Left Ventricular Function and Exercise Tolerance in Patients with Type II Diabetes Mellitus

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Summary

Background: Left ventricular (LV) preload changes may alter exercise tolerance (ET), probably lessening activation of the Maestrini-Starling mechanism. Reduced LV filling (preload) during the diastolic phase, usually impaired in diabetic patients, could affect ventricular function.

Hypothesis: To evaluate the relationship between some echocardiographic LV function indices and ET, 24 patients (age 43–75 years, mean 54 ± 13 years, Group A) with type II diabetes mellitus (DM), not suffering from other pathologies, and for whom the ergometric stress test (EST) resulted in an early interruption because of muscular fatigue and/or dyspnea, and 14 patients (age 38–70 years, mean 53 ± 12 years, Group B) with type II DM and maximal ergometric stress test, used as control group, were studied.

Methods: The EST was performed by increasing the load by 25 W every 2 min; its duration was used as an ET index and correlated with clinical parameters of LV function obtained with M-mode, two-dimensional, and Doppler echocardiography.

Results: No patient in either Group A or Group B showed a high systolic blood pressure value at rest and/or an LV hypertrophy and/or an alteration of systolic functional indices. In neither group was there significant correlation between ET and duration of DM, basal heart rate, basal and max systolic blood pressure, and EF values. Linear regression analysis showed a significant correlation between Doppler parameters

of the diastolic function and ET index in Group A, while there was no significant correlation in Group B.

Conclusion: From these data we can deduce that in absence of left systolic ventricular dysfunction the impairment of LV relaxation in DM can influence exercise tolerance, probably by limiting activation of the contractile reserve.

Key words: diabetes mellitus, ventricular function, exercise tolerance

Introduction

Clinical evidence of cardiac failure can occur in patients with normal systolic ventricular function. Patients with this syndrome suffer from asthenia and exertional dyspnea in the same way as do patients with systolic dysfunction.^{1–6}

A correlation between exercise and ventricular filling parameters has been shown with invasive and noninvasive techniques, but the pathophysiologic mechanism is still unclear.^{4, 7–12}

Since diastolic impairment is found frequently in diabetic patients and in patients with normal systolic function,^{13–18} we evaluated whether there exists a relationship between noninvasive hemodynamic indices of ventricular function (derived from a noninvasive and easily reproducible technique such as Doppler echocardiography) and tolerance to exercise in patients with type II diabetes mellitus (DM) not suffering from coronary artery disease (CAD).

Materials and Methods

In all, 51 patients with type II DM and without anamnestic and clinical evidence of myocardial infarction and/or angina underwent a diagnostic protocol that included (1) an ergometric stress test (EST) and a stress-rest myocardioscintigraphy with Tc 99-sestamibi to exclude the presence of coronary artery disease, and (2) M-mode, two-dimensional, and Doppler echocardiography to assess left ventricular (LV) function.

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Ergometric Stress Test

The EST was carried out with a Lode Corival 300 cycloergometer (Esaote Biomedica, Florence, Italy) following a protocol consisting of a 2-min warm-up period followed by repeated increases of 25 W every 2 min, until the maximum age-related heart rate was reached, and of a 10 min recovery phase. During the test, 12 leads were recorded and heart rate (HR) and blood pressure (BP) were determined (the latter manually with a mercury sphygmomanometer) at the end of the 2 min of each stage, at the maximum work load, and at the first, third, fifth, and tenth min of the recovery.

Criteria for discontinuation of the test were the achievement of the maximum HR (220 beats/min for men and 200 beats/min for women; ST-segment depression > 3.0 mm at 0.08 s from the J point in precordial leads and/or a depression > 2.0 mm in peripheral leads; increasing angor, ventricular arrhythmias, muscular fatigue, intense dyspnea; increase in systolic blood pressure > 240 mmHg and in diastolic blood pressure > 140 mmHg; decrease of > 20 mmHg in systolic blood pressure during exercise.

An ST-segment depression > 1.5 mm at 0.08 s from the J point in precordial leads, an ST depression > 1 mm in peripheral leads or its elevation > 1 mm in more than one lead, and/or precordial angor were considered to have positive significance. Exercise duration in all subjects was used as an index of exercise tolerance and was related to some general and echocardiographic parameters of systolic and diastolic function.

Myocardial Scintigraphy

Myocardial scintigraphy with ^{99m}Tc -mibi single-photon emission computed tomography (SPECT) was performed with a Siemens Orbiter gamma camera (Siemens Basicam, Erlanger, Germany) equipped with a high-resolution collimator (64×64). A single day rest-stress protocol was performed, and for exercise the same EST protocol as described previously was used.

In a tomographic scan at 180° (-45° to 135°), 32 images (40 s/image for the first study and 20 s/image for the second study) were acquired and then reconstructed with a Microdelta Siemens system using a Butterworth filter (cutoff 0.4; n.5).

For data analysis, the left ventricle was divided into 20 segments (total 640 segments), followed by qualitative and quantitative analysis (as the percentage of MIBI uptake detected in each segment compared with a normal area defined as the area with the highest activity).

An activity increase of $> 10\%$ during rest following the stress test was considered to be a sign of stress-induced ischemia.

Echocardiography

An echocardiogram was performed with an Acuson MPX 3 device (Acuson, Mountainview, Calif., USA) equipped

with a 3.5 MHz probe. Two-dimensional and M-mode echocardiograms of the left ventricle were obtained from the parasternal window.

We calculated the left ventricular (LV) and end-diastolic and end-systolic diameters, the thickness of the interventricular septum and of the posterior wall (in diastole and systole) of the left ventricle according to American Society of Echocardiography guidelines.¹⁹ Ejection fraction (EF), obtained with Teicholz's volumes formula, was used as an index of systolic function.²⁰ Transmitral velocity was studied from the apical 4-chamber view, placing the sample volume within the mitral annulus. The tracings of three consecutive beats showing the highest velocity in early filling were analyzed and the mean value obtained was used.

The following parameters were examined: peak velocity of early filling (E wave), peak velocity of late filling (A wave) and their ratio (E/A); time velocity integral of both early (TVIE) and late (TVIA) filling and their ratio. These were calculated as the mean value of at least three consecutive cycles.

Study Population

At the end of this diagnostic approach, 13 patients (25%) with positive Tc 99-sestamibi myocardial scintigraphy, probably related to CAD, were excluded from the study. Of these patients, eight also proved positive during the ergometric stress test, showing a significant ST depression with or without angor during exercise.

The remaining patients, all of whom gave informed consent to the study, were then divided into two groups: Group 1 comprised of 24 patients (age 43–75 years, mean 54 ± 12 , 20 men and 4 women) who did not suffer from other pathologies and in whom the test was interrupted because of dyspnea and/or muscular fatigue before reaching 85% of the age-related predicted HR (reduced exercise tolerance); and Group 2 comprised of 14 patients (age 38–70 years, mean 53 ± 12 , 11 men and 3 women) with normal maximal ergometric test (maximal HR $> 90\%$ of age-related predicted HR) who were considered a control group (normal tolerance to exercise).

All patients were under hypoglycemic therapy with oral antidiabetics, and none took drugs that could interfere with the results of the examination.

In these patients, the presence of microalbuminuria was assessed using a double-antibody I125 radioimmunoassay method (Albumin, Diagnostic Product Corporation, Los Angeles, Calif.). A 3-h morning urine sample was collected. Patients were ambulatory rather than at rest, both before and during the time of collection. Microalbuminuria was considered present if the urinary excretion of albumin was between 20 and 200 $\mu\text{g}/\text{min}$.

Twenty-nine patients (18 in Group 1 and 11 in Group 2) also underwent five simple tests for the assessment of autonomic function (AFT) according to Ewing *et al.*:²¹ (1) HR at rest: HR > 100 beats/min after 5 min of rest in clinostatism was considered pathologic. (2) Beat-to-beat HR variation: a difference between the maximum and minimum HR in each single

cycle < 10 beats/min with the patients breathing six times per min was considered pathologic. (3) Valsalva maneuver: a ratio between the longest R-R interval taken immediately after the test and the shortest R-R interval obtained during the Valsalva maneuver < 1.10 was considered pathologic. (4) HR response to standing: a ratio between the R-R interval at the third beat after standing and the R-R interval at the fifteenth beat < 1 was considered pathologic. (5) BP response to standing: a decrease in systolic BP after 1 min of standing > 30 mmHg was considered pathologic.

Patients with at least two tests with pathologic results were defined as having autonomic neuropathy.

Statistical Analysis

All data are expressed as mean $\pm$ standard deviation. Data analysis was made by Student's *t*-test, when necessary, and by linear regression analysis. In particular, analysis was to define the relationship between exercise tolerance and various clinical parameters (age, duration of diabetes, systolic BP at basal and maximum workload, etc.), and systolic (EF) and diastolic functional parameters (E wave, A wave, and their ratio; TVIE, TVIA and their ratio). A *p* value of < 0.05 was considered significant. Chi-square test or Fisher's exact test was used to assess the difference between nonparametric data.

Results

Clinical characteristics of the patients and the hemodynamic data of their ergometric stress tests are shown in Table I.

The prevalence of diabetes-related organ damage in the two groups proved to be approximately the same, as assessed by the presence of microalbuminuria (25% in Group 1 and 28.5% in Group 2, *p* = NS) and/or disautonomic neuropathy (11.1% in Group 1 and 9% in Group 2, *p* = NS) Table I.

Echocardiographic monodimensional parameters showed no significant irregularity regarding either the thickness or the diameters of the left ventricle in either group (Table II).

TABLE I Clinical characteristics and hemodynamic data at rest and during exercise

	Group 1	Group 2	<i>p</i> Value
Age (years)	54 $\pm$ 12 (43–75)	53 $\pm$ 12 (38–70)	NS
Diabetes duration (years)	6.5 $\pm$ 4 (3–15)	5.8 $\pm$ 3 (3–12)	NS
Microalbuminuria	25% (6/24)	28.5% (4/14)	NS
Autonomic neuropathy	11.1% (2/18)	9% (1/11)	NS
SBP rest (mmHg)	135 $\pm$ 19	145 $\pm$ 15	NS
SBP exercise (mmHg)	192 $\pm$ 21	197 $\pm$ 13	NS
HR rest (beats/min)	80 $\pm$ 12	82 $\pm$ 11	NS
HR exercise (beats/min)	125 $\pm$ 16	142 $\pm$ 8	NS
Time of exercise (s)	410 $\pm$ 85	596 $\pm$ 112	<0.005

Abbreviations: SBP = systolic blood pressure, HR = heart rate, NS = not significant.

Ejection fraction values, within the normal range, showed preserved systolic function. Echo Doppler data showed abnormal ventricular filling parameters in Group 1 compared with those observed in Group 2; in particular, a transmitral flowmetric pattern, similar to the one due to abnormal relaxation, was observed, whereas Group 2 showed no significant impairment of the transmitral velocity pattern (Table II). Deceleration time was prolonged, but not significantly, in Group 1 patients.

No correlation was observed between ET indices and clinical and hemodynamic data in any patient; rest EF obtained through echocardiography also showed no relationship to this index (Table III). On the other hand, a significant correlation between diastolic function and the ET index was made evident by some echo Doppler parameters. In particular, a statistical significance was obtained for the E wave velocity and E/A ratio and tolerance index (Table III).

Discussion

The main factors determining cardiac output increase during exercise are an increase in HR and contractility, changes in LV end-diastolic volume, and stroke volume.²²

Thus, also diastolic dysfunction, affecting LV filling, could limit cardiac output increase with exercise. In normal subjects, exercise is associated with a downward shift in the diastolic component of the LV pressure–volume relationship mediated by beta-receptor activation and diastolic improvement.²³ Diastolic dysfunction, due to myocardial fibrosis with myocyte hypertrophy, pericardial constraint, or exercise-induced ischemia, determines a paradoxical upward shift in the diastolic component of LV pressure–volume relationship during exercise.^{24,25}

TABLE II Echocardiographic mono-, two-dimensional, and Doppler parameters

	Group 1	Group 2	<i>p</i> Value
LVEDD (mm)	52 $\pm$ 11	51 $\pm$ 9	NS
LVESD (mm)	38 $\pm$ 10	37 $\pm$ 10	NS
PWT (mm)	9.3 $\pm$ 0.7	9.1 $\pm$ 0.8	NS
IVST (mm)	10 $\pm$ 0.9	10.1 $\pm$ 0.8	NS
EF (%)	55 $\pm$ 7	58 $\pm$ 6	NS
E wave peak (cm/s)	34 $\pm$ 7	45 $\pm$ 6	<0.005
A wave peak (cm/s)	48 $\pm$ 10	40 $\pm$ 7	<0.05
E/A ratio	0.73 $\pm$ 0.12	1.16 $\pm$ 0.07	<0.0005
TVIE	4.6 $\pm$ 1.2	6.0 $\pm$ 1.3	<0.05
TVIA	5.5 $\pm$ 1.1	4.7 $\pm$ 1.3	NS
TVIE/TVIA ratio	0.83 $\pm$ 0.4	1.46 $\pm$ 0.7	<0.005
AT (ms)	85 $\pm$ 17	90 $\pm$ 15	NS
DT (ms)	136 $\pm$ 31	120 $\pm$ 33	NS

Abbreviations: LVEDD = left ventricular end-diastolic dimension, LVESD = left ventricular end-systolic dimension, PWT = posterior wall thickness, IVST = interventricular septal thickness, EF = ejection fraction, TVIE = time velocity integral of early filling, TVIA = time velocity integral of late filling, AT = acceleration time, DT = deceleration time, NS = not significant.

TABLE III Relationship between clinical characteristics, hemodynamic data, echocardiographic parameters, and tolerance index

	r	p Value
Age	0.48	NS
Duration of diabetes	0.13	NS
SBP rest	-0.17	NS
SBP exercise	0.28	NS
HR rest	0.13	NS
HR exercise	0.77	<0.005
EF	-0.23	NS
E wave	0.68	<0.02
A wave	-0.21	NS
E/A ratio	0.57	<0.05
TVIE	0.65	<0.02
TVIA	-0.34	NS
TVIE/TVIA ratio	0.63	<0.02
AT	0.67	<0.02
DT	-0.40	NS

Abbreviations: SBP = systolic blood pressure, HR = heart rate. Other abbreviations as in Table II.

Patients with DM sometimes show normal LV filling at rest; during exercise, however, LV diastolic impairment, probably due to a condition in which normal LV relaxation is compromised, may become evident.²⁶

In patients with CAD, a strong correlation was observed between exercise capacity and indices of LV diastolic filling during exercise, but there was only a poor correlation between indices of systolic function at rest or during exercise and diastolic filling at rest. One could speculate on the possibility that, in these patients, exercise-induced ischemia could interfere with diastolic filling and thus with diastolic function.²⁷

It is not yet clear how diastolic impairment may cause exercise limitation. Proposed mechanisms take into consideration impaired skeletal muscle flow during exercise, reduced activation of beta-adrenergic receptors, or stimulation of juxta capillary receptors by high pulmonary wedge pressure. Diastolic filling impairment could also interfere with the Frank-Starling mechanism and increase LV end-diastolic pressure and wedge pressure. In patients with markedly impaired diastolic function, increase in LV end-diastolic pressure causes only a small increase in LV end-diastolic volume, and hence in stroke volume.²⁸

Diabetes mellitus is one of the most common causes of diastolic dysfunction of the left ventricle, observed both by echocardiographic and radionuclide techniques.^{14-18, 29, 30}

When the echocardiographic technique is used, the echo-Doppler pattern that mostly characterizes this situation is a configuration of abnormal relaxation with the A wave equal or superior to the E wave.^{14, 31, 32} A similar modification of the transmitral flowmetric pattern was also observed in this study: impairment of the LV filling process was observed in 24 (63%) of the 38 diabetic patients who did not suffer from

other cardiovascular pathologies and/or CAD, as assessed by myocardial scintigraphy.

Franciosa *et al.*,⁸ with invasive techniques, showed a correlation between exercise capacity, defined as the maximum oxygen consumption (VO₂ max), and pulmonary wedge pressure. This correlation, on the other hand, was not observed using other parameters, such as vascular resistances, both peripheral ($r = -0.20$) and pulmonary ($r = -0.26$), at rest. The authors also showed that, during exercise, a reduction of systemic but not pulmonary resistances occurs. Therefore, Franciosa *et al.* concluded that the right ventricle afterload could be an important factor determining the exercise capacity of patients with LV failure.

Using the angioscintigraphic technique, Cuocolo *et al.*⁷ showed that in patients suffering from hypertension, the modifications of LV ejection values during exercise are strictly related to some diastolic functional indices as the percentage of variations in end-diastolic volumes and maximal velocity of LV filling.

According to Kitzman *et al.*¹² a possible pathophysiologic explanation for the reduced exercise tolerance in subjects with preserved systolic functions can be seen in a reduced activation of the Frank-Maestrini-Starling mechanism determined by a reduction in ventricular relaxation.¹² Kitzman has confirmed this hypothesis by demonstrating that normal subjects with low wedge pressure respond to exercise with an increase in LV end-diastolic dimension due to good ventricular relaxation. In patients with cardiac failure, in whom pulmonary wedge pressure at basal conditions was higher, the response to exercise seems to be related not to LV end-diastolic volume increase but to abnormal wedge pressure increase. This caused an upward and leftward shift of the pressure-volume curve: Kitzman concluded that an increase in pressure did not correlate with an increase in LV end-diastolic volume.¹²

Consistent with this hypothesis, our study has shown the existence of a significant correlation between exercise tolerance and LV diastolic functional indices in patients with preserved systolic function. On the other hand, diabetic patients without ventricular filling abnormalities showed no significant alterations in their exercise capacity. In our study, the lack of a significant correlation between some clinical parameters, such as age, duration of diabetes, BP values (systolic and diastolic), and exercise tolerance index allow us to consider these elements to have no influence on the exercise of our patients. This conclusion was also enhanced by the observation of normal exercise capacity in patients of Group 2 who showed preserved diastolic function at rest.

It is also well known that many pathologic conditions accompanying diabetes mellitus can influence exercise tolerance,³³⁻³⁶ but the uniformity in the distribution of the organ damage in our patients could not explain the results of our study.

Moreover, exclusion from the study of diabetic patients with ischemic cardiopathy whose presence could have affected exercise capacity, justifies the lack of a significant correlation between exercise tolerance and both BP and EF.

Conclusion

Based on our data, even without a simultaneous (but invasive) measurement of pressure and volume changes, we conclude that in patients affected by type II diabetes mellitus who demonstrate normal systolic function there exists a close relationship between diastolic filling impairment and exercise tolerance.

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