Left Ventricular Systolic and Diastolic Function in Normotensive Type 1 Diabetic Patients With or Without Autonomic Neuropathy

A radionuclide ventriculography study

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OBJECTIVE — To investigate the relation between diabetic autonomic neuropathy (DAN) and left ventricular (LV) function in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 57 type 1 diabetic patients free of coronary artery disease and arterial hypertension were studied. Diagnosis of DAN was established by autonomic nervous function (ANF) tests, and LV systolic and diastolic functions were assessed by radionuclide ventriculography at rest.

RESULTS — There were 24 patients who had definite DAN, established by the presence of two or more abnormal ANF tests, and 33 subjects were without DAN. DAN patients had impaired LV filling pattern, obvious by a reduced peak filling rate (3.1 ± 1.1 vs. 3.7 ± 0.7 end-diastolic volume [EDV]/s, $P = 0.011$) and first third filling fraction (35.3 ± 19.5 vs. 50.8 ± 16%, $P = 0.002$) as well as an increased time to peak filling (159.4 ± 45.1 vs. 134.2 ± 33.4 ms, $P = 0.02$) after correction for age and heart rate. There were no differences between the two groups with regard to ejection fraction, cardiac output, and cardiac index, whereas the peak emptying rate was greater in DAN patients (4.1 ± 0.8 vs. 3.6 ± 0.8 EDV/s, $P = 0.019$), suggesting LV hypercontractility. DAN patients had an increased heart rate (83.4 ± 11.9 vs. 72.7 ± 9.3 bpm, $P = 0.001$) and slightly higher systolic blood pressure. As a result, LV working load at rest was higher in DAN patients (11,109 vs. 9,096 bpm × mmHg, $P < 0.001$). Moreover, a correlation was found between abnormal LV systolic and diastolic indexes and the number of abnormal ANF tests.

CONCLUSIONS — At rest, DAN patients have impaired LV filling pattern, slightly increased LV systolic function, and a higher LV working load, in comparison to non-DAN type 1 diabetic patients.

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Clinical and epidemiological studies have confirmed that patients with diabetes appear susceptible to heart failure, which is the leading cause of death in these patients (1). Impairment of left ventricular (LV) function is frequent in patients with type 1 diabetes, even in the absence of ischemic, hypertensive, or valvular heart disease (2). Possible mechanisms for a specific diabetic cardiomyopathy include abnormalities of small intramural coronary vessels, deposition of collagen, and lipids and metabolic derangements that alter actomyosin and myosin adenosine triphosphatase activities (3). Although histopathologic and biochemical evidence for a distinct diabetic cardiomyopathy is available, it remains unclear whether these pathologic processes may cause significant LV systolic or diastolic dysfunction. Numerous studies have reported normal LV systolic function at rest in most type 1 diabetic patients (4), whereas others have suggested increased LV systolic function (5,6). Several investigators have shown abnormal LV diastolic function in the majority of type 1 diabetic patients (7–11), whereas others (12) found no evidence of LV diastolic dysfunction at rest in long-term type 1 diabetic patients. It has been suggested that LV dysfunction in type 1 diabetic patients may be related to structural changes of the myocardium or to concomitant diabetic autonomic neuropathy (DAN) (13).

On the basis that the literature is not clear on this issue, we investigated the LV systolic and diastolic function, in relation to DAN, of 57 type 1 diabetic adult patients without evidence of ischemic heart disease or arterial hypertension. We used radionuclide ventriculography (RNV) at rest, which is a reliable method to assess both systolic and diastolic LV function in patients with diabetes (14).

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Abbreviations: ANF, autonomic nervous function; BSA, body surface area; DAN, diabetic autonomic neuropathy; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular; RNV, radionuclide ventriculography; ROI, region of interest; SV, stroke volume; TAC, time-activity curve.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

REARCH DESIGN AND METHODS

Patient selection
The study included 57 long-term type 1 diabetic adult patients. Patients with overt nephropathy, arterial hypertension, or a

history or clinical evidence of cardiovascular or cerebrovascular disease or other systematic disease(s) were excluded from the study. Insulin was the only medication taken by the patients enrolled in the study. Informed consent, approved by the Ethics Committee of the Hospital, was obtained from all subjects before enrollment.

Autonomic nervous function tests

The Monitor ONE NDX devise (QMED Industries, Clark, NJ) was used for the assessment of the autonomic nervous function (ANF) indexes. The ANF tests were performed according to the consensus statement of the American Diabetes Association and the American Academy of Neurology (15). Normal values adopted were those set by Ziegler and colleagues (16,17). The following tests were performed:

- Beat-to-beat variation of R-R interval assessed by *1*) expiration/inspiration index; *2*) mean circular resultant, vector analysis (probably the most reliable ANF index [18]); and *3*) SD
- Valsalva maneuver (Valsalva Index)
- Variation of R-R interval during postural change (30:15 index)
- Variation of systolic blood pressure during postural change (standing)

The presence of definitive DAN was established if two or more of the abovementioned tests were abnormal. Beat-to-beat variation of the R-R interval was considered abnormal on the basis of mean circular resultant. The extent of the disease was represented by the number of the abnormal ANF tests.

RNV

Autologous stannous pretreated erythrocytes were in vivo labeled with 740 MBq (20 mCi)/70 kg $^{99m}TcO_4^-$. A Toshiba GSA 602A single-headed γ-camera was used. Electrocardiogram-gated acquisition was performed at rest in the supine position. Time was given for patients to relax and stabilize their heart rate before starting acquisition. The γ detector, equipped with a general purpose parallel hole collimator, was positioned for best septal view, and the photopeak was set at 140 keV with a 20% window. The cardiac cycle was divided into 32 frames. A dynamic filtration acquisition mode was used, with rejection of cardiac cycles outwith ±10% of the mean R-R interval. Typically, 6,500 kilocounts per study were acquired. After a preliminary temporary and spatial smoothing, tail frames were appropriately corrected for loss of counts due to R-R variation. Using a second derivative edge detection technique, a region of interest (ROI) over left ventricle was automatically produced for each of the 32 frames. ROIs were manually corrected as needed. A background ROI was drawn at the inferolateral edge of the LV. The background substracted time-activity curve (TAC) thus generated was approximated by a 4th order Fourier transformation. The first derivative of the latter, representing the rate of LV volume change, was used as a supplement for accurate measurement of both diastolic events timing and diastolic parameters. Ejection fraction was calculated in the usual manner. Peak emptying rate was defined as the negative peak of the first derivative curve during systole and was expressed in end-diastolic volume (EDV)/s. Likewise, peak filling rate was defined as the peak of the 1st derivative curve at the first half of diastole, expressed in EDV/s. The interval from the lowest TAC point to the time when peak filling rate occurred was defined as time to peak filling rate. The late positive deflection of the first derivative curve was attributed to the atrial contraction, and the atrial contribution to diastolic filling (A/V) was measured from the corresponding TAC segment as the percentage of stroke volume (SV). The first third filling fraction was designated as the percentage of LV filling (or SV) during the first third of diastole. All these parameters for diastolic function assessment have been previously described (19,20). EDV and end-systolic volume (ESV) (and hence SV and cardiac output) were calculated using a previously validated count ratio-based method (21). Cardiac volumes were indexed for body surface area (BSA), which was calculated according to the formula by Dubois and Dubois (22): $BSA = H^{0.725} \times W^{0.425} \times 71.84$. Cardiac workload was calculated as the product of heart rate times systolic arterial pressure.

Table 1—*Demographic characteristics and clinical and biochemical parameters of the two groups of patients as defined by the presence or absence of DAN*

	Patients with <2 measures of DAN	Patients with ≥2 measures of DAN	*P*
n	33	24	—
Females (%)	42.4	58.3	NS
Age (years)	29.8 ± 10.7	40.4 ± 17.3	0.002
BSA (m^2)	1.88 ± 0.23	1.79 ± 0.17	NS
Duration of diabetes (years)	16.0 ± 6.5	21.2 ± 8.9	0.012
HbA_{1c} (%) (normal values 3.8–5.5)	7.38 ± 1.20	8.35 ± 1.59	0.014
Microalbuminuria (mg/24 h) (normal values 0–30)	21.2 ± 42.0	48.6 ± 75.5	<0.0001
Heart rate* (bpm)	72.7 ± 9.3	83.4 ± 11.9	0.001
Systolic blood pressure (mmHg)	124.7 ± 12.9	131.5 ± 15.8	NS
Diastolic blood pressure (mmHg)	79.7 ± 8.1	82.8 ± 9.7	NS
Working load (bpm × mmHg)	9,096 ± 1,763	11,109 ± 1,971	<0.001

Data are means ± SD. *During RNV.

Statistical analysis

Descriptive statistics are presented as means ± 1 SD. The χ^2 test was applied for rate comparisons. The nonparametric Mann-Whitney *U* test was used for comparisons between two independent groups. To adjust data for between-group differences in variables (e.g., heart rate, age, and blood pressure) known or postulated to influence systolic or diastolic RNV parameters, multiple linear regression analysis was used. Using the forward stepwise regression approach, multivariate models incorporating the statistically significant covariates were obtained, allowing for adjustment of data to preselected values of these covariates. The nonparametric Spearman's rank correlation coefficient (r_s) was used to assess the association between systolic or diastolic

Table 2—*Results of ANF tests in the two groups of patients as defined by the presence or absence of DAN*

	Patients with <2 measures of DAN	Patients with ≥2 measures of DAN	*P*
n	33	24	—
HR variability			
Expiration/inspiration index (NV >1.05)	1.41 ± 0.24	1.10 ± 0.06	<0.001
Mean circular resultant (NV >20)	62.0 ± 32.6	17.9 ± 9.6	<0.001
SD (NV >20)	95.2 ± 53.9	27.7 ± 14.6	<0.001
Valsalva index (NV ≥1.21)	1.78 ± 0.29	1.38 ± 0.26	<0.001
30:15 index (NV ≥1.04)	1.37 ± 0.26	1.13 ± 0.17	<0.001
Postural hypotension (NV <20 mmHg)	1.67 ± 4.08	20.6 ± 13.6	<0.001

Data are means ± SD. NV, normal values.

RNV parameters and the number of abnormal ANF tests. Statistical significance was accepted for *P* values <0.05.

RESULTS— Demographic characteristics and clinical and biochemical findings of the study population are displayed in Table 1. DAN patients were older, with longer duration of diabetes, and had higher HbA_{1c} and microalbuminuria levels than patients without DAN. Heart rate was higher in the DAN group. Despite no significant differences in systolic or diastolic arterial pressure, working load was higher in DAN patients.

ANF tests

From the 57 type 1 diabetic patients included in the study, 22 (38.6%), 11 (19.3%), 14 (24.6%), 7 (12.3%), and 3 (5.3%) patients had zero, one, two, three, or four abnormal ANF tests, respectively. Thus, 24 of them were considered to have definite DAN and 33 were without DAN. The two groups of patients significantly differed in the values of all measured ANF tests (Table 2).

RNV

As shown in Table 3, there were no differences between DAN and non-DAN patients in LV systolic function. Concerning diastolic parameters, atrial contribution (%SV) was higher and the first third filling fraction (%SV) was lower in patients with DAN than in patients without DAN. Peak filling rate and time to peak filling did not significantly differ between the two groups. Differences between the two groups were also observed in EDV, ESV, and SV. Only ESV remained significantly lower in the DAN group after indexing for BSA. Cardiac output and cardiac index did not significantly differ between the two groups. Stepwise regression analysis showed that the major covariates of LV systolic and diastolic indexes were age, heart rate, and systolic blood pressure. We adjusted LV function indexes for these covariates (age = 34.4 years, heart rate = 77.3 min, and systolic blood pressure = 128.6 mmHg). After adjustment, ejection fraction values remained similar between groups, but the LV peak emptying rate was greater in the DAN group, suggesting LV hypercontractility (Table 4). After adjustment, the statistically significant difference in atrial contribution disappeared, but the peak filling rate became lower, first third filling fraction remained lower, and time to peak filling (ms) became significantly higher in the DAN group, all suggesting a definite LV diastolic deterioration in DAN patients (Table 4). Nonparametric correlation (Spearman's rank correlation coefficient r_s) was significant between the number of abnormal ANF tests and peak emptying rate, peak filling rate (EDV/s), first third filling fraction, and time to peak filling (ms) (Table 5).

CONCLUSIONS— We have shown in the present study that DAN is closely associated to LV dysfunction at rest in long-term type 1 diabetic patients without arterial hypertension or ischemic heart disease. Our data suggest that LV function of type 1 diabetic patients differs according to the absence or presence of DAN. Type 1 diabetic patients without DAN have no evidence of diastolic or systolic dysfunction. Patients with DAN show deterioration of ventricular filling pattern and a normal or slightly hyperactive LV systolic function at rest. Nonethe-

Table 3—*Systolic, diastolic, and volumetric RNV parameters in the two groups of patients as defined by the presence or absence of DAN*

	Patients with <2 measures of DAN	Patients with ≥2 measures of DAN	*P*
n	33	24	—
Systolic			
Ejection fraction (%) (normal values >55%)	66.9 ± 5.4	68.8 ± 7.9	NS
Peak emptying rate (EDV/s)	3.81 ± 0.65	3.89 ± 0.65	NS
Diastolic			
Atrial contribution (%SV)	17.3 ± 7.1	26.0 ± 11.9	0.002
Peak filling rate (EDV/s)	3.44 ± 0.71	3.43 ± 1.04	NS
First third filling fraction (%SV)	52.7 ± 16.5	32.8 ± 11.9	<0.001
Time to peak filling (ms)	138.6 ± 29.3	153.6 ± 38.7	NS
Volumetric			
EDV (ml)	138.2 ± 29.8	116.3 ± 28.8	0.015
EDV index (ml/m^2)	72.1 ± 13.3	65.2 ± 16.5	NS
ESV (ml)	45.9 ± 12.8	36.5 ± 13.8	0.007
ESV index (ml/m^2)	24.5 ± 6.6	20.4 ± 7.6	0.017
SV (ml)	92.3 ± 20.4	79.8 ± 21.2	0.034
SV index (ml/m^2)	49.4 ± 10.3	44.9 ± 12.7	NS
Cardiac output (ml/min)	6,700 ± 1,654	6,623 ± 1,986	NS
Cardiac index (ml · min^{-1} · m^{-2})	3,586 ± 879	3,735 ± 1,211	NS

Table 4—*Systolic and diastolic RNV parameters in the two groups of patients as defined by the presence or absence of DAN, after correction for age, heart rate, and systolic blood pressure*

	Patients with <2 measures of DAN	Patients with ≥2 measures of DAN	P
n	33	24	—
Systolic parameters			
Ejection fraction (%)	67.3 ± 5.1	68.2 ± 7.7	NS
Peak emptying rate (EDV/s)	3.63 ± 0.79	4.12 ± 0.80	0.019
Diastolic parameters			
Atrial contribution to ventricular filling (%SV)	20.9 ± 5.9	21.2 ± 9.9	NS
Peak filling rate (EDV/s)	3.70 ± 0.68	3.09 ± 1.07	0.011
First third filling fraction (%SV)	50.8 ± 16.0	35.3 ± 19.5	0.002
Time to peak filling (ms)	134.2 ± 33.4	159.4 ± 45.1	0.020

Parameters adjusted for covariates: age = 34.4 years, heart rate = 77.3 bpm, systolic blood pressure = 128.6 mmHg.

Table 5—*Correlation between the number of abnormal autonomic function tests and adjusted systolic and diastolic RNV parameters in the total of the patients*

	R	P
Peak emptying rate (EDV/s)	0.311	<0.05
Peak filling rate (EDV/s)	−0.336	<0.01
First third filling fraction (%SV)	−0.419	<0.01
Time to peak filling (ms)	0.309	<0.05

less, LV working load in these patients is higher than that of type 1 diabetic patients without DAN, thus rendering them suitable candidates for long-term ACE inhibition therapy as an addition to their conventional drug regimen.

We preferred RNV because it has distinct advantages over echocardiography in LV function quantification; namely, data are collected over some hundreds of cardiac cycles, no body habitus is impeding acquisition, and intra- and interobserver variabilities are minimal. LV mass assessment is impossible using RNV, and this is a methodological disadvantage because a slight increase in LV mass index has been reported in normotensive diabetic subjects using echocardiography (23).

In our type 1 diabetic patients, both systolic and diastolic LV function were preserved in the absence of DAN, whereas isolated diastolic impairment was demonstrated in the group of patients with overt DAN. Patients with and without DAN significantly differed with respect to heart rate and age. A methodological difficulty exists in demonstrating alterations in diastolic function under changing hemodynamic or demographic conditions. Age and heart rate are well-known determinants of diastolic function. Diastolic function deterioration has been shown in normal adult hearts with advancing age (24,25), and many studies have revealed a linear relationship between heart rate and LV filling pattern over a wide heart rate range (26,27). We therefore corrected indexes of LV function for age, heart rate, and systolic arterial pressure differences between patients with and without DAN. To our knowledge, no previous study has investigated the relation between DAN and LV diastolic function using data corrected for age, heart rate, and blood pressure. Adjusting LV diastolic indexes for clinical, demographic, and hemodynamic confounders is common in similar studies (23). Even after correction for these covariates, we were able to show that patients with DAN had definite LV diastolic deterioration. Moreover, DAN patients presented LV hypercontractility, because this was suggested by an increased peak emptying rate, although there were no differences in ejection fraction, cardiac output, and cardiac index. Increased LV mass, reported in normotensive diabetic patients (23), could potentially underlie the augmentation of cardiac systolic function observed in our study. Resting working load, however, was greater in the type 1 diabetic patients with DAN when compared with performance in the group without DAN (Table 1). This result was due to a slight increase in systolic blood pressure and a significant increase in heart rate in the DAN group (Table 1), reflecting an increased sympathetic tone in these patients (28). An inverse relationship between the R-R variation and resting work product has been previously shown (13). Moreover, as has been shown by others, the impairment of LV relaxation in diabetes can influence exercise tolerance even in the absence of LV systolic dysfunction, probably by limiting activation of the contractile reserve (29).

All of our patients with DAN presented microalbuminuria, which may be related to the overall LV function. Increased systolic performance (heart rate and contractility) may contribute to renal hyperperfusion and glomerular hyperfiltration observed in type 1 diabetic patients preceding the development of microalbuminuria (albumin excretion rate >30 mg/day) and, in turn, macroalbuminuria (5). Moreover, early diastolic cardiac dysfunction has been found to be correlated with microalbuminuria, which represents an incipient stage of diabetic nephropathy (30). The high incidence of cardiac mortality in type 1 diabetic patients is further increased in the presence of diabetic nephropathy (31). Thus, the overall LV performance in type 1 diabetic patients with DAN may be of important prognostic significance.

Our results seem to be in contradiction to other studies, which have shown the presence of cardiomyopathy in similar patient groups (4–12). The main reason for the different results with regard to LV dysfunction may be that patient selection and exclusion criteria vary considerably between studies. In contrast, most of the above studies revealed normal systolic and diastolic function in type 1 diabetic patients if hypertension, coronary heart disease, autonomic dysfunction, and microangiopathy had been excluded. The different results may also be explained by differences in metabolic control, which seem to be the most important factor for the development of late diabetic complications. The absence of other diabetic complications in our patients can also be interpreted as a consequence of good metabolic control. Reduction in cardiovascular risk factors and intensive diabetes therapy may not only delay the appearance of retinopathy and nephropathy (31–33), but may also have a beneficial effect on cardiac function. Further studies are needed to clarify this point.

Clinical implications

The presence of DAN can help the physician to identify the subset of patients with type 1 diabetes who may need special consideration when exercise training is prescribed. The intentional assessment of diastolic function is advisable for early detection of LV dysfunction before clinical symptoms appear. Type 1 diabetic patients with DAN are suitable candidates for long-term ACE inhibition therapy as an addition to their existing drug regimen. Because the reliability of echocardiographic assessment of LV diastolic function is moderate (34), RNV, which is a more accurate and reliable modality, may be of additional value in view of repeated assessments of LV diastolic function.

In conclusion, DAN is associated with LV diastolic dysfunction. Presence of DAN might serve as an early marker for the evaluation of LV diastolic function and potential initiation of treatment with ACE inhibition therapy.

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