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Left ventricular performance and autonomic dysfunction in patients with long-term insulin-dependent diabetes mellitus

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Abstract Cardiac autonomic neuropathy (CAN) is a very frequent complication of insulin-dependent mellitus type 1, affecting the sympathetic or parasympathetic sections or both. The different impairment in the two sections might modify left ventricular function early. To evaluate this relationship, we studied 61 patients (mean age 39.6±7 years) with type 1 diabetes for more than 10 years, without coronary artery disease (CAD; negative ergometric stress test) and without other pathologies that could interfere with ventricular function. All patients underwent MONO-, 2-dimensional and Doppler echocardiographic examination and radionuclide angiography with ^{99}Tc (RNA). According to the outcome of the Ewing tests, patients were divided into two groups: group A with two or more tests altered (26 patients with CAN) and group B with one or no tests altered (35 patients without CAN). No significant differences between the two groups were found in the systolic function parameters with either technique. In contrast, a pattern of abnormal relaxation was found for the diastolic function parameters: in group A a decrease in E-wave velocity and its time-velocity integral and an increase in A-wave and its time-velocity integral were detected with echocardiography. Moreover, RNA showed a reduced peak filling rate and an increased isovolumic relaxation time. When compared with normal values, an abnormal diastolic filling, defined as two independent echocardiography plus one RNA variable impairment, was found in 15 patients (57.6%) in group A and in only 4 patients (11.4%) in group B ($P<0.001$). Our findings suggest an early involvement of diastolic function in patients with CAN.

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Introduction

Diabetes mellitus is considered one of the main risk factors in the development of cardiac disease (coronary artery disease, CAD, cardiomyopathy, etc.). From many epidemiological studies, people with diabetes seems to have an increased incidence of cardiovascular disease compared with the general population [1–5]. Although CAD in diabetic patients seems to be related to non-insulin-dependent diabetes mellitus (type 2), in young patients with type 1 diabetes mellitus (insulin-dependent) but without CAD, a higher incidence of impairment of both systolic and diastolic function has been shown [6–11].

Moreover, in insulin-dependent diabetic patients, a specific neuropathy has been found that includes an early dysfunction of the autonomic cardiac system [12–14].

In order to evaluate this relationship with cardiac autonomic neuropathy (CAN), 69 type 1 patients underwent non-invasive assessment of left ventricular function.

Materials and methods

A total of 69 patients (age range 16–51 years, mean 39.6±7 years) with type 1 diabetes for more than 10 years was studied. They were selected through a detailed anamnestic and clinical examination from a large population of diabetic patients according to the following criteria: less than 55 years old, no evidence of CAD such as the presence of angina or previous myocardial infaction, no hypertension or hypertensive cardiomyopathy, no peripheral or other overt cardiovascular diseases, no obesity, no history of phaeochromocytoma.

All patients were treated with insulin, and none was taking any other drug that could interfere with cardiac function (such as digitalis or angiotensin-converting enzyme ACE-inhibitors or calcium antagonists, or beta-blockers).

All examinations were performed at least 2 h after insulin administration.

Long-term glycaemic control was assessed by A_1 glycosylated haemoglobin values <9.2% (upper normal limit 7.5%, Cordis).

All patients underwent an ergometric stress test (EST) to assess the presence of latent CAD: it was performed in the upright position on a cycloergometer Lode Corival 300 with load increases of 25 watts every 3 min until reaching the maximal age-predicted heart rate. During the EST, 12 electrocardiogram (ECG) standard leads and blood pressure were monitored and recorded at the end of each stage or at the onset of ECG changes or symptoms. Blood pressure was measured manually at the 2nd min of each stage, before stopping the test and at the 1st, 3rd and 5th min of recovery phase with a cuff sphyngmomanometer. The test was considered positive according to the following: horizontal or downsloping ST depression >2 mm at 60 ms from the J point in at least two leads if asymptomatic and depression >1 mm if associated with increasing angor. T wave inversion during EST was considered positive only if it was associated with angor.

The probability of a negative test to exclude CAD was calculated according to Bayes theorem:

$$P(-)=\frac{\text{spec}\times(1\text{-prev})}{\text{spec}\times(1\text{-prev})+(1\text{-sens})\times\text{prev}}$$

where prev=pre-test probability of CAD, (1-prev)=pre-test probability of no CAD, spec=specificity, (1-sens)=inverse of sensibility. A post-test probability of less than 5% was considered useful in excluding a CAD. Two patients were excluded because of a positive EST (ST depression in one and ST depression and angina in another).

The patients with negative EST (n=67) underwent five simple tests for the assessment of autonomic function (AFT), according to Ewing et al. [14]:

I. Heart rate at rest: after 5 min of rest in clinostatism. More than 100 beats/min after 5 min at rest in clinostatism was considered pathologic.
II. Beat-to-beat heart rate variation: when the difference between the maximum and minimum heart rate in each single cycle was <10 beats/min with the patient breathing at six times per minute, this was considered pathologic.
III. Valsalva maneuver: when the ratio between the longest R-R interval immediately after the test and the shortest R-R interval obtained during Valsalva was <1.10, this was considered pathologic.
IV. Heart rate response to standing: when the ratio between the R-R interval at the third beat after standing and the R-R interval at the fifteenth beat was <1, this was considered pathologic.
V. Blood pressure response to standing: when the decrease in systolic blood pressure after 1 min of standing was >30 mmHg, this was considered pathologic.

All the tests were performed between 1 p.m. and 4 p.m.while the patients were fasting (for at least 3 h); they were also advised not to smoke or consume alcohol or coffee 2 h before the test. Twenty-seven patients (40.2%) with at least two of these tests altered were defined as having diabetic autonomic neuropathy and were included in group A. The remaining patients (n=40, 59.8%) with one or no tests altered were included in group B.

All patients performed a MONO-, 2-dimensional and Doppler echocardiography with a Hewlett Packard device equipped with a 2.25-MHz transducer. The examination was performed on the same day as the AFT, and the interventricular septum thickness (IST), left ventricular posterior wall thickness (PWT), left enddiastolic and endsystolic diameter (LVEDD and LVESD, respectively), left atrium (LA) and aortic diameter (AD) were measured according to the American Society of Echocardiography [15]. Fractional shortening (% FS) and ejection fraction (EF) were calculated. Mitral inflow velocity was recorded by pulse wave Doppler from an apical four-chamber view with the sample volume placed near the tips of the mitral leaflets. The following normalized parameters of ventricular performance were obtained as the average of three cardiac cycles:

- Peak velocity early mitral flow (E)
- Peak velocity late mitral flow (A)
- Ratio between early and late mitral flow velocity (E/A)
- Time velocity integral of early mitral flow (TVIE)
- Time velocity integral of late mitral flow (TVIA)
- Ratio between the time velocity integral of early and late mitral flow (TVIE/TVIA)

After echocardiography, one patient in group A and five patients in group B were excluded for technical inadequacy and/or left ventricular hypertrophy and/or cardiac valve pathology, conditions that could interfere with cardiac function.

Then the patients underwent equilibrium radionuclide angiography (RNA) with ^{99}Tc-albumin (15 mCi given as a bolus), and data were acquired with a Siemens LEM ZLC gamma-camera in left anterior oblique, LAO 45° position. Images were acquired with a digital zoom in frame mode (50 frames/s with a tolerance of 5%). In the supine position 3 million counts were collected. To analyze the data, a left ventricular (LV) region of interest was identified for each patient by a semiquantitative algorithm. A region of background was identified in the enddiastolic frame. Then a background-subtracted curve was generated. LV EF was determined using the following formula:

EF = (enddiastolic – endsystolic)/enddiastolic counts – background counts.

Peak filling rate (end-diastolic counts/s) was computed as the peak positive of the first derivative on the time-activity curve.

The isovolumic relaxation period, from the endsystole to the onset of rapid filling, was computed as the peak of the second derivative on the time-activity curve.

The following indexes of ventricular performance were obtained: EF, peak filling rate (PFR), time to peak filling rate (TPFR), isovolumic relaxation period (IVRP).

At the end of this diagnostic approach the two groups were composed as follow: group A 26 patients and group B 35 patients. All the patients gave their informed consent to the study.

Statistical analysis

All data are expressed as mean±SD. The data were analyzed through paired and unpaired Student's t-test and analysis of variance. $P<0.05$ was considered statistically significant.

A diastolic dysfunction has been defined as two independent echocardiography plus one RNA variables impairment. The normal values of variables with both techniques are indicated in Table 2. Chi-square test or Fisher exact test was used to assess the difference between nonparametric data.

Results

The clinical characteristics and laboratory results of the two groups are given in Table 1. The results of the autonomic function tests are summarized in Fig. 1.

Table 1 Clinical characteristics and laboratory results

	Group A (n=26)	Group B (n=35)	P
Age (years)	43±9	38±11	NS
Gender	13 M/13F	17 M/18F	–
Duration of diabetes (years)	14±6	13±3	NS
Body surface (m^2)	1.7±0.1	1.8±0.1	NS
SBP (mmHg)	130±18	124±17	NS
DBP (mmHg)	82±11	83±11	NS
HR	98±15	87±10	>0.02
Fasting glucose level (mg/dl)	121±14	118±10	NS
Glycosylated haemoglobin	8.2%±0.3%	8.4%±0.5%	NS

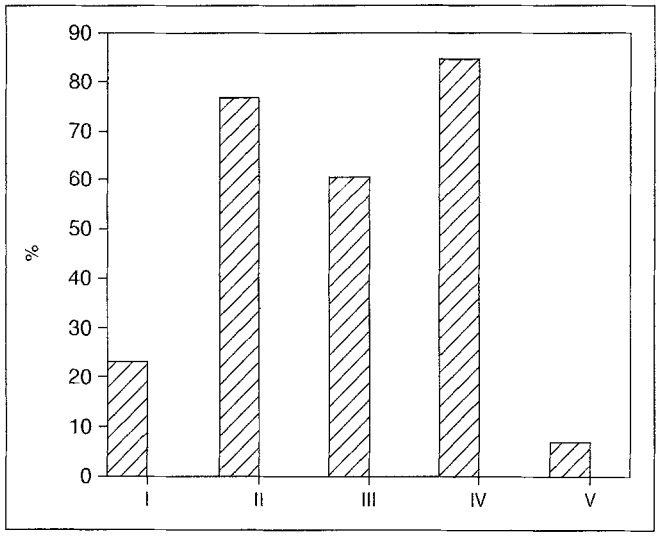

Fig. 1 Incidence of abnormality of each test in the population (%) (*I* heart rate at rest, *II* beat-to-beat heart rate variation, *III* Valsalva maneuver, *IV* heart rate response to standing, *V* blood pressure response to standing)

Table 2 Left ventricular echocardiographic data (*LVEDD* left ventricular enddiastolic diameter, *LVESD* left ventricular endsystolic diameter, *PWT* posterior wall thickness, *IVT* interventricular septum thickness, *LA* left atrium, *AD* aortic diameter)

	Group A (n=26)	GroupB (n=35)	P	Normal values
LVEDD (mm)	46.4±4.9	45.6±3.9	NS	39–50
LVESD (mm)	27.4±3.7	27.2±3.6	NS	23–34
PWT (mm)	9.4±1.1	8.6±1.6	NS	7–11
IVT (mm)	9.4±1.9	9.1±1.6	NS	7–12
LA (mm)	33.1±2.8	33.5±4.8	NS	27–41
AD (mm)	29.2±2.4	27.9±3.4	NS	20–32

From the ergometric data already published in a previous work, we can calculate a post-test probability of CAD in our patients, which was less than 5% [16].

No significant differences were found between the two groups in LVEDD, LVESD, PWT, IST, LA and AD measurements (Table 2). No impairment was found in any parameters of systolic performance in the two groups with either technique: the EF in group A was found to be 71%±6% and 67%±7% and in group B 74%±4% and 71%±9%, respectively, with echocardiography and RNA (Table 3).

The fractional shortening of LV, revealed by echocardiography, was within the normal range in both groups (40.5%±5% in group A and 40.2%±5% in group B).

Many indexes of ventricular filling were available for evaluating diastolic function. The pattern observed with Doppler echocardiography was one of abnormal relaxation: it included a more pronounced, although not significant, reduction of E-wave velocity (52.9±8.7 cm/s in group A and 57.7±7.7 cm/sec in group B). The E-wave time-velocity integral showed a significant decrease in group A vs group B (4.68±0.96 vs 6.23±1.32, P<0.02). A further increase in A-wave velocity in group A over group B was found, but this difference was not significant between the two groups (Table 3).

The E/A ratio (0.86±0.15 in group A and 1.0±0.2 in group B) and the TVIE/TVIA ratio (1.27±0.32 in group A and 1.62±0.67 in group B) were not statistically significantly different between the two groups (Table 3).

Moreover, a significantly longer IVRP was found in group A with respect to group B with echocardiography, while RNA showed a similar increase in IVRP (Table 3).

While diastolic phase indexes obtained through RNA showed only a slight difference in mean PFR and TPFR between the two groups (Table 3), when each parameter was analyzed in comparison with normal values, an abnormal diastolic filling, defined above, was found in 15 pa-

Table 3 Echocardiographic and RNA results (*FS* fractional shortening, *FE* ejection fraction, *E* E-wave maximal velocity, *A* A-wave maximal velocity, *TVIE* time-velocity integral of E-wave, *TVIA* time-velocity integral of A-wave; *IRP* isovolumic relaxation period, *PFR* peak filling rate, *TPFR* time to peak filling rate)

	Group A (n=26)	Group B (n=35)	P	Normal values
Echocardiography				
FS (%)	40.5±5	40.2±5	NS	>30
FE (%)	71±6	74±4	NS	>55
E_{max} (cm/s)	52.9±8.7	57.7±7.7	NS	60–75
A_{max} (cm/s)	61.3±11.0	56.9±6.4	NS	45–55
E/A	0.86±0.15	1.0±0.2	NS	1.1–1.8
TVIE	4.68±0.96	6.23±1.32	<0.02	
TVIA	3.78±0.70	4.26±1.51	NS	
TVIE/TVIA	1.27±0.32	1.62±0.67	NS	
IVRP (ms)	106±33	90±24	<0.05	<75
RNA				
FE (%)	67±7	71±9	NS	>50
PFR (edv/s)	3.1±0.6	3.7±0.9	NS	1.8–3.8
TPFR (ms)	151±14	176±14	NS	120–180
IVRP (ms)	109±19	105±34	NS	<90

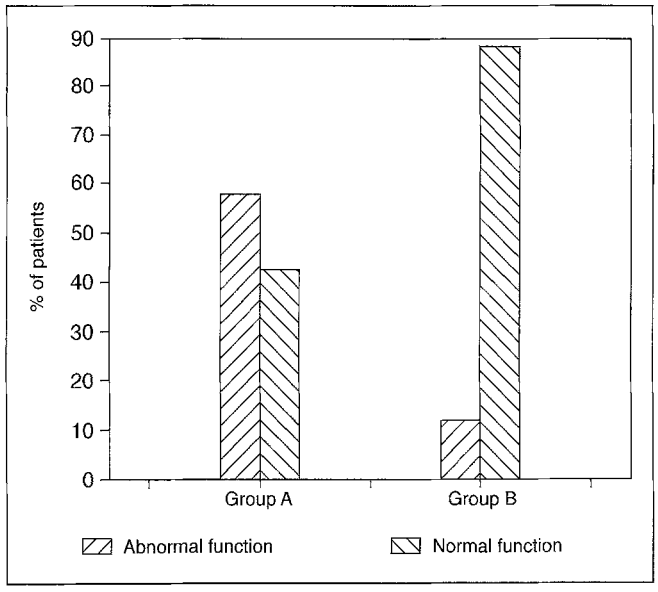

Fig. 2 Percentage of patients with normal and abnormal diastolic performance in the two groups (see text for explanation). $^{*}P<0.001$ (A vs B)

tients (57.6%) in group A and in only 4 patients (11.4%) in group B ($P<0.001$) (Fig. 2).

Discussion

Since 1972 Rubler and co-workers [17], with an autoptic study, have proposed the existence of diabetic cardiomyopathy, and in 1974 Hamby et al. [5] showed the existence of diabetic cardiomyopathy in patients without CAD. From then on many authors found impairment of LV function in patients with type 1 diabetes.

Although some studies also showed a slight increase of LV EF in diabetic patients without other pathologies [17–20], Mustonen and co-workers [21] and Vered and co-workers [6] showed a decrease in EF during a stress test in young diabetic patients. The causes of these impairments could be ascribed to many hypotheses such as the reduction in diastolic relaxation with reduced filling that could affect the enddiastolic volume, metabolic or ultrastructural changes, or microangiopathic involvement.

The impairment does not involve just systolic function and, moreover, diastolic filling seems to be affected earlier than systolic performance in both type 1 and type 2 diabetes mellitus [7–8, 22–30] or in the phase of reduced glucose tolerance that is considered a pre-diabetic state [31]. Zarich and co-workers showed an impairment, nearly absolute, of diastolic function indexes obtained with echocardiography [32]. With the same technique Riggs and co-workers also noted a pattern of abnormal relaxation in young diabetic patients [33]. This pattern was observed by Ferraro and co-workers in patients with type 2 diabetes [34].

The mechanism responsible for LV diastolic dysfunction is still unclear. The onset of LV relaxation impairment showed an alteration in the active process of calcium reuptake in the sarcoplasmic reticulum. This process is controlled through several mechanisms [35, 36].

The impairment of the normal vagal-sympathetic equilibrium could play a role in the development of myocardial dysfunction, and our study has evaluated the relationship between CAN and LV dysfunction. Autonomic dysfunction is a common event in diabetic neuropathy and seems to precede the peripheral neuropathy [37–40]. CAN is present in 20%–40% of patients with type 1 diabetes mellitus and, in accordance with previous data, we found autonomic dysfunction in 42% of our patients.

Similar to other studies, the two groups in our study did not show a significant difference in the parameters of systolic performance with both echocardiography and RNA at rest.

Also in this study, we founded an impairment of diastolic function in our patients; this could be related to the existence of a diabetic cardiomyopathy, but the patients with a Autonomic Nervous System (ANS) dysfunction showed a greater incidence of diastolic alterations than patients without CAN (57.6% vs 11.4%, $P<0.001$).

Diabetic cardiomyopathy, with structural changes in the myocardium, is a late complication of diabetes, and the degree of functional impairment seems to be related also to the duration of diabetes. In our patient groups, we can assume that their similar duration of diabetes cannot play a role in the greater functional impairment observed in group A. Moreover, neither metabolic nor systolic function parameters differed significantly between the two groups, and thus, they could not be considered a pathogenetic mechanism of diastolic impairment. Also, Kahn showed a correlation between diastolic RNA indexes (PFR, TPFR) and the mean values of R-R variation during the Valsalva maneuvre [41], suggesting a greater impairment of diastole in patients with autonomic dysfunction.

Our results suggest that abnormalities in ventricular diastolic performance seem to be more evident in type 1 diabetic patients with ANS impairment and without other cardiovascular diseases.

Although other studies will be necessary to detect the pathogenetic mechanism involved, from this study it can be assumed that impairment of the cardiac autonomic system in type 1 diabetic patients is related to sympathetic and parasympathetic dysfunction, and this can worsen an existing diastolic dysfunction, probably due also to an accompanying diabetic cardiomyopathy.

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