Association Between Left Ventricular Mechanics and Heart Rate Variability in Untreated Hypertensive Patients

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The authors sought to investigate left ventricular (LV) mechanics and heart rate variability (HRV), and their relationship, in untreated hypertensive patients. A total of 63 untreated hypertensive patients and 45 healthy patients were included. All patients underwent 24-hour Holter monitoring and echocardiographic examination (two- and three-dimensional). All parameters of time and frequency domain of HRV were decreased in the hypertensive patients. Two-dimensional LV longitudinal and circumferential deformation was significantly reduced in hypertensive patients. Three-dimensional LV strain in all three directions as well as area strain were reduced in the hypertensive group. In two different models of multivariate regression, two-dimensional LV longitudinal and circumferential strain, as well as three-dimensional LV area strain, remained associated with HRV parameters independently of LV structural and functional parameters. This study showed that LV mechanics and HRV were significantly impaired in untreated hypertensive patients. Two- and three-dimensional echocardiographic LV deformation were independently associated with HRV parameters in the whole study population. *J Clin Hypertens (Greenwich).* 2015;17:118–125. © 2014 Wiley Periodicals, Inc.

Studies have shown that autonomic imbalance, characterized by an increased activity of sympathetic nervous system and a decreased activity of parasympathetic system has been related with different pathological conditions, including cardiovascular diseases.[1] The autonomic imbalance is associated with cardiovascular morbidity and mortality[1] and could be estimated by heart rate variability (HRV) using 24-hour Holter monitoring.

HRV is affected by many modifiable cardiovascular risk factors such as essential arterial hypertension, metabolic syndrome, diabetes, obesity, family history, or work stress, but it is also significantly deteriorated in conditions such as acute myocardial infarction and heart failure. In addition, HRV is closely related with sudden death and cardiovascular mortality.[1–3]

Investigations have revealed that depressed HRV is associated with cardiac, vascular, and renal target organ damage in hypertensive patients.[4–6] The most frequently used markers of cardiac damage in these studies were left ventricular (LV) hypertrophy and pulsed Doppler indexes as parameters of LV diastolic dysfunction.[5–8] To our knowledge, there is no study that has investigated the association between LV mechanics and autonomic imbalance assessed by HRV.

We aimed to determine LV mechanics, evaluated with comprehensive two- and three-dimensional strain analyses, and HRV in untreated hypertensive patients. Additionally, we sought to investigate the relationship between LV mechanics and HRV parameters in the whole study population of hypertensive patients and controls.

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METHODOLOGY

Between September 2012 and December 2013, we enrolled 63 untreated hypertensive patients and 45 normotensive patients without cardiovascular risk factors. Exclusion criteria were age older than 60, antihypertensive treatment, heart failure, coronary artery disease, previous cerebrovascular events, atrial fibrillation, congenital heart disease, valvular heart disease, obesity (body mass index [BMI] $\geq$30 kg/m^2), neoplastic disease, cirrhosis of the liver, kidney failure, or endocrinological diseases including type 2 diabetes mellitus. Patients with nonsinusal rhythms and artificially paced were excluded. Patients with unsatisfactory three-dimensional echocardiographic (3DE) acquisitions (5 participants) were also excluded from any further analyses.

Clinic blood pressure (BP) values were obtained in two separate visits 3 weeks apart. BP was measured by conventional sphygmomanometer in the morning hours by taking the average value of three consecutive measurements in the sitting position 10 minutes apart. BP was calculated as the average values between all the measurements. Arterial hypertension was diagnosed according to the current guidelines.[9]

Anthropometric measures (height and weight) and laboratory analyses (level of fasting glucose, blood creatinine and urea, total cholesterol, and triglycerides) were obtained from all the patients included in the study. BMI and body surface area (BSA) were calculated for each patient. The study was approved by the local

ethics committee, and informed consent was obtained from all of the participants.

24-hour Holter monitoring

Twenty-four–hour Holter monitoring was performed with a three-channel digital Schiller Microvit MT-101 system (Schiller AG, Baar, Switzerland) and analyzed by Schiller software (Schiller AG). The minimum duration of recording was 18 hours (after exclusion of nonsinusal cardiac cycles). Electrocardiographic segments were considered appropriate if they were free of artifacts and ectopic cardiac beats with regular RR intervals that could be easily analyzed by the software. Only time intervals between normal QRS complexes (NN intervals) were used. The RR intervals before and after an ectopic beat were not considered for the calculation of the HRV. The recording was subdivided into 5-minute intervals for the HRV analysis. When a compliance ratio was less than 80% of NN intervals within a 5-minute interval, this time interval was not used for the calculation. When an episode of atrial fibrillation was detected, the QRS complexes during this arrhythmia were not accepted for HRV analysis. The software performed triangular interpolation of RR intervals. The time-series sequences were transformed in power spectral density by using the Fourier transformation. Power spectral density was calculated for 5-minute segments and for the complete recording. Our system has high sampling frequency and resolution (8000 Hz), which enables extremely accurate measure of the R peak.

Time-domain HRV parameters were calculated on 24-hour, daytime, and nighttime recordings after excluding nonsinusal cardiac cycles according to the guidelines.[10] SDNN was defined as the standard deviation of all normal RR intervals. SDANN, which reflects long-term HRV and therefore mainly sympathetic activity or sympathovagal balance, was defined as the standard deviation of the averaged normal RR intervals for all 5-minute segments. rMSSD was calculated as the root mean square of the difference between the coupling intervals of adjacent RR intervals. pNN50, which reflects short-term beat-to-beat HRV and consequently primarily vagal activity, was calculated as the proportion of adjacent RR intervals that varied by more than 50 ms. After power spectral density estimation, four standard frequency-domain HRV measures were calculated for 24-hour, daytime, and nighttime recordings.[10] Low frequency domain (LF) was defined between 0.04 and 0.15 Hz, high frequency domain (HF) was defined between 0.15 and 0.4 Hz, total spectral power (TP) for all intervals up to 0.4 Hz, and ratio of low to high frequency power (LF/HF).

Echocardiography

Echocardiographic examinations were performed using a commercially available Vivid 7 (GE Vingmed, Horten, Norway) ultrasound machine equipped with both a 2.5-MHz transducer and a 3V matrix probe for 3DE dataset acquisitions.

Reported values of all two-dimensional echocardiographic (2DE) parameters were obtained as the average value of three consecutive cardiac cycles. LV diameters, posterior wall, and septum thickness were measured according to the current recommendations.[11] Relative wall thickness was calculated according to the formula. LV ejection fraction (EF) was calculated by using the biplane method. LV mass was calculated by using the Devereux formula[12] and indexed for the height powered to 2.7.

Pulsed-wave Doppler assessment of transmitral LV was obtained in the apical four-chamber view according to the guidelines.[13] Tissue Doppler imaging was used to obtain LV myocardial velocities in the apical four-chamber view, with a sample volume placed at the septal and lateral segments of the mitral annulus during early and late diastole (e′ and a′) and systole (s). The average of the peak early diastolic relaxation velocity (e′) of the septal and lateral mitral annulus was calculated, and the E/e′ ratio was computed.

2DE Strain Analysis

2DE strain analysis was performed by using three apical (long-axis, 4- and 2-chamber) views and three parasternal short-axis views of the LV (basal, just below the mitral level; mid-ventricle, at the papillary muscle level; and apical).[14] Commercially available software (EchoPAC 110.1.2, GE-Healthcare, Horten, Norway) was used for 2DE strain quantitation.

2DE longitudinal strain was calculated by averaging all the values of regional peak longitudinal strain values obtained in three apical views. 2DE circumferential strain and radial strain were assessed as the average of the LV six regional values measured in the parasternal short-axis view at the level of papillary muscles. To evaluate LV twist, tracking points were placed on end-diastolic frame short-axis views obtained at basal and apical LV levels.[14] LV twist values and untwisting rate were calculated by software. LV torsion was calculated when LV twist was divided by end-diastolic LV length.

3DE Examination and 3DE Strain Analysis

A full-volume acquisition of the left ventricle was obtained by harmonic imaging from the apical approach. Six ECG-gated consecutive beats were acquired during end-expiratory breath-hold to generate LV full volume. Depth size and volume size were adjusted to obtain a temporal resolution higher than 30 volumes/s. All datasets were analyzed offline using commercially available software (4D Auto LVQ, GE-Vingmed). The 3DE global deformation parameters: longitudinal strain, circumferential strain, radial strain, and area strain were calculated as weighted averages of the regional values from the 17 myocardial segments at end-systole.[15] If three or more segments were rejected, global strain values were not calculated, and these patients were excluded from any further analyses.

Statistical Analysis

Continuous variables were presented as mean±standard deviation (SD), and the Student *t* test was used to detect differences between the two groups for the variables that showed normal distribution. The differences in proportions were compared using the chi-square test. Pearson's correlation coefficients were used for determining the correlation between different demographic and echocardiographic parameters and HRV parameters in the whole study population including controls and hypertensive patients. Almost all HRV parameters, except SDNN and SDANN, were transformed by natural logarithm, before using the *t* test or linear regressions because of their high positive skewed distribution. The variables that showed *P* values ≤.10 were included into the stepwise multiple regression analyses. We established two models of multivariate regression in all study participants. Model 1 included age, systolic BP, LV mass index, mitral E/e', LV longitudinal and circumferential strain, LV torsion, and LV untwisting rate. Model 2 included age, systolic BP, LV mass index, mitral E/e', and 3D LV area strain. The *P* <.05 was considered statistically significant.

RESULTS

There was no significant difference in age and sex distribution between the two observed groups, whereas BMI and BSA were increased in the hypertensive patients (Table I). Blood glucose, creatinine, and triglyceride levels were similar between hypertensive patients and controls. BP values were higher in hypertensive patients, by definition. Urea and total cholesterol levels were also higher in the hypertensive patients (Table I).

TABLE I. Demographic Characteristics and Clinical Parameters of the Study Population

	Controls (n=45)	Hypertension (n=63)	*P* Value
Age, y	45±8	47±7	NS
Women, %	21 (46)	27 (43)	NS
BMI, kg/m^2	23.9±2.2	25.6±2.5	<.001
BSA, m^2	1.9±0.2	2.03±0.25	<.001
Clinic systolic BP, mm Hg	128±9	146±8	<.001
Clinic diastolic BP, mm Hg	78±6	86±5	<.001
Plasma glucose, mmol/L	5.2±0.5	5.4±0.6	NS
Creatinine, mmol/L	68±7	70±8	NS
Urea, mmol/L	5.3±1.2	5.9±1.4	.02
Triglycerides, mmol/L	1.5±0.3	1.6±0.3	NS
Total cholesterol, mmol/L	5.0±0.6	5.4±0.7	.003

Abbreviations: BMI, body mass index; BP, blood pressure; BSA, body surface area; NS, not significant.

Echocardiographic Conventional Parameters and LV Mechanics

LV diameters and ejection fractions were similar between the groups (Table II). Parameters of LV hypertrophy (interventricular septum and relative wall thickness, LV mass index) were higher in the hypertensive patients (Table II). Traditional parameters of LV diastolic function (transmitral E/A and E/e' ratio, and DT) were deteriorated in the hypertensive patients.

2DE LV strain in all two directions (longitudinal and circumferential) was decreased in the hypertensive patients, whereas radial strain was similar between the groups (Table II). LV twist and torsion, as well as LV untwisting rate, were lower in the hypertensive patients.

3DE LV strain in all directions (longitudinal, circumferential, and radial), as well as area strain, were decreased in the hypertensive patients (Table II).

24-hour Holter Monitoring

Heart rates during 24 hours, day, and night were similar between the hypertensive patients and the controls (Table III). SDNN, SDANN, rMSSD, and p50NN were lower in the hypertensive patients. Twenty-four–hour, daytime, and nighttime LF and HF were also decreased in the hypertensive group (Table III). Similar results were obtained for TP. On the other hand, there was no difference in 24-hour, daytime, and nighttime ratio between LF and HF (LF/HF).

Correlation and Multivariate Regression Analysis

In the total study population, transmitral E/e' ratio, 2DE LV longitudinal and circumferential strain, LV twist and untwisting rate, as well as 3DE LV area strain correlated with SDNN, but, in model 1, only E/e' ratio, 2DE LV longitudinal strain, and circumferential strain were independently associated with SDNN (Table IV). Model 2 revealed that mitral E/e' ratio (β=–0.29, *P*=.031) and 3DE LV area strain (β=0.52, *P*<.001) were independently associated with SDNN.

LV mass index, transmitral E/e' ratio, 2DE LV longitudinal, and circumferential strain correlated with rMSSD, and only longitudinal strain was independently associated with rMSSD according to model 1 in the complete investigated population (Table IV). Model 2 showed that 3DE LV area strain was independently associated with rMSSD (β=0.413, *P*<.001).

Age, LV mass index, transmitral E/e' ratio, 2DE LV longitudinal and circumferential strain, LV twist and LV untwisting rate, and 3DE LV area strain correlated with 24-hour LF in all study participants. Model 1 showed that transmitral E/e' ratio and 2DE LV longitudinal strain were independently associated with 24-hour LF (Table IV), whereas model 2 demonstrated that only 3DE LV area strain was independently associated with 24-hour LF (β=0.47, *P*<.001).

LV mass index, transmitral E/e' ratio, 2DE LV longitudinal and circumferential strain, and 3DE LV area strain correlated with 24-hour HF in controls and hypertensive patients in model 1, but only 2DE longitudinal strain was independently associated with 24-hour HF (Table IV), while model 2 found that 3DE LV area strain was independently associated with 24-hour HF (β=0.406, *P*<.001).

TABLE II. Echocardiographic Parameters of the Study Population

	Controls (n=45)	Hypertension (n=63)	*P* Value
2DE parameters			
LV end-diastolic diameter, mm	49.2±5	50.4±5.3	NS
LV end-systolic diameter, mm	32.3±4.1	33.4±4.4	NS
Interventricular septum thickness, mm	9.2±1.2	10.4±1.3	<.001
Relative wall thickness	0.37±0.04	0.41±0.05	<.001
LA, mm	35.4±3.3	38.3±3.8	<.001
LVM/Ht$^{2.7}$, g/m$^{2.7}$	40.2±5.6	48.1±6.8	<.001
EF, %	64±5	64±4	NS
E/A ratio	1.22±0.25	1.03±0.2	<.001
DT, ms	180±29	206±33	<.001
E/e'_m ratio	5.3±1.7	7.6±2.7	<.001
2DE speckle tracking analysis			
Peak LV systolic strain, %			
Global longitudinal strain	−21.1±2.6	−18.7±2.2	<.001
Global circumferential strain	−22.7±3	−21±3.4	.008
Global radial strain	47.4±12.2	45.5±12.4	NS
LV twist, °	19.3±5.1	17±4.6	.017
LV torsion, °/cm	2.4±0.8	2.1±0.6	.029
LV untwisting rate, °/s	−131±35	−116±30	.019
3DE speckle tracking analysis			
Global longitudinal strain, %	−20.3±2.5	−17.6±2.1	<.001
Global circumferential strain, %	−22±2.7	−19.1±2.5	<.001
Global radial strain, %	44.2±8.1	40.8±7.5	.028
Global area strain, %	−30.5±4.4	−27±3.5	<.001

Abbreviations: 2DE, two-dimensional; 3DE, three-dimensional; A, late diastolic mitral flow (pulse Doppler); E, early diastolic mitral flow (pulse Doppler); e′, average of the peak early diastolic relaxation velocity (e′) of the septal and lateral mitral annulus (tissue Doppler); EF, ejection fraction; Ht, height; IVS, interventricular septum; LA, left atrium; LV, left ventricular; LVM, left ventricular mass; NS, not significant.

TABLE III. Heart Rate Variability Parameters in the Study Population

	Controls (n=45)	Hypertension (n=63)	*P* Value
24-h heart rate, beats per min	73±7	75±8	NS
Daytime heart rate, beats per min	80±8	82±9	NS
Nighttime heart rate, beats per min	62±7	61±8	NS
SDNN, ms	152±44	128±39	.004
SDANN, ms	130±47	114±35	.04
Ln rMSSD, ms	3.4±0.4	3.1±0.5	.002
Ln p50NN, %	1.8±1	1.1±1.2	<.001
Ln 24-h LF, ms^2	6.8±0.8	6.1±0.7	<.001
Ln daytime LF, ms^2	6.9±0.7	6.2±0.8	<.001
Ln nighttime LF, ms^2	6.6±0.8	6±0.9	<.001
Ln 24-h HF, ms^2	5.5±0.7	4.9±0.8	<.001
Ln daytime HF, ms^2	5.3±0.7	4.7±0.9	<.001
Ln nighttime HF, ms^2	5.7±0.8	5±1	<.001
Ln 24-h LF/HF	1.6±0.4	1.7±0.5	NS
Ln daytime LF/HF	1.8±0.5	1.8±0.6	NS
Ln nighttime LF/HF	1.1±0.6	1.3±0.6	NS
Ln 24-h TP, ms^2	7.9±0.5	7.3±0.6	<.001
Ln daytime TP, ms^2	8±0.6	7.4±0.7	<.001
Ln nighttime TP, ms^2	7.9±0.7	7.2±0.6	<.001

Abbreviations: HF, high-frequency domain (0.15–0.40 Hz); LF, low-frequency domain (0.04-0.15 Hz); NS, not significant; p50NN, percentage of adjacent R-R intervals that varied by more than 50 ms; rMSSD, root mean square of the difference between the coupling intervals of adjacent R-R intervals; SDANN, standard deviation of the averaged normal RR intervals for all 5-min segments; SDNN, standard deviation of all normal RR intervals; TP, total power (0.01–0.40 Hz).

Age, LV mass index, transmitral E/e' ratio, 2DE LV longitudinal and circumferential strain, and LV untwisting rate, as well as 3DE LV area strain, correlated with 24-hour TP in the whole study population. Model 1 demonstrated that transmitral E/e' ratio and 2DE LV circumferential strain were independently associated with 24-hour TP (Table V), whereas model 2 showed that transmitral E/e' ratio (β=−0.34, *P*<.001) and 3DE LV area strain (β=0.45, *P*<.001) were independently associated with 24-hour TP.

DISCUSSION

There are several important findings of our investigation that deserve discussion: (1) LV mechanics assessed by 2DE and 3DE strain analysis was significantly deteriorated in the hypertensive patients; (2) HRV was impaired in the hypertensive patients; and (3) LV mechanics, along with LV hypertrophy and diastolic function, were associated with HRV in the whole study population.

In our previous studies we showed that high-normal BP and arterial hypertension impacts LV mechanics evaluated with 2DE and 3DE speckle tracking imaging,[16,17] which is in agreement with the findings from the literature.[18–20] Our results showed that 2DE LV longitudinal strain and radial strain were reduced in hypertensive patients, whereas 2DE radial strain did not differ between the observed groups. On the other hand, 3DE LV radial strain was decreased in the hypertensive patients, which could suggest higher sensitivity of 3DE assessment. 3DE LV area strain, as a combination of longitudinal and circumferential strain, and accurate and reproducible index for quantitative assessment of global and regional LV function, was also depressed in

TABLE IV. Association Between Two-Dimensional Left Ventricular Mechanics and Heart Rate Variability Parameters (Adjusted for Sex and BMI)

	SDNN, ms		Ln rMSSD, ms		Ln 24-h LF, ms^2		Ln 24-h HF, ms^2	
	Correlation r	Multivariate regression β	Correlation r	Multivariate regression β	Correlation r	Multivariate regression β	Correlation r	Multivariate regression β
Model 1								
Age, y	−0.205	–	−0.143	–	−0.301[a]	−0.121	−0.188	–
Systolic BP, mm Hg	−0.108	–	−0.09	–	−0.119	–	−0.12	–
LV mass index, g/m$^{2.7}$	−0.187	–	−0.253[a]	−0.16	−0.295[a]	−0.086	−0.263[a]	−0.146
E/e'_m ratio	−0.364[b]	−0.31[a]	−0.27[a]	−0.171	−0.47[b]	−0.31[a]	−0.297[a]	−0.152
2DE LV longitudinal strain, %	0.418[b]	0.37[b]	0.315[b]	0.278[a]	0.52[b]	0.37[b]	0.378[b]	0.32[b]
2DE LV circumferential strain, %	0.389[b]	0.32[b]	0.278[a]	0.203	0.46[b]	0.227	0.32[b]	0.206
Torsion, °/cm	0.355[b]	0.215	0.218	–	0.322[a]	0.179	0.227	–
Untwisting rate, °/s	0.311[b]	0.186	0.186	–	0.26	–	0.211	–
r^2		0.55		0.4		0.53		0.41

Abbreviations: 2DE, two-dimensional; BMI, body mass index; BP, blood pressure; HF, high-frequency domain (0.15–0.40 Hz); E, early diastolic mitral flow (pulse Doppler); e′, average of the peak early diastolic relaxation velocity (e′) of the septal and lateral mitral annulus (tissue Doppler); LF, low-frequency domain (0.04–0.15 Hz); LV, left ventricular; rMSSD, root mean square of the difference between the coupling intervals of adjacent R-R intervals; SDNN, standard deviation of all normal RR intervals. [a]$P<.05$. [b]$P<.01$.

the hypertensive patients. This is also concurrent with the previous reports.[18]

LV twist, torsion, and untwisting rates were significantly increased in the hypertensive patients in the present investigation, which concurs with other investigations.[21,22] This confirms that both systolic and diastolic LV functions are impaired in the hypertensive population, which could explain the development of systolic or diastolic heart failure in the later course of disease.

Our study showed that time domain parameters SDNN and SDANN, which predominantly reflect the overactivity of sympathetic nervous system, were reduced in the hypertensive patients. The same results were obtained for rMSSD and p50NN, parameters that reflect vagal activity. Frequency domain parameters (LF, HF, and TP) in the hypertensive patients were significantly lower than in the control group during daytime, nighttime, and the entire 24 hours, whereas LF/HF ratio remained the same between the two groups. The data from the literature about LF, HF, and LF/HF in hypertension are still controversial.[23–29] The Atherosclerosis Risk in Communities (ARIC) study did not find any difference in these three HRV parameters between normotensives and untreated hypertensives, while HF and LF were significantly lower in treated hypertensives compared with normotensive controls.[24] The possible explanation could be the usage of only 2-minute ECG data, and not 24-hour Holter monitoring, which we performed in our investigation. In the prospective analysis of the ARIC study participants, investigators demonstrated a statistically significant graded inverse association between the baseline HF and LF/HF ratio on

TABLE V. Association Between Two-Dimensional LV Mechanics and Heart Rate Variability Parameters (Adjusted for Sex and BMI)

	Ln 24-h TP, ms^2	
	Correlation r	Multivariate regression β
Model 1		
Age, y	−0.26[a]	−0.118
Systolic BP, mm Hg	−0.13	–
LV mass index, g/m$^{2.7}$	−0.283[a]	−0.137
E/e'_m ratio	−0.493[b]	−0.432[b]
2DE LV longitudinal strain, %	0.395[b]	0.205
2DE LV circumferential strain, %	0.411[b]	0.311[a]
Torsion, °/cm	0.2	–
Untwisting rate, °/s	0.305[a]	0.133
r^2		0.47

Abbreviations: 2DE, two-dimensional; BMI, body mass index; BP, blood pressure; E, early diastolic mitral flow (pulse Doppler); e′, average of the peak early diastolic relaxation velocity (e′) of the septal and lateral mitral annulus (tissue Doppler); LV, left ventricular; TP, total power (0.01–0.40 Hz). [a]$P<.05$. [b]$P<.01$.

one side, and the risk of incident hypertension on the other side, whereas no clear pattern of correlation was found for LF.[24]

Zaliunas and colleagues[27] reported that the LF and LF/HF ratio decreased, while HF increased, after antihypertensive therapy. The authors explained these changes by decreased sympathetic nervous system activity after initiation of antihypertensive therapy. Mussalo and colleagues[28] found decreased HF and LF in hypertensive patients, whereas LF/HF ratio was similar between normotensive and the hypertensive patients, as we found. Virtanen and colleagues[29] revealed the same results in hypertensive patients of both sexes. Additionally, the investigators demonstrated that increased plasma renin activity was an independent predictor of reduced HF power, which provides one more possible mechanism that could explain impaired HRV in hypertension.[29]

The deterioration of HRV parameters confirms the existence of autonomic imbalance in arterial hypertension. Namely, vagal activity is mainly associated with an HF component, whereas an LF component is more controversial.[10] Some authors consider LF a marker of sympathetic modulation, while others consider it a parameter of both sympathetic and vagal influences.[10] These disturbances in autonomic regulation might partly explain the increased risk of cardiovascular events, even in hypertensive patients with optimal BP control.[30,31]

Our research shows that LV mass index, LV diastolic function estimated by mitral E/e', and LV longitudinal and circumferential mechanical function, as well as 3DE LV area strain, correlate with HRV parameters. Furthermore, LV diastolic function and LV longitudinal strain were independently associated with HRV components. In addition, 3DE LV area strain that represents a composite parameter of longitudinal and circumferential myocardial function was independently associated with HRV parameters. Previously it had been shown that LV mass and interventricular wall thickness, parameters of LV structure, and mitral E/A ratio, as an index of LV diastolic function, were associated with autonomic imbalance.[5–8] However, this is the first study to demonstrate the association between LV 2DE and 3DE mechanics and autonomic nervous system in a hypertensive population.

Autonomic disturbances in arterial hypertension and the relationship between HRV parameters and LV structure, function, and mechanics have not yet been clarified, but they could be explained by several mechanisms. Arterial hypertension is directly (by increased preload and afterload) or indirectly (by atherosclerosis development) associated with LV hypertrophy and LV diastolic dysfunction, which are connected with both LV mechanical function[32] and autonomic imbalance.[5-8] Furthermore, arterial hypertension is associated with oxidative stress and increased concentration of inflammation markers that negatively correlate with LV deformation and HRV simultaneously.[33,34] On the other hand, autonomic disturbances and predominance of sympathetic nervous system in hypertension could contribute to LV remodeling by activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system itself. Both biohumoral systems are related to modification in collagen turnover and consequent myocardial fibrosis that cause increase of myocardial stiffness, reduction of myocardial deformation, development of cardiac hypertrophy, and diastolic dysfunction.

Our results have significant clinical application because they showed, for the first time, the relationship between autonomic nervous system and myocardial deformation in the hypertensive population. This finding shows that LV mechanics evaluated by speckle tracking imaging could also indirectly provide information about the status of autonomic nervous system in hypertensive patients without using additional methods such as 24-hour Holter monitoring. This is especially important for the majority of hypertensive patients who are not candidates for Holter monitoring and who should undergo echocardiographic examination as a part of detection of asymptomatic target organ damage during evaluation, which is highly recommended by current guidelines.[9] In addition, LV strain decreases before LV hypertrophy occurrence and could indicate cardiac damage, as well as autonomic disturbances, before the development of LV hypertrophy or LV diastolic dysfunction identified by traditional echocardiographic Doppler parameters. This should help provide us with the information as to when to start medication therapy and how aggressively. In addition, by using LV strain we could tailor therapy for each patient individually and follow the success of medical treatment. Namely, there are limited data about the influence of medical treatment on HRV that reveal that combination of β-blocker and angiotensin-converting enzyme inhibitor or β-blocker and calcium channel blocker significantly improved HRV in hypertensive patients, better than any other single group of antihypertensive agents.[35,36] These findings indicate that β-blockers still have an important place in the treatment of arterial hypertension, despite their unfavorable position in the latest American Joint National Committee guidelines for management of hypertension (JNC 8), which almost completely sidelined β-blockers.[37]

LIMITATIONS

Our research has several limitations. First, the 2DE and 3DE speckle tracking analysis could be significantly influenced by the quality of ultrasound images, especially during the full-volume acquisition when it is required to include the whole LV cavity and wall while maintaining an adequate frame rate. Second, we excluded all patients with comorbidities and included patients with uncomplicated newly diagnosed hypertension, which reduces potential generalization of our results, especially when taking into account patients with long-lasting hypertension, diabetes, severe obesity,

and older age. Considering the fact that this was a cross-sectional study, we could not determine the causal relationship between the increased BP and LV mechanics or HRV, which represents another potential limitation of this study. Fourth, HRV components are surrogate measurements of the autonomic nervous system and could be poorly associated with direct measurements of muscle sympathetic nerve activity.[38]

CONCLUSIONS

Our investigations showed that LV mechanical function as well as autonomic nervous function are significantly deteriorated in untreated hypertensive patients. The results revealed a significant relationship between LV deformation and HRV parameters. This association could provide significant insight into the pathophysiologic mechanisms that connect HRV, myocardial deformation, and cardiovascular outcomes. Further prospective studies with a larger population of hypertensive patients are required to investigate the long-term prognostic significance of LV mechanical changes and the interaction between HRV and LV deformation on cardiovascular morbidity and mortality in hypertensive patients. Future research should also investigate the influence of different therapeutic approaches to LV mechanics, HRV, and their interaction in order to improve the prognosis of hypertensive patients.

Conflict of interest: None.

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