

Diastolic Dysfunction in Normotensive Men With Well-Controlled Type 2 Diabetes

Importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy

PAUL POIRIER, MD, FRCPC
PETER BOGATY, MD, FRCPC
CAROLINE GARNEAU, MSC

LOUISE MAROIS, RT
JEAN-G. DUMESNIL, MD, FRCPC, FACC

OBJECTIVE — Because a pseudonormal pattern of ventricular filling has never been considered in studies that reported a prevalence of left ventricular diastolic dysfunction (LVDD) between 20 and 40%, our aim was to more completely evaluate the prevalence of LVDD in subjects with diabetes.

RESEARCH DESIGN AND METHODS — We studied 46 men with type 2 diabetes who were aged 38–67 years; without evidence of diabetic complications, hypertension, coronary artery disease, congestive heart failure, or thyroid or overt renal disease; and with a maximal treadmill exercise test showing no ischemia. LVDD was evaluated by Doppler echocardiography, which included the use of the Valsalva maneuver and pulmonary venous recordings to unmask a pseudonormal pattern of left ventricular filling.

RESULTS — LVDD was found in 28 subjects (60%), of whom 13 (28%) had a pseudonormal pattern of ventricular filling and 15 (32%) had impaired relaxation. Systolic function was normal in all subjects, and there was no correlation between LVDD and indexes of metabolic control.

CONCLUSIONS — LVDD is much more common than previously reported in subjects with well-controlled type 2 diabetes who are free of clinically detectable heart disease. The high prevalence of this phenomenon in this high-risk population suggests that screening for LVDD in type 2 diabetes should include procedures such as the Valsalva maneuver and pulmonary venous recordings to unmask a pseudonormal pattern of ventricular filling.

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Epidemiological data indicate a greater risk of cardiovascular morbidity and mortality, particularly congestive heart failure, in diabetic subjects compared with nondiabetic subjects (1). Clinical, epidemiological, and pathological studies attribute the increased occurrence of clinical conges-

tive heart failure in diabetic subjects to diabetic cardiomyopathy, which could take the form of diastolic and/or systolic left ventricular dysfunction (2,3). Left ventricular diastolic dysfunction (LVDD) may represent the first stage of diabetic cardiomyopathy (3), reinforcing the importance of early exami-

nation of diastolic ventricular function in individuals with diabetes.

Numerous studies have attempted to determine the prevalence of LVDD in middle-aged asymptomatic subjects with type 2 diabetes (4–11). However, these studies, which used Doppler assessment of transmitral flow velocity, could have underestimated the prevalence of LVDD (4–11), because they neglected to account for pseudonormal patterns of ventricular filling, which are often noted in the evaluation of left ventricular diastolic function (12–14). Thus, the frequency of LVDD in subjects with diabetes should be reassessed by using methods designed to unmask pseudonormal ventricular filling patterns. In this context, Dumesnil et al. (14) have previously shown that the Valsalva maneuver can be easily used for this purpose and that the results of the technique are in accordance with the results of pulmonary venous recordings (13), which have also been suggested as an alternate means of identifying pseudonormal patterns (12).

Several studies have shown a correlation between glycemic control and LVDD, with associated improvement in cardiac function after adequate treatment (7,15–17). However, other studies have found no such correlation (4,6,11,18). It has been suggested that LVDD is secondary to microvascular disease because an association with retinopathy has been described (7,8). However, this relationship has not been documented consistently (10,11,18). Also, such discrepancies may exist because pseudonormal patterns of ventricular filling were not accounted for in these studies.

The objectives of this study were 1) to more clearly establish the prevalence of LVDD in normotensive subjects with well-controlled type 2 diabetes with Doppler echocardiography using pulmonary flow recordings and the Valsalva maneuver to unmask a pseudonormal pattern and 2) to evaluate more precisely the association between LVDD and indexes of metabolic control in individuals with type 2 diabetes.

From the Quebec Heart Institute and Laval Hospital, Sainte-Foy, Quebec, Canada.

Address correspondence and reprint requests to Paul Poirier, MD, FRCPC, Quebec Heart Institute/Laval Hospital, 2725 Chemin Sainte-Foy, Sainte-Foy, Quebec, Canada, G1V 4G5. E-mail: paul.poirier@crhl.ulaval.ca.

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Abbreviations: CAD, coronary artery disease; IVRT, isovolumetric relaxation time; LVDD, left ventricular diastolic dysfunction; MET, metabolic equivalent; PST, posterior wall thickness; PVA, pulmonary reversed A wave velocity; PVD, pulmonary D wave velocity; PVS, pulmonary S wave velocity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Study population

A total of 46 Caucasian sedentary men with type 2 diabetes, aged 38–67 years, were recruited consecutively among subjects fulfilling the criteria for inclusion in the study. The only exclusion criterion was clinical evidence of cardiovascular or respiratory disease. The exclusion criterion for hypertension was a blood pressure >140/90 mmHg. Subjects were treated with diet and/or oral hypoglycemic agents (sulfonylurea and/or metformin). No subjects used insulin or any cardiovascular medications. Diabetes had to be well controlled according to standard clinical criteria during the 3 months before enrollment. Subjects with diabetic complications such as retinopathy, clinical neuropathy, or macroalbuminuria were excluded. The study was approved by the Laval Hospital Ethics Committee, and all subjects gave written informed consent.

All subjects were determined to be otherwise healthy by medical history and physical examination. A normal resting electrocardiogram and a negative (i.e., no ischemia) symptom-limited graded treadmill exercise test (modified Bruce protocol), supervised by a cardiologist, were prerequisites for participation. Maximum exercise testing was used to exclude subjects with unsuspected clinically significant coronary artery disease (CAD). When silent ischemia and/or hypertension were suspected, myocardial perfusion scintigraphy using perfusion of dipyridamole with thallium²⁰¹ imaging, 24-h ambulatory blood pressure monitoring, and 24-h ambulatory ST-segment monitoring were performed to rule out these conditions (19).

Plasma glucose concentration was measured by a glucose oxidase method (Hitachi 717 Autoanalyzer; Roche, Laval, Canada), and HbA_{1c} was measured by an affinity binding assay (Abbott IMX, Mississauga, Canada). Serum total cholesterol and triglycerides were analyzed enzymatically (Hitachi 717 Autoanalyzer). Serum HDL cholesterol was also analyzed enzymatically after precipitation of LDL and VLDL with phosphotungstate and MgCl₂. LDL cholesterol was calculated with Friedewald's formula. Microalbuminuria was evaluated with Micral-Test II strips (Roche) or measured by immunoturbidimetry (Randox; Cobas Mira, Mississauga, Canada). We calculated BMI as weight (kilograms) divided by height (meters) squared.

Echocardiography

Echocardiograms were recorded with a commercially available ultrasound system (Sonos 1000 or 2500; Hewlett Packard, Andover, MA). Subjects were examined in the left lateral decubitus position using standard parasternal, short-axis, and apical views. All recordings and measurements were obtained by the same observer according to the recommendations of the American Society of Echocardiography (20) and were always performed at midday to avoid the influence of circadian rhythm on left ventricular diastolic function (21). LVDD was evaluated using well-standardized diagnostic criteria (12,13), and all Doppler measurements were assessed at end expiration.

From the transmitral recordings, the following measurements were carried out: peak *E* velocity in centimeters per second (peak early transmitral filling velocity during early diastole), peak *A* velocity in centimeters per second (peak transmitral atrial filling velocity during late diastole), and deceleration time in milliseconds (time elapsed between peak *E* velocity and the point where the extrapolation of the deceleration slope of the *E* velocity crosses the zero baseline). The same measurements were repeated during phase II of the Valsalva maneuver (14). Pulmonary venous flow recordings were obtained from the four-chamber view directed at the right upper pulmonary vein. Sample volume was obtained 1–2 cm into the pulmonary vein, and the following measurements were carried out: peak *S* wave velocity in centimeters per second (peak systolic pulmonary venous inflow velocity during ventricular systole), peak *D* wave velocity in centimeters per second (peak diastolic pulmonary venous inflow velocity during early phase of atrial diastole), and peak *A* wave velocity in centimeters per second (peak reversed systolic wave during atrial contraction). The definitions published by the Canadian consensus on diastolic dysfunction by echocardiography were used to classify diastolic function as follows: normal, impaired relaxation, pseudonormal, and restrictive pattern (13). To distinguish subjects with normal diastolic function from those with a pseudonormalized pattern of ventricular filling, two of the three following criteria had to be met: 1) having an *E*:*A* ratio <1 after the Valsalva maneuver, 2) having the *E*:*A* ratio decrease by ≥25%, and 3) having a pulmonary *A* wave duration longer than the mitral *A* wave duration.

No subject had echocardiographically detectable regional wall motion abnormalities, and each subject had normal ejection fractions. All cardiac valves were examined to rule out significant valvular disease. Left ventricular mass (LVM) was calculated using the following formula (22): $LVM (g) = 0.8 \times 1.04 [(LVEDD + IVST + PWT)^3 - (LVEDD)^3] + 0.6$, where LVEDD is left ventricle end diastolic internal diameter, IVST is interventricular septal thickness, and PWT is posterior wall thickness.

Statistical analysis

The data are presented as means ± SD unless otherwise specified. Comparison among the three groups of subjects for various parameters was carried out by one-way analysis of variance and post hoc Tukey's 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. Paired Student's *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. Subjects with LVDD (spontaneous and pseudonormalized patterns) were pooled together for statistical analysis when appropriate. $P \leq 0.05$ was considered to be statistically significant.

RESULTS

Clinical parameters

Table 1 shows clinical characteristics of subjects separated into the following three groups on the basis of left ventricular diastolic function: normal, impaired relaxation, or a pseudonormalized pattern of left ventricular filling. No subjects had a restrictive pattern. There were no differences in treatment for diabetes or daily dosages of hypoglycemic agents among the three groups. Subjects with normal diastolic function were younger ($P < 0.001$). There were no differences among groups in diabetes duration; BMI; resting heart rate; systolic, diastolic, and mean blood pressure; fasting blood glucose; HbA_{1c}; lipid profile; and microalbuminuria.

Metabolic equivalents (METs), as measured by maximal treadmill performance, differed depending on left ventricular diastolic function. Normal subjects ($n = 18$) performed 11.6 ± 1.8 METs, whereas as a group, subjects with LVDD ($n = 28$) attained 10.2 ± 2.2 METs ($P < 0.05$). There were no differences between groups in maximal

Table 1—Characteristics of 46 men with type 2 diabetes separated on the basis of left ventricular diastolic function

	Normal subjects	Subjects with impaired relaxation	Subjects with a pseudonormalized pattern
<i>n</i>	18	15	13
Age (years)	48 ± 6	57 ± 6*	56 ± 7†
Diabetes duration (years)	4 (1–10)	2.5 (0.25–32)	6.5 (1.5–30)
BMI (kg/m ²)	29.5 ± 3.2	29.9 ± 4.7	30.1 ± 2.0
Resting heart rate (beats/min)	67 ± 9	74 ± 12	72 ± 10
Systolic blood pressure (mmHg)	120 ± 12	124 ± 12	128 ± 8
Diastolic blood pressure (mmHg)	76 ± 8	78 ± 8	77 ± 9
Fasting glucose (mmol/l)	10.1 ± 2.7	9.7 ± 2.7	10.4 ± 2.7
HbA _{1c} (%)	6.5 ± 2.0	6.2 ± 1.3	6.6 ± 1.4
Total cholesterol (mmol/l)	5.3 ± 1.1	5.4 ± 1.1	5.3 ± 0.7
HDL cholesterol (mmol/l)	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.2
LDL cholesterol (mmol/l)	3.2 ± 0.8	3.6 ± 1.0	3.3 ± 0.7
Triglycerides (mmol/l)	2.0 (0.9–11.3)	1.4 (0.8–6.0)	2.1 (1.5–2.8)
Microalbuminuria (<i>n</i>)	6	7	8
Exercise performance (METs)	11.6 ± 1.8	10.3 ± 2.5	10.0 ± 1.8

Data are means ± SD or median (range), unless otherwise indicated. Normal range HbA_{1c}: 4.4–6.6%. **P* < 0.001 vs. normal subjects; †*P* < 0.01 vs. normal subjects.

heart rate (158 ± 14 vs. 155 ± 11 beats/min, respectively) or in predictive heart rate attained during the maximal treadmill test (101 ± 9 vs. 100 ± 7%, respectively).

Echocardiographic measurements (M-mode)

Table 2 shows the M-mode measurement for left ventricular cavity dimensions. All dimensions were within normal limits. There were no differences between groups in aortic root, interventricular septum, posterior wall, left ventricular systolic or diastolic dimensions, right ventricular diastolic dimensions, left ventricular mass, or left ventricular ejection fraction (Table 2). The left atrium was smaller in normal subjects (*n* = 18) compared with all combined subjects (*n* = 28) with LVDD (37.3 ± 4.1 vs. 39.8 ± 3.3 mm, *P* = 0.03).

Transmitral and pulmonary venous Doppler flow velocity recordings

Tables 3 and 4 summarize the results from Doppler-derived diastolic filling indexes in the three groups. Transmitral recordings are reported at baseline and after phase II of the Valsalva maneuver (Table 3). Transmitral and pulmonary venous flow recordings were obtained in 100 and 98% of subjects, respectively. *E* and *A* wave velocity values for the group with normal diastolic function were within the normal range reported for a normal population by the Canadian

consensus recommendations on diastolic dysfunction (13).

There was no difference in isovolumetric relaxation time (IVRT) between groups (Table 3). Before the Valsalva maneuver, subjects with impaired relaxation showed lower *E* wave velocity compared with subjects with normal diastolic function (*P* < 0.001) and subjects with a pseudonormalized pattern (*P* < 0.001). *A* wave velocity was higher in subjects with impaired relaxation compared with subjects with normal diastolic function (*P* < 0.001). As a result,

the *E:A* ratio was smaller in subjects with impaired relaxation compared with subjects with normal diastolic function (*P* < 0.001) or subjects with a pseudonormalized pattern (*P* < 0.001). There was no statistical difference in deceleration time or *A* wave duration among groups.

After the Valsalva maneuver (Table 3), *E* wave velocity decreased in the three groups (*P* < 0.001), whereas *A* wave velocity decreased only in the group with normal diastolic function and in the group with impaired relaxation (*P* < 0.001). As a consequence, the subjects with normal diastolic function and subjects with a pseudonormalized pattern demonstrated a decrease in the *E:A* ratio (*P* < 0.001). The percentage decrease in *E:A* ratio was 12% in the group with normal diastolic function, 9% in the group with impaired relaxation, and 39% in the group with a pseudonormalized pattern (*P* < 0.001 vs. normal and impaired relaxation). All subjects with a normal diastolic function conserved an *E:A* ratio > 1, whereas all subjects with a pseudonormalized pattern showed an *E:A* ratio < 1. Therefore, subjects with a normal diastolic function showed a higher *E:A* ratio than subjects with impaired relaxation (*P* < 0.001) or subjects with a pseudonormalized pattern (*P* < 0.001). Deceleration time increased similarly (~25%) after the Valsalva maneuver in all three groups (Table 3). *A* wave duration decreased only in subjects with normal diastolic function after the Valsalva maneuver (*P* < 0.001).

There were no differences in pulmonary *S* wave velocity (PVs) and pulmonary *D* wave velocity (PVd) among groups (Table

Table 2—Echocardiographic measurements (M-mode) in 46 men with type 2 diabetes separated on the basis of left ventricular diastolic function

	Normal range	Normal subjects	Subjects with impaired relaxation	Subjects with a pseudonormalized pattern
<i>n</i>	—	18	15	13
Aortic root (mm)	20–37	34.3 ± 3.2	35.5 ± 2.1	32.9 ± 2.7
IV septum (mm)	6–11	9.3 ± 1.6	10.3 ± 2.1	9.9 ± 1.3
Posterior wall (mm)	6–11	8.9 ± 1.1	9.5 ± 1.1	9.0 ± 0.9
Left atrium (mm)	19–40	37.3 ± 4.1*	39.6 ± 3.4	39.9 ± 3.4
RV diastolic (mm)	7–23	22.9 ± 2.7	23.3 ± 1.4	22.7 ± 2.8
LV diastolic (mm)	35–57	50.8 ± 3.3	49.2 ± 3.1	49.4 ± 3.0
LV systolic (mm)	20–39	30.4 ± 2.5	30.2 ± 3.5	29.8 ± 4.4
LV mass (kg/m ²)	<131	83.3 ± 15.3	87.7 ± 16.7	83.9 ± 13.1
Ejection fraction (%)	>50	66 ± 5	65 ± 5	66 ± 5

Data are means ± SD, unless otherwise indicated. **P* < 0.05 vs. pooled subjects with LVDD. IV, interventricular; LV, left ventricle; RV, right ventricle.

Table 3—Transmitral Doppler flow velocity recordings before (baseline) and after the Valsalva maneuver in 46 men with type 2 diabetes separated on the basis of left ventricular diastolic function

	Normal subjects	Subjects with impaired relaxation	Subjects with a pseudonormalized pattern
<i>n</i>	18	15	13
Baseline			
IVRT (ms)	106 ± 17	109 ± 11	102 ± 13
E wave (cm/s)	69 ± 11	56 ± 10*	73 ± 12†
A wave (cm/s)	52 ± 9	71 ± 13*	60 ± 14
E:A	1.34 ± 0.17	0.79 ± 0.07*	1.23 ± 0.18†
DT (ms)	189 ± 42	224 ± 51	189 ± 22
A wave duration (ms)	129 ± 16	128 ± 25	120 ± 19
After the Valsalva maneuver			
E wave (cm/s)	48 ± 8‡	38 ± 6‡§	43 ± 9‡
A wave (cm/s)	41 ± 8‡	54 ± 8‡§	58 ± 11§
E:A	1.17 ± 0.16‡	0.72 ± 0.13*	0.74 ± 0.11‡§
DT (ms)	233 ± 61	279 ± 91¶	245 ± 51‡
A wave duration (ms)	110 ± 24‡	120 ± 20	120 ± 20

Data are means ± SD, unless otherwise indicated. * $P < 0.001$ vs. normal subjects; † $P < 0.001$ vs. subjects with impaired relaxation; ‡ $P < 0.001$ before vs. after Valsalva maneuver; § $P < 0.01$ vs. normal subjects; || $P < 0.01$ before vs. after Valsalva maneuver; ¶ $P < 0.05$ before vs. after Valsalva maneuver. DT, deceleration time.

4). Pulmonary reversed A wave duration (PVa) was significantly longer in subjects with a pseudonormalized pattern compared with normal subjects (125 ± 14 vs. 101 ± 11 ms, $P < 0.001$). Again, values in subjects with normal diastolic function were in accordance with reported normal values (13). PVa minus mitral A wave duration was calculated, and, as expected, subjects with a pseudonormalized pattern showed a significantly higher value than those with normal function ($P < 0.001$). There was a very good concordance between PVa minus mitral A wave duration and Valsalva maneuver to discriminate subjects with normal diastolic function from subjects with a pseudonormalized pattern. Indeed, these two evaluations agreed in 17 of 18 subjects with normal diastolic function and 11 of 13 subjects with a pseudonormalized pattern of left ventricular diastolic filling.

There were significant inverse correlations between E:A ratio measurements before the Valsalva maneuver and age ($r = -0.43$, $P = 0.003$), whereas systolic blood pressure ($r = -0.35$, $P < 0.05$) and treadmill performance (METs, $r = 0.39$, $P = 0.011$) were only correlated to E:A ratio measurement after the Valsalva maneuver. There was no correlation between the E:A ratio and lipid profile, the E:A ratio and metabolic control (expressed by HbA_{1c}), the E:A ratio and fasting blood glucose, and the

E:A ratio and left ventricular mass or heart dimensions assessed with M-mode. As expected, mitral E wave velocity correlated with pulmonary venous D wave velocity ($r = 0.41$, $P = 0.006$) and the E:A ratio before the Valsalva maneuver correlated inversely with S:D ratio ($r = -0.516$, $P < 0.001$). Of interest, pulmonary A wave velocity minus mitral A wave velocity indexes correlated with the E:A ratio only after the Valsalva maneuver ($r = -0.379$, $P = 0.012$).

CONCLUSIONS — The major finding of this study is that LVDD is much more prevalent than previously suggested in subjects with type 2 diabetes who are free of

clinically detectable heart disease. In addition to revealing a prevalence of LVDD of $>50\%$, this study also unmasked a significant number of subjects (28%) with a pseudonormal pattern of diastolic filling that has yet to be recognized in previous studies (4–11). In these studies, the Valsalva maneuver and pulmonary venous recordings were not used. Indeed, if we had classified subjects with a pseudonormal pattern as subjects with a normal pattern of left ventricle filling, the prevalence in the present study for LVDD would have been 32%, similar to that previously observed (4).

The recognition of the pseudonormal pattern is all the more important because it is considered an intermediary stage between impaired relaxation and restrictive filling and, thus, is a more advanced stage of LVDD. The pseudonormalization of the filling pattern is caused by higher filling pressures and is detected by the Valsalva maneuver, which acutely decreases filling pressures and unmasks the underlying impaired relaxation. Likewise, if left ventricular stiffness increases, a stronger atrial contraction will be required to fill a less compliant ventricle and will result in an increase in the amplitude and duration of the pulmonary A wave, whereas the mitral A wave will have a tendency to decrease and shorten. Indeed, it was previously shown that a longer duration of the pulmonary venous A wave compared with the mitral A wave predicted an elevated left ventricular end diastolic pressure (23). In this study, this index was significantly different when subjects with normal diastolic function were compared with subjects with a pseudonormalized pattern, and there was very good agreement between these results and those obtained using the Valsalva maneuver. Furthermore, after the Valsalva

Table 4—Pulmonary venous Doppler flow velocity recordings in 46 men with type 2 diabetes separated on the basis of left ventricular diastolic function

	Normal subjects	Subjects with impaired relaxation	Subjects with a pseudonormalized pattern
<i>n</i>	18	15	13
PVs wave (cm/s)	49 ± 9	55 ± 12	57 ± 10
PVd wave (cm/s)	46 ± 12	39 ± 6	43 ± 9
PVa wave (cm/s)	26 ± 5	30 ± 7	29 ± 5
PVa duration (ms)	101 ± 11	115 ± 24	125 ± 14†
PVs:PVd	1.10 ± 0.29	1.47 ± 0.45*	1.36 ± 0.23
PVa–transmitral A wave duration (ms)	−25 ± 20	−13 ± 23	5 ± 18†

Data are means ± SD, unless otherwise indicated. * $P < 0.01$ vs. normal subjects; † $P < 0.001$ vs. normal subjects.

maneuver, the decrease in the *E:A* ratio in control subjects was similar in our diabetic population to previous reports involving subjects with hypertension and CAD, suggesting that this technique is reproducible in different populations (13,14). The strong concordance between the two techniques concomitantly with the increased left atrial size and the lower exercise performance are all consistent with less compliant left ventricle and increased left atrial pressures.

As in previous studies, an *E:A* ratio value of 1.0 was arbitrarily chosen as the lower limit to detect impaired relaxation (13). It has previously been shown that relaxation velocity and, thus, the *E:A* ratio have a tendency to decrease with age (13). However, the values for the *E:A* ratio observed in our impaired relaxation group (0.79 ± 0.07) are significantly lower than the average values reported for age-groups without overt heart disease. Indeed, the mean ± 1 SD in these age-groups is always >1 (13). Nonetheless, age cannot be eliminated as a confounding variable. The value of 1.0 was mostly used to be comparable with previous studies (13,14). It must be emphasized that the main contribution of the present study is not to differentiate the extent of impaired relaxation attributable to age from that attributable to diabetic cardiomyopathy; rather, the main contribution was the finding of a relatively high number of subjects with type 2 diabetes with LVDD and a pseudonormal pattern of left ventricular filling, which has been unrecognized in previous studies. Pseudonormalization represents a more advanced stage of LVDD that has never been recognized as a normally occurring phenomenon in subjects of any age. In addition, in the study of Robillon et al. (9), subjects with diabetes demonstrated a decrease in the *E:A* ratio, reaching a value of 1 at a much younger age (56 years) compared with control subjects (78 years); this value is considered normal for individuals in their seventh decade (13). Thus, progression of LVDD with aging seems markedly accelerated by diabetes (5,6,9).

The clinical significance of these findings in terms of prognosis and treatment remains to be determined. Although no prospective data are available, in retrospective studies, the mitral *E:A* ratio has had equal or even superior prognostic value compared with left ventricular systolic indexes (such as ejection fraction), reinforcing the importance of screening for asymptomatic LVDD (12,24). Because it has been shown that interventions such as aerobic exercise could beneficially influence

diastolic function, the early and accurate detection of LVDD might have therapeutic implications (25). Finally, previous studies have suggested that LVDD can occur in individuals with well-controlled diabetes and without vascular complications (26), and this finding has been confirmed by animal models of diabetes, suggesting that diastolic dysfunction can be ascribed to impaired myocyte handling of calcium independent of microvascular disease (27,28). Thus, LVDD in type 2 diabetes can probably be present within a constellation of different clinical settings.

Study limitations

Subjects with uncomplicated and well-controlled type 2 diabetes are difficult to study because of the high incidence of coexistent CAD and hypertension. In this study, we attempted to rule out ischemia by performing noninvasive tests, such as symptom-limited exercise electrocardiography, dipyridamole-thallium scintigraphy, and 24-h ST segment monitoring, methods which have all been shown to be reliable in excluding CAD (19). Thus, although preclinical atherosclerosis may have been present, it is highly unlikely that it is an important confounding variable in explaining the observed abnormalities in left ventricular diastolic function. Moreover, experimental animal studies support the view that the diabetic state per se affects ventricular performance (27,28). Although the current normal values adjusted for age have large confidence limits, particularly in patients older than 60 years of age (13), pseudonormalized pattern of left ventricular filling represents an advanced stage of LVDD and is considered abnormal, independently of the age of the subject. This study was limited to a small group of well-characterized sedentary men to avoid too many confounding variables. Although several studies evaluating LVDD have included both sexes (4,6–11), further studies using similar techniques with larger populations are needed to assess more precisely the prevalence of this phenomenon in women with type 2 diabetes. Finally, because LVDD was similarly demonstrated in subjects with type 2 diabetes treated with diet or sulfonylureas, the influence of oral hypoglycemic agents cannot account for our results (15,29).

In conclusion, this study is the first to evaluate LVDD in well-controlled type 2 diabetes with the Valsalva maneuver and pulmonary venous inflow recordings in the

left atrium, and it broadens the spectrum of preclinical cardiomyopathy in these subjects. Guidelines on heart disease prevention have repeatedly defined subjects with diabetes as a group at high risk for heart disease for whom the threshold for the initiation of preventive measures should be lower than that for nondiabetic subjects. LVDD is a marker of evolving heart disease (30). Therefore, the high prevalence of LVDD suggested by this study supports the use of echocardiography in the initial clinical evaluation of subjects with type 2 diabetes.

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