Blood pressure pattern and heart rate variability in normotensive patients with type 2 Diabetes Mellitus

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Abstract

Background: ambulatory blood pressure monitoring (ABPM) has shown that almost one third of presumed normotensive patients with type 2 diabetes mellitus have instead masked hypertension. There is also a relationship between cardiovascular autonomic neuropathy and blood pressure patterns even in normotensive patients with diabetes mellitus. The aim of the present study was to analyze the blood pressure patterns in type 2 diabetic patients without any history of hypertension and to establish the connection between heart rate variability parameters, ultrasound parameters and ABPM parameters.

Material and methods: Fifty-two subjects with type 2 diabetes, aged 59 (±6), were consecutively recruited at the internal medicine department of the County Hospital from Cluj. Informed consent was obtained from all participants. A control group of 47 subjects, age and sex matched, was also analyzed.

Results: More than half of the patients had a non-dipping pattern, despite the fact that they are considered normotensive patients. Heart rate variability parameters are lower in the non-dipping group, but the difference is significant only for vagal activity. Left ventricle is thicker in non-dipping group. The mean age of the non-dipping group (61.23 ±2.02 years) was significantly higher than the age of the dipping group (55.11 ±3.88 years) (p<0.01).

Discussions and conclusion: we found a great number of patients with diabetes mellitus and with altered patterns of blood pressure, even if they were previously considered as normotensive. The non-dipping pattern is associated with abnormal values of heart rate variability parameters and with thicker left ventricle walls, but the differences are not always statistical significant. It is important to closely monitorize the patients with diabetes mellitus even if they have normal office blood pressure determinations, mainly those with a history of more than 5 years of the disease.

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Ambulatory blood pressure monitoring (ABPM) has shown that almost one third of presumed normotensive patients with type 2 diabetes mellitus have instead masked hypertension [1]. The thickness of inter-ventricular septum and posterior wall were significantly increased in these patients, as compared with confirmed normotensive patients. ABPM is important for identifying these high-risk patient groups and ensuring early interventions. Also, left ventricle hypertrophy parameters are greater among hypertensive patients with diabetes mellitus, as they had a higher rate of non-dipping pattern. Another study showed that only night-time systolic blood pressure (BP) is associated with cardiovascular and cerebro-vascular morbidity and mortality, in hypertensive patients with type 2 diabetes mellitus [2]. Pulse pressure is another parameter which proved itself very useful in mortality prediction, but also when measured by ABPM. [3].

ABPM allows the evaluation of some important BP parameters such as the 24-h general mean, daytime and nighttime systolic and diastolic BP means, BP loads and the absence of nocturnal drop of BP (dipping), as well as the identification of white-coat and masked hypertension. [4]

On the other hand, there is a relationship between cardiovascular autonomic neuropathy and blood pressure patterns even in normotensive patients with diabetes mellitus, autonomic imbalance being associated with abnormal patterns of 24-hours blood pressure measurements (non-dipping pattern, higher values of nocturnal blood pressure) [5-8].

The aim of the present study was to analyze the blood pressure patterns in type 2 diabetic patients without any history of hypertension and to establish the connection between heart rate variability parameters (as the expression of autonomic balance), ultrasound parameters (accounting for left ventricle dimensions) and ABPM parameters.
Material and methods

Fifty-two subjects with type 2 diabetes, aged 59 (±6), were consecutively recruited at the internal medicine department of the County Hospital from Cluj. Informed consent was obtained from all participants. A control group of 47 subjects, age and sex matched, was also analyzed.

Inclusion criteria were: age under 65 years and values of casual BP within normal range (<140/90 mm Hg) without antihypertensive treatment.

Exclusion criteria were: impaired renal function, clinically significant abnormality of hepatic, haemopoietic, respiratory or endocrine function, history and/or evidence of cerebrovascular or coronary heart disease, arrhythmias, antihypertensive treatment and use of any other medication affecting cardiovascular or autonomic nervous function.

BP monitoring

Non-invasive 24-h ambulatory BP monitoring (ABPM) was performed using an oscillometric recorder. The device was programmed to measure BP every 20 minutes on daytime and every 30 minutes on nighttime, for 24 h. Patients were hospitalized and were following the hospital routines, which allowed a better standardization of recording conditions. Only the 24-h recordings that contained a percentage of measurement errors under 30% were accepted as valid. Systolic (SBP) and diastolic BP (DBP) measurements were averaged for the day and the night periods, according to reported time of waking up and going to bed (6 a.m. and 10 p.m., respectively). The percentage change from day to night in BP was calculated as: (day BP–night BP) 100/day BP. Non-dipper pattern is defined as a reduction with less than 10% from the daytime mean, or a day/night ratio over 0.9.

Blood pressure was also measured with a classical sphyngomanometer at two different moments, in the morning (awake BP, at 6 a.m.) and in the evening (asleep BP, at 10 p.m.), at the
same hour for all the patients. We created two sub groups (dippers and non-dippers) and we compared the results.

Heart rate variability

HRV was measured using a 24-hour ECG monitoring system (Holter Digital recorder AsPEKT 812) in all subjects during normal daily activity. Time domain parameters used are: SDNN expressed in milliseconds (ms) accounts for standard deviation of all NN intervals. SDANN expressed in ms accounts for standard deviation of the averages of NN intervals in all 5 min segments of the entire recording. pNN50 % is the number of pairs of adjacent NN intervals divided by the total number of all NN intervals. Frequency domain parameters used are: low frequency and high frequency components of spectral analysis expressed in squared milliseconds (ms² or normalized units).

Echocardiography

Standard two dimensional and Doppler echocardiography was performed in all the subjects. The standard views and the measurements of heart chambers were performed according to American Society of Echocardiography recommendations [9] and the same clinician performed all the examinations. The following parameters were obtained for the study: left ventricular diastolic diameter, left ventricular systolic diameter, inter-ventricular septum thickness (IVST) and posterior wall thickness (PWT), expressed in millimeters.

Statistical analysis

Continuous variables were expressed as mean (SD). Differences were tested for significance by unpaired Student’s t test. Upper and lower 95% confidence limits for each variable were calculated from the two tails of the Student’s t test distribution. We compared the results among the study group and with control group. A p value <0.05 was considered
significant. Pearson correlation coefficients were used to explore linear relationships between the study variables. Statistics were performed with SPSS for Windows, version 10.0.

**Results**

General characteristics of the DM patients are shown in table 1.

**Place for Table 1**

Characteristics of the DM patients between the two subgroups, dippers and non-dippers, are shown in table 2.

**Place for Table 2**

Heart rate variability parameters in dippers and non-dippers are shown in table 3.

**Place for Table 3**

More than half of the patients had a non-dipping pattern, despite the fact that they are considered normotensive patients. The mean values obtained with ABPM are higher in non-dipping group, but the differences are not statistically significant; Δ day - night (%) parameter is significantly affected in non-dippers, but regarding only systolic blood pressure. The awake systolic BP was not significantly different between the dipping and the non-dipping groups (p>0.05; table 2), but the awake diastolic BP in the non-dipping group was lower (p=0.03). The asleep systolic BP and diastolic BP were, as expected, both significantly higher in the non-dipping group (p<0.05). The mean age of the non-dipping group (61.23 ±2.02 years) was significantly higher than the age of the dipping group (55.11 ±3.88 years) (p<0.01) (table 2). Weight, body mass index (BMI) and duration of diabetes were also significantly higher in non-dippers (table 2). Glycemic control and diabetes treatment did not differ significantly between the two groups. The total cholesterol concentration was significantly lower in the non-dipping group concentrations.
**Heart rate variability parameters**

There are differences between the two groups regarding HRV parameters, but only for HF and HF n.u. (as the expression of parasympathetic activity) the differences are statistical significant (table 3). There are strong positive correlations between HF values and Δ day - night (%) parameter (only regarding systolic blood pressure) \((r = 0.54)\) and also between HF and HF n.u. and office diastolic blood pressure measured in the evening \((r = 0.60\) and \(0.58\), respectively).

**Ultrasound parameters**

Left ventricular diameters, inter-ventricular septum thickness and end-diastolic posterior wall thickness are greater among patients with type 2 diabetes and non-dipper patterns of blood pressure, but the differences are not statistically significant (table 2).

**Discussions**

Only few data are available on the factors involved in 24-h BP pattern in type 2 diabetic patients, [10, 11, 12, 13] and generally include both normotensive and hypertensive patients. A conclusive link between abnormal circadian rhythm of BP and autonomic neuropathy has not been established yet. Lower HRV parameters were found to be related to mean 24-h SBP and our study supports this connection. Recent data tend to indicate a significant relationship between hypertension and autonomic neuropathy in diabetes both in the sense of a correlation of SBP to autonomic test impairment [14, 15] and in the suggestion of hypertension as a risk factor for peripheral neuropathy [16, 17].

HF and HF n.u. (which account for vagal activity) were in fact the only parameters of HRV which significantly correlates with non-dipping pattern in our study, although all the HRV parameters were lower in non-dipping group, suggesting impaired cardiovascular autonomic functioning.
Our study has considered only normotensive type 2 diabetic patients, most of them (over 50%) showing a non-dipping nocturnal pattern of BP, especially in those with abnormal HRV. The differences between groups involved both SBP and DBP, but in slightly different manners.

The decision to exclude type 2 diabetic patients with hypertension or other cardiovascular disease was based on the need to avoid factors potentially interfering with autonomic function assessment such as hypertensive drugs or diseases affecting cardiovascular system [18]. Thus, we cannot exclude that with the occurrence of cardiovascular disease, further factors beyond autonomic function could affect BP circadian pattern in type 2 diabetic patients, as stated in other studies. [19]

Qualitative and quantitative differences in daily activities or nocturnal sleep can affect BP monitoring. In this study day and night periods were fixed intervals. ABPM was performed when patients were hospitalized, thus allowing a better standardization of recording conditions in particular with regard to physical activity [19].

The present study has demonstrated that non-dipping of nocturnal blood pressure in people with type 2 diabetes was strongly associated with increasing age and with a longer disease duration. Other studies (by Nakano et al. [20] and Sturrock et al. [21]) have shown an association between increasing age and non-dipping status in people with diabetes. Of course, determination of the true duration of diabetes is difficult, as type 2 diabetes often remains subclinical for many years before the diagnosis.

In a previous study, glycemic control correlated with non-dipping, with higher levels of glycemic control observed in non-dippers [22]. In our study, also the glycemic control was associated with non-dipping pattern, but the difference was not statistically significant.

The total cholesterol level was significantly lower in the non-dipping cohort, but triglyceride and high-density lipoprotein levels were not significantly different between the two
groups. This may reflect the higher incidence of the use of statins in the non-dippers. It was also apparent that non-dipping status was associated with increased body weight and BMI.

Non-dipping of nocturnal blood pressure is of prognostic importance. Evidence suggests that a blunted reduction in the normal nocturnal blood pressure fall may play a pivotal role in the development of target organ damage [23, 24, 25] such as left ventricular hypertrophy, which is a powerful predictor of cardiovascular mortality [26, 27]. Also in our study, non-dipping pattern was associated with higher values of left ventricle diameters and wall thickness, but the differences between those and dipping pattern were not statistically significant.

**Conclusions:**

Blood pressure determination by ABPM is capable of identifying more adequately stratifying patients at risk for developing chronic complications of DM, and has become an indispensable instrument for BP measurement in these patients. It is of a great importance the fact that blood pressure patterns are modified even in normotensive patients especially associated with heart rate variability changes.
References


