Left Ventricular Diastolic Filling in Diabetes Mellitus With and Without Hypertension

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Left ventricular diastolic filling by Doppler echocardiography was investigated in 84 diabetic patients without evidence of heart disease and in 84 normotensive nondiabetic age- and sex-matched control subjects. Diabetic patients were subdivided into two groups on the basis of the presence of arterial hypertension. Group 1 comprised 41 normotensive diabetic patients (19 men, 22 women, mean age 63.7 ± 9.1 years); Group 2 comprised 43 hypertensive diabetics (15 men, 28 women, mean age 65.6 ± 9.6 years).

Doppler measures of diastolic filling were significantly altered in the two groups as compared with control subjects. Peak atrial flow velocity, velocity integral for the atrial filling period, and atrial filling fraction were increased, whereas the ratio of peak early to peak atrial flow velocity and the ratio of flow velocity integrals were decreased, especially in Group 2 patients.

Thirteen patients in Group 1 (32%) and 17 in Group 2 (40%) had evidence of diastolic dysfunction, as assessed by the presence of at least two independent abnormal indices (outside age-corrected 95% confidence interval).

In each group, patients with altered diastolic filling differed slightly from diabetic patients with normal Doppler indices, tending to increased wall thickness and left ventricular mass.

In conclusion, diastolic filling of the left ventricle is frequently altered in diabetic patients and is adversely affected by arterial hypertension whose coexistence further impairs left ventricular relaxation. Am J Hypertens 1995;8:382–389

KEY WORDS: **Diabetes mellitus, hypertension, diastolic filling, Doppler echocardiography.**

Abnormalities in global left ventricular (LV) function are common in patients with various cardiac disorders and have been described in patients with hypertension and diabetes mellitus, two well-known major risk factors for cardiovascular morbidity and mortality. In particular, the concomitant occurrence of several risk factors greatly increases the risk of developing congestive heart failure and myocardial infarction.[1–5]

Experimental and clinical studies carried out in the last two decades support the concept of diabetic cardiomyopathy and the existence of impaired LV function in the absence of clinical evidence of heart disease.[6–12] Abnormalities of left ventricular relaxation, filling, and compliance in diabetic patients have been demonstrated by various authors,[13–18] but with variable results, and few have reported the effects of hypertension on diastolic performance of the left ventricle.[19,20] The purpose of this investigation was to assess prevalence and correlates of left ventricular diastolic filling abnormalities by Doppler echocardiog-

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raphy in diabetic patients with and without arterial hypertension.

METHODS

Study Population Of 238 patients with adult-onset diabetes mellitus referred to our noninvasive laboratory, we excluded 118 patients: 74 with previous myocardial infarction; 14 with angina pectoris or with a positive exercise electrocardiographic stress test; four with dilated cardiomyopathy; one with mitral valve prosthesis; 14 with mitral or aortic valve dysfunction; three with left bundle block; nine with atrial fibrillation; and one with pacemaker for complete atrioventicular block. A further 11 patients with heart rates >90 beats per minute and 25 with echo-Doppler studies of poor quality were excluded. Thus, analysis was performed on 84 diabetics (34 men and 50 women, mean age 64.7 ± 9.4 years, range 45 to 87).

Each of these patients was matched for sex, age, and heart rate with one of 84 healthy control subjects (control group). All these had normal history and physical examinations, resting and exercise electrocardiograms, two-dimensional and Doppler echocardiograms, blood cell count, and serum chemistry. None was taking drugs.

The diabetic patients were divided into two groups, based on the presence of arterial hypertension. Group 1 comprised 41 patients (19 men and 22 women, mean age 63.7 ± 9.1 years) with isolated diabetes mellitus; eight of these (20%) were insulin-dependent. Group 2 comprised 43 diabetics (15 men and 28 women, mean age 65.6 ± 9.6 years) with mild to moderate arterial hypertension; seven (16%) were insulin-dependent. Antihypertensive drugs were discontinued for at least 72 h before the study. No patient was treated with β-blockers.

No patient had clinical manifestations of congestive heart failure, and systolic function was normal in all. In particular, none had echocardiographically detectable regional wall motion asynergies. All patients gave informed consent to participate in the study.

Echocardiography M-mode, two-dimensional echocardiographic and cardiac Doppler studies were performed using a commercially available echo-Doppler unit (Hewlett-Packard 77025A system) equipped with either a 2.5- or 3.5-MHz transducer. Subjects were studied in left lateral decubitus, utilizing standard parasternal, short-axis, and apical views. M-mode echocardiograms of the LV cavity were made under two-dimensional control at or just below the tips of mitral valve leaflets, at a speed of 100 mm/s. Measurements of interventricular septal thickness (IVST, in cm), posterior wall thickness (PWT, in cm), LV end-diastolic dimension (LVEDD, in cm), LV end-systolic dimension (LVESD, in cm), and left atrial size (LA, in cm) were made according to the recommendations of the American Society of Echocardiography.[21] LV mass (LVM) was calculated by the formula of Devereux and Reichek:[22] LVM (g) = 1.04 [(LVEDD + IVST + PWT)^3 − (LVEDD)^3] − 13.6. LV mass index (LVMI, in g/m^2) was defined as LVM divided by body surface area. Fractional shortening (FS) was calculated according to the formula: FS (%) = 100 · [(LVEDD − LVESD)/LVEDD].

Doppler ultrasound examinations were performed with the transducer at the apical impulse oriented to obtain an apical four-chamber view of the heart. Transmitral blood flow signals were obtained in the pulsed mode by placing the sample volume between the mitral leaflets and adjusting its position until the highest peaks of diastolic flow velocity were obtained. Doppler waveforms were recorded at a speed of 100 mm/s with simultaneous electrocardiogram. All cardiac valves were examined by both pulsed and color Doppler ultrasound to rule out significant valvular disease. From the transmitral recordings, the following measurements were made on three to five consecutive cardiac cycles: peak early diastolic flow velocity (peak E, in cm/s); peak late diastolic flow velocity (peak A, in cm/s); rate of decrease (deceleration) of the flow velocity in early diastole (EF slope, in cm/s^2); velocity integral for the early filing period (E_i, in cm) and the late diastolic filling period (A_i, in cm); and isovolumic relaxation time, measured as the interval from the aortic closure and the onset of the diastolic flow simultaneously recorded by pulsed Doppler (IRT, in ms). In addition, ratio between heights of early and late diastolic flow velocity peaks (E/A ratio), and ratio between velocity integrals (E_i/A_i ratio) were calculated. Atrial filling fraction (AFF, in percent) was derived as the ratio of the atrial component to the total flow velocity integral.

Statistical Analysis The data are presented as mean ± standard deviation. Comparison among the three groups of patients for various parameters was carried out by one-way analysis of variance and Duncan test. A probability value less than .05 was considered significant. Fisher's exact test was used to test for differences between the diabetic groups regarding incidence of diastolic abnormalities.

In individual subjects, normal limits for Doppler variables were defined as the 95% confidence limits of the distribution of control values. Since diastolic filling indices are greatly affected by age,[23,24] control subjects were subdivided into two age-groups: adults aged from 45 to 64 years and elderly aged from 65 to 87 years; upper and lower normal 95% confidence intervals were calculated for each group. The diastolic filling pattern was considered to be abnormal in a given patient when at least two independent Doppler indices were outside the age-corrected 95% confidence interval.

RESULTS

Clinical Parameters Table 1 lists the clinical characteristics of study population. No significant differences in age, height, weight, body surface area or heart rate were found among the groups. The mean duration of diabetic status was similar between Groups 1 and 2, as was the distribution of insulin-dependent subjects. As expected, systolic blood pressure (SBP, in mm Hg) and diastolic blood pressure (DBP, in mm Hg) were significantly higher in the hypertensive patients than in the other groups ($P < .01$ *v* Controls and *v* Group 2).

Echocardiographic Measurements As seen in Table 2, the groups did not differ in left ventricular cavity dimensions (LVEDD and LVESD) or in fractional shortening. Interventricular septal thickness, posterior wall thickness, LV mass, and LV mass index were significantly higher in Group 2 than in controls ($P < .01$). In Group 1, all these measurements were intermediate between those of controls and Group 2, and differences were not significant except posterior wall, which was significantly thicker than in controls ($P < .01$).

Left atrial size was slightly increased in hypertensive-diabetic subjects ($P < .05$ *v* Control group and *v* Group 1).

Doppler Measurements Table 3 summarizes the results of Doppler-derived diastolic filling indices in the three groups. Peak velocity of late LV filling (peak A), velocity integral for the late filling period (A_i), and atrial filling fraction (AFF) were significantly increased, whereas the E/A and E_i/A_i ratios were significantly lower in both diabetic groups than in control subjects. The isovolumic relaxation time was significantly longer in diabetics than in the control group ($P < .01$ in both cases). Hypertensive-diabetic patients showed a more marked alteration in diastolic filling indices than those with isolated diabetes (a greater increase in A, A_i, and AFF and a greater decrease in E/A and E_i/A_i ratios). Peak early filling velocity (peak E), time velocity integral in early diastole (E_i), and EF slope were similar in the three study groups.

Frequency of Filling Abnormalities For each of the Doppler parameters, the observed value was considered abnormal when it exceeded the 95% confidence limits for the corresponding age group. For adult controls the threshold values of the nine Doppler indices considered were as follows: peak E velocity < 42.1, peak A velocity > 90.2, E/A peak velocity ratio < 0.72, isovolumic relaxation time (IRT) > 110, rate of decrease of the flow velocity in early diastole (EF slope) < 209, integrated early filling velocity (E_i) < 5.00, integrated atrial filling velocity (A_i) > 7.26, ratio between velocity integrals (E_i/A_i ratio) < 1.25, percent contribution of atrial to total diastolic filling (AFF) > 44.5. The corresponding figures for elderly controls were <56.1 (peak E), >90.5 (peak A), <0.55 (E/A ratio), >110 (IRT), <108 (EF slope), <4.55 (E_i), >7.78 (A_i), <1.03 (E_i/A_i ratio), >49.2 (AFF).

Overall, 30 of the 84 diabetic patients (36%) had at least two independent abnormal values. Diastolic filling was impaired in 13 diabetic patients in Group 1 (32%), and in 17 patients (40%) in the hypertensive-diabetic group (P = ns). The variables most frequently altered were peak A velocity, E/A ratio, isovolumic relaxation time, E_i/A_i ratio, and atrial filling fraction. Peak A velocity, E/A ratio, and isovolumic relaxation time were abnormal in 22 diabetic patients (respectively, 10, 9, and 9 patients in Group 1 and 12, 13, and 13 patients in Group 2), while the E_i/A_i ratio and AFF were out of the normal ranges in 26 patients (respectively, 10 and 16 patients in both Groups 1 and 2).

Subsequent analysis was carried out on patients in each group with and without altered diastolic function, to evaluate whether the former differed in clinical characteristics or LV structure from the latter (Table 4). Patients with altered diastolic function were

TABLE 1. CLINICAL CHARACTERISTICS OF STUDY POPULATION

	Control Group (n = 84)	Group 1 (n = 41)	Group 2 (n = 43)
Sex (F/M)	50/34	22/19	28/15
Age (yrs)	64.8 ± 9.6	63.7 ± 9.1	65.6 ± 9.6
Weight (kg)	68 ± 14	69 ± 11	72 ± 13
Height (cm)	158 ± 9	160 ± 9	159 ± 9
BSA (m^2)	1.69 ± 0.19	1.71 ± 0.18	1.74 ± 0.16
SBP (mm Hg)	130 ± 13	135 ± 17	174 ± 22*
DBP (mm Hg)	78 ± 8	81 ± 7	96 ± 14*
Duration of diabetes (yrs)		9.1 ± 5.2	10.9 ± 6.9
HR (beats/min)	77.5 ± 7.7	76.8 ± 10.7	75.7 ± 8.8

BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

*P < .01 v *control group and* v *Group 1.*

TABLE 2. M-MODE ECHOCARDIOGRAPHIC MEASUREMENTS

	Control Group	Group 1	Group 2
LVEDD (cm)	4.81 ± 0.46	4.74 ± 0.42	4.90 ± 0.46
LVESD (cm)	2.72 ± 0.44	2.63 ± 0.45	2.79 ± 0.49
FS (%)	43.6 ± 6.4	44.8 ± 6.3	43.1 ± 7.1
IVST (cm)	0.93 ± 0.14	0.98 ± 0.15	1.08 ± 0.25*
PWT (cm)	0.88 ± 0.09	0.96 ± 0.15*	1.00 ± 0.19*
LVM (g)	175 ± 45	191 ± 57	222 ± 76*
LVMI (g/m^2)	104 ± 24	112 ± 31	127 ± 41*
LA (cm)	3.36 ± 0.34	3.32 ± 0.42	3.53 ± 0.37†

LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; FS, fractional shortening; IVST, interventricular septal thickness; PWT, posterior wall thickness; LVM, left ventricular mass; LVMI, left ventricular mass index: LA, left atrium.

*P < .01 v control group.

†P < .05 v control group and v Group 1.

slightly older in both groups, but not significantly. Known duration of diabetic status, LV dimensions, and fractional shortening were similar between subgroups in Group 1 and Group 2. In both groups, patients with altered diastolic filling had only minimal differences with respect to those with normal diastolic filling indices, but consistent with concentric hypertrophy of the left ventricle. In fact, interventricular septal and posterior wall thickness, LV mass, and mass index where slightly increased, but differences were significant only for posterior wall thickness in Group 2 ($P < .05$).

In Group 1, patients with altered diastolic filling had an increased left atrial size with respect to those with normal filling indices ($P < .05$), while in Group 2 left atrial diameter was similar between subgroups.

The duration of diabetes mellitus was slightly higher in both subgroups with altered diastolic function, but not significantly so.

DISCUSSION

Findings of the Present Study This study demonstrates that diastolic transmitral blood flow is abnormal in about one-third of adults with diabetes mellitus, with or without arterial hypertension. Diabetic patients (Group 1) had a significantly higher atrial contribution to LV filling and prolonged isovolumic relaxation time than controls. E/A ratio and E_i/A_i ratio were significantly lower than in control subjects but peak E velocity and early velocity time integral were similar. Analogous differences were seen in the hypertensive-diabetic group (Group 2), in whom diastolic filling was more severely impaired than in Group 1 patients. When analyzing for clinical and echocardiographic variables possibly influencing diastolic indices, hypertensive-diabetic patients showed an increased LV mass with interventricular septum and posterior wall thicker than controls, and values for diabetic-only patients (Group 1) were intermediate between those of controls and Group 2. Analysis of subgroups of diabetics in relation to diastolic filling pattern (Table 4) showed that wall thickness and LV mass tend to increase in patients with altered filling. Left atrial diameter was significantly increased in all hypertensive-diabetics and in diabetics with diastolic dysfunction.

TABLE 3. DOPPLER INDICES OF DIASTOLIC FILLING

	Control Group	Group 1	Group 2
Peak E (cm/s)	58.2 ± 12.5	57.9 ± 14.8	56.5 ± 18.0
Peak A (cm/s)	63.8 ± 14.5	75.0 ± 19.5*	79.6 ± 20.7*
E/A ratio	0.95 ± 0.28	0.81 ± 0.28*	0.72 ± 0.19*
IRT (ms)	87 ± 14	98 ± 19*	101 ± 24*
EF slope (cm/s^2)	306 ± 109	295 ± 103	272 ± 115
E_i (cm)	7.6 ± 1.9	7.3 ± 2.0	7.3 ± 2.4
A_i (cm)	4.8 ± 1.4	5.5 ± 1.8†	5.9 ± 1.7*
E_i/A_i ratio	1.70 ± 0.57	1.43 ± 0.56*	1.28 ± 0.38*
AFF (%)	38.4 ± 6.8	43.0 ± 8.5*	44.9 ± 7.1*

Peak E, peak velocity of early filling; peak A, peak velocity of late filling; IRT, isovolumic relaxation time; EF slope, rate of deceleration of early filling; E_i, time velocity integral of early filling; A_i, time velocity integral of late filling; AFF, atrial filling fraction.

†P < .05 v control group.

*P < .01 v control group.

TABLE 4. SUBGROUP ANALYSIS OF PATIENTS WITH ALTERED DIASTOLIC FILLING; M-MODE MEASUREMENTS AND GENERAL DATA

	Group 1			Group 2		
	Normal DF	Abnormal DF	P	Normal DF	Abnormal DF	P
n	28	13		26	17	
Age (yrs)	64.5 ± 9.6	62.1 ± 8.0	NS	66.5 ± 10.4	64.4 ± 8.4	NS
SBP (mm Hg)	132 ± 17	137 ± 18	NS	169 ± 20	181 ± 25	NS
DBP (mm Hg)	81 ± 8	81 ± 6	NS	92 ± 10	101 ± 16	<.05
Duration of diabetes (yrs)	8.8 ± 4.9	9.7 ± 5.8	NS	10.7 ± 6.6	11.3 ± 7.6	NS
HR (beats/min)	76.3 ± 11.4	77.7 ± 9.5	NS	75.3 ± 8.6	76.4 ± 9.3	NS
LVEDD (cm)	4.70 ± 0.39	4.84 ± 0.48	NS	4.92 ± 0.52	4.87 ± 0.38	NS
LVESD (cm)	2.59 ± 0.46	2.74 ± 0.44	NS	2.80 ± 0.57	2.78 ± 0.35	NS
FS (%)	45.3 ± 6.3	43.5 ± 6.2	NS	43.3 ± 8.0	42.9 ± 6.7	NS
IVST (cm)	0.96 ± 0.13	1.04 ± 0.18	NS	1.03 ± 0.23	1.16 ± 0.27	NS
PWT (cm)	0.95 ± 0.14	1.00 ± 0.18	NS	0.94 ± 0.15	1.09 ± 0.22	<.05
LVM (g)	180 ± 43	213 ± 78	NS	206 ± 62	248 ± 89	NS
LVMI (g/m^2)	108 ± 25	119 ± 39	NS	120 ± 34	138 ± 48	NS
LA (cm)	3.22 ± 0.34	3.54 ± 0.49	<.05	3.50 ± 0.34	3.57 ± 0.42	NS

DF, diastolic filling; other abbreviations as in Tables 1 and 2.

The determinants of late diastolic LV filling are multifactorial, including the preload of the left atrium, its intrinsic contractile state, and the compliance of the left ventricle. Decreased LV compliance could result in a shift in filling from early to late diastole. In this study, however, early filling indices were normal in both diabetic groups, whereas atrial velocities were significantly increased together with prolonged IRT. Recently, Hamada et al[25] reported that prolongation of IRT is associated with increased LV mass due to hypertension and reflects the severity of myocardial hypertrophy. The finding of increased LV mass in our diabetics lends support to the concept that diastolic dysfunction may be, even if partially, dependent on LV hypertrophy. On the other hand, enhanced atrial function could be secondary to increased atrial preload, as evidenced by increased left atrial size or, alternatively, to intrinsic atrial hypercontractility, as suggested by Phillips et al,[26] who showed that, although early filling was normal, atrial velocities were abnormally increased in nondiabetic hypertensives.

Previous Studies Diastolic dysfunction in diabetic patients has been reported by numerous authors; prevalence of diastolic abnormalities varies from 21 to 100%.[13–20] This variability is probably due to different selection criteria and methods for evaluating diastolic function. Airaksinen et al[13] used M-mode echocardiography to reveal diastolic impairment in 53% of their young insulin-dependent patients, while Kahn et al[14] observed via radionuclide ventriculography a 21% prevalence of diastolic dysfunction. Paillole et al[18] and Zarich et al[17] found diastolic filling abnormalities of 69% and 29%, respectively, in insulin-dependent diabetics using Doppler echocardiography. Using a similar technique, Takenaka et al[16] found significant diastolic dysfunction only in diabetic patients who had retinopathy or wall motion asynergies.

Danielsen and coworkers[15] have made an extensive study on cardiac involvement in insulin-dependent diabetes mellitus. They report reduced peak filling rate with prolonged rapid filling period and increased atrial contribution to filling, which suggests decreased compliance in patients with long-standing type-1 diabetes. Subsequently, Danielsen[20] evaluated the factors contributing to LV diastolic dysfunction in diabetic subjects with borderline or mild arterial hypertension. By multivariate analysis, only diabetes, systolic blood pressure, and LV mass showed a significant independent relationship with diastolic filling indices.

A population similar to ours, composed of men and women with types I and II diabetes mellitus and with longstanding hypertension, was studied by Venco et al[19] by M-mode echocardiography. Peak lengthening rate or peak velocity of posterior wall thinning was reduced in all hypertensive-diabetic patients but in only 45% of patients with hypertension alone.

The frequency of diastolic abnormalities our study revealed is similar to that reported by Zarich et al, but is much lower than that reported by Venco et al. This discrepancy may be explained by differences in study population and methods of evaluating LV diastolic function. Patients studied by Venco were about 10 years younger than ours and about 30% of their hypertensive-diabetic patients had decreased systolic function. In their diabetics, coronary artery disease was excluded only on the basis of clinical, electrocardiographic, and echocardiographic evaluation. Sub-

clinical coronary artery disease is frequent in diabetic subjects, who exhibit a higher incidence of asymptomatic ischemia or myocardial infarctions than nondiabetics[27–29] and may itself cause a diastolic impairment.[30,31] Therefore, an underestimation of coronary disease may have resulted in an overestimation of diastolic dysfunction. The different results could also be the consequence of different techniques. We evaluated diastolic function by pulsed Doppler echocardiography while Venco et al used M-mode echocardiography. Recently, Lee et al[32] compared M-mode and Doppler echocardiography for the assessment of rapid ventricular filling, and have found that M-mode indices of diastolic function are more frequently abnormal than Doppler-derived ones in the hypertrophied heart.

Pathogenetic Considerations Diastole is a complex active process requiring energy and is primarily altered in numerous cardiac disease processes even in the preclinical phase and before systolic dysfunction develops.

Several pathophysiologic mechanisms have been postulated to contribute to the genesis of LV diastolic dysfunction in diabetic patients and in hypertensives: coronary artery disease, microvascular changes, interstitial fibrosis, metabolic and neurohormonal alterations.[33–36]

We were unable to evaluate the different roles played by these factors in our study population, although patients with evidence of coronary artery disease from history and noninvasive testing were excluded from analysis. We cannot exclude the possibility that some of our patients had clinically occult coronary artery disease. Myocardial ischemia can affect LV filling but significant coronary artery stenosis must be present to cause diastolic impairment. However, because all diabetics were asymptomatic, had no echocardiographically demonstrable wall motion asynergies or abnormal exercise stress tests, it is unlikely that significant coronary artery disease was present. Moreover, 23 patients had normal myocardial perfusion scintigrams.

It is possible that LV hypertrophy plays an important role in the genesis or aggravation of diastolic dysfunction. Our finding of an increased myocardial mass is in agreement with those of other authors who have evaluated ventricular structure in diabetics. An increased LV mass and an increased wall-thickness-to-radius ratio not related to blood pressure levels were found by Paillole et al[18] and Airaksinen et al[13] in their young normotensive insulin-dependent diabetic patients. Our diabetics, especially those with concomitant hypertension and diastolic abnormalities, had echocardiographic features of intramyocardial restriction with increased wall thickness and normal cavity size. The increased LV mass may be the consequence of an increased myocardial collagen deposition, which leads to abnormal distensibility and altered filling properties of the left ventricle. Rubler et al[6] first found myocardial hypertrophy and fibrosis in patients with diabetic cardiomyopathy. In a recent necropsy study conducted on patients with hypertension, diabetes, or both, van Hoeven and Factor[37] demonstrated that heart weight and interstitial fibrosis were increased in all patients, especially in those with combined diabetes and hypertension. Coexistence of both factors increases the cardiovascular risk in a multiplicative manner, leading to myocardial dysfunction with increased occurrence of congestive heart failure and increased cardiac mortality.

Limitations of the Study The main limitation of this study is that Doppler echocardiography permits only an indirect estimate of diastolic function in relation to LV filling. In addition, LV filling is influenced by a variety of factors such as ventricular relaxation, myocardial stiffness, coronary blood flow, preload, and afterload, and its pattern considerably modifies with aging. The Doppler technique is unable to evaluate directly these factors; furthermore, in combination they may "normalize" an abnormal transmitral flow pattern, thus complicating the evaluation of diastolic filling.[38,39]

Another limitation of this study is the relatively small number of subjects, which may have masked differences between groups, especially regarding the additive influence of arterial hypertension on diastolic dysfunction.

In conclusion, diastolic impairment is frequent in diabetic patients without overt evidence of heart disease, particularly in those with concomitant arterial hypertension. Further studies are needed to evaluate the clinical and prognostic significance of subclinical diastolic abnormalities in diabetic cardiomyopathy and the pathogenic role of the multiple factors affecting myocardial performance in diabetes mellitus.

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