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ORIGINAL ARTICLE

Index of myocardial performance in patients with type 2 diabetes without hypertension and its relationship with clinical and echocardiographic parameters

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Abstract

Background: Diabetes mellitus affects the systolic and diastolic function of the left ventricle (LV). The aim of the present study was to evaluate the index of myocardial performance (IMP), a new Doppler index, in asymptomatic, normotensive patients with type 2 diabetes mellitus (T2DM).

Methods: The study population consisted of 40 asymptomatic normotensive patients with T2DM (22 women, 18 men; mean [±SD] age 49 ± 7 years) and 20 healthy controls (13 women, seven men; mean age 45 ± 4 years). M-Mode and two-dimensional Doppler echocardiography was performed in all subjects to calculate IMP. Venous blood samples were collected for analysis and body mass index (BMI) was calculated.

Results: In normotensive T2DM patients, the mitral E wave was decreased, whereas mitral A wave, mitral E/A ratio, and septal wall thickening were increased compared with values obtained for the control group. The IMP was higher in normotensive T2DM patients than in the control group ($P = 0.004$). There was a significant correlation between IMP and triglyceride (TG) levels ($P < 0.001$), mitral E wave ($P < 0.001$), mitral E/A ratio ($P < 0.001$), ejection fraction ($P = 0.001$), fasting blood glucose ($P = 0.007$), LV systolic dimension ($P < 0.001$), duration of diabetes ($P = 0.017$), and BMI ($P = 0.029$). Stepwise multiple regression analysis demonstrated that only TG levels ($\beta = 0.355$, $t = 2.487$, $P = 0.017$) and the mitral E/A ratio ($\beta = -0.384$, $t = -2.690$, $P = 0.011$) had an independent effect on IMP.

Conclusion: The results of the present study indicate that IMP is increased in normotensive T2DM patients. The findings suggest that increased IMP may be an early sign of diabetic cardiomyopathy in normotensive diabetic patients with preserved LV function.

Keywords: diabetes, echocardiography, myocardial performance.

Introduction

Epidemiological studies have demonstrated that diabetes mellitus (DM) is a significant risk factor for cardiovascular morbidity and mortality.[1–3] It has been reported that the incidence of heart failure in subjects with diabetes is two to fivefold greater than in the normal population, even after controlling for additional risk factors.[4] However, the clinical presentation in DM patients can range from preserved left ventricular (LV) function "diastolic heart" to asymptomatic or symptomatic LV dysfunction. Various methods have been used to demonstrate LV diastolic dysfunction in DM patients, including digitized M-mode, conventional, and tissue Doppler echocardiography, as well as radionuclide studies.[5–7]

Tei et al. defined a new Doppler-derived index of myocardial performance (IMP),[8] which reflects both LV systolic and diastolic function.[9] The IMP is calculated as the sum of the isovolumetric contraction time (IVCT) and the isovolumetric relaxation time (IVRT) divided by ejection time. The IMP has been reported to be useful in determining prognosis after acute myocardial infarction, dilated cardiomyopathy, and primary pulmonary hypertension.[10–12]

The existence of primary myocardial disease in DM patients (i.e. diabetic cardiomyopathy) has been proposed as evidence of myocardial dysfunction in diabetic patients in the absence of ischemic, valvular, or hypertensive heart disease.[13,14] Diastolic dysfunction has been described as an early sign of diabetic heart muscle disease preceding systolic damage.[15] Recently, Pattoneri et al.[16] showed that global myocardial dysfunction may precede diastolic dysfunction and therefore represents the earliest echocardiographic evidence of diabetic cardiomyopathy. However, the mechanisms underlying diastolic dysfunction in DM patients remain largely unknown.

Therefore, the aim of the present study was to investigate global (systolic and diastolic) ventricular function using the Doppler-derived IMP in asymptomatic, normotensive patients with type 2 DM (T2DM) and to determine the relationship between IMP and clinical and echocardiographic variables in T2DM patients.

Methods

Study population

The study population consisted of 40 asymptomatic normotensive T2DM patients who did not have clinical coronary artery disease (CAD; 22 women, 18 men; mean [$\pm$SD] age 49 ± 7 years) and 20 healthy controls (13 women, seven men; mean age 45 ± 4 years). Exclusion criteria included angiographically proven stenosis (>50% of the luminal diameter), a history of myocardial infarction, regional abnormalities in wall motion at rest on echocardiography, significant ECG changes suggestive of myocardial ischemia, significant valvular disease, arrhythmias, heart failure, chronic obstructive pulmonary disease, hypertension, and any other chronic diseases. Diabetes mellitus was diagnosed on the basis of American Diabetes Association criteria.[17] Hypertension was defined according to the recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[18] or on the basis of treatment with antihypertensive medications for a known diagnosis of hypertension.

Blood pressure was measured in all subjects after 15 min rest in the sitting position with a manual sphygmomanometer at least twice on two different occasions. Mean values of three consecutive measurements were taken; normal blood pressure was defined as $\leq 140/90$ mmHg in control subjects and as $\leq 130/80$ mmHg in T2DM patients.

Echocardiographic measurements

Echocardiographic examinations were performed using a 2.5-MHz probe with a Vivid 7 pro echocardiography device (GE Vingmed, Horten, Norway). Echocardiographic imaging was performed according to the recommendations of the American Society of Echocardiography.[19] The LV mass (LVM) was calculated as follows:[20]

$$\mathrm{LVM(g)} = 0.8 \times (1.04 \times ((\mathrm{PWT} + \mathrm{IVS} + \mathrm{LVEDD})^3 - (\mathrm{LVEDD})^3)) + 0.6$$

where PWT is posterior wall thickness, IVS is interventricular septal wall thickness, and LVEDD is LV end-diastolic dimension.

Conventional Doppler echocardiographic measurements

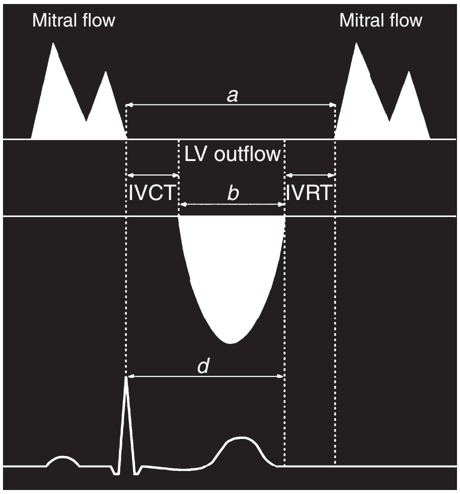
Records were taken with patients in the left lateral decubitus position. Early (E) wave, late (A) wave, the E/A ratio, and E deceleration time of LV inflow velocities were measured by pulse wave Doppler, placing the sample volume between the tips of the mitral valve leaflets in an apical four-chamber window. The IVRT was obtained from the apical five-chamber view by placing the sample volume between the tip of the mitral anterior leaflet and the LV outflow tract. All conventional Doppler measurements were made in five consecutive cycles and mean values were used for statistical comparisons. Systolic and diastolic blood pressures were recorded using conventional sphygmomanometry during echocardiography, as was heart rate.

Doppler-derived IMP

Doppler measurements were used to calculate IMP as follows:

$$\mathrm{IMP} = (a - b)/b$$

where a is the time interval between the end and onset of mitral filling on the transmitral pulsed Doppler and



$$\text{IMP} = \frac{(a-b)}{b} = \frac{(\text{IVCT} + \text{IVRT})}{\text{ET}}$$

Figure 1 Flow Doppler at the mitral valve and at the left ventricular (LV) outflow tract. Measurements of time intervals used to calculate the index of myocardial performance (IMP). The interval *a* is measured from the end to the onset of the mitral inflow waveform; the interval *b* is the left ventricular outflow velocity tracing (ejection time). The IMP was calculated according to Tei et al.[9] as $(a - b)/b$. IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time.

b is the time interval from the beginning to the end of aortic flow on the transaortic pulsed Doppler (Fig. 1). Mean values of three measurements were used for *a* and *b*. All echocardiographic measurements were made by same cardiologist, who was unaware of the patients' clinical data.

The present study was approved by the local ethics committee of the School of Medicine, Mustafa Kemal University, and informed consent was obtained from all subjects prior to their participation in the study.

Statistical analysis

Statistical analyses were performed using SPSS (version 11.0; SPSS, Chicago, IL, USA). Continuous variables are expressed as the mean ± SD, whereas categorical variables are given as percentages. Results for categorical variables were compared using the chi-squared test and Fisher's exact test as appropriate; continuous variables were compared using unpaired *t*-tests and the Mann–Whitney *U*-test as appropriate. Pearson correlations were used to analyze the relationship between indices. Stepwise multivariate linear regression analysis was used to examine the relationship between IMP and correlated variables in the study population.

Results

Clinical characteristics

Baseline clinical characteristics are given in Table 1. There were no significant differences in mean age and sex between the T2DM patient and control groups. However, mean fasting plasma glucose and glycosylated hemoglobin (HbA1c) levels were increased and low-density lipoprotein–cholesterol levels were decreased in normotensive T2DM patients compared with the control group ($P < 0.001$, $P = 0.001$, and $P = 0.048$, respectively). Mean heart rate and triglyceride levels were higher in T2DM patients than in the control group. There were no significant differences in any other clinical and hemodynamic variables between the two groups (Table 1).

The drug therapy regimens used in T2DM patients were as follows: oral hypoglycemic agents in 31 patients; insulin therapy in seven patients; and insulin and oral hypoglycemic agents in two patients. Eighteen T2DM patients were being treated with lipid-lowering therapy and two were taking an angiotensin-converting enzyme inhibitor.

Table 1 Baseline characteristics of normotensive type 2 diabetes mellitus patients and healthy controls

	Normotensive T2DM patients (n = 40)	Control group (n = 20)	P-value
Age (years)	49 ± 7	45 ± 4	0.056
No. women/men	22/18	13/7	0.459
No. smokers	11	5	0.793
BMI (kg/m^2)	27 ± 4	27 ± 3	0.739
Height (cm)	168 ± 9	164 ± 8	0.098
Weight (kg)	78 ± 13	73 ± 11	0.114
Wait circumstance (cm)	100 ± 8	93 ± 11	0.046
Hip circumstance (cm)	102 ± 9	102 ± 6	0.857
SBP (mmHg)	118 ± 12	112 ± 11	0.118
DBP (mmHg)	75 ± 8	75 ± 6	0.859
HR (b.p.m.)	80 ± 10	71 ± 6	<0.001
Duration of DM (months)	80 ± 58	–	
Fasting blood glucose (mg/dL)	188 ± 67	88 ± 8	<0.001
HbA1c (%)	8.9 ± 3.3	5.3 ± 0.1	<0.001
TC (mg/dL)	185 ± 41	187 ± 28	0.885
Triglyceride (mg/dL)	135 ± 66	92 ± 44	0.001
HDL-C (mg/dL)	40 ± 7	42 ± 12	0.496
LDL-C (mg/dL)	109 ± 22	124 ± 24	0.048

Unless noted otherwise, data are the mean ± SD.
BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein–cholesterol; HR, heart rate; LDL, low density lipoprotein–cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

Echocardiographic findings

The LV end-systolic and end-diastolic diameter, left atrial diameter, aortic root, and ejection fraction were similar between T2DM patients and controls, but interventricular septal thickening was greater in normotensive T2DM patients than in the control group (Table 2). In contrast with systolic parameters, mitral E wave and the mitral E/A ratio were decreased and the mitral A wave was increased in normotensive T2DM patients compared with the control group (Table 2).

The calculated IMP was significantly higher in normotensive T2DM patients than in the control group. Ejection time (*b*) was decreased in T2DM patients compared with the control group, whereas there was no change in IVCT + IVRT (*a*). As indicated in Table 3, there was a significant correlation between IMP and triglyceride (TG) levels ($P < 0.001$), mitral E wave ($P < 0.001$), mitral E/A ratio ($P < 0.001$), ejection fraction ($P = 0.001$), fasting blood glucose ($P = 0.007$), LV systolic dimension ($P < 0.001$), the duration of diabetes ($P = 0.017$), and body mass index ($P = 0.029$). Stepwise multiple regression analysis demonstrated that only TG levels ($\beta = 0.355$, $t = 2.487$, $P = 0.017$) and the mitral E/A ratio ($\beta = -0.384$, $t = -2.690$, $P = 0.011$) had an independent effect on IMP (Table 4).

If the mean IMP value calculated for control subjects (0.45 ± 0.12) is accepted as baseline, then IMP was increased in 77% of normotensive T2DM patients ($\geq 0.45 \pm 0.12$). Normotensive T2DM patients were further divided into two groups according to IMP values: group I, IMP < 0.45 ($n = 9$); and group II, IMP > 0.45 ($n = 31$). When these two groups were compared, it

Table 2 Echocardiographic findings for normotensive type 2 diabetes mellitus patients and healthy controls

	Normotensive T2DM patients (*n* = 40)	Control group (*n* = 20)	*P*-value
AoD (cm)	3.0 ± 0.4	2.9 ± 0.3	0.361
LAD (cm)	3.2 ± 0.3	3.2 ± 0.3	0.789
LVESD (cm)	2.8 ± 0.3	2.7 ± 0.4	0.255
LVEDD (cm)	4.7 ± 0.4	4.6 ± 0.4	0.412
Septal wall thickening (cm)	1.1 ± 0.1	0.9 ± 0.1	0.004
Posterior wall thickening (cm)	0.9 ± 0.2	0.9 ± 0.1	0.213
EF (%)	70 ± 7	72 ± 5	0.197
LVM (g)	242 ± 59	209 ± 50	0.028
Mitral E wave (m/s)	0.69 ± 0.15	0.81 ± 0.08	<0.001
Mitral A wave (m/s)	0.82 ± 0.14	0.69 ± 0.10	<0.001
E_{dec} (msec)	172 ± 34	157 ± 40	0.169
IVRT (msec)	117 ± 19	108 ± 23	0.196
Mitral E/A ratio	0.87 ± 0.04	1.20 ± 0.05	<0.001
IMP *a*	423 ± 36	427 ± 23	0.588
IMP *b*	271 ± 19	294 ± 23	0.001
IMP	0.56 ± 0.13	0.45 ± 0.12	0.004

Data are presented as the mean ± SD.
a, time interval between the end and onset of mitral filling on the transmitral pulsed Doppler (see Fig. 1); AoD, aortic dimension; *b*, time interval from the beginning to the end of aortic flow on the transaortic pulsed Doppler (see Fig. 1); E_{dec}, E wave deceleration time; EF, ejection fraction; IMP, Doppler-derived index of myocardial performance (see Fig. 1); IVRT, isovolumetric relaxation time; LAD, left atrial dimension; LVEDD, left ventricular (LV) end-diastolic dimension; LVESD, LV end-systolic dimension; LVM, LV mass; T2DM, type 2 diabetes mellitus.

Table 3 Correlations between the index of myocardial performance and metabolic and echocardiographic parameters

	IMP	
	r	*P*-value
Fasting blood glucose	0.382	0.007
Duration of diabetes	0.307	0.017
Body mass index	0.282	0.029
Triglyceride	0.503	<0.001
High-density lipoprotein–cholesterol	−0.249	>0.05
Low-density lipoprotein–cholesterol	−0.129	>0.05
Aortic dimension	0.380	0.003
Left atrial dimension	0.110	0.402
Mitral E wave	−0.511	<0.001
Mitral A wave	0.187	>0.05
Mitral E/A ratio	−0.484	<0.001
LV systolic dimension	0.466	<0.001
LV diastolic dimension	0.341	0.009
Ejection fraction	−0.408	0.001

IMP, index of myocardial performance; LV, left ventricular.

Table 4 Stepwise multiple regression analysis of variables correlated with the Doppler-derived index of myocardial performance

Correlated variable	Standardized coefficients (β)	*P*-value
Fasting blood glucose	0.039	0.823
Body mass index	0.197	0.159
Triglycerides	0.355	0.017
Presence of diabetes mellitus	0.163	0.303
Mitral E wave	−0.166	0.366
Mitral E/A ratio	−0.384	0.011
LV systolic dimension	0.222	0.097
LV diastolic dimension	0.091	0.502
Ejection fraction	−0.242	0.065

LV, left ventricular.

was found that the decrease in ejection fraction (68 ± 6 vs 75 ± 4; $P = 0.004$), prolongation in IVRT (120 ± 20 vs 105 ± 12, $P = 0.021$), and increase in LV systolic dimension (2.9 ± 0.3 vs 2.5 ± 0.2, $P = 0.003$) were greater in group II than group I T2DM patients. However, there were no significant differences in any other echocardiographic parameters between the two T2DM groups.

Discussion

The results of the present study show that IMP is increased in asymptomatic, normotensive patients with DM despite normal LV ejection fraction, as measured by conventional methods. The IMP was closely correlated with parameters of systolic and diastolic function. Multiple regression analysis also showed that IMP was independently related to TG levels and the mitral E/A ratio.

It is well known that cardiovascular diseases are a significant cause of mortality in diabetic patients. Patients with DM in whom LV function is preserved may have abnormalities in systolic and diastolic cardiac functions, which could predispose them to the development of heart failure. The prevalence of diastolic dysfunction in diabetic patients has been reported to range widely from 30% to 60%.[21] This variation may be due to the use of different methods, study design, and the presence of concomitant disease, such as ischemic heart disease and hypertension. Boyer et al.[7] reported that the prevalence of diastolic dysfunction, as measured by tissue Doppler imaging, was much higher than expected in normotensive diabetic patients. However, the parameters of systolic function may be normal in patients with diastolic dysfunction. There may be some limitations associated with the use parameters of LV systolic function, such as ejection fraction or fractional shortening, in assessing the contractile properties of the LV and the results may not reflect all aspects of systole.

In contrast, IMP is an easy to measure and reproducible Doppler-derived index of combined systolic and diastolic myocardial performance.[22,23] It is defined as the sum of IVCT and IVRT divided by ejection time. The IMP has been used to evaluate combined systolic and diastolic function of both ventricles in various diseases, including ischemic heart disease, pulmonary hypertension, and hypertension. The advantages of the IMP include less dependence on heart rate and blood pressure, no effect of geometric changes to the ventricle on outcome, easy quantitative assessment, suitability for follow-up studies, and cost effectiveness.

Index of myocardial performance in normotensive T2DM patients

In the present study, using the IMP, we found a reduction in global ventricular performance in normotensive T2DM patients compared with matched normal controls. The strength of the IMP is its inclusion of both systolic and diastolic parameters. Tei et al.[9] have reported that IMP is closely correlated with invasive measurements of both systolic and diastolic function. Increases in IMP are due primarily to shortening of the ejection time (*b*). However, prolongation of IVCT + IVRT (*a*) is not significant. In the present study, we found a significant correlation between IMP and systolic and diastolic parameters.

Andersen et al. recently reported increased IMP in diabetic patients with essential hypertension.[24] They suggested that the IMP may support traditional methods used to assess myocardial function in hypertensive diabetic patients. However, it has been reported that the association between diastolic filling abnormalities and DM is not dependent on other confounding variables that frequently coexist with DM, and abnormalities in relaxation are more severe in patients with DM plus hypertension.[25] We did not include diabetic patients with essential hypertension in the present study; regardless, we found a significant increase in IMP in normotensive T2DM patients. In diabetic patients who have no microvascular or macrovascular diseases, diastolic abnormalities have been suggested as the earliest functional effect of a specific diabetic cardiomyopathy.[15] Poulsen et al.[26] showed that IMP was significantly more sensitive than ejection fraction in the prediction of LV dysfunction based on the clinical development of congestive heart failure. Therefore, the results of the present study suggest that impaired global myocardial performance may reflect the earliest period of diabetic cardiomyopathy in diabetic patients without complications or associated disorders.

Although the pathogenesis has not been completely elucidated, the possible effects of diabetes on myocardial disorders have been investigated in many studies. Interstitial accumulation of advanced glycation end-products (including collagen, elastin, and other connective tissue proteins), as well as fibrosis in the myocardium,[27] small vessel disease,[28] diminished intracellular Ca^{2+} handling,[29] silent myocardial ischemia,[30] and fasting plasma glucose levels[31] may be the cause of systolic and diastolic abnormalities in diabetic patients.

It is likely that metabolic abnormalities may play a major role in diabetic patients without hypertension and known coronary artery disease. The results of the present study showed that plasma TG levels were significantly higher in the diabetic group than in the control group, and that IMP was related to higher TG levels. Metabolic abnormalities due to diabetes mellitus may also affect cardiac performance independent of hemodynamic overload.[32] In addition, Di Bonito et al.[33] have demonstrated a relationship between diastolic dysfunction and reduced insulin sensitivity in diabetic patients, suggesting that insulin resistance may contribute to the pathogenesis of cardiac dysfunction.

Study limitations

The main limitation of the present study is that the sample investigated is small. Patients with probable coronary artery disease who had a history and electrocardiographic, echocardiographic, and stress test findings typical of this disorder were excluded from the study. However, it is well known that diabetic patients may have asymptomatic coronary artery disease. In addition, we did not measure insulin resistance and albuminuria in the present study, which may explain the pathogenesis of diastolic abnormalities in diabetic patients. Furthermore, the existence of a pseudonormal LV filling pattern was not evaluated in the present study.

Conclusions

In conclusion, early changes in LV performance were shown by the Doppler-derived IMP during the early stage of diabetes in normotensive T2DM patients. The findings suggest that an increased IMP may be an early sign of diabetic cardiomyopathy in asymptomatic diabetic patients without hypertension. In addition, LV global dysfunction may be due to metabolic abnormalities in addition to hemodynamic abnormalities in the early stage of T2DM without hypertension. Therefore, using the Doppler-derived IMP is a simple, cost-effective, and reproducible method by which to determine systolic and diastolic abnormalities in normotensive diabetic patients.

Disclosure

The authors report no conflicts of interest. The contents of this paper have not been published or communicated elsewhere.

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