

Echocardiographic Correlates of Blood Pressure in Normoalbuminuric Prehypertensive Adults with Type 1 Diabetes Mellitus: An Ambulatory Blood Pressure Monitoring Study

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Citation

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Abstract

Aim: To investigate the relation between echocardiographic parameters and 24-hour ambulatory blood pressure monitoring (ABPM) in normoalbuminuric pre-hypertensive adults with type 1 diabetes mellitus (T1DM) without clinical evidence of nephropathy or cardiovascular autonomic neuropathy.

Methods: Adult patients who were diagnosed as T1DM and pre-hypertensive were categorized as dippers and non-dippers on the basis of 24-hour ambulatory blood pressure measurement and their echocardiographic parameters were compared. An oscillometric portable monitor took twenty-four hour blood pressure measurements automatically. A comprehensive echocardiographic evaluation was performed focusing on the left ventricular (LV) dimensions, LV mass index, relative wall thickness (RWT), left atrial (LA) dimension and LV ejection fraction.

Results: Of the 23 T1DM pre-hypertensive patients, 11 were categorized as dippers and 12 as nondippers. There were no differences between the dipper and the nondipper T1DM pre-hypertensive patients with respect to age, gender, body mass index, clinical and ABPM for average day-time systolic and diastolic blood pressure levels. Left ventricular (LV) internal diameters, LV septal and posterior wall thicknesses, LV ejection fraction (LVEF) were all similar in both groups. Left atrial diameter and LV mass index were found higher in the nondipper T1DM patients. There was no significant difference between two groups in terms of RWT although there was a trend for it to be higher in the nondipper group.

Conclusion: Among prehypertensive T1DM patients evaluated by ambulatory BP monitoring, nondippers had higher LV mass index and left atrial dimensions compared with dippers. This may presage worse long term cardiovascular outcomes in nondippers.

INTRODUCTION

The advent of 24-hour ambulatory blood pressure (ABPM) monitoring has made it possible to record blood pressure (BP) during daily activities and during sleep (1). The typical circadian pattern in normotensive subjects, also preserved in many essential hypertensive patients, is characterized by an increase of BP during early morning and a nocturnal decrease during sleep; but this may not be seen in a certain groups, in which the BP does not decrease at night (2). The hypertensive patients can be defined as 'dippers' when the average nocturnal BP decreases by >10% of average

daytime BP and as 'nondipper' the decrease is <10% of daytime BP (3, 4). Elevated blood pressure levels are more frequently observed in patients with Type 1 diabetes mellitus (T1DM) than in the general population (5,6,7). This association conveys a significant increase in morbidity and mortality due to atherosclerosis, microvascular complications such as retinopathy, nephropathy and premature cardiovascular disease (6, 7). Ambulatory blood pressure monitoring (ABPM) is better correlated with target organ damage from hypertension (HT) than clinic blood pressure readings (8, 9). The correlation between ABPM and urinary albumin excretion rate (UAER) in T1DM has been

found to be stronger than the correlation between clinic blood pressure (BP) and UAER ($_{10}$).

Echocardiographic studies have enhanced our understanding of the etiology of hypertensive left ventricular (LV) hypertrophy and dysfunction in epidemiologic studies over the past two decades. Echocardiography provides visualization of structural or functional abnormalities, which appear long before the detection by clinical means.

The 2003 European Society of Cardiology guidelines define blood pressure between 130/85 and 139/89 mmHg as “high normal”, while the 2003 Joint National Committee VII guidelines introduced a new category of “prehypertension” (BP between 120/80 and 139/89 mmHg). Evidence is available that high normal or pre hypertensive blood pressure is associated with an adverse risk profile and an increased risk of cardiovascular events.

To the best of our knowledge the echocardiographic correlates of ABPM has never been reported in uncomplicated prehypertensive T1DM patients. The aim of this study was to investigate the relation between the echocardiographic parameters with ABPM in normoalbuminuric prehypertensive T1DM adults without clinical evidence of or cardiovascular autonomic neuropathy.

RESEARCH DESIGN AND METHODS

STUDY POPULATION

Patients attending the internal Medicine service of the Istanbul Naval Hospital, who were diagnosed as T1DM according to the American Diabetes Association with clinic BP recording in the prehypertensive range and were also categorized according to their dipping status were selected for the study. Informed consent was obtained from all participants. Exclusion criteria were: Previous treatment with antihypertensives, body mass index ≥ 30 Kg/m², presence of any type of cardiac valve disease, not having sinus rhythm, impaired global or segmental LV wall motion, presence of retinal changes on fundoscopy, presence of persistent microalbuminuria (three determinations), use of drugs other than insulin, presence of cardiovascular autonomic neuropathy, or the presence of any other chronic disease in addition to DM. All T1DM patients were treated with two injections a day of neutral protamine Hagedorn (NPH) insulin with variable doses of short-acting insulin before meals that were individually adjusted based on self-blood glucose monitoring results. Research design and methods

BLOOD PRESSURE MEASUREMENTS

Twenty-four hour ABPM measurements were taken automatically in the non-dominant arm by an oscillometric portable monitor (SpaceLabs, Medical Inc, Model: 92512, Redmond WA) every 20 minutes from 07.00 to 22.00 and every 30 minutes from 22.00 to 07.00 h. Day time was defined between 07.00 to 22.00 and night time was defined between 22.00 to 07.00 h. All the cuff sizes were selected according to the arm circumference of the subjects. The monitor was programmed to reject heart rate (HR) values over 110 and lower 50 beats/min (bpm), and SBP>260 and <60 mmHg and DBP >150 and <40 mmHg. All the patients were advised to maintain their daily activities and avoid vigorous exercise during the ABPM. The T1DM patients were recorded the time they went to bed and the time they awoke, exercise periods, if they napped during the day, the time of their meals and, for the patients, the time of insulin injections and any hypoglycemic episodes. Then the recordings of the monitor were downloaded to a PC-compatible computer and the ABPM analyzed for;

1. Mean HR, average SBP, average DBP during awake or sleep over the 24-h period,
2. Percentage nocturnal decline of SBP and DBP calculated as: [(mean daytime BP-mean night time BP)/mean day-time BP] x100 (normal $\geq 10\%$).

The ABPM recordings were considered enough and accepted for the diagnosis when at least 80% of all day measurements were recorded and utilized for the diagnosis. Normal considered subjects have $\geq 50\%$ of BP measurements within the normal range. Pre-hypertension was defined as the systolic blood pressure between 120/139 and the diastolic between 80/89 mmHg ($_{11}$). The average day time measured by ABPM was taken into account while defining the study population, uncomplicated prehypertensive type 1 DM patients group.

BIOCHEMICAL MEASUREMENTS

The routine biochemical measurements were fasting and postprandial blood glucose levels, plasma triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol levels were all compared statistically with ABPM outcomes Fasting blood glucose level for the diagnosis of diabetes mellitus was considered as 110 mg/dl (6.1 mmol/L) ($_{12, 13}$). The definition for DM, was in accordance with the report of the committee of the Japan Diabetes Society for classification

and diagnostic criteria of DM; which fasting plasma glucose is 7.0 mmol/L (126 mg/dl) or higher and/or plasma glucose 2 hour after 75 gr of glucose load as 11.1 mmol/L (200 mg/dl) or higher (₁₃). Type I status was diagnosed according to the World Health Organization and American Diabetes Association criteria (_{14, 15})

ECHOCARDIOGRAPHIC MEASUREMENTS

All cases underwent a complete two-dimensional transthoracic echocardiographic and Doppler study in the left lateral decubitus position from multiple windows. All studies were performed with Vingmed system V (GE, Horten, NORWAY) echocardiograph by using a 2.5 MHz transducer. Left ventricular dimensions were obtained using the parasternal short-axis view at the level of the papillary muscle. M-mode measurements were obtained using the leading-edge technique in accordance with recommendations as previously described (₁₆). Gain, depth and sector angles were individualized for 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 outcomes (Mitral E and A wave, E/A, mitral E wave deceleration time, isovolumetric relaxation time) were utilized to calculate the diastolic function of the LV. Left ventricular ejection fraction was measured according to Teicholz formula and the LV mass according to Devereux formula and the LV mass were indexed to body surface area (_{17, 18}). LV hypertrophy was considered present when LV mass index was >125 g/m² in men and 110 g/m² in women (_{18, 19, 20}). Relative wall thickness (RWT) was calculated as (LV Septal wall thickness+LV Posterior wall thickness)/LV internal diameter in diastole. Increased RWT was considered when this ratio is >0.43, which this value has been validated previously (₁₉)

REPRODUCIBILITY OF THE ECHOCARDIOGRAPHIC OUTCOMES

Intraobserver variability was assessed in ten 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 provided by the same company were performed offline by a second observer who was unaware of the results of the first examination. Variability was calculated as mean percent error, derived as the difference between the two sets of measurements, divided by the mean of the observations.

Echocardiograms were read offline with an interobserver reproducibility of 90% and the intra and interobserver variability for measurements derived from M-mode analysis and Doppler-derived parameters (mitral E, A) ranged from 1.2%-7.5%, respectively. The mathematical average of these measurements was used for statistical analysis.

DETERMINATION FOR THE AUTONOMIC NEUROPATHY AND RETINOPATHY

Autonomic nervous system function was evaluated by;

1. Heart rate variation: This was assessed from the measurements of R-R intervals during deep breathing and expressed as the mean of three measurements of HR at maximum inspiration and at full expiration. Normal is >15 bpm, borderline 11-14 bpm, and abnormal ≤10 bpm.
2. Increase in DBP during isometric exercise with a dynamometer (handgrip test) mean of three measurements was taken (₂₁). Normal is ≥16 mmHg, borderline 11-15 mmHg and abnormal is ≤10 mmHg.

At least one abnormal result or one borderline result in each of the two tests was accepted as presence of autonomic dysfunction.

An ophthalmologist performed retinal examination with fundus photography in all subjects with T1DM. Retinal alterations were described as previously reported (₂₂).

STATISTICAL ANALYSIS

Values of selected variables were summarized by standard descriptive statistics and expressed as mean ± SD. The statistical software SPSS, version 11.5 was utilized for all data processing. Independent-Samples T test (Mann-Whitney U test when Levene test is significant) and chi-square tests were used to compare continuous and categorical variables between groups, respectively. Median analysis was performed where appropriate using the Kruskal-Wallis test. All the echocardiographic variables were compared with HR, SBP, and DBP during the day and night both for T1DM and control groups were evaluated by Pearson correlation analysis. All tests considered 95% confidence interval and the statistical significance were defined by a p value < 0.05.

RESULTS

There were 23 patients with T1DM and prehypertension. 11 T1DM patients were categorized as dipper prehypertensive and 12 T1DM patients were as nondipper hypertensive. Characteristics of T1DM dipper and nondipper prehypertensive patients are shown in Table 1. There were no difference between the dipper and the nondipper T1DM prehypertensive patients with respect to age, gender, body mass index (BMI), clinical and ABPM for SBP and DBP levels. Echocardiographic outcomes were given in Table 2 for dipper and nondipper groups of pre-hypertensive T1DM patients.

Figure 1

Table 1: Characteristics of type 1 diabetes mellitus patients

Parameters	Dipper (n:11)	Nondipper (n:12)	p
Age (Year)	26±5	28±4	0.3
Male (%)	82(19)	83(21)	0.31
BMI (kg/m ²)	27±3	28±4	0.5
Heart Rate (Rate/minute)	75±17	72.7±12.2	0.7
Clinical SBP (mmHg)	129±4	131±5	0.3
Clinical DBP (mmHg)	71±6	67±8	0.19
Daytime SBP (mmHg)	133±11	129±6	0.3
Daytime DBP (mmHg)	80±5	77±3	0.1
Nighttime SBP (mmHg)	114±8	113±8	0.76
Nighttime DBP (mmHg)	70±7	69±8	0.75

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Figure 2

Table 2: Echocardiographic characteristics of type 1 diabetes mellitus patients

Parameters	Dipper	Nondipper	P
LA (mm)	32±3	35±6	0.016
EF (%)	66±7	63±5	0.43
LVIDD (mm)	48±4	51±6	0.12
LVIDS (mm)	31±5	33±5	0.14
IVS (mm)	10±1	11±3	0.48
LVPW (mm)	9±1	9±2	0.16
RWT	0.40±0.01	0.42±0.05	0.8
LVMI(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
IVRT (sec)	136.2±4.38	133.7±15.2	0.68

LA: Left atrium, EF: Left ventricle ejection fraction, LVIDD: Left ventricle internal diameter in diastole, LVIDS: Left ventricle internal diameter in systole, IVS: Interventricular septal wall thickness, LVPW: Left ventricular posterior wall thickness, LVMI: Left ventricular mass index, RWT: Relative wall thickness, IVRT: Isovolumic relaxation time.

Left ventricular internal diameters, LV septal and posterior wall thicknesses, LVEF were all similar in the dipper as well

as the nondipper T1DM pre-hypertensive groups.

Left atrial diameter and LV mass index were found higher in the nondipper T1DM pre-hypertensive patients. There was no statistical difference between the two groups by means of RWT but it was found higher in the nondipper group as compared to the dipper T1DM pre-hypertensives. (0.40 ± 0.01 vs 0.42 ± 0.05 , $p: 0.08$).

DISCUSSION

Our study has clearly shown the statistical correlations between the echocardiographic and ABPM measurements in uncomplicated pre-hypertensive T1DM patients according to their dipping status. Pre-hypertensive subjects are more prone to develop target organ damage whose nighttime BP does not drop. As previously reported our study has confirmed that left atrial dimension and LV mass index was found higher in the nondipper T1DM patients as compared with the dipper T1DM patients (_{2, 23}). Although the RWT did not differ statistically, nondipper T1DM pre-hypertensives tend to have thicker LV, which may suggest early cardiac involvement.

The nondippers often had higher clinic or ABPM BP compared with dippers attributable, which may lead to a chronic increase in hemodynamic load of the heart. The LV characteristics between dipper and nondipper T1DM patients could be due to differences in daytime BP rather than in the extent of nocturnal BP dip (₂₄). In our study, the influence of ABPM profile on echocardiographic parameters were demonstrated an increased eccentricity in patients with nondipper hypertension compared to dipper hypertension, which was consistent with the literature (₂₅). There have been some reports of nondipper hypertensives having greater LV hypertrophy and diastolic dysfunction compared dipper hypertensives (_{12, 26, 27}).

We chose to enroll subjects who were never treated with antihypertensive therapy, also excluding obese ($\text{BMI} \geq 30$ kg/m²) patients and utilized a high cut-off BP value and chose a fixed time interval for the day (between 7 A.M. to 10 P.M.) and night (between 10 P.M. to 7 A.M.) time definition while others used different definitions (narrow time spans, methods related to bedtime and rising, or sleeping and waking determined from diary or position recorder). Recently it has been demonstrated that the correlation between LV characteristics with day and nighttime ABPM does not vary with different definitions of day and night (₂₈). By using these criteria, we have found no differences

between dipper and nondipper T1DM patients with regard to LV diameter, LV thicknesses, LV mass and LV systolic and diastolic function. The extent of the nocturnal BP fall did not correlate with any morphofunctional parameter of the LV measurements and LV diastolic function in both dipper and nondipper T1DM patients. Our results regarding with the nocturnal BP behavior is not statistically relevant to cardiovascular remodeling, because dipping and nondipping status can change in a short time interval at the same population (29,30,31). However, comparing the clinical BP measurement with 24-hour ABPM, the latter enables us more reliable BP measurements as well as allows detecting and measuring the differences between day and night time BP, which is an important prognostic laboratory finding.

The reduced nocturnal decline in BP in T1DM pre-hypertensive patients in our study, which has also been reported previously, may be attributable to incipient nephropathy or be a sign of early autonomic neuropathy (32). Twenty-four hour ABPM is more sensitive than occasional BP measurement in detecting early increase in BP load in pre-hypertensive T1DM patients without any cardiac autonomic dysfunction. Also 24-hour ABPM avoids the problem of elevated readings regarding with the 'white coat' phenomenon and allows the detection of abnormalities of the BP circadian rhythm, which are associated with a greater degree of target organ damage in pre-hypertensive T1DM patients (32,33,34,35,36,37).

Left atrial diameter and LV mass index were found higher in the nondipper T1DM patients. We also have found that there was no statistical difference between dipper and nondipper groups by means of RWT, there was a trend for higher RWT in the nondipper group.

Our study suggests that among prehypertensive Type 1 diabetics undergoing ambulatory BP monitoring, nondippers have higher mean LA dimensions and LV mass index compared to dippers. This may indicate early cardiac involvement in nondippers may constitute a subgroup where more diligent efforts to treat the abnormality and/or prevent progression to hypertension may be indicated.

STUDY LIMITATIONS

Most of our subjects are young male that we couldn't perform 24-hour ABPM in sufficient number of female and older subjects. Another limitation is classifying individuals on the basis of a nocturnal BP pattern, which were evaluated with a single 24-hour BP monitoring. Evaluation of the LV

diastolic function was only based from the mitral inflow Doppler recordings, which cannot rule out pseudonormalization for the LV diastolic function evaluation. The design of this study is a cross-sectional rather than a longitudinal.

Exclusion of high heart rates makes us hard to diagnose autonomic neuropathy, which is a phenomenon occur during the course of T1DM reported previously (27).

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