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Influence of Autonomic Neuropathy upon Left Ventricular Dysfunction in Insulin-Dependent Diabetic Patients

PATRICIA T. MONTEAGUDO, M.D., PH.D., VALDIR A. MOISÉS, M.D., PH.D.,* OSVALDO KOHLMANN, JR., M.D., PH.D.,†
ARTUR B. RIBEIRO, M.D., PH.D.,† VALTER C. LIMA, M.D., PH.D.,* M. TERESA ZANELLA, M.D., PH.D.

Endocrinology, *Cardiology, and †Nephrology Divisions, Department of Medicine, Escola Paulista de Medicina, UNIFESP, São Paulo, Brazil

Summary

Background: Diabetic cardiomyopathy is a well-defined complication of diabetes that occurs in the absence of ischemic, vascular, and hypertensive disease.

Hypothesis: The study was undertaken to test the relationship among autonomic neuropathy (AN), 24-h blood pressure (BP) profile, and left ventricular function.

Methods: Nineteen type-1 diabetic patients underwent autonomic tests and echocardiographic examination. Patients were divided according to the presence (AN+) or absence (AN−) of AN.

Results: In the AN+ group (n = 8), the E/A ratio at echo was lower than in the AN− group (n = 11) (1.1 ± 0.3 vs. 1.6 ± 0.3; $p < 0.005$). Systolic and diastolic BP reductions during sleep were smaller in the AN+ than in the AN− group (6.6 ± 6.6 vs. 13.0 ± 4.3%; $p < 0.03$ for systolic and 12.8 ± 6.8 vs. 20.0 ± 4.0% for diastolic BP reduction; $p < 0.03$, respectively). Considering all patients, the E/A ratio correlated inversely with awake diastolic BP (r − 0.63; $p = 0.005$); sleep systolic BP (r − 0.48; $p = 0.04$), and sleep diastolic BP (r − 0.67; $p = 0.002$). The AN correlated with diastolic interventricular septum thickness (r 0.57; $p = 0.01$), sleep systolic BP (r 0.45; $p = 0.05$), sleep diastolic BP (r 0.54; $p = 0.02$), and correlated inversely with systolic and diastolic sleep BP reduction (r − 0.49; $p = 0.03$ and r − 0.67; $p = 0.002$, respectively). Finally, E/A ratio and AN score correlated between themselves (r − 0.6; $p = 0.005$).

Conclusion: Our results suggest that left ventricular diastolic dysfunction may be detected very early in type-1 diabetic patients with AN. Parasympathetic lesion and nocturnal elevations in BP could be the link between AN and diastolic ventricular dysfunction.

Key words: diabetic cardiomyopathy, autonomic neuropathy, left diastolic dysfunction, type-1 diabetes, insulin-dependent diabetes

Introduction

Diabetic cardiomyopathy (DMCM) is a well-defined complication of diabetes that occurs in the absence of ischemic, vascular, and hypertensive disease.[1,2] The Framingham Study was the first epidemiologic study that presented the existence of a specific diabetic heart disease, showing an incidence of congestive heart failure that was substantially increased among diabetic patients.[3]

Most studies showed that the diastolic abnormalities of DMCM occur nearly 10 years before the appearance of systolic dysfunction.[4,5] However, in a prospective study, Shapiro observed that congestive heart failure occurred in 30% of diabetic patients with diastolic dysfunction and no systolic dysfunction.[6] In this context, the association with hypertension has cumulative effects.[7,8]

Nevertheless, the pathophysiologic factors that influence the development of DMCM are not completely understood. In this study, the relationship among autonomic neuropathy (AN), 24-h blood pressure (BP) profile, and diastolic left ventricular (LV) function was analyzed in 19 insulin-dependent diabetic patients.

Address for reprints:

Dra. Patrícia T. Monteagudo
Clínica de Hipertensão
Hospital de Rim e Hipertensão
Escola Paulista de Medicina – UNIFESP
Rua Borges Lagoa, 960, andar térreo
Vila Clementino, CEP 04024-000
São Paulo, Brazil

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Patients and Methods

The entry criteria were the diagnosis of type-1 diabetes (DM-1), patients < 55 years of age, absence of any acute or chronic disease, no use of beta blockers, no history of coronary heart disease, normal electrocardiogram, normal systolic LV function on echocardiogram, and serum creatinine < 1.5 mg/dl. Before clinical and laboratory evaluation, patients were oriented to improve their glycemic control so that their blood glucose would remain < 200 mg/dl. All antihypertensive agents were withdrawn 15 days prior to the evaluation and no medication other than insulin was administered. The study was approved by the Institutional Ethical Committee and all patients signed informed consent.

Autonomic neuropathy was evaluated according to standard procedures of the San Antonio Conference.[9, 10] The tests performed were heart rate at rest, heart rate response to deep breathing, Valsalva maneuver, BP variation from supine to upright posture (postural hypotension), and sympathetic cutaneous reflex. The result obtained in each test was compared with the result obtained in a normal, age-matched control group. Nineteen healthy individuals who work at the Hospital were selected and volunteered to serve as a control group. For each test, values out of the range determined by the mean value ± 2 standard deviations (SD) of the control group were considered abnormal and had score 1. Values out of the range determined by the mean ± 3 SD had score 2, while normal tests had score 0. The degree of AN was quantified by the sum of the scores that ranged from 0 to 8. Presence of AN was determined if at least two tests were abnormal (total score ≥ 2). Eight diabetic patients had an AN score ≤ 1 and were considered free of AN. Clinical data and cardiovascular tests of the control group and of diabetic patients with and without AN are shown in Table I.

Twenty-four hour ambulatory BP monitoring was performed during normal daily activities. Patients were advised not to rest in bed and not to refrain from exercising during the day so that daily activities would not differ substantially. Blood pressure was measured every 15 min between 6:00 A.M. and 11:00 P.M. and every 20 min thereafter, using an oscillometric ambulatory BP recorder (SpaceLabs 90202, Redmond, Wash.). Patients were requested to record their activities and the wake-up and sleep time. Systolic and diastolic BP readings were averaged for the time of wake-up (awake BP) and for the time of sleeping (sleep BP), based on the patients' records. The percentage change in both systolic and diastolic BP from the wake-up time to sleep time was calculated as

$$\Delta BP = (\text{awake BP} - \text{sleep BP}) \times 100 / \text{awake BP}$$
$$(\Delta \text{ awake-sleep BP}).$$

M-mode and two-dimensional echocardiography recordings and phonogram were obtained on an Esaote Biomedica (model SIM 5000, Florence, Italy) with a mechanical transducer of 2.5 MHz, in accordance with the recommendations of the American Society of Echocardiography.[11] Left ventricular mass was corrected for body weight as LV mass index. Systolic function was evaluated by ejection fraction and LV fractional shortening. Doppler patterns of diastolic function were described in a recent review[12] and were evaluated by measurements of A and E waves, E/A ratio, atrial deceleration time, and isovolumetric relaxation time.

After overnight fasting, blood samples were obtained for blood glucose, serum creatinine, and glycosilated hemoglobin (HbA1).

Statistical Analysis

Data are expressed as means ± SD. Urinary albumin excretion rates were logarithmically transformed ($\log_{10}$) to achieve a near-normal distribution. These data are presented as the geometric mean multiplied or divided by the tolerance factor

TABLE I Clinical and neurological evaluation in control group and in diabetes mellitus-1 patients with autonomic neuropathy positive (AN+) or negative (AN−)

		DM-1 patients	
	Controls	AN−	AN+
Number of patients (female/male)	19 (13/6)	8 (6/2)	11 (8/3)
Number of hypertensive patients	—	3	5
Age (years)	30.4 ± 8.6	27.8 ± 13.1	34.3 ± 9.9
Body mass index (kg/m^2)	22.5 ± 1.4	22.1 ± 1.5	22.5 ± 2.9
Diabetes duration (years)	—	9.3 ± 2.4	15.8 ± 8.5[a]
Heart rate at rest (beats/min)	69 ± 10.2	83 ± 14.9	92 ± 6
Heart rate response to deep breathing (beats/min)	22.8 ± 5.8	24.5 ± 8.9	7.9 ± 4.9
Valsalva maneuver	1.49 ± 0.21	1.66 ± 0.33	1.38 ± 0.38
Systolic BP variation with posture (1/5 min)	−3 ± 5 / −1 ± 6	4 ± 6 / 7 ± 7	−15 ± 7 / −8 ± 11
Altered sympathetic cutaneous reflex (n)	0	2	4
Range of AN score	—	0–1	2–7

Mean ± standard deviation.

[a] $p < 0.05$ vs. DM-1 without AN.

Abbreviations: DM = diabetes mellitus, AN = autonomic neuropathy, BP = blood pressure.

(= antilog to SD of $\log_{10}$ transformation). Unpaired Student's *t*-test, the Mann-Whitney U-test, and analysis of variance (ANOVA) were used where appropriate. Correlation between variables was tested by Spearman correlation coefficient. Differences were considered significant if $p < 0.05$.

Results

Table I shows demographic and autonomic cardiovascular test results in controls and in the two subgroups of diabetic patients divided according to the presence or absence of AN. Eleven of 19 patients had AN, and 5 of these were hypertensive, whereas 3 of the 8 without AN were hypertensive. There were no significant differences between patients with and without AN regarding age, gender distribution, and body mass index. However, the presence of AN was associated with longer duration of diabetes.

Table II shows blood pressure data for both groups of diabetic patients divided by the presence or absence of AN. Both groups with and without AN had similar levels of HbA1c (6.5 ± 1.1 vs. 6.4 ± 4.3%) and serum creatinine (0.7 ± 0.1 vs. 0.9 ± 0.3 mg/dl), respectively. However, albuminuria was higher in the group with AN (15.8x ÷ 6.3 vs. 125.9x ÷ 6.3, $p < 0.03$). With respect to 24-h BP pattern, the presence of diabetic AN was associated with higher sleeping diastolic BP levels and reduced systolic and diastolic BP reductions during sleep (Table II) (Fig. 1A).

Table III contains left echocardiographic parameters for both diabetics groups studied. As is shown, patients with AN had a higher diastolic interventricular septum compared with those without AN. Patients with AN tended to have higher A wave values and lower E/A ratio than AN-free patients (Fig. 1B).

Our results showed that the E/A ratio correlated inversely with awake diastolic (r − 0.63; $p = 0.005$), but not with systolic BP; with sleep systolic (r − 0.48; $p = 0.04$) and diastolic BP (r − 0.67; $p = 0.001$); and with diastolic interventricular septum thickness (r − 0.48; $p = 0.04$). Furthermore, the score of AN directly correlated with diastolic interventricular septum thickness (r 0.57; $p = 0.01$); sleep systolic (r 0.45; $p = 0.05$) and diastolic BP (r 0.43; $p = 0.06$); and inversely with systolic and diastolic BP reductions during sleep (r − 0,49; $p = 0.03$ and r − 0.67; $p = 0.002$, respectively). Finally, a correlation was found between E/A ratio and AN score (r − 0.63; $p = 0.005$). This correlation was even observed between E/A ratio and heart rate response to deep breathing (r 0.71; $p = 0.001$).

TABLE II Average 24-h, awake, sleep, and Δ awake-sleep values of systolic and diastolic blood pressure in DM-1 patients with autonomic neuropathy positive (AN +) or negative (AN −)

	AN −	AN +	p Value
Systolic blood pressure			
24-h (mmHg)	131 ± 14	135 ± 15	NS
Awake (mmHg)	135 ± 14	137 ± 15	NS
Sleep (mmHg)	117 ± 12	128 ± 16	NS
Δ Awake -sleep (%)	13.0 ± 4.3	6.6 ± 6.6	0.03
Diastolic blood pressure			
24-h (mmHg)	83 ± 9	89 ± 11	NS
Awake (mmHg)	86 ± 9	92 ± 11	NS
Sleep (mmHg)	70 ± 8	80 ± 12	0.05
Δ Awake -sleep (%)	20.0 ± 4.0	12.8 ± 6.8	0.03

Mean ± standard deviation.

Abbreviation: NS = not significant. Other abbreviations as in Table I.

Discussion

Our results clearly demonstrated that patients with AN have diastolic dysfunction as assessed by E/A ratio. In our study, both the magnitude of E/A ratio and of the degree of AN were negatively related to the BP reduction during sleep. Thus, AN may affect left diastolic function through changes in BP profile. Autonomic parasympathetic failure, which occurs earlier in the development of diabetic neuropathy,[13–16] would be responsible for the smaller decrements in BP during the night. However, other hemodynamics mechanisms could be responsible for this alteration in BP profile. Sympathetic lesion and sodium and water retention that occur for the maintenance of BP during upright position in some patients would also contribute to the higher BP values during the night.[17–19] This volume retention during the day could overload the heart at night and would therefore be responsible for the development of functional and structural changes of the heart.

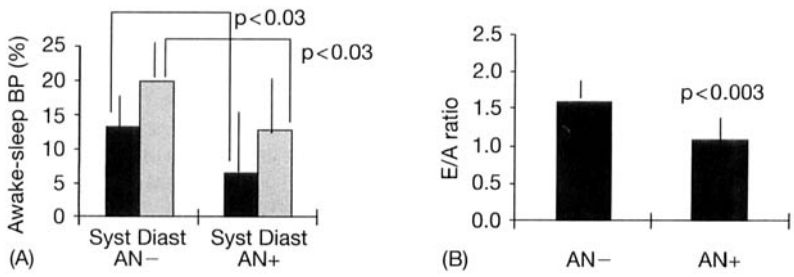

FIG. 1 The presence of autonomic neuropathy (AN) and percentage systolic (syst) and diastolic (diast) blood pressure (BP) reduction during sleep (A) and the E/A ratio (B).

TABLE III Echocardiography left ventricular parameters in DM-1 patients with autonomic neuropathy positive (AN +) or negative (AN −)

DM-1 patients	AN −	AN +	p Value
Morphologic parameters			
Diastolic posterior wall (mm)	7.8 ± 0.7	9.0 ± 2.2	0.08
Diastolic interventricular septum (mm)	8.0 ± 0.8	9.4 ± 2.1	0.05
Diastolic diameter (mm)	25.6 ± 3.1	26.2 ± 3.1	NS
Left ventricular mass index (g/m^2)	82.0 ± 16.3	80.1 ± 27.3	NS
Systolic function			
Ejection fraction (%)	0.77 ± 0.07	0.76 ± 0.04	NS
Fractional shortening (%)	39.5 ± 6.2	38.3 ± 3.3	NS
Diastolic function			
E wave (cm/s)	82 ± 16	70 ± 14	NS
A wave (cm/s)	53 ± 11	66 ± 17	0.07
E/A ratio	1.6 ± 0.3	1.1 ± 0.3	0.003
Atrial deceleration time (ms)	198 ± 31	197 ± 32	NS
Isovolumetric deceleration time (ms)	81 ± 45	86 ± 16	NS

Mean ± standard deviation.
Abbreviations as in Tables I and II.

Several other features of diabetic patients with AN may explain our data: as we showed, patients with AN had higher cardiac rate with lower variability (beat to beat) associated to diastolic dysfunction, as was also demonstrated by Willenheimer *et al.*[20] and Irace *et al.*,[21] although others did not show similar results.[22] These findings could result from lower parasympathetic activity to the heart. Parasympathetic denervation may induce slower ventricular relaxation, leading to a decrease in the velocity of the passive, early diastolic mitral flow (decreased E) and a compensatory increase in the velocity of the flow caused by the atrial contraction (elevated A), resulting in low E/A ratio.[21,23]

Considering that patients with AN presented with tachycardia and that a fixed heart rate may compromise ventricular relaxation,[24] it is reasonable to postulate that AN triggered the diastolic dysfunction. Although diastolic ventricular function evaluation may be confounded by tachycardia,[25] the E/A ratio minimizes the influence of heart rate, so it is the most reliable marker of diastolic dysfunction in these patients.[12] This is supported by experimental studies.[26] Furthermore, the relaxing effects of catecholamines on the myocardium, which facilitate calcium uptake by the sarcoplasmic reticulum, may be compromised in AN.[27]

We also found in patients with AN a mild stiffening of the left ventricle, as also reported by Gotzsche *et al.*[28] Therefore, early decreases in LV compliance together with disturbances in relaxation and an increase in atrial pressure are possible contributing factors to diastolic dysfunction. Our results confirm previous observations that diabetic patients with AN have impaired ventricular diastolic filling in comparison with patients free of AN.[29,30]

Conclusion

We have shown that left ventricular diastolic dysfunction may be detected very early in type-1 diabetic patients with AN. Parasympathetic lesion and nocturnal elevations in BP could be the link between AN and diastolic ventricular dysfunction.

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