Preclinical Diabetic Cardiomyopathy: Relation of Left Ventricular Diastolic Dysfunction to Cardiac Autonomic Neuropathy in Men With Uncomplicated Well-Controlled Type 2 Diabetes

Paul Poirier, Peter Bogaty, François Philippon, Caroline Garneau, Claudette Fortin, and Jean-G. Dumesnil

Diabetic cardiomyopathy is an ill-defined entity. This study was designed to explore the possible association between left ventricular diastolic dysfunction (LVDD) and cardiac autonomic neuropathy (CAN) independently from metabolic control. Three groups of 10 age-matched men each with well-controlled type 2 diabetes were studied: (1) subjects with normal diastolic function, (2) subjects with LVDD characterized by impaired LV relaxation, and (3) subjects with a more severe form of LVDD characterized by a pseudonormalized pattern of LV filling. No subject had evidence of clinical diabetic complications, coronary artery disease (CAD), hypertension, congestive heart failure, or thyroid or overt renal disease, and all had a negative maximal exercise test. LVDD was evaluated by Doppler echocardiographic and CAN was evaluated using spectral analysis of heart rate variability (HRV; time and frequency domains) from 24-hour Holter recordings. Findings showed that the high frequency power (HF: 0.15 to 0.4 Hz) tends to decrease with worsening diastolic function; 5.0 ± 0.2 ms^2 (mean ± SE) in group 1, 4.2 ± 0.3 ms^2 in group 2, and 3.9 ± 0.4 ms^2 ($P = .03$) in group 3, respectively, whereas the low frequency power (LF: 0.04 to 0.15 Hz) was similar between groups. In the time domain, the mean squared differences of the successive RR intervals (rMSDD) also showed the same pattern, ie, 31.0 ± 2.8 ms, 23.8 ± 1.6 ms, and 21.5 ± 2.9 ms in groups 1, 2, and 3, respectively ($P = .03$). The E/A ratio correlated significantly with indices of parasympathetic modulation (HF; $r = 0.448$, $P = .013$; rMSDD: $r = 0.457$, $P = .011$; pNN50: $r = 0.425$, $P = .019$). LVDD and CAN are associated in patients with otherwise uncomplicated well-controlled type 2 diabetes. The parameters defining these 2 abnormalities may serve to better define diabetic cardiomyopathy as a distinct entity and could eventually become useful prognostic indicators as it has been shown in nondiabetic populations.

SUBJECTS WITH diabetes mellitus have a poorer cardiovascular prognosis than individuals without diabetes[1]; the vast majority of subjects with diabetes will die from heart disease.[2] Up to 60% of unselected populations with type 2 diabetes have autonomic neuropathy.[3-6] In subjects with diabetes, a reduction in heart rate variability (HRV) is associated with an adverse cardiovascular prognosis[2,7] and stroke.[4] The most frequently reported autonomic abnormalities are a slight increase in heart rate and an altered HRV that have been ascribed to vagal damage.[8,9] Autonomic neuropathy is a frequent complication of diabetes and is often clinically inapparent.[2,10]

Left ventricular diastolic dysfunction (LVDD) may represent the first stage of diabetic cardiomyopathy, which is an ill-defined entity.[11-13] Recently in a population-based sample of adults with type 2 diabetes, a distinct diabetic cardiomyopathy, independent of age, arterial pressure, LV mass, and systolic function, was described.[11] The prevalence of LVDD in middle-aged asymptomatic subjects with type 2 diabetes is estimated to be about 30%.[14-16] However, in subjects with type 2 diabetes, a pseudonormal pattern of LV filling that is often noted in the evaluation of LVDD[17,18] suggests that LVDD may be more frequent (45% to 60%) than previously suspected.[19-21] Interestingly, although the pseudonormalized pattern of ventricular filling was not assessed, an association between cardiac autonomic neuropathy (CAN) and LVDD has been described in subjects with type 1[10] and type 2 diabetes.[22] However, the presence of comorbidities such as poor metabolic control, hypertension, significant coronary artery disease (CAD), proliferative retinopathy, impaired LV systolic function, and the absence recognition of the pseudonormalized pattern of ventricular filling limit the interpretation of these results.[10,22] The pseudonormal pattern is especially important since it represents a more advanced stage of LVDD. The association between a pseudonormal pattern of ventricular filling and cardiac dysautonomy has never been evaluated in subjects with diabetes. The objective of this study was to evaluate the association between stages of LVDD and the degree of CAN in normotensive men with well-controlled type 2 diabetes without clinical evidence of heart disease.

SUBJECTS AND METHODS

Study Population

From a previous study,[19] we have constituted 3 age-matched groups of men with type 2 diabetes without clinical evidence of cardiovascular disease including hypertension (blood pressure > 140/90 mm Hg) or respiratory diseases on the basis of their LV function to evaluate cardiac autonomic nervous system between the groups. The groups were separated as follows: (1) subjects with normal LV diastolic function (n = 10), (2) subjects with an impaired relaxation pattern of LVDD (n = 10), and (3) subjects with a pseudonormalized pattern of LVDD (n = 10). All subjects underwent a maximal treadmill exercise test and in subjects with exercise-induced ST-segment depression, myocardial perfusion imaging with thallium 201 was performed to exclude CAD.[16] Also excluded were subjects with diabetic complica-

From the Institut Universitaire de Cardiologie et de Pneumologie, Laval Hospital, Ste-Foy, Québec, Canada.

Received October 22, 2002; accepted January 22, 2003.

C.G. was supported in part by a scholarship from the Association du Diabète du Québec. This work was supported in part by the Fonds de la Recherche en Santé du Québec (FRSQ) granted to P.P.

Address reprint requests to Paul Poirier MD, PhD, FRCPC, FACC, Associate Professor/Laval University Faculty of Medicine, Institut Universitaire de Cardiologie et de Pneumologie, Laval Hospital, 2725 Chemin Sainte-Foy, Sainte-Foy, Quebec, Canada G1V 4G5.

0026-0495/03/5208-0044$30.00/0

doi:10.1016/S0026-0495(03)00091-X

tions such as retinopathy, macroalbuminuria, or any clinical signs or symptoms of autonomic dysfunction; subjects who were involved in regular physical training; subjects using insulin, cardiovascular drugs, or medication known to influence the autonomic nervous system; and subjects with regional or global wall motion abnormalities or valvular disease on echocardiography. Subjects were treated with diet and/or oral hypoglycemic agents (sulfonylurea and/or metformin) and their diabetes had to be well controlled during the last 3 months.[23] The Laval Hospital Ethics Committee approved the protocol, and all subjects gave written informed consent.

Biochemistry

Plasma glucose concentration, glycated hemoglobin A_{1C} (normal range, 4.4% to 6.6%), serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides (TG) were analyzed as previously described.[16,19] Low-density lipoprotein (LDL)-cholesterol was calculated using Friedewald's formula.[24] LDL-cholesterol was not calculated in 2 subjects because the TG level was ≥6.0 mmol/L. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Echocardiography

Standard parasternal, short-axis, and apical views were performed in accordance with the recommendations of the American Society of Echocardiography and the same observer obtained all recordings and measurements.[19] LVDD, using transmitral and pulmonary veins recordings, was evaluated using well-standardized criteria.[17,19] The following parameters were obtained: peak *E* velocity in cm/s (peak early transmitral filling velocity during early diastole), peak *A* velocity in cm/s (peak transmitral atrial filling velocity during late diastole), deceleration time in ms (time elapsed between peak *E* velocity and the point where the extrapolation of the deceleration slope of the *E* velocity crosses the zero baseline), isovolumic relaxation time (time elapsed between aortic valve closure and mitral valve opening), and E/A ratio (peak *E* wave velocity divided by peak *A* wave velocity). To diminish the high filling pressures encountered in the pseudonormalized pattern of LV filling, the same measurements were repeated during phase II of the Valsalva maneuver.[17]

Pulmonary venous flow recordings were obtained from the 4-chamber view directed at the right upper pulmonary vein. Sample volume placed 1 to 2 cm into the pulmonary vein for the measurement of peak *A* wave velocity in cm/sec (peak reversed systolic wave during atrial contraction). The reference values from the Canadian Consensus on Diastolic Dysfunction were used to identify the group without LVDD.[17] To distinguish the latter from those with a pseudonormalized pattern of ventricular filling, 2 of the 3 following criteria had to be met: (1) the E/A ratio was less than 1 after the Valsalva maneuver; (2) the E/A ratio decreased by ≥25% after the Valsalva maneuver; and (3) pulmonary *A* wave duration was longer than mitral *A* wave duration.[19]

Left ventricular mass (LVM) was calculated with the following formula[25]: $LVM\ (g) = 0.8 \times 1.04\ [(LVEDD + IVST + PWT)^3 - (LVEDD)^3] + 0.6$, where LVEDD was the left ventricle end diastolic dimension, IVST the interventricular septal thickness, and PWT the posterior wall thickness.

Heart Rate Variability

HRV was derived from a 24-hour Holter monitoring system (Marquette Electronics, Milwaukee, WI) in all subjects during normal daily life activity. HRV derived from 24-hour ambulatory monitoring is reproducible and free of placebo effect.[26] Using frequency domains, power in the low frequency (LF: 0.04 to 0.15 Hz), an index of both sympathetic and parasympathetic activity, and power in the high frequency (HF: 0.15 to 0.4 Hz), an index of solely parasympathetic activity, were calculated. The LF/HF ratio is the power in low frequency divided by the power in high frequency. Using time domains, the standard deviation of the RR intervals (SDNN), the square root of the mean squared differences of successive RR intervals (rMSDD), and the standard deviation of the average RR intervals calculated over 5-minute periods (SDANN) were determined. pNN50 is the proportion of interval differences of successive NN intervals greater than 50 ms. NN or RR intervals are the normal-to-normal intervals that include all intervals between adjacent QRS complexes resulting from sinus node depolarizations in the entire 24-hour electrocardiogram recording.

Statistical Analysis

The data are presented as mean ± SD unless otherwise specified. Comparison among the 3 groups of subjects for various parameters was performed by 1-way analysis of variance (ANOVA) and the post hoc Tukey test for multiple comparisons. When normality and/or equal variance testing conditions were not met, the Kruskal-Wallis rank test and/or the Dunn test for multiple comparisons were used, respectively. Student's paired *t* test was used to evaluate the responses to the Valsalva maneuver within groups. Pearson's linear correlation coefficients were calculated for pairs of continuous variables. Logarithmic transformation was used for variables not normally distributed. A *P* value less than .05 was considered statistically significant.

RESULTS

Clinical Parameters

Table 1 shows clinical characteristics of the 3 groups. No subject had a restrictive pattern of ventricular filling. There were no differences in treatment for diabetes, daily dosages of hypoglycemic agents, diabetes duration, BMI, resting heart rate, diastolic and mean blood pressure, fasting blood glucose, glycated hemoglobin A_{1c}, and lipid profile. Although within normal limits, systolic blood pressure was lower in normal subjects compared to subjects with a pseudonormalized pattern of ventricular filling ($P = .043$).

Echocardiographic Measurements (M-mode)

All measurement for LVM cavity dimensions were within normal limits. There were no differences between groups in aortic root, posterior wall, LV systolic or diastolic or right ventricular diastolic dimensions, LVM, or LV ejection fraction (data not shown).

Transmitral and Pulmonary Venous Doppler Flow Velocity Recordings

Table 2 summarizes the results from Doppler-derived diastolic filling indices for the 3 groups. Transmitral recordings are reported at baseline and during phase II of the Valsalva maneuver (Table 2). LV diastolic function using transmitral and pulmonary venous flow recordings was measured in all subjects. *E* and *A* wave velocity values for the group with normal diastolic function were within the accepted normal range.[17]

Before the Valsalva maneuver (Table 2), subjects with impaired relaxation showed lower *E* wave velocity compared to subjects with normal diastolic function ($P = .025$) and subjects with a pseudonormalized pattern ($P = .036$). *A* wave velocity was higher in subjects with impaired relaxation compared to normals ($P < .001$) and subjects with a pseudonormalized pattern ($P = .002$). Consequently, the E/A ratio was smaller in subjects with impaired relaxation compared to subjects with normal diastolic function ($P < .001$) and subjects with a

Table 1. Characteristics of 30 Men With Type 2 Diabetes Separated on the Basis of Left Ventricular Diastolic Function

	Normal (n = 10)	Impaired Relaxation (n = 10)	Pseudonormalized Pattern (n = 10)
Age (yr)	51 ± 4	56 ± 4	54 ± 7
Diabetes duration (yr)	4 ± 3	3 ± 3	10 ± 10
BMI (kg/m^2)	28.7 ± 3.0	29.3 ± 4.2	30.2 ± 1.9
Resting HR (beats/min)	66 ± 8	75 ± 13	71 ± 8
Systolic BP (mm Hg)	115 ± 11	125 ± 12	127 ± 8‡
Diastolic BP (mm Hg)	72 ± 7	79 ± 8	76 ± 9
Fasting glucose (mmol/L)	10.6 ± 3.2	10.2 ± 2.9	10.7 ± 2.6
HbA_{1c} (%)*	6.7 ± 2.4	5.9 ± 1.2	6.7 ± 1.6
Total-cholesterol (mmol/L)	5.8 ± 1.3	5.4 ± 1.2	5.4 ± 0.7
HDL-cholesterol (mmol/L)	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3
LDL-cholesterol (mmol/L)	3.6 ± 1.0	3.6 ± 1.1	3.3 ± 0.8
Triglycerides (mmol/L)†	2.9 (1.3-11.3)	2.2 (1.0-6.0)	2.2 (1.5-2.8)
Microalbuminuria (+)	4	6	7

NOTE. Data are the mean ± SD

*Normal range HbA_{1c}: 4.4% to 6.6%.

†Triglycerides are expressed as the median (range).

‡$P < .05$ *v* normal subjects

Abbreviations: BMI, body-mass index; HR, heart rate; BP, blood pressure.

pseudonormalized pattern ($P < .001$). There was no statistical difference in isovolumetric relaxation time, deceleration time, or *A* wave duration among groups.

After the Valsalva maneuver (Table 2), *E* wave velocity decreased in the 3 groups ($P < .001$), whereas *A* wave velocity decreased only in those with normal diastolic function or with impaired relaxation ($P < .005$). As a consequence, a decrease in the E/A ratio was observed in subjects with normal diastolic function ($P = .01$) and with a pseudonormalized pattern ($P < .001$). The decrease in E/A ratio was 13% in the group with normal diastolic function, 11% in the group with impaired relaxation, and 40% in the group with a pseudonormalized pattern ($P < .001$ *v* normal and impaired relaxation). All subjects without LVDD conserved an E/A ratio greater than 1, whereas all subjects with a pseudonormalized pattern showed an E/A ratio less than 1. Therefore, subjects with normal diastolic function showed a higher E/A ratio than subjects with impaired relaxation ($P < .001$) and subjects with a pseudonormalized pattern ($P < .001$). Deceleration time increased similarly (29% to 33%) following the Valsalva maneuver in all 3 groups (Table 2). Pulmonary reversed *A* wave duration (PVa) was significantly longer in subjects with a pseudonormalized

Table 2. Transmitral and Pulmonary Doppler Flow Recordings in 30 Men With Type 2 Diabetes Separated on the Basis of Left Ventricular Diastolic Function

	Normal (n = 10)	Impaired Relaxation (n = 10)	Pseudonormalized Pattern (n = 10)
Baseline			
E wave (cm/s)	69 ± 13	56 ± 10*	68 ± 7†
A wave (cm/s)	52 ± 10	74 ± 14‡	55 ± 8§
E/A	1.35 ± 0.14	0.77 ± 0.06‡	1.27 ± 0.19§
IVRT (ms)	109 ± 15	110 ± 12	105 ± 12
Deceleration time (ms)	188 ± 32	229 ± 57	188 ± 24
A wave duration (ms)	128 ± 20	128 ± 24	119 ± 21
PVa duration (ms)	100 ± 9	115 ± 28	125 ± 16*
PVa − Ma duration (ms)	−28 ± 14†	−13 ± 22	6 ± 22¶
During the Valsalva maneuver			
E wave (cm/s)	45 ± 9	36 ± 3*	40 ± 8
A wave (cm/s)	39 ± 8	53 ± 9‡	54 ± 8¶
E/A	1.17 ± 0.14	0.69 ± 0.12‡	0.75 ± 0.12¶
Deceleration time (ms)	245 ± 54	294 ± 102	250 ± 55
A wave duration (ms)	108 ± 27	121 ± 23	116 ± 21

NOTE. Data are the mean ± SD

*$P < .05$ *v* normal subjects.

†$P < .05$ *v* subjects with impaired relaxation.

‡$P < .005$ *v* normal subjects.

§$P < .005$ *v* subjects with impaired relaxation.

¶$P < .005$ *v* normal subjects.

Abbreviations: IVRT, isovolumetric relaxation time; PVa, reversed systolic wave in the pulmonary veins, Ma, transmitral *A* wave.

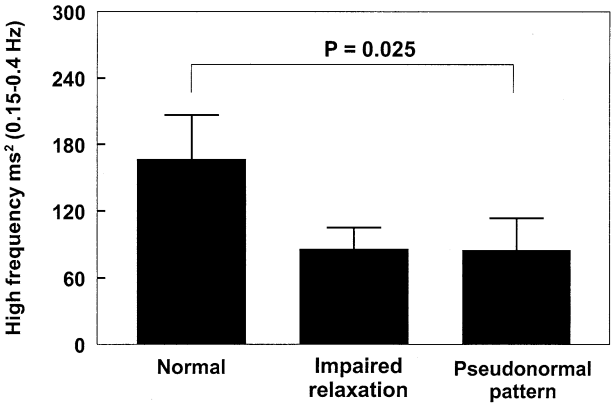

Fig 1. HF (ms^2) in 30 men with type II diabetes separated on the basis of LV diastolic function. Values are mean ± SD.

pattern compared to normal subjects (125 ± 16 *v* 100 ± 9 ms, $P = .019$). PVa wave duration minus mitral *A* wave duration was calculated and, as expected because of high left atrial filling pressure, subjects with a pseudonormalized pattern showed a significantly higher value than those without LVDD ($P = .002$).

HRV Indices

Several HRV indices from frequency and time domains are described in Fig 1 and Table 3. In the frequency domain, there was no difference in LF (0.04 to 0.15 Hz) or LH/HF ratio among groups (Table 3), whereas HF (0.15 to 0.4 Hz) decreased as the diastolic function worsened ($P = .03$, Fig 1). Moreover, HF was decreased in subjects with a pseudonormalized pattern of ventricular filling compared to controls ($P = .03$). In the time domain, there were no differences in SDNN, SDANN, or mean NN among groups. However, rMSSD also decreased as the diastolic function worsened (Table 3, $P = .03$). Thus, the indices of parasympathetic modulation (HF and rMSSD) were decreased as the LV diastolic function worsened in our cohort.

There were significant inverse correlations between E/A ratio and age ($r = -0.40$, $P = .028$) and systolic blood pressure ($r = -0.425$, $P = .019$). There was no correlation between E/A ratio and lipid profile, metabolic control (expressed by HbA_{1c}), fasting blood glucose, LVM, or heart dimensions. E/A ratio correlated significantly with indices evaluating parasympathetic modulation in both the frequency domains (HF: 0.15 to 0.4 Hz, $r = 0.448$, $P = .013$) and the time domains (rMSSD: $r = 0.457$, $P = .011$; pNN50: $r = 0.425$, $P = .019$).

DISCUSSION

The current findings suggest that preclinical manifestations of diabetic cardiomyopathy, ie, LVDD and cardiac dysautonomy, are associated and this maybe independent of metabolic control. Although the pathogenesis and pathophysiology of diabetic cardiomyopathy remain unclear and are probably multifactorial,[12,27,28] LVDD is frequent in subjects with diabetes.[11,19-21] The LV elastic recoil, the rate of myocardial relaxation, chamber compliance, and loading conditions, all affect LV diastolic function. The association between LVDD and CAN depicted in this study may be the hemodynamic consequence of disturbed parasympathetic flow to the heart and/or an abnormal afferent parasympathetic inflow from carotid and aortic baroreflexes and atrial receptors. Whether efferent or afferent, parasympathetic denervation may induce slowed ventricular relaxation, leading to a fall in the velocity of the passive, early diastolic transmitral flow (*E* wave) and a compensatory increase in the flow velocity caused by atrial contraction (*A* wave). This is further reinforced by findings suggesting that diastolic dysfunction is caused by impaired myocyte handling of calcium, since the latter depends in part on autonomic nervous stimulation.[29] Therefore, LVDD and cardiac dysautonomy may well be related through a common pathophysiological pathway at the preclinical stage, which may better define the presence of diabetic cardiomyopathy.

Subjects with type 2 diabetes clearly show a widespread abnormality in their autonomic modulation that impacts heart rate, blood pressure, and the microvasculature.[30] Consistent with our results, it is thought that neural damage affects parasympathetic nerves earlier and to a greater degree than it affects the sympathetic nerves. The reduction in cardiac vagal modulation may be seen not only at the cardiac level, but also at the vascular level.[10] As such, in this study, there was a trend toward higher resting heart rate in all subjects with LVDD compared to subjects with normal diastolic function (73 ± 11 *v* 66 ± 8; $P = .09$) and an increase in systolic blood pressure (Table 1).

It has generally been accepted that autonomic neuropathy is a consequence of long-term hyperglycemia[31] and uncontrolled diabetes negatively affects the progression of autonomic neuropathy.[2,5] Also, suboptimal glucose control has been associated with abnormal LV relaxation,[11] but abnormal relaxation is also associated, in subjects with type 2 diabetes, with renal microvascular disease and arterial stiffening, again supporting a systemic pathological process.[32] Metabolic control at least in

Table 3. Heart Rate Variability Indices in 30 Men With Type 2 Diabetes Separated on the Basis of Left Ventricular Diastolic Function

	Normal (n = 10)	Impaired Relaxation (n = 10)	Pseudonormalized Pattern (n = 10)
LF ms^2 (0.04-0.15 Hz)	554 ± 180	444 ± 298	349 ± 332
LF/HF	4.12 ± 1.84	5.32 ± 2.14	5.10 ± 2.86
SDANN (ms)	129 ± 23	130 ± 55	111 ± 25
rMSSD (ms)	31 ± 9	24 ± 5	22 ± 9*
pNN50 (%)	8.8 ± 5.1	4.9 ± 2.5	4.3 ± 4.8
NN (ms)	753 ± 83	797 ± 156	728 ± 85
SDNN (ms)	139 ± 24	141 ± 54	117 ± 26

NOTE. Data are the mean ± SD

*$P < .05$ *v* normal subjects.

Abbreviations: LF/HF, low frequency/high frequency ratio; SDANN, standard deviation of the average NN intervals calculated over 5 minutes periods; rMSSD, the square root of the mean squared differences of successive NN intervals; pNN50, the proportion of interval differences of successive NN intervals >50 ms; NN, normal-to-normal intervals between adjacent QRS complexes resulting from sinus node depolarizations; SDNN, standard deviation of the NN intervals.

the last few months prior the study was excellent. Moreover, since abnormal LV relaxation in diabetes mellitus has been recently shown to be similar in degree to the well-known impaired relaxation associated with hypertension without diabetes,[11] a common link independent of hyperglycemia or insulin resistance may be suspected. Accordingly, Liu et al have demonstrated in a large cohort of subjects that plasma insulin is not related to diastolic stiffness.[11]

On the other hand, subclinical autonomic neuropathy may develop in the absence of long-term hyperglycemia since autonomic neuropathy may be present in nondiabetic subjects with a family history of type 2 diabetes.[33] There is a large variability in the susceptibility of the subject with diabetes to develop complications inherent to this disease.[2] It is also plausible that clinical methods for the diagnosis of diabetic neuropathy are insufficiently sensitive[6,34] and that HRV may represent a useful screening tool in the early assessment of CAN (much as the Valsalva maneuver may unmask the pseudonormalized pattern of ventricular filling). Additionally, HRV is accepted as a method to evaluate subclinical cardiac neuropathy in individuals at increased risk of cardiac-related mortality[2,5] and is more widely available than other more sophisticated method of evaluation such as myocardial m[^{123}I]iodobenzylguanidine scintigraphy.[22,34,35]

It is unlikely that impaired diastolic function was simply due to increased heart rate, since there was no difference in heart rate between the subjects with impaired relaxation and the group with a pseudonormalized pattern of ventricular filling. However, a structural cause for the diastolic dysfunction cannot be excluded. Advanced glycosylation end-products (AGEs) cause diastolic dysfunction in animal model of diabetes.[36] Indeed, interstitial accumulation of AGEs, which include collagen, elastin, and other connective tissue proteins, have been reported in human diabetic hearts.[37,38] Also, increased LVM may be associated with progressive autonomic neuropathy[39] and it is of note that subjects with abnormal diastolic function have higher, although within normal range, interventricular septum thickness. Although several studies evaluating LVDD have included both gender,[15,40-47] further studies using the same evaluation technique are needed to assess the prevalence of this phenomenon in women or minorities with type 2 diabetes.

In conclusion, the present study describes an association between the degree of LV diastolic dysfunction and the degree of cardiac dysautonomy in well-characterized subjects with type 2 diabetes free of clinically overt heart disease. These clinical noninvasive tools can better define and detect diabetic cardiomyopathy at a very early stage. These findings should lead to further studies to advance understanding of this clinical entity and may have implications in the evaluation and definition of the poor prognosis associated with this high-risk population.

ACKNOWLEDGMENT

We are grateful to Dr Claude Garceau, Dr Jean Guimond, and Louise Marois for skillful technical assistance.

REFERENCES

1. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. JAMA 281:1291-1297, 1999

2. Forsblom CM, Sane T, Groop PH, et al: Risk factors for mortality in type II (non-insulin-dependent) diabetes: Evidence of a role for neuropathy and a protective effect of HLA-DR4. Diabetologia 41: 1253-1262, 1998

3. Bellavere F, Balzani I, De Masi G, et al: Power spectral analysis of heart-rate variations improves assessment of diabetic cardiac autonomic neuropathy. Diabetes 41:633-640, 1992

4. Toyry JP, Niskanen LK, Lansimies EA, et al: Autonomic neuropathy predicts the development of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke 27:1316-1318, 1996

5. Toyry JP, Niskanen LK, Mantysaari MJ, et al: Occurrence, predictors, and clinical significance of autonomic neuropathy in NIDDM. Ten-year follow-up from the diagnosis. Diabetes 45:308-315, 1996

6. Toyry JP, Partanen JV, Niskanen LK, et al: Divergent development of autonomic and peripheral somatic neuropathies in NIDDM. Diabetologia 40:953-988, 1997

7. La Rovere MT, Bigger JTJ, Marcus FI, et al: Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 351:478-484, 1998

8. Ewing DJ, Martyn CN, Young RJ, et al: The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 8:491-498, 1985

9. Ziegler D, Laux G, Dannehl K, et al: Assessment of cardiovascular autonomic function: Age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. Diabet Med 2:166-175, 1992

10. Willenheimer RB, Erhardt LR, Nilsson H, et al: Parasympathetic neuropathy associated with left ventricular diastolic dysfunction in patients with insulin-dependent diabetes mellitus. Scand Cardiovasc J 32:17-22, 1998

11. Liu JE, Palmieri V, Roman MJ, et al: The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: The Strong Heart Study. J Am Coll Cardiol 37:1943-1949, 2001

12. Taegtmeyer H, McNulty P, Young ME: Adaptation and maladaptation of the heart in diabetes: Part I: General concepts. Circulation 105:1727-1733, 2002

13. Raev DC: Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients. Diabetes Care 17:633-639, 1994

14. Nicolino A, Longobardi G, Furgi G, et al: Left ventricular diastolic filling in diabetes mellitus with and without hypertension. Am J Hypertens 8:382-389, 1995

15. Di Bonito P, Cuomo S, Moio N, et al: Diastolic dysfunction in patients with non-insulin-dependent diabetes mellitus of short duration. Diabet Med 13:321-324, 1996

16. Poirier P, Garneau C, Bogaty P, et al: Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. Am J Cardiol 85:473-477, 2000

17. Rakowski H, Appleton C, Chan KL, et al: Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: From the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. J Am Soc Echocardiogr 9:736-760, 1996

18. Appleton CP, Jensen JL, Hatle LK, et al: Doppler evaluation of left and right ventricular diastolic function: A technical guide for obtaining optimal flow velocity recordings. J Am Soc Echocardiogr 10:271-292, 1997

19. Poirier P, Bogaty P, Garneau C, et al: Diastolic dysfunction in

type 2 diabetes men without hypertension or coronary artery disease: Importance of the Valsalva maneuver in screening patients. Diabetes Care 24:5-10, 2001

20. Zabalgoitia M, Ismaeil MF, Anderson L, et al: Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. Am J Cardiol 87:320-323, 2001

21. Whalley GA, Bagg W, Doughty RN, et al: Pseudonormal diastolic filling unmasked with glyceryl trinitrate in patients with type 2 diabetes with poor metabolic control. Diabetes Care 24:1307-1308, 2001

22. Mustonen J, Mantysaari M, Kuikka J, et al: Decreased myocardial 123I-metaiodobenzylguanidine uptake is associated with disturbed left ventricular diastolic filling in diabetes. Am Heart J 123:804-805, 1992

23. Standards of medical care for patients with diabetes mellitus. Diabetes Care 25:213-229, 2002

24. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

25. Guidelines from the Canadian Cardiovascular Society and the Canadian Hypertension Society on the echocardiographic determination of left ventricular mass. Task Force of the Echocardiography Section. Can J Cardiol 11:391-395, 1995

26. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 17:354-381, 1996

27. Bell DS: Diabetic cardiomyopathy. A unique entity or a complication of coronary artery disease? Diabetes Care 18:708-714, 1995

28. Rodrigues B, Cam MC, McNeill JH: Metabolic disturbances in diabetic cardiomyopathy. Mol Cell Biochem 180:53-57, 1998

29. Flarsheim CE, Grupp IL, Matlib MA: Mitochondrial dysfunction accompanies diastolic dysfunction in diabetic rat heart. Am J Physiol 271:H192-H202, 1996

30. Bernardi L, Rossi M, Leuzzi S, et al: Reduction of 0.1 Hz microcirculatory fluctuations as evidence of sympathetic dysfunction in insulin-dependent diabetes. Cardiovasc Res 34:185-191, 1997

31. Cohen JA, Jeffers BW, Faldut D, et al: Risks for sensorimotor peripheral neuropathy and autonomic neuropathy in non-insulin-dependent diabetes mellitus (NIDDM). Muscle Nerve 21:72-80, 1998

32. Grandi AM, Santillo R, Bertolini A, et al: Microalbuminuria as a marker of preclinical diastolic dysfunction in never-treated essential hypertensives. Am J Hypertens 14:644-648, 2001

33. Foss CH, Vestbo E, Froland A, et al: Autonomic neuropathy in nondiabetic offspring of type 2 diabetic subjects is associated with urinary albumin excretion rate and 24-h ambulatory blood pressure: The Fredericia study. Diabetes 50:630-636, 2001

34. Kreiner G, Wolzt M, Fasching P, et al: Myocardial m-[^{123}I]iodobenzylguanidine scintigraphy for the assessment of adrenergic cardiac innervation in patients with IDDM. Comparison with cardiovascular reflex tests and relationship to left ventricular function. Diabetes 44: 543-549, 1995

35. Mantysaari M, Kuikka J, Mustonen J, et al: Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [^{123}I]metaiodobenzylguanidine. Diabetes 41:1069-1075, 1992

36. Norton GR, Candy G, Woodiwiss AJ: Aminoguanidine prevents the decreased myocardial compliance produced by streptozotocin-induced diabetes mellitus in rats. Circulation 93:1905-1912, 1996

37. van Hoeven KH, Factor SM: A comparison of the pathological spectrum of hypertensive, diabetic, and hypertensive-diabetic heart disease. Circulation 82:848-855, 1990

38. Regan TJ, Lyons MM, Ahmed SS, et al: Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest 60:884-899, 1977

39. Gambardella S, Frontoni S, Spallone V, et al: Increased left ventricular mass in normotensive diabetic patients with autonomic neuropathy. Am J Hypertens 6:97-102, 1993

40. Hiramatsu K, Ohara N, Shigematsu S, et al: Left ventricular filling abnormalities in non-insulin-dependent diabetes mellitus and improvement by a short-term glycemic control. Am J Cardiol 70:1185-1189, 1992

41. Gough SC, Smyllie J, Barker M, et al: Diastolic dysfunction is not related to changes in glycaemic control over 6 months in type 2 (non-insulin-dependent) diabetes mellitus. A cross-sectional study. Acta Diabetol 32:110-115, 1995

42. Celentano A, Vaccaro O, Tammaro P, et al: Early abnormalities of cardiac function in non-insulin-dependent diabetes mellitus and impaired glucose tolerance. Am J Cardiol 76:1173-1176, 1995

43. Takenaka K, Sakamoto T, Amano K, et al: Left ventricular filling determined by Doppler echocardiography in diabetes mellitus. Am J Cardiol 61:1140-1143, 1988

44. Beljic T, Miric M: Improved metabolic control does not reverse left ventricular filling abnormalities in newly diagnosed non-insulin-dependent diabetes patients. Acta Diabetol 31:147-150, 1994

45. Astorri E, Fiorina P, Gavaruzzi G, et al: Left ventricular function in insulin-dependent and in non-insulin-dependent diabetic patients: Radionuclide assessment. Cardiology 88:152-155, 1997

46. Robillon JF, Sadoul JL, Jullien D, et al: Abnormalities suggestive of cardiomyopathy in patients with type 2 diabetes of relatively short duration. Diabet Metab 20:473-480, 1994

47. Tarumi N, Iwasaka T, Takahashi N, et al: Left ventricular diastolic filling properties in diabetic patients during isometric exercise. Cardiology 83:316-323, 1993