

# LEFT VENTRICULAR SYSTOLIC FUNCTION IN SELECTED TYPE 1 DIABETIC PATIENTS WITH OR WITHOUT DIABETIC RETINOPATHY AND MICROALBUMINURIA

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**SUMMARY** – Vascular endothelial dysfunction is a basic etiologic factor for the development of late clinical complications in patients with diabetes mellitus type 1, such as diabetic retinopathy, diabetic nephropathy (which is characterized at the very beginning by microalbuminuria), and left ventricular cardiac dysfunction. The aims of this study were to determine the prevalence of asymptomatic left ventricular systolic dysfunction in patients with diabetes mellitus type 1 and with or without diabetic retinopathy and microalbuminuria, and to correlate the duration of diabetes with the dynamics of diabetic retinopathy, microalbuminuria and asymptomatic left ventricular dysfunction development in these patients. One-hundred and twenty selected patients with diabetes mellitus type 1 were examined by ophthalmologist and cardiologist. All patients underwent ergometric testing and two-dimensional (2-D) echocardiography with pulsed Doppler. Patients were divided into three groups according to their fundus findings and microalbuminuria: (1) patients without diabetic retinopathy and without microalbuminuria (n=40); (2) patients with diabetic retinopathy without microalbuminuria (n=40); and (3) patients with diabetic retinopathy and microalbuminuria (n=40). All three groups of patients with diabetes mellitus type 1 (with low cardiovascular risk, regulated blood sugar, and without diabetic neuropathy) had echocardiographic values in the normal range. We found no statistically significant correlation between the duration of diabetes mellitus type 1 and echocardiographic values.

**Key words:** *Diabetes mellitus, type 1; Retinopathy; Albuminuria; Ventricular function, left*

## Introduction

Diabetes mellitus type 1 (DM1) is a complex, polygenetic, chronic, autoimmune disease characterized by selective destruction of  $\beta$ -cells in pancreatic islets<sup>1,2</sup>. Diabetes mellitus (DM) causes generalized microangiopathy in late stages and is the most important cause of cardiovascular diseases<sup>3</sup>. Endothelial dysfunction is the most important etiologic factor for

microangiopathy, and affects mostly small vessels in the retina, renal glomeruli, peripheral nerves, and all cardiovascular system components including small blood vessels, great arteries and the heart<sup>4-6</sup>.

Microangiopathic heart changes are the same as in other organs, so these patients often, in the beginning, have asymptomatic dysfunction of the left ventricle<sup>7,8</sup>. Regarding diffuse microangiopathy in patients with DM, we can suppose that patients with diabetic retinopathy (which appears frequently and before microalbuminuria), as a sign of systemic microangiopathy, also have myocardial microangiopathy, which may cause systolic dysfunction of the left ventricle. Systolic heart dysfunction implies more dif-

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ficult left ventricular discharge, which manifests with lower ejection fraction (EF)<sup>9</sup>.

The aim of this study was to determine left ventricular systolic dysfunction in patients with DM1 and clinically (un)evident diabetic retinopathy (DR) with or without associated microalbuminuria, and to evaluate correlation between the duration of DM1 and the first appearance of DR, microalbuminuria, and asymptomatic left ventricular dysfunction.

## Material and Methods

### Statistics

Data analysis was performed with the help of the SPSS17.0 statistical package. Distribution of categorical and metric variables was performed and the distribution of metric variables tested (normal or gaussian, Kolmogorov Smirnov test). If the distribution of metric variables proved normal, parametric methods (ANOVA and Duncan test; ANCOVA) were used to test differences among the three test groups. If the distribution of metric variables was not normal, nonparametric methods were used (Kruskal-Wallis analysis of variance and Mann-Whitney test). We used  $\chi^2$ -test to determine the association of categorical variables with the three groups of patients. Logistic regression analysis was used for each variable (cardiac function) separately to assess correlation of the test variables with DR and DR together with microalbuminuria. Results were interpreted at the level of  $p < 0.05$ .

### Methods

We examined 154 patients with DM1. Inclusion criteria were the onset of the disease at the age between 12 and 30 years; duration of the disease  $\geq 5$  years; regulation of glycemia expressed as HbA<sub>1c</sub> value  $< 9\%$ ; systolic blood pressure  $\leq 130$  mm Hg, diastolic blood pressure  $\leq 80$  mm Hg; absence of diabetic autonomic neuropathy, absence of complete opacification of the optic media and of other vascular ophthalmic diseases; absence of other heart, kidney and hematologic anomalies and diseases.

We excluded 34 patients because of hypertension ( $n=14$ ), presence of autonomic diabetic neuropathy ( $n=7$ ), poor metabolic control of the disease ( $n=6$ ), positive coronary reserve test ( $n=4$ ), lens opacification ( $n=2$ ), and urinary tract infection ( $n=1$ ). All patients

voluntarily participated in the study ( $N=120$ ) and signed the informed consent form.

All patients underwent direct and indirect ophthalmoscopy in mydriasis, stereo fundus photography, and fluorescein angiography. Fundus photography and fluorescein angiography were done with a fundus camera (Zeiss FF 450 plus IR). Apart from urinary sediment analysis, turbidimetric evaluation of microalbuminuria in 24-h urine was also done twice in all patients, 15 days apart, using the MULTIGENT immunoassay on the ARCHITECT cSYSTEMS (Abbott Diagnostics). If the mean value of two measures of microalbuminuria was  $\geq 30$  mg/24 h, it was considered as positive finding. Patients with DM1 ( $N=120$ ) were divided into three groups according to funduscopy and microalbuminuria findings: group 1, patients without DR and without microalbuminuria ( $n=40$ ); group 2, patients with DR without microalbuminuria ( $n=40$ ); and group 3, patients with DR and microalbuminuria ( $n=40$ ).

Ophthalmologist evaluated the autonomic nerve system by measuring pupil cycle time (PCT)<sup>10</sup>. The mean PCT value was obtained by calculating it from values measured on each eye. We considered the time to 954 milliseconds (msec) and the difference between the two eyes of 70 msec as reference values<sup>11-13</sup>. In order to exclude the presence of coronary disease or to evaluate its severity, coronary reserve was tested by cardiologist (Bruce's protocol) using ergometric testing (Marquette Electronics Inc., CASE 12, USA). Echocardiography was performed by the same cardiologist using standardized two-dimensional (2-D) technique on the ultrasound machine VIVID 3-s/w version 1.2 E, with 1.7 MHz probe. We measured left ventricular diameter at the end of diastole (LVIDd); left ventricular diameter at the end of systole (LVIDs); diastolic septal thickness (IVSd); left ventricular posterior wall thickness in diastole (LVPWd); and left atrial diameter (LA) at the level of aortal valve. All values were expressed in centimeters (cm). From LVIDd and LVIDs values, we calculated systolic function of the left ventricle expressed as EF. EF of the left ventricle (ratio between stroke volume and end diastolic volume) was expressed as percentage (%) and calculated according to the formula:  $EF = (LVIDd^3 - LVIDs^3) : LVIDd^3 \times 100$ . The EF value  $> 50\%$  was considered normal.

*Table 1. Number of patients with diabetic retinopathy according to groups*

	Total (N=120)	Group 1 (N=40)	Group 2 (N=40)	Group 3 (N=40)
Without diabetic retinopathy (n)	40	40	0	0
Diabetic retinopathy (n):	80	0	40	40
nonproliferative (n)	68	0	37	31
proliferative (n)	12	0	3	9

*Table 2. Mean (median) age and duration of diabetes mellitus type 1 (DM1)*

	Total (N=120)	Group 1 (N=40)	Group 2 (N=40)	Group 3 (N=40)	P <sup>†</sup>
Age (years)	33 (17-59)	20.5 (17-45)	41.5 (18-59)	43.5 (17-58)	<0.001
Duration of DM1 (years)	11 (5-34)	6.5 (5-22)	16 (5-31)	17.1 (5-34)	<0.001

DM1 = diabetes mellitus type 1; <sup>†</sup>Kruskal-Wallis test (post hoc: Mann-Whitney test)

## Results

The study included 120 patients with DM1, 64 (53.3%) men and 56 (47.7%) women.

Out of 120 study patients, 40 had DM1 without microangiopathic complications (group 1); 40 patients

had DR along with DM1 (group 2); and 40 patients had DM1, DR, and microalbuminuria (group 3) (Table 1).

The mean age (median) of all patients (N=120) was 33 years. The lowest age median was recorded in group

*Table 3. Descriptive values ( $\bar{X} \pm SD$ ) or medians (min-max) of echocardiographic variables in all groups*

	Total (N=120)	Group 1 (N=40)	Group 2 (N=40)	Group 3 (N=40)	P
LVIDd (cm)	4.7±0.49	4.7±0.50	4.7±0.43	4.7±0.56	0.580*
LVIDs (cm)	2.8 (1.7-3.9)	2.7 (1.9-3.9)	2.8 (1.9-3.6)	2.9 (1.7-3.94)	0.245 <sup>†</sup>
IVSd (cm)	0.916±0.13	0.873±0.13	0.944±0.11	0.93±0.14	0.883*
LVPWd (cm)	0.96±0.12	0.934±0.12	0.99±0.12	0.96±0.13	0.379*
LA (cm)	3.18±0.43	3.05±0.42	3.22±0.41	3.26±0.44	0.635*
EF (%)	71.7±6.60	73.8±5.80	70.3±5.90	70.2±7.60	0.264*

LVIDd = left ventricular diameter at the end of diastole; LVIDs = left ventricular diameter at the end of systole; IVSd = diastolic septal thickness; LVPWd = left ventricular posterior wall thickness in diastole; LA = left atrial diameter; EF = ejection fraction; \*ANCOVA (covariables: age, duration of disease; post hoc: Fisher LSD test); <sup>†</sup>Kruskal-Wallis test (post hoc: Mann-Whitney test)

Table 4. Distribution of patients and odds ratio (univariate logistic regression) according to groups and duration of diabetes mellitus type 1 (DM1) considering median values of ejection fraction (EF)  $\leq 71$

Predictor		EF (%)		p <sup>†</sup>	Odds ratio (95% CI)	p <sup>‡</sup>
		$\leq 71$	$> 71$			
Group	1*	16	24	0.106	1.4 (0.92-2.22)	0.119
	2	25	15			
	3	23	17			
Duration of DM1 (yrs)	$\leq 11$ *	28	34	0.064	2.0 (0.96-4.1)	0.065
	$> 11$	36	22			

DM1 = diabetes mellitus type 1; EF = ejection fraction; \*values reported as basal values; <sup>†</sup> $\chi^2$ -test; <sup>‡</sup>logistic regression

1. The age of group 2 ( $Z=5.4$ ;  $p<0.001$ ) and group 3 ( $Z=5.2$ ;  $p<0.001$ ) patients was significantly higher than in group 1. The median age of group 2 and group 3 patients was twofold that in group 1 (Table 2).

The mean (median) duration of DM1 was 11 years (lower quartile: 7 years, upper quartile: 18.5 years). The duration of the disease in all patients was  $\geq 5$  years. The duration of DM1 was significantly higher in group 2 ( $Z=5.7$ ;  $p<0.001$ ) and group 3 ( $Z=5.8$ ;  $p<0.001$ ) than in group 1. In groups 2 and 3, the median of DM1 duration was twofold that in group 1.

Table 3 shows echocardiographic measures. In groups 2 and 3, echocardiographic values differed significantly from those recorded in group 1, but all were within the reference values. Therefore, we aimed to determine the relationship between the median of EF and DR, microalbuminuria, and duration of DM1. EF values were classified into two categories:  $\leq$ median and  $>$ median.

Table 5. Odds ratio (multivariate logistic regression) for incidence of ejection fraction  $\leq 71\%$  according to duration of diabetes mellitus type 1 (DM1) and age

Predictor	Odds ratio	95% CI	p	
Duration of DM1 (years)	$\leq 11$ *	1.6	0.57-4.5	0.366
	$> 11$			
Age (years)	$\leq 33$ *	1.3	0.48-3.8	0.576
	$> 33$			

DM1 = diabetes mellitus type 1; \*values reported as basal values

We performed  $\chi^2$ -test in order to determine EF distribution according to DM1 duration ( $\leq 11$  years and  $> 11$  years) and groups. This was followed by univariate logistic regression. The  $\chi^2$ -test and univariate logistic regression according to groups as predictor provide answer to the EF correlation with diabetic retinopathy and microalbuminuria.

Multivariate 'forward stepwise (WALD)' analysis was performed to determine the relation of EF with the duration of DM1 ( $\leq 11$  years and  $> 11$  years) and age ( $\leq 33$  years and  $> 33$  years) as predictors.

Left ventricular EF (expressed in %) was not significantly correlated with the group (DR and microalbuminuria) ( $\chi^2=4.49$ ;  $p=0.106$ ), but group 1 was significantly different from groups 2 and 3 together ( $\chi^2=4.3$ ;  $p=0.038$ ) (Table 4). Neither univariate logistic regression ( $p=0.065$ ) nor multivariate logistic regression (predictors: duration of DM1 and age) yielded significant correlation of EF  $\leq 71\%$  with the duration of DM1 ( $p=0.366$ ) (Table 5).

Echocardiographic values, age and duration of the disease did not significantly differ between group 2 (DM1 and DR) and group 3 (DM1, DR and microalbuminuria) patients. Since patients in these groups were older than group 1 patients (DM1 without complications), we matched the group 2 and 3 patients with group 1 patients according to age and duration of DM1. We obtained two groups of 26 patients each, matched for age and DM1 duration. The mean (median) age in group 1 was 22 years (min-max: 17-45 years), and in the other group of patients it was 21

Table 6. Descriptive values of echocardiographic variables ( $\bar{X} \pm SD$ ) or median (min-max) in group 1 patients, and in groups 2 and 3 patients, adjusted for duration of diabetes type 1 and age

	Group 1 (N=26)	Groups 2 and 3 (N=26)	P
LVIDd (cm)	4.7±0.55	4.7±0.49	0.829*
LVIDs (cm)	2.7 (2.3-3.9)	2.8 (1.9-3.7)	0.647†
IVSd (cm)	0.88±0.13	0.89±0.10	0.633*
LVPWd (cm)	0.94±0.13	0.95±0.10	0.715*
LA (cm)	3.18±0.43	3.13±0.40	0.374*
EF (%)	73±6.0	71±6.4	0.370*

LVIDd = left ventricular diameter at the end of diastole; LVIDs = left ventricular diameter at the end of systole; IVSd = diastolic septal thickness; LVPWd = left ventricular posterior wall thickness in diastole; LA = left atrial diameter; EF = ejection fraction; \*T-test; †Mann-Whitney test

years (min-max: 18-49 years) ( $p=0.978$ ). Echocardiographic results in groups 1, 2 and 3, matched according to age and DM1 duration, did not show any significant difference (Table 6).

## Discussion

In patients with DM1, tests offer better possibilities of determining the relation between microangiopathic complications than in patients with diabetes mellitus type 2 because DM1 develops in younger patients with less adjunctive variables associated with metabolic syndrome and senile atherosclerotic factors.

The results of our study showed that the mean echocardiographic values were within the normal range in all three groups of patients with DM1 (N=120) (group 1 without microangiopathic complications, group 2 with DR, and group 3 with DR and microalbuminuria). Data analysis showed significant difference in echocardiographic variables in patients without complications (group 1) as compared with either patients with DR or those with DR and microalbuminuria (groups 2 and 3). There was no significant difference between the patients with DM1 and DR and those with DM1, DR and microalbuminuria. Left ventricular systolic dysfunction values were within the normal range in all patients. Borow *et al.* did not find

any left ventricular systolic or diastolic dysfunction in patients with DM1<sup>14</sup>.

Some authors found significant correlation between left ventricular systolic dysfunction in patients with DM1 when compared with normal population<sup>15-17</sup>. Some other authors found normal left ventricular systolic function and their patients showed pathologic values only on physical exercise<sup>18</sup>. Other authors report on normal echocardiographic values of left ventricular systolic function in patients with DM1 even during physical exercise<sup>19</sup>.

Most authors describe normal left ventricular systolic function in DM1 patients free from microangiopathic complications and with low cardiovascular risk (normotensive patients without cardiac autonomic neuropathy, dyslipidemia, coagulation dysfunction, and proteinuria), and with regulated glycemia<sup>20-24</sup>.

Our results showed that there was no significant correlation between DR and EF <71%, and between DR and microalbuminuria on the one hand and EF <71% on the other. It was also confirmed that there was no correlation between EF <71% and duration of the disease. Raev also examined the relation between EF and duration of DM1 and reports a rare occurrence of systolic dysfunction until the age of 18<sup>23</sup>.

Rajan and Gokhale report normal EF (mean value 73%) in the group of patients with DM1 and microangiopathic complications<sup>21</sup>, while Konduracka *et al.* report abnormal systolic function in 185 examined patients with DM1 and mean duration of the disease of 22.8 years<sup>24,25</sup>. On the contrary, Raev reports deterioration of systolic function in 39% of patients with DM1 and microangiopathic complications (retinopathy, nephropathy and autonomic neuropathy)<sup>26</sup>. Some authors think that hypertension and cardiac autonomic neuropathy (which is present in more than 40% of patients) have great influence on systolic dysfunction development, so with this perspective we can observe the incidence of systolic dysfunction in the previously mentioned study<sup>27-30</sup>.

In an attempt to correct our data, we matched patients according to age and duration of DM1, but we did not obtain any significant difference among the matched groups in any of the echocardiographic variables or EF.

The most important reasons for different results found in other studies may be different inclusion and

exclusion criteria (especially hypertension, neuropathy, and poor blood glucose regulation), and different diagnostic methods employed to reveal complications<sup>31</sup>.

Based on the data gathered on 120 patients with DM1, we have drawn the following conclusions:

1. Mean values of all echocardiographic variables examined in this study were within the normal range in each of the three groups of examined patients with DM1 (with low cardiovascular risk, and without diabetic neuropathy).
2. There were significant differences in echocardiographic variables in the group of patients without complications (group 1) when compared with the group of patients with DR and microalbuminuria together (groups 2 and 3).
3. There was no significant difference in echocardiographic variables between the group of patients with DM1 and DR and the group of patients with DM1, DR and microalbuminuria.
4. There was significant correlation between the duration of DM1, the presence of DR and microalbuminuria.
5. Systolic function, expressed as left ventricular EF, was normal in all patients.
6. There was no significant correlation between DR and EF <71%, or between DR, microalbuminuria and EF <71%.
7. There was no correlation between EF <71% and duration of the disease.

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#### Sažetak

### SISTOLIČKA FUNKCIJA LIJEVE KLIJETKE U ODABRANIH BOLESNIKA SA ŠEĆERNOM BOLESTI TIP 1 S DIJABETIČNOM RETINOPATIJOM I MIKROALBUMINURIJOM ILI BEZ NJIH

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Endotelno-vaskularna disfunkcija je temeljni čimbenik u etiologiji razvoja kasnih kliničkih komplikacija u bolesnika sa šećernom bolesti tip 1 (ŠBT1) uključujući dijabetičnu retinopatiju, dijabetičnu nefropatiju (u samom početku obilježenu mikroalbuminurijom) i disfunkciju lijeve srčane klijetke. Ciljevi rada bili su odrediti asimptomatsku sistoličku disfunkciju lijeve srčane klijetke u bolesnika sa ŠBT1 i klinički (ne)evidentnom dijabetičnom retinopatijom i s mikroalbuminurijom ili bez nje, te utvrditi povezanost trajanja ŠBT1 s pojavom dijabetične retinopatije, mikroalbuminurije i asimptomatske sistoličke disfunkcije lijeve srčane klijetke. Ispitano je 120 odabranih bolesnika sa ŠBT1 (normotenzivni, bez dijabetične neuropatije), koji su s obzirom na nalaz fundoskopije (oftalmoskopski, fundus fotografija i fluoresceinska angiografija) i mikroalbuminurije (turbidimetrijskom metodom) svrstani u tri skupine: 1) bolesnici bez dijabetične retinopatije i bez mikroalbuminurije (n=40); 2) bolesnici s dijabetičnom retinopatijom bez mikroalbuminurije (n=40); 3) bolesnici s dijabetičnom retinopatijom i mikroalbuminurijom (n=40). Kod svih bolesnika izvršeno je ergometrijsko testiranje i ehokardiografsko ispitivanje dvodimenzijom (2-D) i pulsnom Doppler-ehokardiografskom tehnikom. Kod sve tri skupine bolesnika sa ŠBT1 (niskog profila kardiovaskularnog rizika, uredne reguliranosti i bez dijabetične neuropatije) srednje vrijednosti ehokardiografskih varijabla bile su unutar referentnih vrijednosti. Nismo utvrdili statistički značajnu povezanost između trajanja ŠBT1 i ispitivanih ehokardiografskih varijabla.

**Ključne riječi:** Šećerna bolest tip 1; Retinopatija; Albuminurija; Srčana klijetka, lijeva, funkcija