

Study of beta-blocker treatment effects in diabetic hypertensive patients with different dipper profiles: is there a link with the prognosis?

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Abstract

Ambulatory blood pressure monitoring (ABPM) in diabetic patients (DM) with high blood pressure (HBP) is useful to show the dipping status and effectiveness of hypertensive treatment. 163 consecutive DM type 2 patients with HBP treated with beta-blockers (β B), angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers (CCB), angiotensin receptor blockers (ARB) and diuretics, were subjected to 24-hour ABPM. We assessed the BP (blood pressure) circadian variation, the variability of resting mean heart rate (MHR), and the correlations with various drug combinations. There were 55 dippers (33.75%), 79 non-dippers (48.45%), 22 reverse dippers (12.50%) and 7 extreme-dippers (4.30%). Dippers had lower medium arterial pressure (MAP) – 88.45 mmHg and MHR - 71.35 beats per minute (bpm) compared with 91.63 mmHg and 74.27 bpm found in non-dippers ($p=0.006$; $p=0.05$). Dippers was treated with ACEI (65.46%), ARB (18.19%), CCB (40.00%), combinations of these (10.91%), β B (60.00%), and diuretics (74.55%). Non-dippers treated with β B (68.36%) had lower 24-hour MHR - 72.46 bpm vs. 78.20 bpm ($p=0.017$) of those without β B, night MHR - 73.90 bpm vs. 82.02 bpm ($p=0.0004$) and day MHR - 74.61 bpm vs. 81.76 bpm ($p=0.005$). The non-dipper diabetics had increased MAP and MHR compared to dippers, but non-dippers treated with beta-blockers had significantly low MHR and MAP than those without BB. Treatment of BP with beta-blockers does not significantly influence lowering MHR and MAP in dippers profile. The effect of reducing MHR on the non-dipper profile could be beneficial for the prognosis of these patients.

Keywords: Beta-blockers, non-dipper, ambulatory blood pressure monitoring, mean heart rate, hypertension.

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Introduction

The major advantages of ambulatory blood pressure monitoring (ABPM) are that it can identify white-

coat and masked hypertension, measurement in real-life settings, nocturnal readings, stronger prognostic evidence, and give abundant information from a single measurement session [1].

In a recent study, the results showed that 24-hour ABPM is a stronger prognostic tool and predicts mortality with more accuracy than clinical measurement [2].

The prevalence of high blood pressure (HBP) among patients with diabetes mellitus (DM) was twice that of the general U.S. adult population in a 2005-2008 study (57.3% versus 28.6%). Also, the prevalence of abnormalities in the circadian pattern was remarkably high in a series of diabetic hypertensives [3, 4].

It is well known that cardiovascular events occur more frequently in the morning as blood pressure (BP) levels have been shown to increase during the period from night to early morning. In recent years, clinical research using home BP monitoring has clarified that morning BP and BP surge are more closely related to the cardiovascular risk than clinical BP [5].

An extremely important application of ABPM in hypertension is related to its ability to evaluate the changes in BP induced by antihypertensive therapy with greater accuracy and in a much more detailed fashion than clinic BP measurements, offering information on the actual 24-hour BP coverage by a given antihypertensive regimen [6].

Non-dippers with diminished nocturnal blood pressure (BP) and a riser's pattern with higher nocturnal than daytime BP are known to have advanced organ damage of the brain, heart, and kidney and have a poorer prognosis compared with normal dippers [5].

Non-dipping is frequent in diabetes; in those patients, ABPM should be performed at least once for the better risk stratification of hypertension [7, 8].

Our study investigates the circadian BP variation in hypertensive type 2 DM patients and the effects of hypertension medication. A second point was assessing the resting 24-hour heart rate (HR) variability and the correlation with antihypertensive treatment.

Material and Methods

Ethics statement

This study was approved by the Ethics Committee of the Emergency County Hospital Baia Mare, Romania. Written informed consent was obtained from all enrolled patients. Patients' records/information were anonymized and de-identified before the analysis.

Study population

One hundred sixty-three consecutive hypertensive type 2 DM patients with ambulatory follow-up at the Diabetes and Nutrition Ward of the Emergency County Hospital Baia Mare, Romania, were subjected to 24-hour ABPM from February 2018 to January 2019.

Data collection

General data, weight, height, waist circumference, and body mass index (BMI) details were collected. Before installing the ABPM, BP values were standardly measured as recommended by the 2013 European Society of Cardiology Hypertension Guidelines [8]. The medical history was recorded for each patient, especially HBP and cardiovascular diseases (CVD), dyslipidemia, diabetes mellitus type, and the recording of its complications: polyneuropathy, nephropathy, peripheral arterial disease (PAD). Each patient underwent electrocardiography (ECG) to show any possible left ventricular hypertrophy (LVH) and possible ischemic or rhythm disorders. The results of standard blood tests were recorded: glucose, urea, creatinine, total cholesterol, LDL and HDL-cholesterol, triglycerides, uric acid, glycated hemoglobin (HbA1C). A spot urine sample was collected in the morning and checked for the presence of albuminuria and urinary albumin/creatinine ratio (ACR). Microalbuminuria was defined as an ACR from 30 to 299 mg/g. For each patient, the antihypertensive and antidiabetic treatment was recorded: beta-blockers (β B), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), diuretics (Diur), alpha-blockers (AB), as well as combinations of the above.

ABPM

In this study, a validated BTL-08 ABPM II machine was used. The median values of the systolic and diastolic BP with the differences given by the circadian cycles and also the resting HR for each patient was recorded and analyzed: Mean Sys (the systolic mean) and Mean Dias (the diastolic mean), Mean HR – MHR (the heart rate mean), MAP (the mean arterial pressure) and PP (the pulse pressure). To obtain reliable data of patient's BP and HR variations, the ABP Monitor was worn for 24 hours, and BP recordings were made at intervals of 0.5 hours from 06.00 to 22.00 and at one-hour from 22.00 hrs to 06.00 hrs. Dippers were defined as those individuals with a mean 24-hr ambulatory BP, which dropped >10%. Non-dippers are those individuals with a

drop of 0-9%. Reverse dippers are those whose dip is less than 0%, and extreme dippers are those individuals whose drop in BP is greater than 20%.

Nocturnal non-dipping of BP is defined according to the nocturnal systolic and diastolic BP dip. Normal ambulatory BP during the day is <135/<85 mm Hg (HBP threshold - 135/85 mmHg) and <120/<70 mm Hg at night (HBP threshold- 120/70 mmHg) with a 24-hour average <130/80 mmHg [7].

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS Inc., Chicago, Illinois, USA), version 20.0. Results are summarized as counts and percentages for qualitative variables and mean ± standard deviation (SD) for quantitative variables. Comparisons of means and proportions were made using the Student t-test and chi-square test, respectively. A p-value < 0.05 defined the level of statistical significance.

Results

In the study population, out of a total of 163 patients, there were 55 dippers (33.75%), 79 non-dippers (48.85%), 22 reverse dippers (13.50%) and 7 extreme-dippers (4.30%). Epidemiological characteristics correlated to different dipper profiles are shown in Table 1. Non-dippers have higher mean BP, mean albuminuria, and ACR ratio but lower uric acid levels than dippers. Extreme dippers were 8 years younger than the other patients and had significantly lower mean BP, mean HbA1C, and uric acid than dippers and non-dippers. Peripheral arterial disease is also less prevalent in this category of patients. History of acute myocardial infarction and higher mean albuminuria and ACR, but less acid uric is more present in reverse dippers compared with dipper patients.

Table 2 shows the mean BP values and MHR of patients correlated to different dipper profiles. Dippers had lower MAP/24h - 88.45 mmHg and MHR - 71.35 beats per minute (bpm) compared

Table 1. Epidemiological characteristics correlated to different dipper profiles.

	Total	Dippers	Non-dippers	P ₁	Extreme dippers	P ₂	Reverse dippers	P ₃
Patients: N, (%)	163	55 (33.75)	79 (48.45)	-	7 (4.30)	-	22 (13.50)	-
Age: years	64.17 ± 9.52	64.81 ± 8.80	64.25 ± 9.82	NS	56.14 ± 12.99	0.02	64.81 ± 7.52	NS
Sex/male N, (%)	76 (42.95)	27 (16.57)	37 (22.70)	NS	2 (1.23)	NS	10 (6.14)	NS
Urban residence N, (%)	96 (58.90)	33 (20.25)	49 (30.07)	NS	3 (1.84)	NS	11 (6.75)	NS
Body mass index (BMI), kg/m ²	34.40 ± 8.07	34.07 ± 5.21	34.62 ± 9.25	NS	30.55 ± 5.81	NS	35.62 ± 9.31	NS
History of AMI N, (%)	24 (14.73)	6 (3.68)	11 (6.75)	NS	0	-	7 (4.30)	NS
Stable angina pectoris: N, (%)	77 (47.24)	25 (15.34)	37 (22.70)	NS	2 (1.23)	NS	13 (7.98)	NS
Heart failure: N, (%)	48 (29.45)	19 (11.66)	20 (12.27)	NS	1 (0.62)	NS	8 (4.91)	NS
Stroke N, (%)	16 (10.66)	7 (4.66)	5 (3.33)	NS	0	-	4 (2.66)	NS
Peripheral chronic arterial disease N, (%)	52 (34.66)	18 (12)	28 (18.66)	NS	2 (1.33)	NS	4 (2.66)	NS
Diabetic polyneuropathy N, (%)	123 (82)	41 (27.33)	59 (39.33)	NS	6 (4)	NS	17 (11.33)	NS
Diabetic nephropathy N, (%)	65 (43.33)	22 (14.66)	31 (20.66)	NS	4 (2.66)	NS	8 (5.33)	NS
Diabetic retinopathy: N, (%)	36 (24)	14 (9.33)	15 (10)	NS	1 (0.66)	NS	6 (4)	NS

Mean blood glucose (mg%)	248.78 ± 97.75	235.28 ± 84.76	267.70 ± 106.38	NS	169.42 ± 64.23	NS	236.27 ± 85.53	NS
Mean HbA1 C (%)	9.71 ± 1.67	9.59 ± 1.64	9.90 ± 1.66	NS	8.22 ± 0.78	NS	9.78 ± 1.82	NS
Mean total cholesterol (mg/dl)	9.71 ± 1.67	197.80 ± 59.19	186.04 ± 50.80	NS	206.82 ± 26.08	NS	182.00 ± 30.67	NS
Mean serum triglycerides (mg/dl)	208.43 ± 126.82	221.62 ± 129.57	209.58 ± 134.79	NS	254.5 ± 126.76	NS	159.81 ± 74.88	0.03
Mean uric acid (mg/dl)	6.45 ± 1.97	6.82 ± 1.58	6.34 ± 2.25	NS	6.00 ± 1.36	NS	5.90 ± 2.04	0.03
Mean serum urea (mg/dl)	46.34 ± 22.73	46.04 ± 23.80	45.85 ± 23.16	NS	39.15 ± 16.59	NS	51.77 ± 20.28	NS
Mean serum creatinine (mg/dl)	1.11 ± 0.53	1.18 ± 0.57	1.09 ± 0.55	NS	0.92 ± 0.51	NS	1.09 ± 0.37	NS
Mean microalbuminuria (mg/l)	83.67 ± 133.57	71.57 ± 108.23	99.37 ± 140.41	NS	78.5 ± 114.76	NS	63.06 ± 164.45	NS
Mean urinary albumin/creatinine ratio (mg/g)	98.00 ± 176.75	76.75 ± 133.94	113.69 ± 169.58	NS	70.68 ± 123.22	NS	101.56 ± 281.76	NS

N - numbers, % - percentage, AMI - acute myocardial infarction, HbA₁C - glycated haemoglobin. P₁, P₂, P₃, compare non-dippers, extreme dippers and reverse dippers to dippers, NS - non-significative.

Table 2. Mean BP values and mean HR of patients correlated to different dipper profiles.

Mean Holter Values	Total patients N=163	Dippers N=55	Non-Dippers N=79	P ₁	Extreme Dippers N=7	P ₂	Reverse Dippers N=22	P ₃
MAP/24h	90.47 ± 10.41	88.45 ± 11.67	91.63 ± 10.46	0.006	88.57 ± 8.24	NS	89.50 ± 6.74	NS
Mean HR/24h	73.43 ± 10.60	71.35 ± 11.05	74.27 ± 9.85	0.05	77.57 ± 13.04	NS	73.04 ± 11.31	NS
Pulse Pressure/24h	61.98 ± 13.96	61.58 ± 13.48	62.01 ± 14.68	NS	57.14 ± 10.60	NS	64.45 ± 13.78	NS
MAP Day	92.55 ± 10.96	94.30 ± 12.42	92.60 ± 10.64	NS	96.85 ± 9.31	NS	86.63 ± 5.79	0.007
Mean HR Day	75.96 ± 11.64	74.45 ± 12.25	76.87 ± 10.79	0.22	82.0 ± 14.78	NS	74.59 ± 11.90	NS
Pulse Pressure Day	61.60 ± 14.12	62.67 ± 14.29	60.94 ± 14.43	NS	60.57 ± 12.97	NS	61.59 ± 13.65	NS
MAP Night	85.76 ± 11.22	81.30 ± 10.83	88.13 ± 10.73	0.0004	74.14 ± 7.84	0.09	92.04 ± 8.10	0.001
Mean HR Night	69.06 ± 10.01	67.13 ± 10.44	69.92 ± 9.38	0.016	69.71 ± 11.27	NS	70.54 ± 11.35	NS
Pulse Pressure Night	62.82 ± 15.40	61.12 ± 14.51	63.30 ± 16.18	NS	63.00 ± 8.90	NS	68.00 ± 15.00	0.05

BP - blood pressure, HR-mean heart rate, MAP-mean arterial pressure, P1 compares non-dippers vs. dippers, P2 compares extreme-dippers vs. dippers, P3 compares reverse dippers versus dippers.

with 91.63 mmHg and 74.27 bpm found in non-dippers (p= 0.006; p=0.05). MHR /24 h in non-dippers are significantly higher than in dippers - 74.27 bpm vs. 71.85 bpm, p=0.18 and marginally higher

than in dippers day MHR - 76.87 bpm vs. 74.45 bpm, p=0.22 and night MHR 69.92 bpm vs. 67.16 bpm, p=0.10. Extreme dippers compared with dippers had lower MAP/24h- 88.57mmHg vs. 89.45

mm Hg, and also lower night MAP - 74.14 mm Hg vs. 81.31 mm Hg, $p=0.09$. Day MHR in extreme dippers is higher than in dippers - 82.00 bpm vs. 74.45 bpm, and marginally higher for MHR /24 h - 77.57 bpm vs. 71.85 bpm, $p=0.08$. The reverse dippers compared with dippers have MAP/24h, day and night MAP significantly higher with 4-6 mm Hg and also the night pulse pressure - 68.00 vs. 61.12, $p=0.05$. MHR/24h, day and night MHR in reverse dippers are non-significantly higher with 2-3 bpm than dippers. MAP night was 88.13 bpm in non-dippers vs. 81.30 bpm in dippers, being significantly higher, $p=0.0004$. In reverse-dipper, MAP night was 92.04 bpm, $p=0.001$.

ACEI were used in 97 patients (59.51%), ARB in 35 patients (21.48%), CCB in 55 patients (33.75%), βB (nebivolol, carvedilol) in 109 patients (66.88%), and diuretics in 121 patients (74.24%).

Dippers (N=55) were treated predominantly with ACEI in 36 patients (65.46%), CCB in 22 patients (40.00%), vasodilating βB in 33 patients (60.00%), diuretics in 41 patients (74.55%), ARB in 10 patients (18.19%) and different combinations of these drugs like ACEI/ARB + CCB in 6 patients (10.91%). Dippers treated with vasodilating βB had lower 24-hour MHR - 71.66 bpm vs. 72.13 bpm, $p=0.87$; day MHR was 73.93 bpm vs. 75.22 bpm, $p=0.70$ and night MHR - 67.78 bpm vs. 66.22 bpm, compared to those without βB (Table 3).

Non-dippers treated with vasodilating βB (N=54 out of 79, 68.36%) had lower 24-hour MHR - 72.46 bpm vs. 78.20 bpm, $p=0.017$, morning MHR - 73.48 bpm vs. 79.44, $p=0.032$. Day MHR was 74.61 bpm vs. 81.76, $p=0.005$ and night MHR was 73.90 bpm vs. 82.02 bpm, $p=0.0004$, compared to those without βB (Table 3). Non-dippers taking βB had significantly lower MAP/24h values - 90.05 mmHg vs. the MAP/24h value of those without βB - 95.04, $p=0.049$. MAP morning was 93.57 mmHg vs. 99.44 mmHg, $p=0.037$; MAP day was 91.12 mmHg vs.

95.80 mmHg, $p=0.068$ and MAP night was 86.59 mmHg vs. 91.48 mmHg, $p=0.023$.

This pattern is also present for the rest of the patients: 3 (42.86%) in extreme dippers (N=7) and 19 (86.37%) in reverse dippers (N=22) were treated with vasodilating βB , and we noted the same lowering HR (4-6 bpm) effect.

Discussion

The 2018 European guidelines on the treatment and management of HBP do not recommend personalized treatment according to the circadian hypertensive status [1, 9]. However, different studies contribute to the evidence that supports a personalized treatment approach in the non-dipper BP pattern. [11].

Our study demonstrated that non-dipping or reverse dipping of nocturnal BP in people with type 2 DM is a frequent status (48.45% + 13.50% of patients) and is also associated with a higher day, night and 24-hour MHR value compared to dippers. Studies from different countries recorded the incidence of BP non-dipping among people with diabetes at 43%, 46%, and 49%, respectively [11-13].

Nocturnal non-dipping of HR predicts future cardiovascular events in hypertensive patients [14, 15]. An analysis of prospective studies in patients with HBP found that night-time HR measured by ambulatory recordings was a better predictor of mortality than elevated HR in the clinic [16]. There is also evidence of an association in patients with type 2 DM: in 11,140 patients who participated in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, a higher resting HR rate was associated with a significantly

Table 3. Mean HR and MAP of patients treated with vasodilating βB vs. those without βB therapy.

Mean HR Values	Dippers treated with βB N=33	Dippers without βB N=22	P	Non-Dipperstreated with βB N=54	Non-Dippers Without βB N=25	P
Mean HR /24 h	71.66 ± 12.44	72.13 ± 8.82	NS	72.46 ± 10.53	78.20 ± 7.70	0.017
Mean HR Morning	72.87 ± 13.67	72.81 ± 9.80	NS	73.48 ± 11.94	79.44 ± 9.76	0.032
Mean HR Day	73.93 ± 13.67	75.22 ± 10.01	NS	74.61 ± 11.03	81.76 ± 8.59	0.005
Mean HR Night	67.78 ± 11.98	66.22 ± 7.76	NS	73.90 ± 9.53	82.02 ± 7.97	0.0004
MAP/24h	89.90 ± 12.14	88.77 ± 11.16	NS	90.05 ± 10.22	95.04 ± 10.58	0.049
MAP Morning	92.87 ± 14.40	91.86 ± 10.91	NS	93.57 ± 11.29	99.44 ± 11.92	0.037
MAP Day	94.66 ± 12.88	93.77 ± 11.97	NS	91.12 ± 10.37	95.80 ± 10.73	0.068
MAP Night	81.90 ± 11.11	80.40 ± 10.58	NS	86.59 ± 10.55	91.48 ± 10.55	0.023

HR-heart rate, N- number, βB - betablockers, $p \leq 0.05$

increased risk of all-cause mortality (fully adjusted HR 1.15 per 10 beats/minute [95% CI 1.08, 1.21], $P < 0.001$), cardiovascular death and major cardiovascular outcomes without adjustment after adjusting for age, sex and multiple covariates [17]. Non-dipping HR was defined as a night/day HR ratio greater than 0.90 in a prospective study where the risk of future cardiovascular events was shown to be 2.4 times higher in those whose HR does not exhibit the typical nocturnal decline. The relationship was independent of the non-dipping of systolic BP and was not dependent on the diabetes status or BP level [18]. At first look, this ratio is not seen in our patients because most of them (66.88 %) were already treated with vasodilating β B (Table 2). However, these ratios become evident if we compare the night MHR vs. day MHR of dipping (22 patients) and non-dipping patients not treated with β B (25 pts.): 66.22 bpm/72.40 bpm, and 75.22 bpm/81.76 bpm, respectively. Interestingly, these ratios become lower if we compare the night MHR vs. day MHR of dipping (33 pts.) and non-dipping patients treated with β B (54pts.): 67.78 bpm/68.76 bpm, and 73.93 bpm/74.61 bpm, respectively (Table 3). Patients in our study were treated with vasodilating β B such as carvedilol and nebivolol that have shown a neutral or beneficial effect on metabolic parameters in DM hypertensive patients [19, 20].

Even if there is convincing evidence that HR is a significant risk factor for cardiovascular disease, there are no outcome studies of HR-lowering in hypertension with tachycardia. In June 2015, a panel of experts gathered in a consensus conference updating recommendations on the management of the hypertensive patients with elevated heart rate (HR), previously released in 2006. They could not make practical therapeutic suggestions for the management of such patients, but they suggested to routinely include HR measurement in the assessment of the hypertensive patient [21]. In this context, the importance of our study is to add another evidence about the importance of measuring HR in DM hypertensive patients and also to suggest a possible approach by using vasodilating β B. Higher HR levels may impair the prognosis and should be routinely assessed, especially in non-dippers, reverse dippers and extreme dippers, cases in which this is more frequent, as shown by our study. Regarding the definition of elevated HR, the above-mentioned consensus of the European Society of Hypertension (ESH) state that in the absence of specific data to determine this criterion, any threshold used to define tachycardia is arbitrary, but a value at least 80 bpm is compatible with the published data [22].

In our study, in dipper patients with β B vs. those without β B, the mean HR/24h decrease was not significant (71.66 bpm vs. 72.13 bpm), in contrast to non-dippers treated with β B vs. those

without β B: the decrease of mean HR/24h was statistically significant: 72.46 bpm vs. 78.20 bpm, $p = 0.017$. Mean HR day of non-dippers with β B vs. those without β B was 74.61 bpm vs. 81.76 bpm, $p = 0.005$, and the mean HR night of dippers with β B vs. those without β B was 73.90 bpm vs. 82.02 bpm, $p = 0.0004$. These facts suggest the possible importance of beta-blockers in the non-dipper profile of diabetic hypertensive patients, which is associated with an increased risk of CV events and more frequent complications of DM and HBP [5, 7, 8].

Further research is needed to provide evidence to support the optimum HR to be achieved and to evaluate if the effects of HR reduction in hypertensive patients with elevated HR have long-term benefits. Our study has shown that ABPM is a potential method that could also be used to determine the optimum HR to be achieved and/or the HR threshold at which treatment should be started, especially in those with high CV risk, like DM hypertensive patients.

Limitations of the study

To our knowledge, this is the first Romanian study to report the association of a higher HR with non-dipper and reverse-dipper pattern of BP in type 2 DM patients. Additionally, we only investigated the circadian BP pattern. In contrast, a larger number of patients, a better description and identification of possible confounders and multiple ABPM over a more extended period may provide more prognostic information regarding the importance of nocturnal non-dipping of HR in hypertensive DM patients.

Conclusions

The present study demonstrated that non-dipping or reverse dipping of nocturnal BP in people with type 2 DM is a frequent status (>60% of patients). Most of them also have a higher resting HR value than dippers, which may impair the long-term prognosis. ABPM should be performed in every hypertensive diabetic patient to identify the dipper/no dipper status. It is also important to routinely include HR measurement in the clinical assessment but further research should clarify the importance of HR-lowering in type 2 DM hypertensives patients. Finally, the study stresses the possible importance and impact on the prognosis of vasodilating β B treatment in diabetic hypertensive patients, especially in those with a non-dipper profile, which is associated with increased CV risk.

Conflict of Interest

The author confirms that there are no conflicts of interest.

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