Left ventricle geometry affects coronary flow reserve in diabetic patients

Sol ventrikül geometrisi diyabetli hastalarda koroner akım rezervini etkiler

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ABSTRACT

Objectives: The aim of this study was to investigate the association between coronary flow reserve (CFR) and left ventricle (LV) geometric patterns in patients with newly-diagnosed diabetes mellitus (DM).

Study design: We studied 116 patients with newly-diagnosed DM and 31 healthy control subjects. Echocardiographic examination was performed on all subjects. Four different geometric patterns were identified in diabetic patients, according to LV mass index (LVMI) and relative wall thickness (RWT) [NG: Normal geometry; CR: Concentric remodeling; EH: Eccentric hypertrophy; CH: Concentric hypertrophy]. CFR was calculated as the hyperemic to resting coronary diastolic peak velocities ratio.

Results: Compared with controls, CFR was decreased in diabetic patients ($p<0.05$). The lowest CFR values were observed in the CH group compared with control and other groups ($p<0.05$, for all). Also, CFR values of the CR and EH groups were lower than NG and the control group ($p<0.05$, for all). CFR was associated with LV geometry ($r=-0.449$, $p=0.001$), LVMI ($r=-0.401$, $p<0.001$), RWT ($r=-0.247$, $p=0.008$), HbA1c ($r=-0.576$, $p<0.001$) and mitral valve E/A ratio ($r=0.239$, $p=0.01$) in bivariate analysis. CFR was independently associated with LV geometry ($\beta=-0.449$, $p<0.001$), LVMI ($\beta=-0.192$, $p=0.016$), and HbA1c ($\beta=-0.576$, $p<0.001$) in multivariate analysis.

Conclusion: CFR was impaired in newly-diagnosed DM. The degree of this deformation increases from normal geometry towards to concentric hypertrophy. This condition suggests that myocardial structural remodeling due to diabetes might be effective on CFR.

ÖZET

Amaç: Bu çalışmamızda yeni diabetes mellitus tanısı konmuş hastalarda sol ventrikül geometrik paternleri ile koroner akım rezervi (KAR) arasındaki ilişkiyi değerlendirmeyi amaçladık.

Çalışma planı: Çalışmamıza yeni diabetes mellitus tanısı konmuş 116 hasta ile sağlıklı 31 olguluk kontrol grubu dahil edildi. Tüm hastalara ekokardiyografik değerlendirme yapıldı. Diyabetli hastalar sol ventrikül kitle indeksi ve göreceli duvar kalınlığına göre dört gruba ayrıldı (NG: Normal geometri; KR: Konsantrik remodelling; EH: Ekzantrik hipertrofi; KH: Konsantrik hipertrofi). KAR koroner hiperemik diyastolik en yüksek hızının istirahatteki en yüksek hıza oranı olarak hesaplandı.

Bulgular: Kontrol grubu ile kıyaslandığında diyabetli hasta grubunda KAR azalmış bulundu ($p<0.05$). En düşük KAR, kontrol grubu ve diğer gruplar kıyaslandığında KH grubunda saptandı ($p<0.05$, hepsi için). Aynı zamanda, KAR değeri KR ve EH grubunda NG ve kontrol grubuna göre daha düşük bulundu. İki değişkenli analizde KAR, sol ventrikül geometrisi ile ($r=-0.449$, $p=0.001$), sol ventrikül kitle indeksi ($r=-0.401$, $p<0.001$), göreceli duvar kalınlığı ($r=-0.247$, $p=0.008$), HbA1c ($r=-0.576$, $p<0.001$) ve mitral kapak E/A oranı ile ($r=0.239$, $p=0.01$) ilişkili bulundu. Çok değişkenli analizde, KAR sol ventrikül geometrisi ($\beta=-0.449$, $p<0.001$), sol ventrikül kitle indeksi ($\beta=-0.192$, $p=0.016$) ve HbA1c ($\beta=-0.576$, $p<0.001$) ile bağımsız ilişkili saptandı.

Sonuç: Yeni diabetes mellitus tanısı konmuş hastalarda KAR bozulmuştur. Bu bozulmanın derecesi normal geometriden konsantrik hipertrofiye doğru artmaktadır. Bu durum diabete bağlı miyokardın yapısal yeniden şekilllenmesinin KAR üzerine etkili olabileceğini düşündürmektedir.

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Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in people with diabetes mellitus (DM).[1] Left ventricular hypertrophy (LVH) is a marker of subclinical CVD and may reflect the accumulated effect of exposure to risk factors unrecognized or underrepresented by classic risk equations. LVH is associated with CV morbidity and mortality, independent of established risk factors such as age, sex and diabetes.[2,3] Diabetes is associated with LVH, and a large proportion of patients with DM without known CVD have LVH.[4,5]

DM is thought to directly affect cardiac structure and function, a condition labeled diabetic cardiomyopathy.[6] In fact, recent evidence seems to suggest that diabetic cardiomyopathy is characterized by diastolic dysfunction, which becomes more apparent in the presence of hypertension or myocardial ischemia.[6] Moreover, DM deteriorates microvascular as well as macrovascular function. The function of coronary microcirculation may be clinically evaluated by quantization of the coronary flow reserve (CFR), i.e. the ratio between hyperemic and resting coronary flow. In the absence of significant stenosis of the epicardial coronary arteries, the reduction of CFR represents a reliable marker of coronary microvascular dysfunction.[7,8] A reduction of CFR has been demonstrated using different techniques in diabetic patients without coronary artery stenosis.

The association between LV mass index (LVMI) and CFR in patients with DM has been investigated in previous studies.[9] However, the association between left ventricle (LV) geometric patterns, which incorporate normal LV structure and concentric remodeling (CR) in addition to LVH, and CFR has not yet been investigated.

In the current study, we hypothesized that LV structure affects CFR in patients with DM. Furthermore, the relationship between CFR and different LV geometric patterns was investigated in patients with newly-diagnosed DM.

PATIENTS AND METHODS

The present study prospectively included 116 (82 female, 34 male and mean age: 48.7±10 years) patients with newly-diagnosed DM and 31 (18 female, 13 male and mean age: 49.7±10 years) age- and sex- matched healthy control subjects. Type 2 DM was defined according to the Standards of Medical Care in Diabetes of the American Diabetes Association.[10] The control group had multiple fasting blood glucose (FBG) measurements <100 mg/dl. These healthy subjects were enrolled from the non-medical staff of our hospital or their relatives, and had normal electrocardiogram, normal echocardiographic examinations and no risk factors for CAD.

Abbreviations:

ASE	*American Society of Echocardiography*
BMI	*Body mass index*
CFR	*Coronary flow reserve*
CH	*Concentric hypertrophy*
CR	*Concentric remodeling*
CVD	*Cardiovascular disease*
DM	*Diabetes mellitus*
EH	*Eccentric hypertrophy*
FBG	*Fasting blood glucose*
HT	*Hypertension*
IVST	*Interventricular septal thickness*
LAD	*Left anterior descending*
LVDd	*LV diastolic dimension*
LVEF	*Left ventricular ejection fraction*
LVH	*Left ventricular hypertrophy*
LVM	*LV mass*
LVMI	*LV mass index*
PWT	*Posterior wall thickness*
RWT	*Relative wall thickness*

We excluded patients with a history of CAD, symptoms or electrocardiographic signs of ischemia on stress tests, atrial fibrillation, left bundle brunch block, systolic or diastolic heart failure, hypertension (HT), taking any medical treatment, or having an inadequate acoustic window to obtain left anterior descending coronary artery (LAD), M-Mode tracings with insufficient quality for quantitative measurements, those currently smoking, with primary valvular heart disease, hypertrophic cardiomyopathy, regional wall motion abnormalities, left ventricular ejection fraction (LVEF) <50%, major non-cardiovascular diseases, cerebrovascular disease and renal insufficiency (serum creatinine: >1.5 mg/dl in men and >1.4 mg/dl in women). Patients whose CFR <2 also underwent coronary computed tomography angiography, and those with any abnormality were also excluded. Of the 179 patients, 28 on the positive exercise test, and 34 for other reasons were excluded from the study.

After taking detailed medical history and complete physical examination, each participant was questioned for the major cardiovascular risk factors such as age, sex, DM, smoking status and HT. In addition, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and initial heart rate were recorded. All patients underwent transthoracic echocardiography (TTE) and treadmill exercise test (TM Pro 2200, Tepa). The study was conducted according to the recommendations set forth by the Declaration of Helsinki on Biomedical Research Involving Human Subjects. The Institutional Ethics Committee

approved the study protocol and each participant provided written informed consent.[11]

Blood pressure measurements used in the study were taken with a mercury sphygmomanometer at the time of echocardiography. BMI was computed as weight divided by height squared (kg/m^2). Body surface area of all subjects was computed (m^2).

Echocardiography

Standard 2D and Doppler echocardiographic examinations were performed using commercially available equipment (Vivid-7, GE Vingmed Sound, Horten, Norway) with a 2.5-3.5 MHz transducer. A simultaneous electrocardiographic recording was also obtained for each patient. All echocardiographic examinations were performed and analyzed by one observer (GYK). All patients were examined at rest in the left lateral decubitus position. Interventricular septal thickness (IVST), posterior wall thickness (PWT) and (LVDd) were measured at end-diastole according to the established standards of the American Society of Echocardiography (ASE).[12] LVEF was calculated using Simpson's method. Pulsed Doppler recordings of mitral flow velocities were obtained from the apical 4-chamber view by placing the sample volume between the tips of the mitral leaflets. Peak early (E) and late diastolic (A) transmitral filling flow velocities, and E/A ratio were measured. LV mass (LVM) was calculated according to the ASE-recommended formula:[12]

$$LVM=0.8x\{1.04[(LVDd+IVST+PWT)^3-(LVDd)^3]\}+0.6$$

Thereafter, LVMI was obtained using the following formula: LVM/body surface area. Relative wall thickness (RWT) was measured at end diastole as the ratio of:

(2xLV posterior wall thickness)/LVDd.

LVH was defined as LVMI values >125 g/m^2 in men and >110 g/m^2 in women.[13] Increased RWT was accepted as ≥0.45.[14]

Pattern of Left Ventricular Geometry

Geometric patterns were based on the upper normal limits for LVMI and RWT: *(i)* normal geometry (NLV; normal LVMI and normal RWT); *(ii)* Concentric remodeling (CR; normal LVMI and increased RWT); *(iii)* eccentric hypertrophy (EH; increased LVMI and normal RWT); and (iv) concentric hypertrophy (CH; increased LVMI and increased RWT).[14,15]

CFR Measurements

Visualization of the distal LAD was performed with a modified, foreshortened, 2-chamber view obtained by sliding the transducer on the upper and the medial part from an apical 2-chamber view. The color Doppler visualization of coronary flow in the LAD artery was obtained with a 5 MHz shallow-focus phased-array transducer over the epicardial part of the anterior wall, with the color Doppler velocity range set in the range of 10-20 cm/s. The LV was imaged on the long-axis cross section, and the ultrasound beam was then inclined laterally. The spectral Doppler signals of the distal LAD displayed the characteristic biphasic flow pattern, with a diastolic dominant flow and a smaller systolic component (Figure 1). Peak systolic and diastolic velocities were measured at baseline and under hyperemic conditions obtained with i.v. infusion of

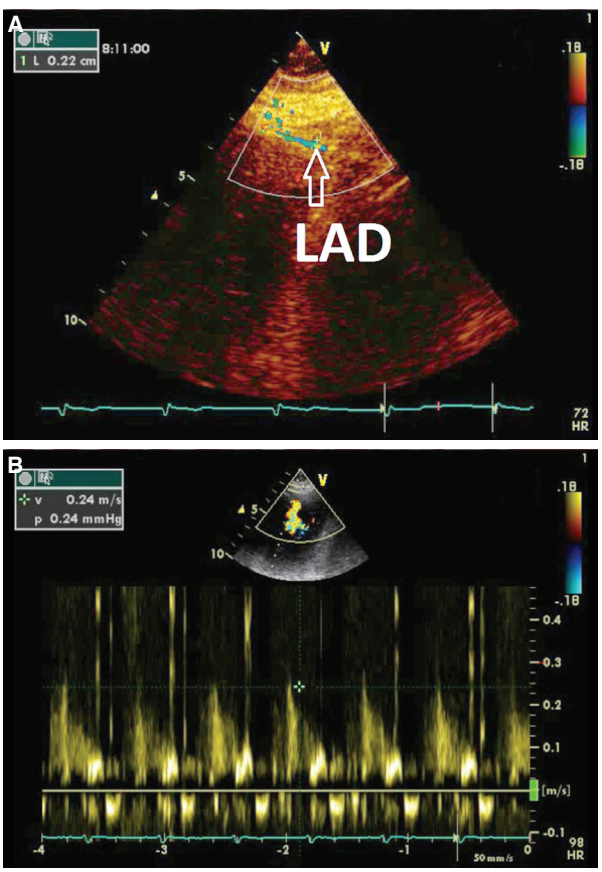

Figure 1. Assessment of CFR. **(A)** Mid to distal segment of the LAD coronary artery in color-coded transthoracic Doppler echocardiography. **(B)** Spectral Doppler coronary blood flow in mid to distal segment of the LAD.

adenosine (140 µgr.kg^{-1}.min^{-1}) over 3-6 minutes. An average peak diastolic velocity was calculated from more than three cardiac cycles, and blood pressure and heart rate were also measured for the same cycles. The CFR was calculated as the ratio of hyperemic to baseline peak diastolic velocities.[7]

Statistical analysis

All analyses were performed using the SPSS software (Statistical Package for the Social Sciences, Version 17.0, SSPS Inc., Chicago, IL, USA). Continuous variables were expressed as mean values±SD, and categorical variables as percentages. Analysis of normality was performed with the Kolmogorov-Smirnov test. Comparisons of continuous variables between the two groups were performed using the independent samples t-test. Comparison among multiple groups was performed by one-way analysis of variance (ANOVA) with LSD post hoc test for continuous variables. Associations of coronary flow reserve with demographical, clinical and echocardiographic parameters were assessed by the Pearson correlation coefficient. Independent relationships of coronary flow reserve were assessed by multiple linear regres-

Table 1. Clinical characteristics, laboratory and echocardiographic findings of groups

Variables	Patients (n=116)	Controls (n=31)	*p*
	Mean±SD	Mean±SD	
Age (years)	48.7±10	49.7±10	NS
Sex, female (%)	70.7	58.1	NS
Body mass index (kg/m²)	32.6±6.2	29.6±4.3	NS
Body surface area (m²)	1.9±0.18	1.9±0.17	NS
Fasting blood glucose (mg/dL)	161.0±74.4	92.5±8.3	**<0.001**
Total cholesterol (mg/dL)	208.4±47.0	202.6±39.1	NS
Low-density lipoprotein (mg/dL)	139.0±40.0	135.5±37.7	NS
High density lipoprotein (mg/dL)	45.1±10	45.3±11.2	NS
Triglyceride (mg/dL)	171.3±89.6	147.0±88.8	NS
Creatinine (mg/dL)	0.73±0.15	0.72±0.16	NS
Hemoglobin (g/dL)	13.6±1.4	14.2±1.4	NS
HbA1c (%)	7.80±1.8	5.26±0.35	**<0.001**
Systolic blood pressure (mmHg)	130.1±20.8	129.3±16.6	NS
Diastolic blood pressure (mmHg)	72.9±13.8	78.2±12.1	NS
Heart rate (beats/min)	81.7±14.1	77.5±10.6	NS
Posterior wall thickness (cm)	0.99±0.11	0.95±0.10	NS
Interventricular septal thickness (cm)	1.0±0.10	1.0±0.13	NS
Left ventricle end diastolic diameter (cm)	4.6±0.4	4.7±0.4	NS
Left ventricle end systolic diameter (cm)	2.9±0.3	3.0±0.3	NS
EF (%)	65.8±5.0	66.0±6.0	NS
Mitral E velocity	0.67±0.14	0.75±0.15	0.010
Mitral A velocity	0.75±0.18	0.67±0.15	0.031
E/A ratio	0.91±0.26	1.1±0.36	**0.001**
Relative wall thickness	0.43±0.58	0.40±0.39	**0.003**
Left ventricule Mass (g)	164.2±35.2	171.2±38.8	NS
Left ventricule mass index (g/m²)	92±18.2	82±11.4	**0.001**
Coronary flow reserve	2.47±0.39	2.79±0.44	**<0.001**

NS: Not significant; SD: Standard deviation; EF: Ejection fraction.

sion analysis. For multiple regressions, factors with p<0.001 in bivariate correlation test were selected. Standardized β-regression coefficients and their significance from multiple linear regression analysis are reported. A two-tailed p-value of 0.05 was considered statistically significant.

RESULTS

In the present study, of the 116 diabetic patients, 47 (40.5%) had NLV, 26 (22.4%) exhibited CR of the LV, 22 (18.9%) exhibited EH, and 21 (18.1%) had CH. Of the 31 control subjects, all had both normal LV mass and normal RWT.

Baseline and Echocardiographic Characteristics of Normal and Diabetics Groups

Clinical and echocardiographic characteristics of normal and diabetic subjects are presented in Table 1. There were no statistical differences in gender, age, body surface area and heart rate between controls and diabetic subjects (p>0.05 for all). Compared with the control group, the diabetic patients had significantly higher LVMI, RWT, HbA1c, FBG and mitral valve A

Table 2. Clinical characteristics, laboratory and echocardiographic findings according to the type of left ventricular geometry

		Patient group				
	Control group (n=31)	Normal left ventricle (n=47)	Concentric remodelling (n=26)	Eccentric hypertrophy (n=22)	Concentric hypertrophy (n=21)	*p**
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age	49.7±9.9	47.0±10.5	47.8±10.4	52.3±8.5	49.6±9.4	0.259
Gender (Male/Female [n])	18/13	36/11	17/9	15/7	14/7	0.541
BMI (kg/m^2)	29.6±4.3[a]	32.4±6.3	33.7±7.3	31.7±5.5	32.5±5.6	0.139
SBP (mmHg)	119±16.6	120±19.6	121±27	122±21.3	124±13.4	0.711
DBP (mmHg)	64.7±10.1	63.5±15.5	62.9±12.5	64.4±10.8	60.2±13.9	0.792
LVEF (%)	65.9±5.6	66.4±5.0	65.0±4.3	66.4±5.4	64.6±5.1	0.627
Mitral E velocity	0.75±0.15[b]	0.71±0.14[bb]	0.65±0.13	0.67±0.13	0.60±0.17	**0.005**
Mitral A velocity	0.67±0.15[c]	0.71±0.16	0.78±0.18	0.77±0.17	0.79±0.20	0.068
E/A ratio	1.15±0.36[d]	1.0±0.29[dd]	0.91±0.21[ddd]	0.83±0.18	0.70±0.17	**<0.001**
CFR	2.8±0.44[e]	2.6±0.4[ee]	2.5±0.3[eee]	2.4±0.3[eeee]	2.1±0.36	**<0.001**
RWT	0.36±0.039[f]	0.38±0.047[f]	0.47±0.053[ff]	0.42±0.040[fff]	0.47±0.052	**<0.001**
LVMI (g/m^2)	82.5±11.4[g]	81.1±15.7[gg]	86.3±10.5[g]	103.8±2.9	109.3±13.3	**<0.001**
HbA1c	5.2±0.3[h]	7.2±1.6[hh]	7.3±1.4[hhh]	8.2±1.6[hhhh]	9.2±2.4	**<0.001**

*: Anova; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVEF: Left ventricle ejection fraction; CFR: Coronary flow reserve; RWT: Relative wall thickness; LVMI: Left ventricle mass index.

[a]p=0.013 *vs.* control group;

[b]p=0.014 *vs.* control group, p<0.001 *vs.* concentric hypertrophy group; [bb]p=0.006 *vs.* concentric hypertrophy;

[c]p=0.028 *vs.* control group, p=0.026 *vs.* concentric hypertrophy group, p=0.044 *vs.* eccentric hypertrophy group;

[d]p=0.001 *vs.* control group, p<0.001 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [dd]p=0.041 *vs.* control group, p=0.002 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [ddd]p=0.01 *vs.* concentric hypertrophy group;

[e]p=0.004 *vs.* control group, p<0.001 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [ee]p=0.015 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [eee]p=0.002 *vs.* concentric hypertrophy group; [eeee]p=0.0027 *vs.* concentric hypertrophy group;

[f]p<0.001 *vs.* control group, p<0.001 *vs.* concentric hypertrophy group; [ff]p<0.001 *vs.* eccentric hypertrophy group; [fff]p<0.001 *vs.* concentric hypertrophy group;

[g]p<0.001 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [gg]p=0.043 *vs.* control group, p<0.001 *vs.* eccentric hypertrophy group, p=0.001 *vs.* concentric hypertrophy group;

[h]p<0.001 *vs.* normal left ventricle group; p<0.043 *vs.* control group, p<0.001 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [hh]p=0.017 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [hhh]p=0.037 *vs.* eccentric hypertrophy group, p<0.001 *vs.* concentric hypertrophy group; [hhhh]p=0.043 *vs.* concentric hypertrophy group.

Table 3. Bivariate and multivariate relationships of coronary flow reserve to clinical, demographic, and echocardiographic variables in patients with diabetes mellitus

	Pearson correlation coefficient	*p*	Standardized β-regression co efficient	*p*
Age	-0.14	NS		
Body mass index (kg/m^2)	-0,012	NS		
Relative wall thickness	-0.247	**0.008**	-0.158	NS
Left ventricule mass index	-0.401	**<0.001**	-0.192	0.016
HbA1c	-0.576	**<0.001**	-0.487	**<0.001**
Left ventricule geometry	-0.449	**0.001**	-0.298	**0.001**
Left ventricle end diastolic diameter	-0.069	NS		
Left ventricle end systolic diameter	-0.123	NS		
Left ventricle ejection fraction	0.070	NS		
Heart rate (pulse/min)	0.038	NS		
Mitral E velocity	0.181	NS		
Mitral A velocity	0.026	NS		
E/A ratio	0.239	**0.01**	-0.070	NS
Systolic blood pressure	0.061	NS		
Diastolic blood pressure	0.140	NS		

NS: Not significant.

velocity (p<0.05 for all). CFR, mitral valve E/A ratio, mitral valve E velocity were lower in patients compared with control subjects (p<0.05 for all).

Differences of Baseline Characteristics and Echocardiographic Findings among LV geometric Patterns

Clinical characteristics, laboratory and echocardiographic findings according to the type of left ventricular geometry are presented in Table 2. CFR, mitral valve E velocity, mitral valve E/A ratio of all geometric patterns in diabetic patients were lower than those in the control group (p<0.05 for all). Besides RWT, LVMI and HbA1c of all geometric patterns in diabetic patients were higher than those in the control group (p<0.05 for all) (Table 2).

CFR of NLV geometric pattern was higher than that of the EH and CH groups (p=0.015 and p<0.001 respectively), but similar to that of the CR and control group (p=0.128 and p=0.084 respectively). CFR of the CR group was higher than that of the CH group (p=0.02), but similar to that of the EH group (p=0.362). CFR of the CH group was lower than that of the EH group (p=0.02) (Figure 2).

Mitral valve E/A ratio of NLV geometric pattern was lower than that of the CR, EH and CH groups (p=0.041, p=0.002 and p<0.001 respectively). Mitral valve E/A ratio of the CR group was lower than that of the CH group (p<0.01), but similar to that of the EH group (p=0.305). Mitral valve E/A ratio of the CH group was similar to that of the EH group (p=0.132).

HbA1c of NLV geometric pattern was lower than that of the EH and CH groups (p=0.017 and p<0.001 respectively), but similar to that of the CR group (p=0.945). HbA1c of the CR group was lower than that of the CH and EH group (p<0.001 and p=0.037 respectively). HbA1c of the CH group was higher than that of the EH group (p=0.043) (Figure 3).

Bivariate and Multivariate Associations of CFR

In the patients group (n=116), there was a correlation between CFR and RWT, LVMI, HbA1c, LV geometry and mitral valve E/A ratio (Table 3). All significant (p<0.05) parameters in the bivariate analysis (LVMI, LV geometry, E/A ratio, HbA1c) were selected in the multivariate model.

Multiple linear regression analysis showed that CFR was independently correlated with LV geometry

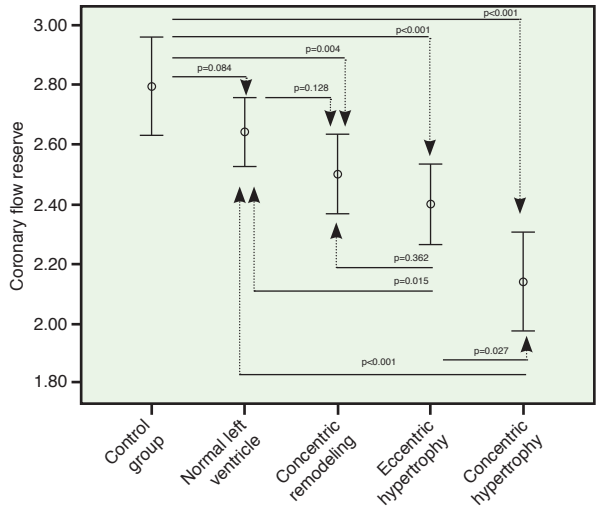

Figure 2. Comparison of groups according to CFR.

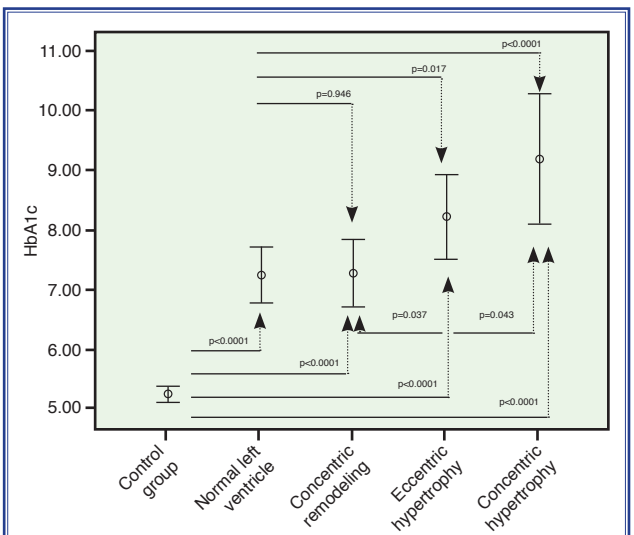

Figure 3. Comparison of groups according to HbA1c.

(β=-0.298, p=0.001), HbA1c (β=-0.487, p<0.001) and LVMI (β=-0.192, p=0.016) (Table 3).

DISCUSSION

To the best of our knowledge, this is the first report to evaluate the association between geometric patterns of LV with CFR in newly-diagnosed diabetic patients. The main findings of this study were that; (i) mean CFR values of all geometric patterns were significantly decreased compared to control group, and (ii) CFRs were independently related to LV geometry, LVMI and HbA1c.

CFR is an important indicator in coronary endothelial function and microcirculation in diabetic patients.[16] In the absence of significant stenosis of the epicardial coronary arteries, reduction of CFR represents a reliable marker of coronary microvascular dysfunction.[16,17] A reduction of CFR was demonstrated in diabetic patients without coronary artery stenosis.[18]

Previous studies have demonstrated an inverse association between CFR and LV diastolic and systolic function in diabetic patients.[18-20] The study of Strauer BE et al.[21] reported that the markedly-reduced coronary flow reserve in diabetic patients may play a key role in the induction and perpetuation of coronary insufficiency in myocardial ischemia, in diastolic and systolic dysfunction, and in the initiation of diabetic cardiomyopathy. On the other hand, LVH causes LV diastolic dysfunction that alters the coronary flow reserve because of coronary flow occurs predominantly at diastole. In the present study, CFR was correlated with diastolic dysfunction assessed with E/A ratio, but not independently associated in the multivariate analysis. In the present study, a strong association between left ventricle geometry and CFR may enhance the relation between CFR and E/A.

Left-ventricular hypertrophy is an independent hallmark of cardiovascular risk in the general population.[22] It develops frequently in diabetic patients, independent of the effect of concomitant risk factors.[23] Notably, the presence of LV hypertrophy is associated with microvascular dysfunction in both diabetic and hypertensive patients.[24] The adjusted CFR in the present study confirmed a previously-observed association with LVMI.[25] In the present study, the reduction of CFR showed a strong, inverse relation with LV geometry in the diabetic population. Although four different geometric patterns have been demonstrated in DM, the relation between coronary flow reserve and different geometric patterns has not yet been investigated in DM patients.

We precisely analyzed LV functional parameters in diabetic patients after classifying them into 4 different LV geometric patterns. A previous study reported that patients with concentric hypertrophy had the highest mortality and cardiovascular event rate, followed by those with eccentric hypertrophy.[26] These findings are consistent with our finding that CFR was lower in concentric hypertrophy in diabetic patients. These results suggest that microvascular dysfunction assessed with

echocardiography may be associated with a worse prognosis in patients with concentric hypertrophy.

In the present study, elevated LV mass was associated with lower CFR, that suggested a poor prognosis for diabetes. Therefore, decrease in CFR values, particularly in hypertrophic geometries (CH, EH) may be the consequence of the effect of LVH on microvascular dysfunction. This condition may be plausible. Furthermore, this geometric pattern is the end-point of DM that both LVMI and RWT increased. Earlier reports showed the adverse effect of LVMI on microvascular functions.[24]

Reduced CFR is an important feature of a hypertrophied ventricle.[26] Although reduced CFR may not affect left ventricular function at rest, it may lead to impaired subendocardial wall function and reduced subendocardial coronary perfusion during periods of stress in the hypertrophied myocardium.[24] Repeated stress and subendocardial ischemia lead to subendocardial fibrosis, which also impairs systolic function. Both the subendocardial ischemia and fibrosis alter left ventricular diastolic function, thereby also impairing systolic function. All of these mechanisms are linked by reduced CFR, which accelerates the progression from compensated left ventricular hypertrophy to failure.[27,28]

CFR of NLV geometric pattern was higher than that of the EH and CH groups but similar to that of the CR and control group. CFR of the CR group was higher than that of the CH group. This condition may be related to the observation of a concentric remodeling in the early stages of DM.

In the present study, HbA1c is independently associated with CFR. Similar results were also observed in other studies.[19,21] The association of CFR with metabolic indexes such as HbA1c was confirmatory that poor glycemic control implies worse prognosis, which may at least be partially attributable to myocardial disease.[29] Chronic hyperglycemia alters the chemical constitution of cell proteins, giving rise to functional and structural changes in tissues. In autopsy studies, a greater degree of myocardial fibrosis with collagen deposition was demonstrated in cases with DM when compared to non-diabetic patients. These data suggest that chronic hyperglycemia could be operative in enhancing myocardial extracellular protein deposition and fibrosis, resulting in increasing LVM and promoting contractile dysfunction.[30,31]

In our study, mitral valve E velocity and mitral valve E/A ratio were significantly lower in DM patients compared to the control group. This finding is compatible with Galderisi et al.[9] that the IRT and E/A ratio were impaired in diabetic patients. We evaluated the diastolic functions using pulse wave Doppler echocardiography, but we did not perform further investigation such as tissue Doppler imaging. Therefore, the relation with only E/A and CFR is not enough to make a certain decision to explain diastolic dysfunction in our patient cohort.

Another limitation of our study is the duration of DM. Since we included newly-diagnosed diabetic patients in our study, most of them did not have former glucose levels and HbA1c. So we do not have certain claims about their duration of diabetes.

In conclusion, CFR was impaired in newly-diagnosed DM. The degree of this deformation increases from normal geometry towards to concentric hypertrophy. This condition suggests that myocardial structural remodeling due to diabetes might be effective on CFR.

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Key words: Blood flow velocity; coronary circulation; diabetes mellitus; echocardiography; hypertrophy, left ventricular.

Anahtar sözcükler: Kan akım hızı; koroner dolaşım; diabetes mellitus; ekokardiyografi; hipertrofi, sol ventrikül.