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Myocardial work in hypertensive patients with and without diabetes: An echocardiographic study

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Abstract

We aimed to investigate myocardial performance using pressure-strain loops in hypertensive patients with and without type 2 diabetes mellitus (DM). This cross-sectional study included 165 subjects (55 controls, 60 hypertensive patients without DM, and 50 hypertensive patients with DM) who underwent complete two-dimensional echocardiographic examination (2DE) including two-dimensional speckle-tracking echocardiography. Pressure-strain curve was used to determine global myocardial work index, constructive work, wasted work, and work efficiency in all study participants. Left ventricular (LV) longitudinal and circumferential strains gradually reduced from controls throughout hypertensive subjects to patients with DM and hypertension. Global myocardial work index gradually increased from controls, throughout hypertensive patients to subjects with hypertension and DM (1887 ± 289 vs 2073 ± 311 vs 2144 ± 345 mm Hg%, $P = .001$). Constructive work increased in the same direction (2040 ± 319 vs 2197 ± 344 vs 2355 ± 379 mm Hg%, $P < .001$). Work efficiency and wasted work did not differ between three observed groups. Glycosylated hemoglobin and systolic blood pressure were associated with global myocardial work and constructive work independently of age, body mass index, LV structural and functional parameters in all hypertensive participants. In conclusion, pressure-strain curve showed that myocardial work was significantly affected by hypertension and diabetes. Diabetes demonstrated an additional negative effect on myocardial work in hypertensive patients.

1 | INTRODUCTION

Myocardial deformation represents one of the most important innovations in the echocardiographic field in the last two decades because it considers many parameters that provide insight information about myocardial function beyond standard echocardiographic indices.[1] This primarily refers to left ventricular (LV) ejection fraction that has always been considered as a reference standard parameter of LV systolic function. However, the growing body of evidence showed that myocardial deformation and primarily LV longitudinal strain represents superior predictor of adverse outcome.[2,3] Even though the parameters of myocardial deformation have many advantages that overcome limitations of LV ejection fraction and other conventional echocardiographic parameters, there is a continuous discussion about load influence on LV strain.[4]

Myocardial work is a novel set of parameters that involve afterload and overcome the load dependency of LV ejection fraction and LV strain. This is dynamic non-invasive method that takes into account myocardial deformation and blood pressure. This method was developed almost three decades ago, but it considered invasive measurements obtained during heart catheterization, which is impractical for everyday clinical practice. Russell et al[5] developed a non-invasive method to calculate myocardial work using LV pressure-strain loops obtained from speckle tracking and showed strong correlation with myocardial glucose metabolism. This method has been used in patients with heart failure and prediction of response to cardiac resynchronization therapy, as well as in patients with confirmed or suspected coronary artery disease.[6-9] Clemmensen et al[10] reported significant correlation between echocardiography-derived myocardial work and myocardial external efficiency evaluated by positron emission tomography in patients with cardiac amyloidosis, which supports use of echocardiography in evaluation of myocardial work and confirms that cardiac catheterization is not the only adequate method for assessment of myocardial work.

However, data about myocardial work in hypertensive and diabetic patients are scarce and recent studies included only patients with isolated diabetes mellitus (DM) or hypertension, without consideration of patients with both conditions.

The aim of this article was to evaluate myocardial work, using pressure-strain loops, in hypertensive patients with and without DM.

2 | METHODOLOGY

This was a cross-sectional study that involved 55 control subjects, 60 patients with hypertension, and 55 patients with hypertension and type 2 DM. The patients were referred to the echocardiographic examination as the part of the screening program conducted at the University Hospital "Dr Dragisa Misovic – Dedinje," Belgrade, Serbia. Therefore, the majority of hypertensive patients were recently diagnosed and echocardiographic examination was performed before initiation of antihypertensive therapy. Exclusion criteria were as follows: heart failure, coronary artery disease, more than mild valve disease, atrial fibrillation, neoplastic disease, liver cirrhosis, or kidney failure. Coronary artery disease was excluded by anamnestic data, echocardiographic examination, and cardiopulmonary exercise test which was conducted with ECG monitoring and therefore is superior to regular ECG exercise test. Neither of included patients had any symptom or sign of coronary artery disease.

Anthropometric measures (height and weight) and laboratory analyses (fasting glucose level, HbA1c, total cholesterol, triglycerides, and creatinine) were taken from all study participants. Body mass index (BMI) and body surface area (BSA) were calculated for each patient. Diabetes was diagnosed according to the current recommendations.[11] Arterial hypertension was defined as clinic systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg on two separate occasions or regular taking antihypertensive treatment. One of BP measurements was taken at the time of echocardiographic examination. Data regarding medication usage was obtained of all participants included in the study. The study was approved by the local Ethics Committee in Belgrade and written informed consent was obtained from all the participants.

2.1 | Echocardiography

Vivid 7 ultrasound machine (GE Healthcare) was used for echocardiographic examination. The values of all parameters were obtained as the average value of three consecutive cardiac cycles. LV diameters, interventricular septum, and posterior wall thickness were measured according to the guideline recommendations.[12] LV ejection fraction (EF) was evaluated by using the biplane method. LV mass was calculated by using the formula of the American Society of Echocardiography[12] and indexed for BSA. Left atrial (LA) volume was evaluated using the biplane method and indexed for BSA. Transmitral Doppler inflow and tissue Doppler velocities were obtained according to the guidelines.[13]

2.2 | LV strain analysis and myocardial work analysis

2D strain imaging was performed by using three consecutive cardiac cycles.[14] Q-analysis (EchoPAC version 202, GE Healthcare) was used for evaluation of 2D strain. Speckle-tracking analysis of the LV was performed in three apical (4- and 2-chamber, long-axis) views and parasternal short-axis view at the papillary muscle level. Longitudinal strain was assessed in apical views and circumferential and radial strains in short-axis parasternal view. The automatic tracking of the endocardial contour provided by software was manually verified, and the region of interest was revised to confirm the inclusion of the whole LV thickness in all echocardiographic views. The software divided the LV into six segments in each of 4-chamber, 2-chamber, apical long-axis views and calculated longitudinal strain, whereas short-axis view at the papillary muscle level was used for assessment of circumferential and radial strains.[14]

Myocardial work assessment was performed using the same software. After calculation of LV global longitudinal strain, values of brachial blood pressure were inserted, and the time of valvular events was determined by echocardiography.[15] Pulse-wave Doppler signal at mitral valve and aortic valve level of the apical long-axis view was used for determination of the time of valvular events. The software provided non-invasive pressure-strain loops by synchronizing longitudinal strain, blood pressure, and data about the time of valvular events. The area of the loop served as global myocardial work index, which corresponds with total work within the area of LV pressure-strain loop, from mitral valve closure to mitral valve opening. Additional indices of myocardial work were also calculated: global constructive work (myocardial work performed during LV shortening in systole and LV lengthening during the isovolumic relaxation phase); global wasted work (myocardial work performed during LV lengthening in systole and LV shortening in isolvolumic relaxation phase); and global work efficiency (constructive work divided by the sum of constructive and wasted work).[15]

2.3 | Statistical analysis

Continuous variables were presented as mean ± standard deviation and were compared by the analysis of equal variance using age and BMI as covariates (ANCOVA), as majority of variables showed normal distribution. Tukey HSD post hoc analysis was used for the comparison between different groups. The Mann-Whitney *U* test for non-normally distributed continuous variables was used for variables that did not show normal distribution. Differences in proportions were compared by the χ^2 test. The univariable and multivariable regression analyses were used to evaluate the relationship between demographic, laboratory and echocardiographic parameters and global myocardial work and constructive work. Intra-class correlation coefficients (ICC) were used for assessment of reproducibility. The *P*-value < .05 was considered statistically significant.

3 | RESULTS

Hypertensive patients with DM were older than control subjects (Table 1). Gender distribution was similar between groups (Table 1). BMI and heart rate were higher in hypertensive DM patients than controls (Table 1). SBP and DBP were higher in hypertensive patients with and without DM than in controls, which was expected by definition (Table 1). Fasting glucose and HbA1c were higher in hypertensive patients with DM than in controls and hypertensive patients. Total cholesterol and triglycerides levels were higher in hypertensive patients with DM than in controls and hypertensive participants (Table 1). Serum creatinine in hypertensive patients with DM was higher than in controls.

3.1 | Conventional echocardiographic measurements

LV diameters and ejection fraction did not differ between three groups (Table 2). Interventricular septum, LV posterior wall thickness, and LV mass index gradually increased from controls to hypertensive patients with DM (Table 2). Parameters of LV diastolic function, E/A, and E/e′ ratio, gradually deteriorated from controls to hypertensive patients with DM (Table 2). LA volume index gradually increased from controls to hypertensive patients with DM (Table 2).

3.2 | 2D strain analysis and myocardial work

2D longitudinal and circumferential strains were significantly lower in hypertensive patients with and without DM than in controls (Table 3). There was no difference in radial strain between observed groups.

Global myocardial work and global constructive work were significantly increased in hypertensive patients with and without DM

TABLE 1 Demographic characteristics and clinical parameters of study population

	Controls (n = 55)	HT (n = 60)	DM + HT (n = 50)	*P*
Age (y)	51 ± 7	54 ± 8	56 ± 8[a]	.004
Female (%)	26 (48)	28 (47)	24 (48)	.990
BMI (kg/m^2)	26.2 ± 2.0	27.1 ± 2.2	27.4 ± 2.4[b]	.015
Heart rate (beats/min)	70 ± 8	73 ± 9	75 ± 9[b]	.013
SBP (mm Hg)	128 ± 9	147 ± 11[a]	145 ± 10[a]	<.001
DBP (mm Hg)	72 ± 8	93 ± 9[a]	90 ± 8[a]	<.001
Antihypertensive therapy (%)	–	19 (32)	29 (58)	–
Antidiabetic therapy (%)	–	–	28 (56)	–
Fasting glucose level (mmol/L)	5.3 ± 0.7	5.1 ± 0.9	6.7 ± 1.2[a,c]	<.001
HbA1c (%)	5.1 ± 0.7	5.3 ± 0.8	7.0 ± 1.0[a,c]	<.001
Triglycerides (mmol/L)	1.6 ± 0.4	1.8 ± 0.5	2.4 ± 0.5[a,c]	<.001
Total cholesterol (mmol/L)	5.0 ± 0.9	5.3 ± 1.0	6.1 ± 0.9[a,c]	<.001
Serum creatinine (umol/L)	80 ± 10	83 ± 12	89 ± 11[a]	.041

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; HT, arterial hypertension; SBP, systolic blood pressure.

[a] $P < .01$ vs controls.

[b] $P < .05$ vs controls.

[c] $P < .01$ vs HT.

TABLE 2 Echocardiographic parameters of left ventricular structure and function in the study population (adjusted for age, BMI, triglycerides, and creatinine levels)

	Controls (n = 55)	HT (n = 60)	DM + HT (n = 50)	*P*
LVEDD (mm)	46 ± 4	47 ± 5	48 ± 5	.096
IVS (mm)	9.0 ± 1.0	10.1 ± 1.2[a]	10.7 ± 1.3[a]	<.001
PWT (mm)	8.7 ± 1.0	9.5 ± 1.1	10.0 ± 1.0	<.001*
LAVI (mL/m^2)	26.7 ± 3.7	30.8 ± 4.0[a]	32.4 ± 4.4[a]	<.001
LVMI (g/m^2)	70 ± 10	83 ± 12	92 ± 15	<.001**
EF (%)	63 ± 3	62 ± 3	62 ± 3	.134
E/A ratio	1.11 ± 0.18	0.87 ± 0.23[a]	0.81 ± 0.20[a]	<.001
E/e´	6.5 ± 2.3	9.3 ± 2.6[a]	9.8 ± 3.0[a]	<.001

Abbreviations: A, late diastolic mitral flow (pulse Doppler); DM- type 2 diabetes mellitus; E, early diastolic mitral flow (pulsed Doppler); e′, average of the peak early diastolic relaxation velocity of the septal and lateral mitral annulus (tissue Doppler); EF, ejection fraction; HT, arterial hypertension; IVS, interventricular septum; LAVI, left atrial volume index; LVMI, left ventricular mass index; LVEDD, left ventricle end-diastolic dimension; PWT, posterior wall thickness.

[a]$P < .01$ vs controls.

*$P < .05$ for all comparisons.

**$P < .01$ for all comparisons.

TABLE 3 Speckle-tracking assessment of the left ventricular function in the study population

	Controls (n = 55)	HT (n = 60)	DM + HT (n = 50)	*P*
Two-dimensional mechanical parameters				
Longitudinal strain (%)	−21.3 ± 2.6	−18.6 ± 2.2[a]	−17.7 ± 2.0[a]	<.001
Circumferential strain (%)	−22.1 ± 2.9	−19.5 ± 2.4	−18.3 ± 2.3	<.001*
Radial strain (%)	41.8 ± 10.1	40.3 ± 10.6	38.5 ± 9.3	.247
Myocardial work				
Global myocardial work index (mm Hg%)	1887 ± 289	2073 ± 311[a]	2144 ± 345[a]	<.001
Global constructive work (mm Hg%)	2040 ± 319	2197 ± 344	2355 ± 379	<.001*
Global wasted work (mm Hg%)	87 ± 40	96 ± 45	108 ± 52	.072
Global work efficiency (%)	95 ± 3	96 ± 3	95 ± 3	.123

Abbreviations: DM, type 2 diabetes mellitus; HT, arterial hypertension.

[a]$P < .01$ vs controls.

*$P < .05$ for all comparisons.

than in controls (Table 3). Global wasted work and global work efficiency were similar between three groups (Table 3).

3.3 | Regression analyses

Univariable regression analysis showed significant association between sex, SBP, HbA1c, total cholesterol, E/e′, LVEF and LV mass index and global myocardial work (Table 4). SBP, HbA1c, total cholesterol, E/e′, and LVEF were associated with global constructive work (Table 4). SBP, HbA1c, and E/e′ were independently associated with global myocardial work index. SBP and HbA1c were independently associated with global constructive work (Table 4).

3.4 | Reproducibility

The interclass correlations coefficients (ICC) for the inter-observer variability were 0.938 (95% CI: 0.894-0.962) for global myocardial work index, 0.948 (95% CI: 0.912-0.971) for global constructive work, 0.922 (95% CI: 0.872-0.974) for global wasted work, and 0.976 (95% CI: 0.947-0.993) for global work efficiency.

The ICC for the intra-observer variability were 0.951 (95% CI: 0.917-0.979) for global myocardial work index, 0.960 (95% CI: 0.935-0.975) for global constructive work, 0.948 (95% CI: 0.927-0.986) for global wasted work, and 0.987 (95% CI: 0.960-0.995) for global work efficiency.

TABLE 4 Univariable and multivariable regression analysis of different demographic and echocardiographic parameters and parameters of myocardial work in patients with hypertension with/without diabetes

	Global myocardial work index (mm Hg%)				Global constructive work (mm Hg%)			
	β	*P*	β	*P*	β	*P*	β	*P*
Age (y)	−0.014	.596	−0.010	.610	−0.032	.468	−0.044	.377
Sex (women)	0.179	.037	0.114	.109	0.021	.548	0.062	.284
BMI (kg/m^2)	−0.105	.109	−0.092	.211	−0.120	.095	−0.095	.115
SBP (mm Hg)	0.445	<.001	0.510	<.001	0.569	<.001	0.480	<.001
HbA1c (%)	0.231	<.001	0.204	.018	0.293	<.001	0.227	.010
Total cholesterol (mmol/l)	0.154	.041	0.097	.194	0.133	.050	0.080	.093
E/e′ ratio	0.210	.001	0.169	.046	0.250	<.001	0.121	.079
LV mass index (g/m^2)	0.170	.042	0.123	.119	0.142	.063	0.105	.092
LVEF (%)	0.206	.022	0.142	.093	0.156	.048	0.088	.163

Abbreviations: BMI, body mass index; E, early diastolic mitral flow (pulsed Doppler); e′, average of the peak early diastolic relaxation velocity of the septal and lateral mitral annulus (tissue Doppler); HbA1c, glycosylated hemoglobin; LV, left ventricle; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

4 | DISCUSSION

The current study provided several interesting findings that deserve further discussion: (a) global myocardial work index and global constructive work were significantly higher in hypertensive patients with and without diabetes than in controls; (b) there was no difference in global wasted work and global work efficiency between controls and hypertensive patients, irrespective of DM; (c) SBP and HbA1c were independently of sex, BMI and conventional echocardiographic parameters associated with global myocardial work index and global constructive work in hypertensive participants.

Our data confirmed findings from the previous studies regarding reduced longitudinal and circumferential strains in hypertensive patients with and without DM.[15,16] Recent studies showed that arterial pressure was one of the most important independent predictors of an accelerated decline in GLS during a follow-up period.[17,18] BP correlated negatively with LV longitudinal and circumferential strain,[15,16] which showed afterload dependency of LV mechanics. Interestingly, our results showed significant difference in LV circumferential, but not longitudinal strain, between patients with hypertension and those with concomitant DM. The most reasonable explanation is a small sample size and inability to achieve statistical significance in post hoc analysis.

The evaluation of myocardial work is conventionally relied on invasive pressure measurements, which significantly reduced feasibility of this technique. Russell et al[5] recently developed non-invasive method for assessment of myocardial work using regional LV pressure-strain loop area that corresponded well with invasive measurements and directly measured myocardial work, as well as myocardial metabolism evaluated by positron emission tomography. Pressure-strain loop area demands measuring valvular timing events by echocardiography, LV longitudinal strain assessment, and peripheral blood pressure.

Present findings revealed that global myocardial index and constructive work were significantly higher in hypertensive patients with and without DM than in controls. Furthermore, DM had an additional impact on global constructive work, but not on global myocardial work index, in hypertensive patients. Increased global myocardial work index in hypertensive patients has been already found in hemodynamic studies that used LV pressure-volume loop tracings.[19] In hypertensive patients, LV pumps against increased arterial pressure, which initially reduces LV stroke volume and increases energy necessary for LV pump function, and consequently elevates global myocardial work index.[19] This was found in our study and in some recently published data.[20] Chan et al found significantly increased global myocardial and constructive work in patients with SBP > 160 mm Hg, but not in those with SBP between 140 and 159 mm Hg.[20] Global wasted work gradually increased from controls, throughout patients with SBP between 140 and 159 mm Hg, to those with SBP > 160 mm Hg. Global myocardial efficiency decreased in the same direction. However, for both parameters, statistical significance was not reached due to a small sample size. Similar changes in LV structure (LV hypertrophy) and mechanics (reduced LV longitudinal strain) were observed in both groups of hypertensive patients comparing with controls, but statistical significance was not obtained due to aforementioned issue with small sample size.

Mansour et al demonstrated significant influence of acute BP elevation during stress echocardiography on myocardial work in patients without coronary artery valve disease.[21] Patients were divided in two groups according to the peak SBP during stress test and threshold was SBP of 180 mm Hg. Hypertension was present in third patients with peak SBP > 180 mm Hg and diabetes in 13% of these patients.[21] There was no difference between groups in indices of myocardial work at rest. However, the authors revealed that global myocardial, constructive, and wasted work was significantly higher in patients with peak SBP > 180 mm Hg than in patients with peak SBP < 180 mm Hg, while there was no difference in global work efficiency between two observed groups.[21] LV longitudinal strain did not differ between these groups neither at rest nor during stress.

Recently published data about DM patients showed that LV global myocardial work index was improved in patients who were treated 12 months with glucagon-like peptide-1 receptor agonist (liraglutide) alone or in combination with the sodium glucose co-transporter-2 (empagliflozin).[22] The patients with combined therapy experienced significant improvement also in global constructive and wasted work.[22] Interestingly, in parallel with improvement of myocardial work, LV longitudinal, circumferential, and radial strains also significantly increased in these groups of DM patients. The reduction of HbA1c was also the highest in the same groups of patients (19.5% and 28.1%, respectively), which reflected the effect of these therapeutic approaches.

Our data showed that indices of myocardial work were deteriorated in hypertensive patients comparing with normotensive controls, but these parameters were even worse in hypertensive patients with concomitant DM. This is in line with recently published studies,[19-23] but also adds some novelties such as concomitant effect of hypertension and diabetes on myocardial work. The present findings revealed that only constructive myocardial work was higher in patients with concomitant hypertension and DM comparing with those who had only hypertension. We could only hypothesize that constructive myocardial work might be more sensitive marker for evaluation of myocardial work impairment in hypertensive patients with DM.

Clinical implications of myocardial work are seen in patients with early stage of disease when LV is not significantly remodeled (hypertension, diabetes, and chemotherapy-induced cardiotoxicity) and potentially in patients with heart failure with preserved ejection fraction. Indices such as global myocardial and constructive work are important parameters because they represent positive LV work and they should be used complementary with other measurements of LV function—LVEF and LV longitudinal strain. The main advantage of myocardial work is the implementation of blood pressure in its calculation and therefore overcoming the influence of afterload, which is inevitable with LV longitudinal strain.

4.1 | Limitations

The present study should be interpreted in reflection of several limitations. First, the patients with other comorbidities were excluded from this study, which limited the potential generalization of obtained results. Second, echocardiographic evaluation of LV mechanics could be influenced by the quality of ultrasound images. Third, subclinical coronary artery disease was not possible to exclude because coronary angiography was not performed in study participants. However, echocardiographic examination and cardiopulmonary exercise test accompanied with ECG monitoring during exercise test excluded possibility for relevant coronary artery disease. Forth, the cross-sectional nature of this study does not allow estimation of causal relationship between hypertension, diabetes, and LV myocardial work.

5 | CONCLUSION

The present investigation showed that LV myocardial work and mechanics were significantly deteriorated in hypertensive patients with and without diabetes. Diabetes additionally affected myocardial work in hypertensive patients. Study revealed that blood pressure and HbA1c, parameter of long-term glucose control, were associated with myocardial work independently of age, sex, BMI and LV function and hypertrophy. Further follow-up investigations with large population of patients are warranted to evaluate a prognostic impact of myocardial work on cardiovascular outcome in hypertensive patients with or without diabetes.

CONFLICT OF INTEREST

None.

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