Original Article

Decreased Vagal Dependent Time-Domain Heart Rate Variability in Hypertensive Patients with Left Ventricular Diastolic Dysfunction

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ABSTRACT

Objectives: To evaluate the role of the autonomic nervous system in determining the appearance of diastolic ventricular dysfunction in patients with previously unrecognized and untreated essential hypertension.

Methods: We studied 100 middle-aged and pharmacologically untreated hypertensive subjects (88 men and 12 women) and 50 normotensive subjects (44 men and 6 women) as a control group (group I). All patients were referred from the outpatient clinic in Farwania Hospital with blood pressure more than 140/90 mmHg as detected by ambulatory blood pressure monitoring with an auscltatory device. Echocardiography was done to assess left ventricular diastolic function. Exercise ECG test was done to exclude patients with ischemic heart disease. Holter ECG monitor was done for all subjects to assess heart rate variability. Hypertensive patients were classified into two groups: group II included 50 patients with diastolic dysfunction and group III included 50 patients with normal ventricular diastolic function.

Results: With respect to age, gender, left ventricular mass index and left ventricular systolic function there were no significant difference between all groups of study (P = NS). The hypertensive patients of group II had a significant decreased E/A ratio ($P < 0.05$), a significant decreased r-MSSD and p-NN50 ($P < 0.05$) and a significant increased daytime and nighttime heart rate ($P < 0.05$) than subjects and patients of groups I and III. There was a significant correlation between vagal dependent parameter (r-MSSD) and E/A ratio ($r = 0.875$, $P < 0.05$). Stepwise logistic analysis revealed no significant relation between age, gender and ambulatory systolic and diastolic blood pressure and the presence of left ventricular diastolic dysfunction in hypertensive patients.

Conclusion: Left ventricular diastolic dysfunction in hypertensive patients without left ventricle hypertrophy is related to reduced parasympathetic activity and this supports the use of non-pharmacologic treatment that increases diastolic vagal tone.

KEY WORDS : ambulatory blood pressure monitoring, autonomic nervous system, diastolic dysfunction, heart rate variability

INTRODUCTION

At rest and during mild exercise, the heart rate is mainly under vagal control. Both heightened sympathetic activity and reduced vagal tone can be found in early stages of hypertension[1]. Contrary to the large volume of literature on the involvement of the sympathetic branch of the autonomic nervous system in hypertension, only a few publications are concerned with vagal activity[2]. Julius *et al*[3], concluded that patients with borderline hypertension and hyperkinetic circulation simultaneously exhibit an increase in sympathetic and a decrease in parasympathetic tone. A similar conclusion was reached by Korner *et al*[4], who reported significantly smaller vagal effects on heart rate in hypertension. The cause and time of occurrence of cardiac impairment in patients with essential hypertension are not precisely known. It has been shown that diastolic left ventricular dysfunction is the earliest cardiac abnormality in this patient population and it may precede ventricular hypertrophy[5]. Age and pressure load are considered possible determinants, whereas the role of autonomic nervous system is still being debated[6]. Animal studies have suggested that a high sympathetic tone may favor the development of hypertrophy, but the role of the autonomic nervous system in the genesis of cardiac abnormalities is unclear[7]. Some studies have reported increased sympathetic activity in hypertensive patients with cardiac hypertrophy, findings not confirmed by other authors. Furthermore, no data concerning the role of depressed baroreflex sensitivity determining cardiac impairment in these patients is available[8].

Szlachcic *et al*[9], found that there was a greater reliance on atrial systole for diastolic filling in hypertensive patients. The E/A ratio, a commonly utilized index of diastolic function, was also

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significantly reduced in these patients and even in hypertensive patients with adequately controlled blood pressure.

Measurement of heart rate variability based on 24-hour Holter recordings provides a reliable and sensitive noninvasive measurement of autonomic input to the heart[10-12].

The aim of the study was to evaluate the role of the autonomic nervous system in determining the appearance of left ventricular diastolic dysfunction in patients with previously unrecognized and untreated essential hypertension.

SUBJECTS AND METHODS

One hundred pharmacologically untreated hypertensive patients (90 men and 10 women) and 50 normotensive subjects (44 men and 6 women) were included in the study. All patients were referred by their physicians to the Non-Invasive Cardiac Laboratory, Medicine Department, Farwania Hospital, with systolic and/or diastolic blood pressure above 140 and 90 mmHg respectively, between February 2001 and June 2002. Twenty one subjects were referred to find out if they were dippers or non-dippers, 29 subjects were referred to confirm casual blood pressure measurment, 30 subjects were discovered accidentally during routine examination and 20 subjects presented for preoperative assessment for elective non-cardiovascular surgery.

Exclusion criteria included patients with coronary artery disease, diabetes mellitus, cerebrovascular disease, significant valvular disease, irritability, anxiety, palpitation and pregnant women. Exclusion was based on medical history, physical examination, routine biological chemical tests, treadmill exercise ECG and echocardiography to avoid confounding factors.

Ambulatory Blood pressure measurements

Ambulatory blood pressure was recorded with an auscultatory device (Accutracker II). Correct positioning of the mirophone was done by prior palpation of the brachial artery. Ambulatory BP was recorded during daytime (6 am to 10 pm) at one hour intervals and during night time (10 pm to 6 am) at 2-hour intervals. Awake and asleep BPs were calculated for twenty four hours and data were edited automatically. Readings with a quality failure code (ECG connection giving erratic heart beats or missing them completely, Korotkoff sounds that were too weak or not detected loose cuff or air leak) were rejected.

Echocardiographic study

Two-dimensional and M-mode echocardiography were performed for all patients with the use of a Toshiba, Power Vision, and a 3.5 MHZ phased array transducer. All echocardiographic studies were performed by the same cardiologist. Measurements were performed according to the recommendations of the American Society of Cardiology[13]. The leading edge to leading edge convention was used. Left ventricular dimensions were measured at or immediately below the tips of mitral leaflets and averaged over 5 heart cycles. Left ventricular mass and left ventricular mass index were also calculated.

Pulsed Doppler echocardiography was obtained from the standard apical four-chamber view. Mitral inflow velocity was recorded with the sample volume at mitral annulus level. The transducer was then manipulated to obtain the maximal flow velocity as assessed by the auditory and spectral outputs. The Doppler measurements were made at least three cardiac cycles using the darkest part of the spectral recording and were averaged[9]. The following measurements were obtained, peak velocity of early left ventricle filling (E), peak velocity of late left ventricular filling (A) and the ratio between early and late flow velocity (E/A).

There were three groups of patients

Group I: 50 normotensive subjects.
Group II: 50 hypertensive patients with left ventricular diastolic dysfunction.
Group III: 50 hypertensive patients with normal left ventricular diastolic function.

Twenty- four hour Holter monitor and heart rate variability

All subjects and patients of the study underwent continuous ambulatory 3-channel Holter monitoring for 24 hours. During analysis, only cycles in which beats had normal morphologic characteristics and were within 25% of the preceding cycle length were selected for calculation for heart rate variability. The QRS filter window excluded the coupling of all ectopic beats and their compensatory pause. Time domain measurements were obtained from normal to normal sinus beats including the mean R-R interval and its SD (SDNN), the percentage of successive R-R intervals that deviated by > 50% from the prior R-R interval (p-NN50), the root mean square of successive RR interval differences (rMMD) and the SD of the average of R-R intervals in 5-minutes segments of the 24-hour recording (SDANN)[14].

Statistical analysis

Continuous variables are summarized as mean ± standard deviation (SD). All data were compared using the ANOVAtest. Comparison between the two groups was performed with the t-test for continuous variables and chi-square test for categorical variables.

A P-value < 0.05 was considered statistically significant and < 0.01 was considered statistically highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with left ventricular diastolic dysfunction. The strength of the association with diastolic dysfunction is presented as 95% confidence intervals. Potential confounding clinical variables were entered as independent variables.

Simple linear regression (least-square method) was used for correlation of the parameters of the study: Y = b + aX Where, a = slope and b = intercept.

RESULTS

There were no significant difference (P = NS) between subjects and patients of all groups in the study when considering age, gender, left ventricular mass index and left ventricular systolic function (Table 1).

There were a significant decrease in r-MSSD and p-NN50 in hypertensive patients with diastolic dysfunction (P < 0.05) than the subjects of control group and hypertensive patients with normal diasolic function (Fig. 1 & 2).

There was a significant impaired left ventricular diastolic function in hypertensive patients of group II as detected by a significant decrease in E/A ratio (P < 0.05) than the subjects of the control group and hypertensive patients of group III.

There was a significant increase in day time and night time heart rate in the hypertensive patients with diastolic dysfunction than subjects of the control group and hypertensive patients with normal diastolic function of left ventricle (102.3 ± 7.4 versus 71.4 ± 5.6 and 76.5 ± 4.9 beat/minute, respectively, P < 0.05). But there was no significant difference between hypertensive patients of group II and III for ambulatory systolic and diastolic blood pressure (165.6 ± 8.9 versus 160.9 ± 7.8 mmHg and 108.5 ± 6.6 versus 110.3 ± 4.8 mmHg, respectively, P = NS).

There was a significant correlation between vagal dependent parameter (r-MSSD) and diastolic dysfunction (E/A ratio) in the hypertensive patients of group II (n = 50, Y = 0.11 + 0.02X , r = 0.875, P < 0.05).

Stepwise logistic analysis revealed no significant relation between age, gender and ambulatory awake, asleep and 24-hour systolic and diastolic blood pressure in our selected subjects (Table 2).

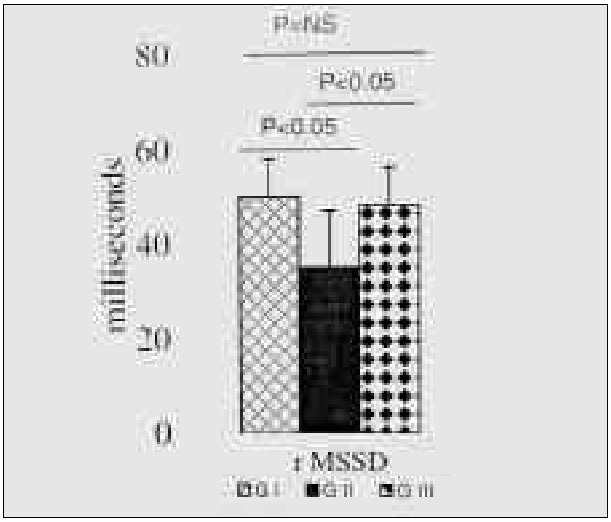

Fig. 1: Significant changes were observed for rMSSD in hypertensive patients with diastolic dysfunction

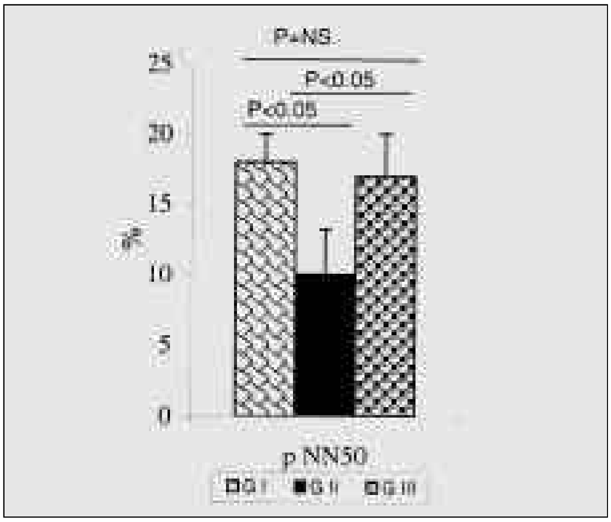

Fig. 2: Significant changes were observed in pNN50 in hypertensive patients with diastolic dysfunction

Table 1

Clinical and echocardiographic data in all groups of the study (mean ± SD)

	Group I	Group II	Group III	P-value
Age (years)	45.4 ± 6.2	47.4 ± 7.9	44.3 ± 3.19	NS
Male n (%)	44 (88%)	42 (84%)	46 (92%)	NS
Female n (%)	6 (12%)	8 (16%)	4 (8%)	NS
LVMI (gm/m^2)	110.3 ± 6.1	115.47 ± 3.9	112.15 ± 5.2	NS
LVFS (%)	40.5 ± 3.2	42.6 ± 2.3	40.16 ± 2.2	NS
E/Aratio	1.5 ± 0.2	0.66 ± 0.3	1.36 ± 0.4	*

* = E/Aratio of group II was significantly decreased (p = 0.05) than other both groups and no significant difference (P= NS) between group I & II, LVFS = left ventricular fractional shortening, LVMI = left ventricle mass index, n = number

Table 2

Stepwise logistic analysis of patients with versus without left ventricular diastolic dysfunction when considering age, gender, clinic systolic blood pressure and ambulatory systolic blood pressure monitoring

	R	SE	P - value	95% CI
Age	0.1421	0.0878	NS	0.554 - 1.231
Gender	0.0258	0.0789	NS	0.923 - 1.176
Awake ABP	0.0815	0.0536	NS	0.668 - 1.108
Asleep ABP	0.0432	0.0049	NS	0.776 - 1.027
24-hour ABP	0.0143	0.0178	NS	0.661 - 0.992

No.of observations = 150, ABP= ambulatory blood pressure,
CI = confidence interval, R = regression coefficient, SE = standard deviation

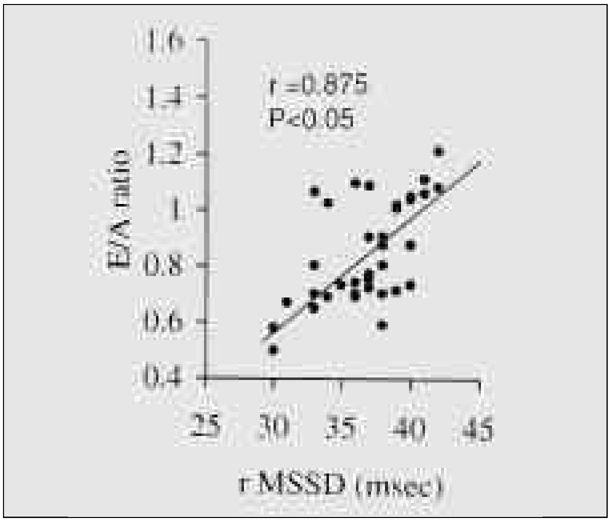

Fig. 3: Correlation between vagal dependent parameter and diastolic dysfunction

DISCUSSION

Heart rate variability has been widely demonstrated to be a reliable measure of autonomic nervous system dysfunction[15,16] although multivariate analysis did not identify it as an independent parameter in predicting the occurrence of left ventricular diastolic dysfunction. This was significantly different in our hypertensive patients with and without diastolic dysfunction, and is in agreement with Pitzalis *et al*[17], as they reported that diastolic dysfunction is related to impaired baroreflex heart rate response and age. Age itself is capable of modifying reflex cardiac activity, since it has been shown that baroreflex sensitivity tends to decrease with aging[18]. Furthermore, from a mathematical point of view, it is also possible that the small changes in the values of E/A ratio at different ages (although hardly significant in clinical terms) may play a greater change in diastolic function than the changes in the presence of reduced baroreflex sensitivity[19]. We found that there was a significant decrease in parameters of vagal dependent time domain heart rate variability in patients with left ventricular diastolic dysfunction in spite of the fact that there was no significant difference with regards to the age between subjects of all the groups studied. Also, our selection of the subject population (subjects with previously unknown and untreated essential hypertension), allowed us to evaluate the role of autonomic nervous system activity in a very early disease phase. An impaired sympathovagal balance during the early phases of hypertension has been revealed by various methods[20,21]. However, these methods generally placed greater emphasis on increased sympathetic tone and only a few evaluated the presence of impaired tonic[22] and reflex vagal activity[23].

Our study suggested that hypertensive patients with diastolic dysfunction show an impaired vagal dependent autonomic function. Pitzalis *et al*[15] found that patients without left ventricular diastolic dysfunction had a partial reflex control of circulation which is completely lost in those with left ventricular diastolic dysfunction.

The cross sectional nature of the present study does not allow us to explore further, the reason for this correlation or, to identify a causal link between the cardiac abnormality and autonomic nervous system activity imbalance. It may be that the two abnormalities are coincidental and different mechanisms are possible. A reduced baroreflex heart rate response and depressed E/A ratio may coexist only at a more advanced disease stage. However, our patients with diastolic dysfunction did not have significantly higher blood pressure values than the other hypertensive patients. Impaired diastolic filling of the left ventricle may increase the firing of the cardio-pulmonary receptors that have a tonic inhibitory effect on arterial baroreflex responsiveness through the sympathetic afference[24,25]. This reduced restraint from the heart might occur at the same time as an increased positive feedback mechanism. In addition, a reduction in the inhibitory effects on sympathetic drive exerted by cardiopulmonary receptors with vagal afferent, as well as resetting arterial baroreceptors, might also favor the progression of sympathetic activation characterizing early hypertension[26,27]. With increasing blood pressure, the balance in the autonomic control mechanisms is shifted towards a preponderance of sympathetic efferent activity in hypertensive and borderline hypertensive patients. No branch of the autonomic nervous system can be viewed as independent of one another; the net effect on the heart will always reflect either activity. Thus reduced vagal inhibition can be expected as the physiologic response to increased sympathetic activation and *vice versa*[28,29].

Limitation of the study

Although we only measured diastolic ventricular filling, we used E/Aratio as an indirect measure of diastolic dysfunction, as it is a generally accepted method. Other methods of analyzing diastolic dysfunction, such as radioisotopic or contrastographic ventriculogarphy, are more accurate, but are also more difficult to obtain.

CONCLUSION

Left ventricle diastolic dysfunction in hypertensive patients without left ventricular hypertrophy is related to reduced parasympathetic activity and this supports the use of non-pharmacologic treatment that increases vagal tone. Further prospective studies are needed to assess the causal nature of the relationship between impaired vagal function and left ventricle functional abnormalities in hypertensive patients.

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