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Isolated and Preclinical Impairment of Left Ventricular Filling in Insulin-Dependent and Non-Insulin-Dependent Diabetic Patients

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Summary

Background: Diabetes mellitus can induce a pattern of myocardial pathology known as specific diabetic cardiomyopathy, even if this is not clearly specified.

Hypothesis: The aim of our study was to evaluate the presence of preclinical myocardial damage in insulin- and non-insulin-dependent diabetic patients and controls by assessment with Doppler echocardiography.

Methods: Twenty insulin-dependent diabetic (IDDM) patients, 10 non-insulin-dependent diabetic (NIDDM) patients, and 12 healthy individuals (C) as controls, matched for age, gender, and without overt cardiovascular disease, were assessed in this study.

Results: Systolic function parameters presented normal values in the three groups, with the exception of a slight reduction in ventricular volume indices in the NIDDM group. Diastolic function was clearly impaired in both groups of patients versus that in healthy controls. In particular, ventricular filling was impaired in the NIDDM compared with the IDDM patients, especially the peak early filling rate E ($p<0.001$). Moreover, in the IDDM group, the duration of diabetes ($p<0.01$) and glycosilated hemoglobin value (HbA1C, $p<0.02$) were higher than in the NIDDM group. Multiple regression analysis showed a significant inverse correlation between HbA1C and peak late filling rate A ($R^2 = 0.28$) in both groups of patients and a direct correlation between velocity time integral E and age, duration of diabetes, and HbA1C ($R^2 = 0.46$). The two groups presented a small, homogeneous number of cases with initial microangiopathy and borderline autonomic neuropathy, associated with microalbuminuria. Doppler echocardiography showed an early impairment of left ventricular filling, as well as an early preclinical alteration of myocardial function in diabetic patients, especially in the NIDDM group.

Conclusion: These early signs of cardiomyopathy could constitute a predisposing condition toward the high cardiac morbidity and mortality rate in diabetic patients.

Key words: diabetes mellitus, Doppler echocardiography, diabetic cardiomyopathy, diastolic function

Introduction

The existence of a specific diabetic cardiomyopathy has been suggested to be partly involved in the development of cardiac failure in diabetic patients, as demonstrated by its high incidence in this population.[1–4] Isolated impairment of left ventricular (LV) function, such as a preclinical myocardial defect in diabetic patients without overt heart disease, has been extensively discussed. In these diabetic patients, LV systolic function was seen to be normal, while abnormal diastolic filling was found[1–5] also in relation to the duration of diabetes and the presence of microangiopathy and diabetic autonomic neuropathy. In young, stable, well-compensated patients, the evaluation of LV systolic and, in particular, diastolic function showed quite contradictory results.[5–10] These studies were largely carried out in patients with insulin-dependent diabetes mellitus (IDDM), although a small number of reports on ventricular systolic and diastolic impairment have also been published on non-insulin-dependent diabetic (NIDDM) patients.[11–13]

We performed an analysis of LV function in two groups of IDDM and NIDDM patients and in a group of nondiabetic controls, all free of any cardiovascular disease known to affect myocardial function. In this paper, we report our results concerning LV ventricular systolic and diastolic function, as analyzed by Doppler echocardiographic examination.

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Patients and Methods

The study was carried out in 20 patients with IDDM (15 men, 5 women, age 33–54 years), 10 patients with NIDDM (6 men, 4 women, age 38–50 years), and a control (C) group of 12 healthy individuals (7 men, 5 women, age 32–49 years). All subjects gave informed consent.

All patients in the IDDM and NIDDM groups and the controls were without overt heart disease, as shown by clinical history, physical examination, and electrocardiogram (ECG). There were no cardiovascular risk factors other than diabetes (i.e., smoking, high blood pressure, hypercholesterolemia). Moderate signs of microangiopathy at the observation of fundus oculii were observed in two patients in the IDDM group and in two patients in the NIDDM group, and there was no evidence of renal failure due to diabetic nephropathy. All patients were examined for the presence of microalbuminuria, an important parameter in the evaluation of renal function; only the patients with microangiopathy showed overt microalbuminuria.

The IDDM patients received no treatment other than insulin; the NIDDM patients were treated with hypoglycemic agents, except for three who were treated with diet alone. Body mass index (BMI) was similar in the three groups considered; the diabetic patients did not present recent ketoacidosis. A glycosylated hemoglobin (HbA_{1C}) measurement was taken from all patients within 15 days of Doppler echocardiography examination with a high-pressure liquid chromatography (HPLC) assessment (normal range 4.5–6.2) (Table I). Autonomic neural function was assessed by heart rate response to the Valsalva maneuver, deep breathing, and standing, and by blood pressure response to standing.[14] None of the patients was subjected to an evaluation of insulin blood levels at Doppler echocardiographic examination.

All patients were examined in the fasting state and without insulin treatment at about 10 A.M., after a 15-min rest period in the recumbent position. Each patient was given a complete Doppler echocardiographic examination by two expert observers, who were totally blinded as to the patients' conditions. An ATL Apogee CX ultrasonograph device with 3.5 MHz, Doppler pulsed wave (PW) and continuous wave, and color PW transducer was used in the examination. Left ventricular function, ventricular and atrial diameter, wall thickness, and chamber volume were measured according to the recommendations of the American Society of Echocardiography.[15]

Doppler PW analysis of LV diastolic filling was performed with apical four-chamber views and with sample volume at the tips of the mitral leaflets in the position providing the best color-flow projection. Three cardiac cycles were averaged for the following measurements: peak early filling rate (E), peak late filling rate (A), early/late (E/A) ratio, and velocity time integral of both E (E-VTI) and A (A-VTI). Isovolumetric relaxation time was assessed with the sample volume in an intermediate position between mitral and aortic flow signal; moreover, the ratio between pre-ejection period and LV ejection time (PEP/LVET) was calculated. In all patients, a 12-lead ECG was recorded, with no pathologic findings.

The results were expressed as mean ± standard deviation. Student's *t*-test for impaired data with a level of significance of 5% was used for testing differences between groups. Variance analysis (ANOVA test) was used when appropriate, and any relationships between the parameters were tested with multiple regression analysis.

TABLE I Clinical data in insulin-dependent and non-insulin-dependent diabetic patients versus healthy controls (C)

	IDDM	NIDDM	C
Age (years)	41.4 ± 8.9	44.7 ± 5.4	40.5 ± 7.0
Male/female	15/5	6/4	7/5
BMI	24.34 ± 2.77	24.78 ± 3.25	23.85 ± 2.53
HR (beats/min)	71.2 ± 10.8	68.0 ± 9.7	73.1 ± 10.5
SBP (mmHg)	137.0 ± 10.5	139.5 ± 10.1	136.3 ± 9.5
DBP (mmHg)	83.5 ± 6.9	85.5 ± 4.9	85.5 ± 5.2
DD (years)	16.54 ± 8.14	5.80 ± 4.13[b]	
HbA_{1C}	9.48 ± 1.23	8.26 ± 1.20[a]	

[a] $p<0.02$.
[b] $p<0.001$.
Abbreviations: IDDM = insulin-dependent diabetic, NIDDM = non-insulin-dependent diabetic, BMI = body mass index, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, DD = duration of disease, HbA_{1C} = glycosylated hemoglobin.

Results

All IDDM patients, NIDDM patients, and controls, matched for age, gender, and BMI, presented a normal scintigraphic examination, with regular blood pressure, heart rate, and BMI (Table I). Most patients belonging to the IDDM and NIDDM groups had cardiovascular autonomic responses in the normal range; a baseline abnormal response was observed in seven IDDM and four NIDDM patients for only one of the four types of programmed tests (Valsalva maneuver and deep breathing). The duration of diabetes was longer in the IDDM than in the NIDDM patients, and the HbA_{1C} values were higher in the IDDM patients.

Ventricular ejection fraction, interventricular septum, posterior wall thickness, left atrial diameter, end-systolic volume index, and cardiac index were homogeneous in the three groups (Table II). End-diastolic volume index was significantly different between the NIDDM patients and the controls, while the IDDM group, as far as homogeneity is concerned, was in between the aforementioned two groups. The same results were obtained for LV fractional shortening and for the PEP/LVET ratio; in the IDDM group, the homogeneity of these two parameters was in between the NIDDM and C groups (Table II).

Analysis of LV filling clearly showed differences between both groups of diabetic patients and controls (Table III). Emphasizing the presence of an impaired diastolic function, peak early filling rate E was lower and peak late filling rate A was higher in the IDDM and NIDDM patients versus the controls, with a reduction in the E/A ratio; the values were similar

TABLE II Echocardiographic parameters of systolic function in insulin-dependent and non-insulin-dependent diabetic patients versus healthy controls (C). Variance analysis among the three groups.

	IDDM	NIDDM	C	Homogeneity of the groups
EF (%)	63.42 ± 6.51	64.70 ± 7.85	62.95 ± 4.82	NIDDM = IDDM = C
LVFS (%)	33.72 ± 5.98	30.39 ± 3.23	36.76 ± 6.19	NIDDM ≠ C; IDDM in between the two groups (F = 3.6; p = 0..036)
IVS (mm)	9.30 ± 1.89	9.80 ± 1.65	9.05 ± 1.27	NIDDM = IDDM = C
PW (mm)	9.64 ± 1.34	9.40 ± 1.45	8.92 ± 1.18	NIDDM = IDDM = C
EDVI (ml)	54.9 ± 9.0	49.4 ± 6.1	54.1 ± 10.4	NIDDM ≠ C; IDDM in between the two groups (F = 4.8; p = 0.014)
ESVI (ml)	19.9 ± 4.6	17.4 ± 4.5	21.7 ± 3.7	NIDDM = IDDM = C
SV (ml)	63.9 ± 13.8	59.0 ± 8.4	62.3 ± 19.4	NIDDM = IDDM = C
CI (l)	2.44 ± 0.61	2.15 ± 0.25	2.68 ± 0.48	NIDDM = IDDM = C
LAD (mm)	34.6 ± 3.9	34.8 ± 2.8	33.4 ± 1.7	NIDDM = IDDM = C
PEP/LVET	0.385 ± 0.083	0.447 ± 0.118	0.318 ± 0.061	NIDDM ≠ C; IDDM in between the two groups (F = 5.9; p = 0.005)

Abbreviations: IDDM = insulin-dependent diabetic, NIDDM = non-insulin-dependent diabetic, C = controls, EF = ejection fraction, LVFS = left ventricular fractional shortening, IVS = interventricular septum, PW = posterior wall thickness, EDVI = end-diastolic volume index, ESVI = end-systolic volume index, SV = stroke volume, CI = cardiac index, LAD = left atrial diameter, PEP/LVET = pre-ejection period/left ventricular ejection time, ≠ =non-homogeneous, = = homogeneous.

regarding E-VTI, A-VTI, and E/A VTI. Therefore, the two groups of diabetic patients presented different values as to peak early filling rate E, E-VTI, and A-VTI, with a more pronounced diastolic impairment in the NIDDM group.

In the NIDDM group, Doppler echocardiography findings for diastolic function were more strongly impaired than in the IDDM group, although significant differences were observed only for E, E-VTI, and A-VTI. Furthermore, IVRT was longer in diabetic patients, both IDDM and NIDDM, compared with controls (Table III).

The relationship between Doppler echocardiographic parameters and clinical data was tested. Multiple regression analysis showed a negative correlation between HbA_{1C} and peak late filling rate A ($R^2 = 0.28$), and a positive correlation between E-VTI and age, duration of diabetes, and HbA_{1C}, respectively ($R^2 = 0.48$; p = 0.054; p = 0.01; p = 0.04).

Discussion

The impairment of LV function in diabetes has been discussed in recent years using different data for defining the existence of a specific cardiomyopathy.[3,4] In selected groups of patients without overt cardiovascular disease, a preclinical im-

TABLE III Echocardiographic parameters of diastolic function in insulin-dependent and non-insulin-dependent diabetic patients versus controls (C). Variance analysis among the three groups.

	IDDM	NIDDM	C	Homogeneity of the groups
E (ms)	0.825 ± 0.144	0.688 ± 0.111	0.991 ± 0.073	NIDDM ≠ IDDM ≠ C (F = 17.5; p<0.001)
A (ms)	0.623 ± 0.0995	0.660 ± 0.176	0.478 ± 0.089	NIDDM = IDDM, both ≠ versus C (F = 7.96; p = 0.0013)
E/A	1.342 ± 0.399	1.112 ± 0.355	2.110 ± 0.337	NIDDM = IDDM, both ≠ versus C (F = 27.3; p<0.001)
E-VTI	12.05 ± 2.72	9.06 ± 1.71	16.58 ± 1.56	NIDDM ≠ IDDM, ≠ C (F = 149.1; p<0.001)
A-VTI	6.40 ± 1.60	6.80 ± 2.09	4.91 ± 1.24	NIDDM = C, both ≠ versus IDDM (F = 42.7; p<0.001)
E/A-VTI	2.014 ± 0.739	1.501 ±0.395	3.588 ± 1.009	NIDDM = IDDM, both ≠ versus C (F = 26.3; p<0.001)
IVRT (ms)	87.50 ± 21.72	102.00 ± 19.32	71.91 ± 16.55	NIDDM = IDDM, both ≠ versus C (F = 8.51; p<0.001)

Abbreviations: E = peak early filling rate, A = peak late filling rate, E-VTI = velocity time integral E, A-VTI = velocity time integral A, IVRT = isovolumetric relaxation time. Other abbreviations as in Table II.

pairment of cardiovascular function can be assessed by noninvasive techniques, as shown in previous studies.[5–10, 16] Systolic ventricular performance usually is regular;[6, 10, 12, 17] the fact that it was occasionally impaired during ergometric stress was due to different ventricular load conditions rather than to truly impaired ventricular contractility.[6] Only in our NIDDM patients was it possible to observe a slight decrease in volumetric indices versus the controls. Left ventricular fractional shortening and end-diastolic volume index were impaired in diabetic patients, especially in the NIDDM group.

The most accurate and earliest markers of an impaired ventricular function likely to progress toward cardiac insufficiency is diastolic dysfunction, analyzed using noninvasive techniques.[1, 5, 11, 13, 18] In our study, both IDDM and NIDDM patients showed an isolated impairment of ventricular filling, without clear signs of cardiovascular involvement. In the IDDM patients, a finding of diastolic abnormality is quite controversial;[10] furthermore, in one of our previous studies, which involved a group of treated and well-compensated IDDM patients and in which radionuclide angiography was used,[19] a normal ventricular filling rate was reported.

Diastolic function appeared clearly impaired in both the IDDM and NIDDM groups, matched for age, gender, and BMI, with a more pronounced impairment in the NIDDM patients. A decrease in peak early filling rate E associated with increased peak late filling rate A and prolonged IVRT was seen in both groups of patients, but was more marked in the NIDDM group. Besides, E-VTI showed a significant decrease and A-VTI an increase in diabetic patients; both parameters were more altered in NIDDM than in IDDM patients. Despite featuring a more pronounced diastolic abnormality, the NIDDM group had a shorter clinically recognized duration of diabetes and lower HbA_{1C} values compared with the IDDM patients, but obviously the vascular and myocardial damage started in an indefinable prediabetic stage.[20]

It can be assumed that IDDM patients are quite well identified from diabetes mellitus onset. Clinical features appeared in IDDM as soon Langehrans' islets are damaged by viral or autoimmune events. Therefore, in NIDDM an overt clinical feature appeared slowly. Vascular and myocardial damage started before the dysmetabolic events become clear, while hyperinsulinemia, microalbuminuria, advanced glycosylated end products, and lipidic abnormalities could lead to a reduction in ventricular compliance. A comparison between the two diabetic groups indicates no difference in the incidence of microangiopathic complications and/or autonomic neuropathy; in addition, microangiopathy or autonomic neuropathy do not seem to induce a parametric impairment of ventricular function prominently;[6] otherwise, these clinical features presented a weak correlation with ventricular dysfunction.

The mechanism by which diabetic disease might induce diastolic dysfunction remains to be clarified. The histologic findings typical of diabetes are well known, especially in the vascular and myocardial structures, as is the possible neurohumoral mechanism that may induce cardiovascular dysfunction.[1, 13, 21, 22] A possible explanation of diastolic impairment might be that it is the consequence of an increased LV mass/body surface area in NIDDM patients, even if this was ruled out in our patients. The mechanism causing LV hypertrophy is still not clear; in the absence of high blood pressure levels, such as in our patients, a different process might be involved: as an example, hyperinsulinemia or, alternatively, associated metabolic abnormalities may lead to lower LV compliance[1, 23, 24] which, if longstanding, may enhance LV mass.[25] Therefore, a development of ventricular muscle stiffness due to elevated tissue calcium levels, associated with a defective sarcoplasmic reticular calcium-ATPase and a redistribution of myosin isoenzymes from the most active V_1 form to the least active V_3 form, was experimentally demonstrated in NIDDM patients who have pathologic mechanisms that are quite different from IDDM.[24] Vascular wall changes and increased LV mass, typically associated with generalized cardiovascular metabolic disease,[26] might be the primary consequence of NIDDM.

Conclusion

An impairment of left ventricular diastolic filling as an early sign of ventricular dysfunction was observed to be prevalent in NIDDM patients compared with IDDM patients, none of whom displayed evidence of any cardiovascular disease. Reduced diastolic function was not related to any sign of autonomic neuropathy or to metabolic control, duration of diabetes, or presence of microangiopathy. Moreover, these abnormalities were not well represented in our patients.

Our findings erased some important considerations in the field of therapeutic approach to diabetes. Patients need to be treated in the early stage of diabetes to prevent the development of diabetic cardiomyopathy. Diabetic heart is at increased risk of damage from both macrovascular and microvascular insults; the metabolic perturbations of diabetes alone result in myocardial dysfunction. With recognition and control of dysmetabolic state (e.g., hyperinsulinemia) in diabetic patients, the development of diabetic heart disease may be retarded. If good control of dysmetabolic state was not achieved early, it is important to consider diastolic abnormality as a possible risk factor worsening the prognosis of diabetic patients, especially those with NIDDM, even without overt cardiovascular features.

The observation of an isolated impairment of diastolic function that may be detected in other cardiovascular diseases (i.e., hypertension, coronary artery disease, cardiomyopathy), might be considered to be one of the factors inducing a higher incidence of cardiac morbidity and mortality among diabetic patients, particularly those how are non-insulin-dependent.

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