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Correlations between ambulatory blood pressure variables and left ventricular parameters and geometry in patients with mild to moderate hypertension and type 1 diabetes mellitus

Hafif-orta derece hipertansiyon ve tip 1 diabetes mellitus olan hastalarda ambulatuvar kan basıncı değerleri ile sol ventrikül parametreleri ve geometrisi arasındaki ilişkiler

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Background: We investigated the efficiency of ambulatory blood pressure monitoring (ABPM) in detecting early alterations in blood pressure (BP) in young patients with mild to moderate hypertension and type 1 diabetes mellitus (DM), and sought correlations between ABPM values and the type of left ventricular (LV) hypertrophy.

Methods: The study included 23 young adults (19 males, 4 females; mean age 26±5 years) with mild to moderate hypertension and type 1 DM. The patients were evaluated by casual BP measurements and 24-hour ABPM monitoring and were classified as dippers and nondippers according to the nocturnal decrease in BP compared to daytime values (>10% and <10%, respectively). All patients underwent complete two-dimensional transthoracic echocardiography and Doppler evaluations. The results of ABPM were evaluated in relation to left ventricular parameters and geometry. Measurements of BP were compared with a control group consisting of 25 age-matched healthy individuals (21 males, 4 females; mean age 28±4 years).

Results: Eleven patients were classified as dippers and 12 patients as nondippers. There were no significant differences between dipper and nondipper patients with respect to age, gender, body mass index, clinical features, and casual and ABPM recordings. All echocardiographic M-mode variables were similar in both patient groups. Concentric hypertrophy was the most frequent LV geometric pattern in the dipper group (45.5%), followed by normal geometry (27.3%), concentric geometry (18.2%), and eccentric hypertrophy (9.1%). In the nondipper group, the most common pattern was eccentric hypertrophy (41.7%), followed by concentric hypertrophy (25%), concentric remodeling (25%), and normal geometry (8.3%). The incidence of eccentric hypertrophy was significantly higher in nondippers (p=0.017).

Conclusion: Nondipping status revealed by ABPM may have a significant impact on LV geometry and determine the type of LV hypertrophy in hypertensive patients with type 1 DM.

Key words: Blood pressure determination/methods; blood pressure monitoring, ambulatory; diabetes mellitus, type 1; hypertension/complications; hypertrophy, left ventricular/etiology.

Amaç: Hafif-orta derece hipertansiyonlu, tip 1 diabetes mellitusu (DM) olan genç hastalarda, erken kan basıncı değişikliklerinin değerlendirilmesinde ambulatuvar kan basıncı ölçümünün (AKBÖ) etkinliği değerlendirildi ve AKBÖ verileri ile sol ventrikül hipertrofi tipleri arasındaki ilişkiler araştırıldı.

Çalışma planı: Çalışmada hafif-orta derece hipertansiyonu ve tip 1 DM olan 23 genç erişkin hasta (19 erkek, 4 kadın; ort. yaş 26±5) incelendi. Kan basıncı klinik olarak ve 24 saatlik AKBÖ ile ölçüldü. Hastalar, gece kan basıncı gündüz basıncından %10'dan fazla düşmüş ise dipper, %10'dan az düşmüş ise non-dipper olarak sınıflandırıldı. Tüm hastalar ikiboyutlu transtorasik ekokardiyografi ve Doppler ile değerlendirildi ve AKBÖ bulgularının sol ventrikül parametreleri ve geometrisi ile ilişkisi araştırıldı. Ayrıca, hasta grubunun kan basıncı ölçümleri, yaş uyumlu 25 sağlıklı gönüllüden oluşan kontrol grubuyla (21 erkek, 4 kadın; ort. yaş 28±4) karşılaştırıldı.

Bulgular: On bir hastada dipper, 12 hastada non-dipper durum saptandı. İki hasta grubu arasında yaş, cinsiyet, beden kütle indeksi, klinik özellikler, klinik olarak ve AKBÖ ile ölçülmüş kan basınçları açısından anlamlı farklılık bulunmadı. M-mod ekokardiyografik değişkenler dipper ve non-dipper olgularında benzerdi. Dipper olgularında en sık rastlanan LV geometrisi konsantrik hipertrofi (%45.5) idi; bunu normal geometri (%27.3), konsantrik geometri (%18.2) ve eksantrik hipertrofi (%9.1) izlemekteydi. Non-dipper olgularında ise en yaygın tür eksantrik hipertrofi (%41.7) iken, konsantrik hipertrofi, konsantrik remodeling ve normal geometriye sırasıyla %25, %25 ve %8.3 oranlarında rastlandı. Eksantrik hipertrofi sıklığı non-dipper olgularında anlamlı derecede fazla bulundu (p=0.017).

Sonuç: Tip 1 DM'li hipertansif hastalarda AKBÖ ile ortaya konan non-dipper durumu sol ventrikül geometrisini önemli derecede etkileyerek sol ventrikül hipertrofisi tipini belirleyebilir.

Anahtar sözcükler: Kan basıncı tayini, yöntem; kan basıncı izlemesi, ambulatuvar; diabetes mellitus, tip 1; hipertansiyon/komplikasyon; hipertrofi, sol ventrikül/etyoloji.

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Elevated blood pressure (BP) levels are more frequently observed in patients with type 1 diabetes mellitus (DM) than in the general population.[1] The advent of 24-hour ambulatory blood pressure monitoring (ABPM) has made it possible to record blood pressure (BP) during daily activities and during sleep.[2] The typical circadian pattern in normotensive subjects, also present in many patients with essential hypertension, is characterized by an increase in BP during early morning and a nocturnal decrease during sleep; but this pattern may not be observed in some patients in which BP does not decrease at night.[3] Hypertensive patients can be defined as 'dippers' when the nocturnal decrease in BP is >10%, and as 'nondippers' when it is <10%, compared to daytime BP values.[4] Ambulatory blood pressure monitoring is better correlated with target organ damage secondary to hypertension than casual clinical BP reading is and it is more sensitive than occasional BP measurements.[5] It also avoids the problem of elevated readings due to white-coat phenomenon.[6] Studies with this technique are very rare in young patients with type 1 DM and are focused on left ventricular geometry and left ventricular hypertrophy (LVH).[7] In this study, we aimed to investigate the efficiency of ABPM in detecting early alterations in BP in young patients having mild to moderate hypertension and type 1 DM and sought correlations between ABPM values and the type of LVH.

PATIENTS AND METHODS

Study population. The study included 23 adults (19 males, 4 females; mean age 26±5 years) with type 1 DM, who were selected among patients attending the internal medicine service of the Istanbul Naval Hospital. The patient group was compared with a control group consisting of 25 age-matched healthy individuals (21 males, 4 females; mean age 28±4 years). All the subjects were adequately informed about the nature, design, and aim of the study and gave their consent to participate in the study.

Type 1 diabetes mellitus was defined by absolute insulin deficiency and acute onset, and detection of two fasting plasma glucose levels of 126 mg/dl or greater. Hypertension was defined as a mean systolic blood pressure (SBP) ≥140 mmHg and a mean diastolic blood pressure (DBP) ≥90 mmHg.

Exclusion criteria were as follows: casual systolic and diastolic blood pressure readings on three consecutive measurements out of the normal range defined by the Joint National Committee VII report; the presence of any type of cardiac valve disease, absence of sinus rhythm, impaired global or segmental left ventricular (LV) wall motion; presence of retinal changes on fundoscopy, presence of persistent microalbuminuria (on three separate determinations), drug therapy other than insulin, presence of cardiovascular autonomic neuropathy, or presence of any other chronic disease in addition to DM.

All type 1 DM patients were treated with two daily injections of neutral protamine Hagedorn (NPH) insulin and with variable doses of short-acting insulin before meals that were individually adjusted based on self-blood glucose monitoring results.

Control subjects did not receive any chronic medications for the past six months and underwent a detailed clinical and laboratory examination to rule out the presence of any illness or medically abnormal condition.

Blood pressure measurements. Following casual SBP and DBP measurements, 24-hour ABPM was obtained automatically in the nondominant arm by an oscillometric portable monitor (SpaceLabs, Medical Inc, Model: 92512, Redmond WA, USA) every 20 minutes from 07.00 to 22.00 and every 30 minutes from 22.00 to 07.00 hours. Daytime was defined as the time interval between 07.00 to 22.00 hours and nighttime as the time interval between 22.00 to 07.00 hours. Cuff size was selected in accordance with the arm circumference of the subjects. The monitor was programmed to reject heart rates higher than 110 beats/min and lower than 50 beats/min, SBP >260 mmHg and <60 mmHg, and DBP >150 mmHg and <40 mmHg. All the patients and controls were advised to maintain their daily activities and avoid vigorous exercise during ABPM monitoring. All the participants were asked to record the time they went to bed and the time they woke up, exercise periods, daytime naps, meal times and, for the patients, the time of insulin injections and any hypoglycemic episodes. The recordings of the monitor were downloaded to a PC-computer and the ABPM data were analyzed for *(i)* mean heart rate, SBP, and DBP during awake and sleep times, and *(ii)* percentage decline in nocturnal SBP and DBP calculated using the following formula: [(mean daytime BP–mean night-time BP)/mean daytime BP]x100, with normal values being ≥10%.

The ABPM recordings were considered sufficient when at least 80% of all daily measurements were recorded and utilized for diagnosis.

Echocardiographic measurements. All cases underwent a complete two-dimensional transthoracic echocardiographic and Doppler evaluation in the left lateral decubitus position from multiple windows. All evaluations were performed with a Vingmed system V echocardiograph (GE, Horten, Norway) using a 2.5-MHz transducer. Left ventricular dimensions were obtained using the parasternal short-axis view at the

Table 1. Characteristics of patients with type 1 diabetes mellitus (mean±SD)

	Dipper (n=11)	Nondipper (n=12)	*p*
Age (years)	26±5	28±4	0.3
Body mass index (kg/m^2)	27±3	28±4	0.5
Heart rate (beat/min)	75±17	72.7±12.2	0.7
Systolic blood pressure (mmHg)			
Clinical	129±4	131±5	0.3
Daytime	133±11	129±6	0.3
Nighttime	114±8	113±8	0.76
Diastolic blood pressure (mmHg)			
Clinical	71±6	67±8	0.19
Daytime	80±5	77±3	0.1
Nighttime	70±7	69±8	0.75

level of the papillary muscle. M-mode measurements were obtained using the leading-edge technique in accordance with the recommendations previously published.[8] Gain, depth and sector angles were individualized for the best measurement. In each echocardiographic method, M-mode traces were recorded at a speed of 50 mm/sec and the Doppler signals at 100 mm/sec and measurements of at least three cardiac cycles were averaged in sinus rhythm. Doppler parameters (mitral E and A wave, E/A, mitral E wave deceleration time, isovolumetric relaxation time) were used to estimate the diastolic function of the LV. Left ventricular ejection fraction was measured according to the Teichholz's formula, the LV mass according to the Devereux formula, and the LV mass was indexed to body surface area.[9,10] Left ventricular hypertrophy was considered to be present when LV mass index was greater than 125 g/m^2 in men, and 110 g/m^2 in women.[11] Relative wall thickness (RWT) was calculated using the following formula: (LV septal wall thickness+LV posterior wall thickness)/LV internal diameter in diastole. A ratio of >0.43 was considered to show increased RWT, a value previously validated.[12] Left ventricular geometry was based upon LV mass index and RWT as previously reported.[7]

Reproducibility of the echocardiographic outcomes. Intraobserver variability was assessed in 10 patients by repeating the measurements on two occasions under the same basal conditions. To test the interobserver variability, the measurements, which were obtained from the recordings inside the Echo-Pac system provided by the manufacturer were performed offline by a second observer who was blind to the results of the first examination. Variability was calculated as the mean percent error, derived as the difference between the two sets of measurements, divided by the mean value obtained in the observations. Echocardiograms were read offline with an interobserver reproducibility of 90% and the intra- and interobserver variabilities for measurements derived from M-mode analysis and Doppler-derived parameters (mitral E, A) ranged from 1.2% to 7.5%. The averages of these measurements were used for statistical analysis.

Statistical analysis. Selected variables were expressed by standard descriptive statistics and with mean±SD values. Data were processed on the SPSS statistical software, version 11.5. Independent samples t-test (Mann-Whitney U-test when Levene test was significant) and chi-square test were used to compare continuous and categorical variables between groups, respectively. Median analysis using the Kruskal-Wallis test was performed where appropriate. All the echocardiographic variables were compared with SBP and DBP during the day and night and were evaluated by the Pearson correlation analysis. Multiple regression analysis was used to predict the echocardiographic variables among ABPM results. The results were expressed with 95% confidence intervals and a *p* value of less than 0.05 was considered significant.

RESULTS

Of 23 patients with type 1 DM and mild to moderate hypertension, 11 patients were classified as dippers and 12 patients as nondippers. Characteristics of the patients are shown in Table 1. There were no significant differences between the dipper and nondipper patients with respect to age, gender, body mass index (BMI), clinical features, and ABPM recordings for systolic and diastolic blood pressures.

Echocardiographic parameters of dipper and nondipper patients are given in Table 2. Left ventricular internal diameters, LV septal and posterior wall thicknesses, and LVEF were similar in two patient groups. Left atrial diameter (p=0.016) and LV mass index (p=0.036) were significantly higher in nondipper patients. Relative wall thickness was higher in nondippers, though the difference was not statistically signifi-

Table 2. Echocardiographic characteristics of the patients (mean±SD)

	Dipper (n=11)	Nondipper (n=12)	*p*
Left atrium (mm)	32±3	35±6	0.016
Left ventricle ejection fraction (%)	66±7	63±5	0.43
Left ventricle internal diameter in diastole (mm)	48±4	51±6	0.12
Left ventricle internal diameter in systole (mm)	31±5	33±5	0.14
Interventricular septal wall thickness (mm)	10±1	11±3	0.48
Left ventricular posterior wall thickness (mm)	9±1	9±2	0.16
Relative wall thickness	0.40±0.01	0.42±0.05	0.8
Left ventricular mass index (g/m^2)	123±29	148±46	0.036
Mitral E wave (m/sec)	0.74±0.12	0.79±0.17	0.9
Mitral A wave (m/sec)	0.64±0.15	0.66±0.16	0.54
E/A	1.09±0.43	1.14±0.31	0.18
Mitral E wave deceleration time (sec)	194.6±45.3	225.6±48.1	0.06
Isovolumic relaxation time (sec)	136.2±4.38	133.7±15.2	0.68

cant. Right atrial diameter (p=0.048), EF (p=0.01), and BMI (p=0.018) were found as the echocardiographic correlates of clinical SBP. Clinical DBP was correlated only with BMI (p=0.043).

There were no differences between male and female subjects both in the patient and control groups in terms of mean heart rate and casual clinical BPs. The mean SBP and DBP levels during daytime in the patient group were not statistically different from those of the controls. Albeit not significant, nighttime SBP and DBP were higher in the patient group (p>0.05).

Concerning the LV geometric patterns in dipper and nondipper patients (Table 3), concentric hypertrophy was the most frequent LV geometric pattern in the dipper group (45.5%), followed by normal geometry in 27.3%, concentric geometry in 18.2%, and eccentric hypertrophy in 9.1%. In the nondipper group, the most common pattern was eccentric hypertrophy (41.7%), followed by concentric hypertrophy (25%), concentric remodeling (25%), and normal geometry (8.3%). The incidence of eccentric hypertrophy was significantly higher in the nondipper group (41.7% *vs* 9.1%, p=0.017).

Statistical correlations between echocardiographic and ABPM variables are summarized in Table 4. Multiple regression analysis showed that the only predictor of EF among the ABPM variables was nighttime maximal DBP level (ß=–0.033).

DISCUSSION

Our study demonstrated statistically significant correlations between the echocardiographic parameters and ABPM variables in uncomplicated type 1 DM patients. Hypertensive subjects in whom nighttime BP levels do not decrease are more prone to severe target organ damage. In agreement with previous reports, our study showed increased left atrial dimensions and left ventricular mass index in nondipper patients.[3,7,13] Nondippers often have higher clinical or ABPM values compared to dippers associated with a chronic increase in hemodynamic load of the heart and the differences in LV characteristics between dipper and nondipper type 1 DM patients may be due to differences in daytime BP rather than the extent of nocturnal BP dip.[14] In our study, the influence of ABPM profile on echocardiographic parameters was evaluated and although no statistically significant changes were found in terms of LV measurements, LV eccentricity was increased in patients with nondipper hypertension. In untreated patients with normal glucose tolerance, insulin and insulin growth factor-1 are strong independent determinants of LV geometry.[15]

There are some studies reporting that insufficient declines in the extent of nocturnal BP are associated with increased LV hypertrophy, LV diastolic impairment, and deterioration in cardiovascular characteristics.[16-18] To avoid confounding effects on nocturnal BP, we enrolled subjects who never received antihy-

Table 3. Left ventricular geometrical patterns in the patient group

	Dipper (n=11)		Nondipper (n=12)		
LV patterns	n	%	n	%	*p*
Normal geometry	3	27.3	1	8.3	0.04
Eccentric hypertrophy	1	9.1	5	41.7	0.017
Concentric hypertrophy	5	45.5	3	25.0	0.1
Concentric remodeling	2	18.2	3	25.0	0.5

Table 4. Correlations between echocardiographic and ambulatory blood pressure measurement variables

Parameters	ABPM variable	*p*
Aortic root diameter	Maximum nighttime SBP	0.041
	Maximum all DBP	0.01
	Average nighttime DBP	0.035
Left atrium	Average all SBP	0.034
Right atrium	Maximum daytime SBP	0.001
	Average all SBP	0.035
	Average all DBP	0.027
	Minimum all SBP	0.035
	Average daytime SBP	0.004
	Average nighttime DBP	0.038
	Maximum nighttime DBP	0.014
Left ventricle ejection fraction	Average all DBP	–0.013
	Minimum all SBP	0.045
	Maximum daytime DBP	–0.039
	Maximum nighttime SBP	0.025
	Minimum nighttime DBP	–0.008
Interventricular septal wall thickness	Maximum all SBP	0.004
	Maximum all DBP	0.014
	Maximum daytime SBP	0.003
	Maximum daytime DBP	0.011
	Average nighttime DBP	–0.011
	Minimum all DBP	–0.037
Left ventricular posterior wall thickness	Average all DBP	–0.009
	Minimum all DBP	–0.045
End-diastolic volume	Average all SBP	–0.017
	Average all DBP	0.028
	Average nighttime SBP	0.005
	Average nighttime DBP	0.008
	Minimum nighttime SBP	0.011
	Minimum nighttime DBP	0.024
	Maximum nighttime SBP	0.03
End-systolic volume	Maximum all DBP	0.011
	Maximum daytime DBP	–0.025
	Average daytime DBP	0.005
	Average nighttime SBP	0.043
	Minimum nighttime SBP	0.042
Left ventricle internal diameter in diastole	Average all SBP	0.016
	Average all DBP	0.033
	Minimum nighttime SBP	0.009
	Minimum nighttime DBP	0.024
	Average nighttime SBP	0.004
	Average nighttime DBP	0.008
	Maximum nighttime SBP	0.029
Left ventricle internal diameter in systole	Minimum all SBP	0.03
	Minimum all DBP	0.036
	Maximum all SBP	0.025
	Minimum daytime DBP	0.022

pertensive therapy, excluded obese patients (BMI ≥30 kg/m^2), used a high cut-off value for BP, and chose fixed time intervals for daytime (between 7 AM to 10 PM) and nighttime (between 10 PM to 7 AM) recordings. Recently, it has been demonstrated that the correlation between daytime and nighttime ABPM and LV characteristics is not influenced by different definitions of the day and night.[19] We found no differences between dipper and nondipper type 1 DM patients with regard to diameter, thickness, mass and systolic and diastolic functions of the left ventricle. The extent of nocturnal fall in BP was not correlated with any morphofunctional LV parameters and LV diastolic function both in dipper and nondipper groups. Our results related to the nocturnal BP behavior are not correlated with cardiovascular remodeling, but this lack of correlation between the nocturnal BP dip found in a single 24-hour ABPM monitoring and cardiovascular remodeling should be interpreted with caution. Previous reports demonstrated that the reproducibility of nighttime BP decreases is low and dipping and nondipping statuses within the same population are subject to changes within a short time.[20,21] However, compared to clinical BP measurements, 24-hour ABPM monitoring enables more reliable BP measurements and allows to detect and evaluate the differences between daytime and nighttime BPs, which is an important prognostic laboratory finding.

We found no significant differences between dipper and nondipper type 1 DM patients with regard to left ventricular measurements, left ventricular mass index, and both systolic and diastolic functions of the LV. These findings are consistent with the literature.[22]

The influence of hypertension on LV geometry is a complex clinical process, since the remodeling of the LV depends on the hemodynamic conditions of preload, afterload, LV contractility, and the severity and duration of hypertension.[23] Our study confirmed the influence of BP profile on LV geometry, with a significantly higher incidence of eccentric hypertrophy in nondippers Concentric hypertrophy is associated with much higher volume and pressure loads in nondipper hypertensive patients and eccentric LVH in nondippers may be due to increased overall load.

Study limitations. Most of our subjects were young males; with enrollment of more females and older subjects, 24-hour ABPM would increase statistical significance. Another limitation was that we classified subjects on the basis of a nocturnal BP pattern obtained from a single 24-hour ABPM monitoring. Evaluation of the LV diastolic function was only based on mitral inflow Doppler recordings, which cannot rule out pseudonormalization of the LV diastolic function. Finally, the cross-sectional instead of longitudinal design may also present a limitation.

In conclusion, the results of the present study suggest that ABPM, which detects early alterations in BP in mild to moderate hypertensive type 1 DM young individuals, is a sensitive technique compared to casual clinical BP measurement. In nondippers, ABPM values that do not show sufficient decreases during nighttime have a great impact on LV geometry and may determine the type of LVH. While concentric LVH is more common among dipper hypertensive patients with type 1 DM, eccentric LVH is more common among nondippers.

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