Original Article

Diastolic Dysfunction in Diabetic Normotensive Patients, Regardless of the Presence of Microangiopathy

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Objective

To assess the Doppler-echocardiographic changes in normotensive patients with type II diabetes mellitus, in the presence or absence of signs of microangiopathy.

Methods

Patients with type II diabetes mellitus were submitted to funduscopy contrasted with fluorescein and dosage of microalbuminuria for diagnose of microangiopathy and divided into two groups: DMII (patients without microangiopathy, n=19) and DM+A (patients with microangiopathy, n=13). All of them were submitted to a Doppler-echocardiography and the results were compared with normotensive patients of same sex and age (group C, n=20), by using the ANOVA, followed by the test of Tukey. In all comparisons the significance level p<0.05 was adopted.

Results

There were no differences among the groups regarding the systolic function indicators or left ventricular mass. Differences compatible with diastolic dysfunction in the two groups of diabetic were observed, regardless of the presence of microangiopathy, which showed significantly higher values of the times of isovolumetric relaxation of the left ventricle (TIRLV, ms): (DMII= 97±22.2; DM+A= 107±28.2 and C= 80±10.7; p<0.05), and lower values of the maximum speeds of the wave of fast ventricular filling (E, cm/s): (DMII= 69±17.5; DM+A= 75±19.7 and C= 84±14.5, p<0.05 between DMII and C). There was no difference among the groups concerning the E/A rate.

Conclusion

Normotensive patients with type II diabetes mellitus and without clinical signs of cardiovascular compromising showed signs of diastolic dysfunction, non-associated to the presence of microangiopathy.

Key words

echocardiogram, left ventricle, cardiomiopathy, diabetes mellitus

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Clinical, epidemiological and hystopathologic evidences indicate the existence of a specific cardiopathy related to the diabetes mellitus[1]. Indeed, non-invasive assessments of the cardiac function in diabetic individuals frequently show the existence of abnormalities in both systolic and diastolic functions of the left ventricle, which can be evinced by means of many diagnostic methods. However, despite the regular use of the term diabetic cardiomiopathy, there is still a considerable debate on the exact nature and cause of the cardiac dysfunction found in diabetic individuals, non-carriers of coronary atherosclerosis and hypertension, which are pathologic conditions frequently associated to diabetes mellitus and that can lead to a cardiac dysfunction, according to the literature.

The existence of diabetic cardiomyopathy was first suggested by Rubler et al.[1], who described myocardial hypertrophy and fibrosis, in addition to prominent endothelial and sub-endothelial proliferation, indicating that the changes in the small vessels could be involved in the pathogenesis of the myocardial dysfunction.

From that initial description, and to this moment, there have still been disputes concerning the importance of the disease in the small vessels, of interstitial fibrosis, and the metabolic disturbance in the pathogenesis of diabetic cardiomyopathy[2-15].

Rossen[15] has debated that, although the correlation of cardiomyopathy with microangiopathy is doubtful, it may exist, having in mind the similarities among the abnormalities in the coronary microvascular function, which are observed in the diabetes mellitus and the idiopathic dilated cardiomyopathy.

Gutierrez and Higuchi [14], in our milieu, accept three hypotheses to explain what they call of contingent causal effect of the diabetes as for the cardiac disease: 1) microangiopathy; 2) direct action on the cardiac fiber of the metabolic disturbances caused by the hyperglycemia, among other factors; 3) changes in the extracellular matrix, caused by a greater level of glycation in its components, with consequent changes in the muscular structure.

So far, the studies that have compared the ventricular function of diabetic patients with or without microangiopathy[10,15-20] have shown conflicting results. Recently, Liu et al.[21] has found a relation between the presence of urinary loss of albumin and the diastolic dysfunction, in three analyzed groups: absence of albuminuria, microalbuminuria and macroalbuminuria. Despite the differences among the groups, the multivariable analysis has shown the albuminuria as an independently associated variable with systolic and diastolic dysfunction, after that adjustment for age, sex, body mass index, systolic blood pressure, duration of diabetes mellitus,

coronary artery disease, and left ventricle mass index. Once the microalbuminuria is a endothelial dysfunction marker in the glomerular arteriole, Bell[22] though valid to postulate that the myocardial endothelial dysfunction causes an increase of healing and rigidity, also considering that such low-cost urinary test could anticipate a Doppler echocardiographic examination, which, although more sensitive to detect the diastolic dysfunction, it has a higher cost. After the diastolic dysfunction was documented, the therapy aiming at preventing the progression of the disease to cardiac insufficiency should have started.

By having in view that the echocardiographic examination is described as a sensitive method for the early detection of diabetic cardiomyopathy[8], the present study aims at identifying whether the presence of microangiopathy is associated to cardiac structural and functional changes in non-hypertensive and asymptomatic diabetic patients, from the cardiovascular point of view.

Methods

All procedures were submitted to and approved by an Ethics Committee in Research Involving Human Beings.

A control-case cross examination was carried out involving 32 patients with diabetes mellitus, aged between 40 and 65 years old, and 20 normal voluntaries, with comparable age and sex. All participants in the study were submitted to a complete clinical assessment with a cardiologist.

The exclusion criteria were as follows: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; signs or symptoms of cardio-respiratory disease; use of cardiovascular action drugs; acoustic fenestra unsuitable for the analysis of the echocardiogram.

The diabetic patients were submitted to laboratory tests for the assessment of renal function and of lipidic profile, and also a funduscopy contrasted with fluorescein and an examination of urine collected in 12 hours for the detection of microalbuminuria. The diagnosis of retinopathy and/or microalbuminuria was the criterion to define the presence of microangiopathy.

The DM+A group consisted of patients with signs of microangiopathy (n=13); and the DM group for patients without microangiopathy (n=19); and the control group of clinically normal voluntaries (n=20).

The funduscopy consisted of direct and indirect ophthalmoscopy under mydriasis; retinography with aneritra light, fluorescenic angiography, through the injection 2.5 ml of intravenous sodic fluorscein at 10%. For the documentation of fluoresceinic angiography and retinography, the TRC-FE model Topcon equipment and a 400-ASA Tri-X Pam Kodak film were used. The diagnosis of retinopathy was based on the presence of at least one microaneuryism in one of the eyes, or in the other changes such as hemorrhages, hard exudates, soft (cotton-like) exudates, and fibrovascular proliferation[23].

The urinary excretion of albumina was determined by means of a turbidimetry, by using the Behring Turbidimeter® and the 0.3μg/ml sensitivity Turbiquant® reactive agents. The examination was performed in urine collected for 12 hours in a sterile flask and without any preservatives. The samples containing bacteriuria $> 10^5/mm^3$ were disregarded. The result was regarded as positive for values greater than 15μ/min.

All procedures were carried out by a single qualified echocardiographer, who did not have any knowledge on the group the individuals belonged to. The examinations were done by means of an ATL Apogee CX 200, equipped with a 2.0-3.5MHz multifrequency ultrasonic transducer and image record system. During the procedure, the patient stayed in left lateral decubitus, with the left upper member slightly flexed under the head. An electrocardiographic derivation was continuously monitored.

The images were obtained by following the recommendations of American Society of Echocardiography[24], from usual echocardiographic sections. The sequence of measurements was: final systolic dimension of the outlet way of the LV (OWLV), anteroposterior diastolic diameter of the left atrium (LA), final diastolic diameter (dLV), final systolic diameter (sLV), diastolic thicknesses of the IVS and of the posterior wall of LV (PW). Such dimensions were used for the calculation of:

$$\text{LV mass index (LVMI, g/m}^2) = \frac{\{[(dIVS + dPWLVd + DdLV)^3 - DDLV^3]x1.04\}-13.6}{BS}$$

$$\text{Fraction of ejection (FE)} = \frac{[7/(2.4+DdLV)] \times DdLV^3 - [7/(2.4+DsLV)] \times DsLV^3}{[7/(2.4+DdLV)] \times DdLV^3}$$

Percentage of variation of the ventricular diameter (%ΔD)= [(dLV - sLV) / deV] x 100

The evaluations of the flows followed the recommendations of the Canadian Consensus[25] for the Doppler-echocardiographic measurements, obtaining the following variables: c1) maximum speed of fast ventricular filling (peak of E wave, cm/s); c2) maximum speed of tardive filling, after atrial contraction (peak of A wave, cm/s); c3) deceleration time of E wave (DTE, ms), corresponding to the time interval between the peak of E wave and its extrapolation to the base line. Also with the pulsated Doppler, simultaneous flow curves at the outlet and inlet ways of the LV were obtained. The time interval between the end of the systolic flow and the beginning of the transmitral flow corresponded to the isovolumetric relaxation time of the LV (VIRT). The analysis of the systolic flow in the OWLV allowed for the calculation of the following variables: systolic index (SI, mL/BS) = (OWLV2 x 0.785 x IOWLV)/BS, in which OWLV is the measurement of the outlet way of the LV, IOWLV is the integral of the systolic flow in the OWLV and BS is the body surface; cardiac output (CO, L/min)= SV x HR.

The comparisons among the groups were done through ANOVA, followed by the test of Tukey. The level of significance $p<0.05$ was considered in all cases.

Results

Diabetic patients with microangiopathy showed average values of microalbuminuria of 36 mcg/min. In the same way, the most frequent changes observed in the contrasted fundoscopy were the presence of microaneurysms, a clinical picture classified as non-proliferative diabetic retinopathy[23]. From the 13 patients of DM+A group, 9 showed isolated eyegrounds change, 2 only microalbuminuria and 2 showed both changes.

Table I shows the age, the body weight, the body surface and the hemodynamic variables of the diabetes mellitus with microan-

Table I - Age, body weight, body surface and hemodynamic variables of the individuals from diabetes mellitus with microangiopathy (DM + A), diabetes mellitus without microangiopathy (DM) and control (C) groups. The values of the means, their respective standard deviations and the results of the statistic test are shown

Variable	Groups			Result of the statistic test
	DM + A	DM	C	
Ag (years)	55.00±6.90	50.90±8.47	51.20±9.41	1.06 (p>0.05)
BW (Kg)	71.60±11.24	72.30±12.54	68.50±14.97	0.45 (p>0.05)
BS (Kg/m²)	1.81±0.18	1.79±0.18	1.76±0.24	0.27 (p>0.05)
SBP (mmHg)	120.00±13.60	±11.50	112.00±10.57	2.11 (p>0.05)
DBP (mmHg)	79.00±8.20	±7.90	76.00±5.90	1.24 (p>0.05)
HR (bpm)	71.00±8.40[ab]	74.00±10.30[b]	65.00±9.40[a]	4.82 (p<0.05)

Ag - age; BW - body weight; BS - body surface; SBP and DBP - systolic and diastolic blood pressure, respectively; HR - heart rate. Small letters represent statistically significant difference among the groups (ANOVA and Tukey).

giopathy (DM + A), diabetes mellitus without microangiopathy (DM) and control (C) groups. The values of the means, their respective standard deviations, and the results from the statistic test are shown. Concerning the age, body weight and body surface variables, the 3 groups were statistically similar among each other. The comparison of hemodynamic data evinced that the groups do not differ in relation to the systolic blood pressure and diastolic blood pressure. Concerning the heart rate, the DM group showed a value, statistically significant, greater than the C group value (74±10.30 bpm vs. 65±9.40 bpm, $p< 0.05$). In table II, the cardiac morphometric variables, normalized for the body surface were observed. They were obtained through the M-mode echocardiogram, from the diabetes mellitus with microangiopathy (DM + A), diabetes mellitus without microangiopathy (DM) and control (C) groups. Significant differences among those three groups were not observed.

The variables of systolic function, obtained through Doppler echocardiography, from the three groups studied are in table III. There were no statistic differences among them and, in table IV, the variables of diastolic function. The maximum sped of fast ventricular filling (E) was similar in the DM + A (75±19.70 cm/s) and DM (69±17.50 cm/s) groups. The value obtained in that last group was significantly lower than that observed in the control group (84±14.50 cm/s). The isovolumetric relaxation time of the left ventricle (IRTLV) showed statistically similar values in the DM + A (107±28.20 ms) and DM (97±22.20 ms) patients. Both groups were different from the control group, which showed a significantly lower value (80±10.70 ms).

Discussion

The absence of differences among the patient groups, in relation to the morphometric and systolic function variables, was not surprising. The inclusion and exclusion criteria were very specific and restricted the patient sampling, which was already discussed. That fact, despite having contributed to decrease the power of evincing potential among the groups, was in accordance to the proposal of assessing the association between the presence of signs of diabetic microangiopathy and cardiac morphofunctional changes in groups that are similar in all the other aspects, except the lesion of small vessels. It was also necessary to restrict the

Table II - Cardiac morphometric variable, normalized for the body surface (BS), obtained through the M - mode echocardiogram, in the individuals from the diabetes mellitus with microangiopathy (DM + A), diabetes mellitus without microangiopathy (DM) and control (C) groups. The values of the means, their respective standard deviations and the results of the statistic test are shown

Variable	Groups			Result of the statistic test
	DM + A	DM	C	
LA/BS (cm/m²)	1.81±0.21	1.90±0.25	1.89±0.27	0.56 (p>0.05)
dLV/BS (cm/m²)	2.52±0.20	2.56±0.45	2.67±0.23	0.95 (p>0.05)
sLV/BS (cm/m²)	1.53±0.17	1.50±0.30	1.51±0.22	0.06 (p>0.05)
MILV (g/m²)	90.60±26.80	90.70±36.00	80.10±22.00	0.83 (p>0.05)

LA - left atrium; dLV and sLV - diastolic and systolic diameters of the left ventricle, respectively; MILV - mass index of the left ventricle; ANOVA.

Table III - Variables of systolic function, obtained through Doppler-echocardiography in the individuals from the diabetes mellitus with microangiopathy (DM + A), diabetes mellitus without microangiopathy (DM) and control (C) groups. The values of the means, their respective standard deviations and the results of the statistic test are shown

Variable	Groups			Result of the statistic test
	DM + A	DM	C	
Delta d	0.39±0.06	0.41±0.05	0.43±0.07	1.91 (p>0.05)
FE	0.69±0.07	0.72±0.05	0.74±0.07	2.23 (p>0.05)
CO (L/min)	4.25±0.98	4.20±1.26	3.94±1.29	0.33 (p>0.05)
SI (mL/m²)	32.80±6.00	32.30±10.80	34.00±6.90	0.23 (p>0.05)
FSS (g/cm²)	51.60±12.20	49.40±12.90	47.00±14.10	0.49 (p>0.05)

Delta d - fraction of shortening of the left ventricle (LV); FE - fraction of ejection of LV; CO - cardiac output; SI - systolic index; FSS - final systolic stress of LV; ANOVA.

Table IV - Variables of diastolic function, obtained through Doppler-echocardiography in the individuals from the diabetes mellitus with microangiopathy (DM + A), diabetes mellitus without microangiopathy (DM) and control (C) groups. The values of the means, their respective standard deviations and the results of the statistic test are shown

Variable	Groups			Result of the
	DM + Angio	DM	C	statistic test
E (cm/s)	75.00±19.70[ab]	69.00±17.50[a]	84.00±14.50[b]	4.15 (p<0.05)
A (cm/s)	80.00±16.20	71.00±16.70	75.00±14.90	1.52 (p>0.05)
E/A	0.94±0.28	0.99±0.26	1.16±0.30	2.69 (p>0.05)
DTE (ms)	181.00±51.00	192.00±36.40	188.00±42.10	0.31 (p>0.05)
TIRLV (ms)	107.00±28.20[b]	97.00±22.20[b]	80.00±10.70[a]	7.61 (p<0.05)

E - maximum speed of the fast ventricular filling; A - maximum speed of the wave of tardive ventricular filling; E/A - rate between E and A speeds; DTE - deceleration time of the E wave; TIRLV - time of isovolumetric relaxation of the left ventricle. Small letters represent statistically significant difference among the groups (ANOVA and Tukey).

analysis to the diabetic patients non-carrier of other cardiovascular diseases. Besides, that has been the problem faced by researchers interested in the subject. For example, many studies with greater casuistry have concluded on left ventricular dysfunction associated with diabetes, by including normotensive and hypertensive patients in the same group[16,26,27]. Cosson et al.[8] attributed the published contradictory results to the lack of homogeneity of the population studied and the uniformity of the echocardiographic indexes used. So, our conclusions are only applicable to groups of individuals with similar characteristics to those assessed in the present study.

The study by Framingham[22] showed that diabetic women had a left ventricle mass 10% greater than those non-diabetic. The Tayside study[28] showed that the ventricular hypertrophy was present in 32% of the normotensive diabetic patients, who did not use drugs that inhibited the enzyme of conversion of the angiotensin and did not have coronary disease. Besides, hypertensive and diabetic women showed a greater level of left ventricular hypertrophy and increase of the left atrium, when compared to non-diabetic hypertensive ones[29]. While the myocardial fibrosis seems to be related to the hyperglycemia, the left ventricular hypertrophy has been more related to the insuline-resistence syndrome[30,31]. Although the left ventricular hypertrophy is more prevailing in diabetic patients and such fact is related to ventricular dysfunction [22,32], there was no variation in the left ventricular mass in our casuistry.

Despite the rest-preserved systolic function, a considerable proportion of those patients showed diastolic changes at the Doppler-echocardiographic examination. Those findings are in accordance to the clinical observations by other authors who showed the diastolic diabetes mellitus[8,32,33].

The study by Framingham convincingly showed that diabetic patients show addition risk for the development of cardiomyopathy and cardiac insufficiency[34]. However, the nature of such association reported in that classic epidemiological study wa.s not completely clear. The identification, in which many of the patients with clinical signs of cardiac failure objectively showed preserved systolic function, caused a huge interest in researchers and clinicians on the condition of the diastolic ventricular function in those patients[8,32,33].

This diastolic compromising that precedes the systolic changes in the evolution of the functional changes in the diabetic heart has been observed even in the absence of coronary artery disease and left ventricular hypertrophy. Many reports have shown prevalence's from 30 to 60% of diastolic dysfunction in well-controlled and normotensive diabetic individuals[22,32,35-37].

An interesting finding in the present study was the increase of the isovolumetric relaxation time in the diabetic patients, when compared to the controls. Despite such increase, in the average, is not of sufficient magnitude to extrapolate the values regarded as normal, it can be acknowledged that some level of compromising of the myocardial relaxation process must be current in those patients.

The myocardial relaxation happens as a consequence of the removal of the ion Ca^{2+} from the cytoplasm to the inside of the sarcoplasmic reticule, after the myocardial contraction, in a complex and active process, with great consumption of ATP and involving many proteins. Therefore, the extension of the myocardial relaxation time can be the result from a large quantity of potential subcellular changes that may impair the relaxation.

The extension of the myocardial relaxation time influences the fast ventricular filling and could be the mechanism subjacent to the observation of decreased values at the peak of the E wave. The ventricular filling depends fundamentally on the atrioventricular pressure gradient, during that stage in the cardiac cycle. That pressure gradient is directly influenced by the intra-atrial pressure and, therefore, by its volume, and inversely influenced by the intraventricular pressure. So, the delayed or incomplete myocardial relaxation promotes an increase in the ventricular diastolic pressure, a reduction in the transmitral gradient and a decrease of the speed of the initial diastolic flow. There is also the possibility that myocardial interstitial changes, with the increase of collagen concentration, have taken part in the induction process of the diastolic function[38].

On the contrary we expected, we did not observe significant changes between the two groups of diabetic patients. Although in the literature, the presence of albuminuria in diabetic individuals identifies that high risk of presence of cardiovascular disease, our data suggest, that its presence is not related to diastolic dysfunction of the left ventricle. Such change is regarded as the initial manifestation of diabetic cardiomyopathy[21,33]. In that aspect, it is relevant to consider the size of the sample. That means, differences among the groups could be statistically demonstrated, if the number of patients were greater. However, given the similarity among the average values of the diastolic function index in the DM and DM+A groups, only the inclusion of hundreds of patients in the study would allow for the demonstration. Despite such limitations, we regarded as valid the disclosure of the results in the present study, by having in view that similar studies can be carried out and, together, allow for in the future solving that relevant matter concerning the physiopathology of the cardiomyopathy of the diabetic individual.

Finally, we regard as great importance the observation that

normotensive diabetic patients and without clinical signs of cardiac disease show suggestive changes of diastolic dysfunction, when compared to their non-diabetic controls. Those results reinforce the need for similar additional studies, searching to clarify the physiopathology, the ways of prevention and the treatment of such dysfunction.

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