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Study of circadian blood pressure and rest heart rate variation in hypertensive diabetic type 2 patients: value of 24-hours ambulatory blood pressure monitoring

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Abstract

Ambulatory blood pressure monitoring (ABPM) in diabetic patients (DM) with hypertension (HBP) is useful to detect the abnormalities in circadian pattern. 150 consecutive DM type 2 patients with HBP treated with angiotensin converting enzyme inhibitors (ACEI), beta-blockers (βB), calcium channel blockers (CCB), angiotensin receptor blockers (ARB) and diuretics, performed under 24 hours' ABPM. We assessed the BP circadian variation, variability of resting mean heart rate (MHR), and the correlations with the various treatments. There were 49 dippers (32.67%), 75 non-dippers (50%), 19 reverse dippers (12.67%) and 7 extreme-dippers (4.66%). Dippers had lower MAP – 88.85 mmHg, and MHR – 71.79 beats per minute (bpm) as compared to 91.54 mmHg and 75.48 bpm found in non-dippers (p = 0.009; p = 0.05). Dippers was treated with ACEI/ARB (63.2%), CCB (38.7%), combinations of both (38.7%), βB (24.4%), and diuretics (16.3%). Non-dippers treated with βB (53.3%) had lower 24 h MHR – 72.73 bpm vs 78.8 bpm (p = 0.006), night MHR – 73.9 bpm vs 82.02 bpm (p = 0.0001) and day MHR – 74.90 bpm vs 79.05 bpm (p = 0.002). In extreme dippers 3 patients (42.8%), and 7 (36.8%) in reverse dippers, were treated with βB and we noted the same lowering of HR effect. Non-dipping or reverse dipping of nocturnal BP in diabetics is a frequently observed status. Furthermore, most of them also have a higher resting HR and that may impair their long-term prognosis. Furthers research should clarify the role of agents that reduces HR in DM hypertensive patients.

Keywords: ambulatory blood pressure monitoring (ABPM), hypertension (HBP), diabetes, dipper, non-dipper, heart rate

Introduction

A recent outcome study has shown that 24 hours ambulatory blood pressure monitoring (ABPM) is a stronger prognostic tool than clinic measurement and predicts mortality more accurately [1]. The prevalence of hypertension (HBP) among diabetes mellitus (DM) patients was reportedly twice that of the general U.S. population of adults in a survey conducted from 2005–2008 at 57.3% versus 28.6%. Additionally, the prevalence of abnormalities in the

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circadian pattern was remarkably high in the series of diabetic hypertensives [2, 3]. Non-dippers with diminished nocturnal blood pressure (BP) and with a pattern of rising, with higher nocturnal BP than daytime, are known to have advanced organ damage such as of the brain, the heart, and the kidney, and poorer prognosis as compared to normal dippers [4]. Non-dipping is frequent in diabetics and ABPM should be performed at least once for such patients for the better risk stratification of hypertension [5,6]. Our study investigates the circadian BP variation in hypertensive DM type 2 patients and the effects of hypertension medication. A second point was the assessment of the resting 24 hours heart rate (HR) variability.

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 prior to the analysis.

Study population

150 consecutive hypertensive DM type 2 patients with ambulatory follow-up at the Diabetes and Nutrition Ward of Emergency County Hospital Baia Mare, Romania, under 24-hours ABPM, performed from February 2018 to October 2018.

Data collection

General data, height, weight, waist circumference and body mass index (BMI) details were collected. Before installing the ABPM, the values of BP were standard measured, as recommended by the 2013 European Society of Cardiology Hypertension guidelines [7]. The medical history was recorded for each patient, especially HBP and cardiovascular diseases (CVD), dyslipidaemia, the type of diabetes mellitus and the recording of its complications – polyneuropathy, nephropathy, peripheral chronic arterial disease (PAD). Each patient underwent electrocardiography (ECG) to illustrate any possible left ventricular hypertrophy (LVH) and ischemic or rhythm disorders. Current sanguine test results were recorded: glucose, urea, creatinine, total cholesterol, LDL and HDL-cholesterol, triglycerides, uric acid, and glycated haemoglobin (HbA1 C). Morning spot samples of urine was collected and checked for the presence of albuminuria and urinary albumin/creatinine ratio (ACR). Microalbuminuria was defined as an ACR from 30 to 299 mg/day. For each patient, the antihypertensive and antidiabetic treatment was recorded: diuretics (Diur), beta blockers (βB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), alpha blockers (AB), as well as a combination 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 provided by the circadian cycles and also the resting HR for each patient, was recorded and analysed: Mean Sys (the systolic mean) and Mean Días (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 hrs and BP recordings were made at intervals of 0.5 hours, from 06.00 to 22.00 hrs, and at 1-hour intervals, from 22.00 hrs to 06.00 hrs. Dippers are defined as those individuals with a mean 24 hr ambulatory BP, which dropped to >10%. Non-dippers are those with a drop of 0–9%. Reverse dippers are at less than 0% and extreme dippers are those individuals whose drop in BP is more 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 the 24 hrs average at < 130/80mmHg [7].

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SSPS Inc., Chicago, Illinois, USA) version 20.0 software. The results are summarized as counts and percentages for qualitative variables and as the mean ±

standard deviation (SD) for quantitative variables. Comparisons of means and proportions were done using a student t-test and a 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 150 patients, included 49 dippers (32.67%), 75 non-dippers (50%), 19 reverse dippers (12.67%) and 7 extreme-dippers (4.66%). Epidemiologically, the characteristics correlated to different dipper profiles are shown in Table 1. Non-dippers have a significantly higher mean BP, mean albuminuria and ACR ratio, but less uric acid than dippers. Extreme-dippers were 8 years younger than other patients and had significantly lower mean BP, mean HbA1 C and uric acid than dippers and non-dippers. PAD 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 as compared to dippers patients.

Table 2 shows the mean BP values and MHR of patients correlated to different dipper profiles. Dippers had lowers MAP/24h – 88.85 mmHg, and MHR – 71.79 beats per minute (bpm) as compared to 91.54 mmHg and 75.48 bpm found in non-dippers (p = 0.009; p = 0.05), respectively. MHR/24 h in non-dippers are significantly higher than in dippers – 75.48 bpm vs 71.79 bpm (p = 0.05) and marginally higher than in dippers, with the day MHR at 77.10 bpm vs 74.4 bpm (p = 0.09), and the night MHR at 70 bpm vs 67 bpm (p = 0.09). Extreme dippers compared to dippers had significantly lower MAP/24h at 80.57 mmHg vs 88.85 mmHg (p = 0.007) and also lower night MAP at 73.14 mmHg vs 80.83 mmHg (p=0.07). Day MHR in extreme dippers are significantly higher than in dippers at 82 bpm vs 77 bpm (p = 0.03) and marginally higher for MHR/24h – 79.5 bpm vs 75.4 bpm (p = 0.08). The reverse dippers compared to dippers have higher MAP/24h, and significantly higher day and night MAPs at 4–6 mmHg and night pulse pressure – 62.68 vs 62.68 (p = 0.05). MHR/24h and day and night MHR in reverse dippers are non-significantly higher, with 2–3 bpm more than in dippers.

ACEI/ARB was used in 120 patients (80%), CCB dihydropyridine in 65 patients (43.3%), vasodilating βB (nebivolol, carvedilol) in 62 patients (41.3%), CCB non-dihydropyridine in 5 patients (3.3%) and diuretics in 45 patients (30%).

Dippers (N = 49) were treated predominantly, with ACEI/ARB in 31 patients (63.2%), CCB in 19 patients (38.7%), vasodilating βB in 12 patients (24.4%), diuretics in 8 patients (16.3%) and different combinations of these drugs like ACEI/ARB + CCB in 19 patients (38.7%). Dippers treated with vasodilating βB had lower 24h MHR – 70.13 bpm vs 76.2 bpm (p = 0.001), night MHR – 71.62 bpm vs 79.12 bpm (p = 0.021) and day MHR – 72.90 bpm vs 77.52 bpm (p = 0.001), akin to those without βB – Table 3.

Non-dippers treated with vasodilating βB (N = 40 from 75, 53.3%) had lower 24hr MHR – 72.73 bpm vs 78.8 bpm (p = 0.006), night MHR – 73.92 bpm vs 82.02 bpm (p = 0.0001) and day MHR – 74.90 bpm vs 79.05 bpm (p = 0.002), than those without βB – Table 3.

This pattern is also present for the rest of patients: 3 (42.8%) in extreme dippers (N = 7) and 7 (36.8%) in reverse dippers (N = 19) were treated with vasodilating βB. We noted the same effect of lowered HR (4–6 bpm). In total, 62 patients were treated with βB (41.3 %) alone or in combinations and had lower MAP – 90.01 mmHg vs 95.01 mmHg (p = 0.048) and lower 24h/ MHR – 72.73 bpm vs 78.43 bpm (p = 0.006).

Discussion

The 2016 European Guidelines on cardiovascular disease prevention in clinical practice indicates the assessment of dipping/non-dipping patterns in chronic kidney diseases, obstructive sleep apnea and DM patients, but the new 2018 guidelines on treatment and management of HBP do not recommend personalized treatment, according to the circadian hypertensive status [8, 9]. However, different studies contribute evidences that support a personalized treatment approach in the non-dipper BP pattern. [10, 11]

Table 1. Epidemiologically characteristics correlated to different dipper profiles.

	TOTAL	DIPPERS	NON-DIPPERS	P_1	EXTREME DIPPERS	P_2	REVERSE DIPPERS	P_3
Patients: N, (%)	150	49 (32.67)	75 (50)	-	7 (4.66)	-	19 (12.67)	-
AGE: years	63.94 ±9.7	64.63± 8.84	64.06± 10.02	NS	56.14± 14.08	0.03	64.57± 8.19	NS
Sex/male N, (%)	70 (46.67)	24 (16)	35 (23.33)	NS	2	NS	9 (6)	NS
Urban residence N, (%)	89 (59.33)	30 (20)	46 (30.66)	NS	3 (2)	NS	10 (6.66)	NS
Body mass index (BMI), kg/m^2	30.3± 8.63	29.37± 5.12	31.50± 9.40	NS	27.55±	NS	31.13± 9.98	NS
History of AMI N, (%)	23 (15.33)	6 (4)	11 (7.33)	NS	0	_	7 (4)	0.05
Stable angina pectoris: N, (%)	69 (46)	21 (14)	35 (23.33)	NS	2 (1.33)	NS	11 (7.33)	NS
Heart failure: N, (%)	44 (29.33)	16 (10.66)	19 (12.66)	NS	1 (0.66)	NS	8 (5.33)	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)	0.0001	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

Table 1. Continued from previous page.

	TOTAL	DIPPERS	NON-DIPPERS	P_1	EXTREME DIPPERS	P_2	REVERSE DIPPERS	P_3
Mean blood glucose (mg%)	240.43±99.04	236.75±86.65	271.25±107.30	0.05	169.42±64.23	0.05	239.95±86.26	NS
Mean HbA1 C (%)	9.70±1.6	9.69±1.68	9.9±1.65	NS	8.22±0.78	0.02	9.46±1.22	NS
Mean total cholesterol (mg/dl))	193.07±51.59	202.57±60.4	188.07±51.16	NS	206.82±26.08	NS	184.00±31.85	NS
Mean serum triglycerides (mg/dl)	213.2±129.79	233.52±132.43	211.97±137.58	NS	254.5±126.76	NS	154.56±67.31	0.01
Mean uric acid (mg/dl)	6.53±2.	7.13±1.49	6.44±2.26	0.05	6.00±1.36	0.06	5.40±1.97	0,0002
Mean serum ureea (mg/dl)	46.54±22.69	46.96±24.73	46.16±27.71	NS	39.15±16.59	NS	50.27±12.67	NS
Mean serum creatinine (mg/dl)	1.12±0.55	1.2±0.59	1.1±0.56	NS	0.92±0.51	NS	1.08±0.37	NS
Mean microalbuminuria (mg/l)	104,8±120.05	77.62±112.	116.87±109.42	0.05	78.5±114.76	NS	146.4±169.66	0.04
Mean urinary albumin/creatinine ratio (mg/g)	91,73±17.52	73.43±13.59	105.36±15.6	0.04	70.68±12.22	NS	117.47±29.43	0.001

N – numbers, % - percentage, AMI – acute myocardial infarction, HbA1 C - glycated haemoglobin, P_1, P_2, P_3, compare non- dippers, extreme dippers and reverse dippers with 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=150	Dippers N=49	Non-Dippers N=75	P_1	Extreme Dippers N=7	P_2	Reverse Dippers N=19	P_3
MAP /24 h	90.28±8.47	88.85±5.40	91.54±5.71	0.009	80.57±8.24	0.007	92.63±7.22	0.02
Mean HR /24 h	73.6±10.68	71.79±11.26	75.48±9.97	0.05	79.57±13.04	0.08	73.31±11.08	NS
Pulse Pressure /24h.	61.42±13.79	60.91±13.8	61.41±14.61	NS	57.14±10.60	NS	64.36±11.63	NS
MAP Day	92.40±8.94	90.71±6.22	92.54±7.82	NS	86.85±9.31	NS	96.84±6.12	0.005
Mean HR Day	76.17±9.72	74.40±8.46	77.10±8.91	0.09	82.0±9.78	0.03	74.89±11.53	NS
Pulse Pressure Day	61.04±14.00	61.93±14.62	60.34±14.35	NS	60.57±12.97	NS	61.63±12.01	NS
MAP Night	85.54±11.37	80.85±10.61	88±10.95	0.0004	73.14±7.84	0.07	92.15±8.64	0.001
Mean HR Night	69.14±10.17	67.0±10.67	70.06±9.34	0.09	69.71±11.27	NS	70.78±11.53	NS
Pulse Pressure Night	64.32±15.21	61.04±15.00	62.68±16.13	NS	63.0±8.90	NS	68.68±12.24	0.05

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

Our study demonstrated that non-dipping or reverse dipping of nocturnal BP in people with type 2 DM is a frequently observed status (50% + 12.67% of patients), and is also associated with a higher day, night and 24 h/MHR as compared to the dippers. Studies from different countries recorded the incidence of BP non-dipping among people with diabetes at 43%, 46% and 49%, respectively [12-14].

Nocturnal non-dipping of HR predicts future cardiovascular events in hypertensive patients [15, 16]. 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 [17]. There is also evidence of an association in patients with DM type 2 – 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 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, and after adjusting for age, sex and multiple covariates [18].

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 whom 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 [19]. At first glance, this ratio is not seen in our patients because most of them (41.3%) were already being treating with vasodilating βB – Table 2. However, these ratios become evident if we compare the night MHR vs day MHR of dipping and non-dipping patients, non-treated with βB: 79.12 bpm/77.52 bpm, respectively, vs 82.02 bpm/79.05 bpm, respectively. Interestingly, these ratios reduce if we compare the night MHR vs day MHR of dipping and non-dipping patients treated with βB: 71.62 bpm/ 77.05 bpm, respectively, vs 73.92 bpm/74.9 bpm, respectively – Table 3. Patients in our study were treated with vasodilating βB, such as carvedilol and nebivolol, that have shown neutral or beneficial effect on metabolic parameters in DM hypertensive patients [20, 21].

Moreover, even that are convincing that HR is an important risk factor for cardiovascular disease,

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

Mean HR Values	Dippers treated with βB N=12	Dippers without βB N=37	p	Non -Dippers treated with βB N=40	Non-Dippers Without βB N=35	p
Mean HR /24 h	70.13	76.2	0.001	72.73	78.08	0.006
Mean HR Day	72.9	77.52	0.001	74.9	79.05	0.002
Mean HR Night	71.62	79.12	0.02	73.9	82.02	0.0001

there are no outcome studies of HR lowering in tachycardia hypertension. In June 2015, a panel of experts gathered in a consensus conference updating recommendations on the management of the hypertensive patient 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 the routine inclusion of HR measurement in the assessment of the hypertensive patient [22].

In this context, the importance of our study is to add more evidence regarding the importance of measuring HR in DM hypertensive patients and also to suggest a possible approach through the use of a vasodilating βB. Higher HR may impair the prognosis and also should be routinely assessed, especially in non-dipper, reverse dipper and extreme dipper patients, where our study shows that it is more frequent. Regarding the definition of elevated HR, the above mentioned ESH consensus states that in the absence of specific data to determine this criterion, any threshold used to define tachycardia is arbitrary but a value of at least 80 bpm is compatible with the published data [22]. Further research is required 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 shows 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 initiated, especially in those with high CV risk, like DM hypertensive patients.

Another issue demonstrated in our study is the association of microalbuminuria and a higher ACR in the non-dipping and reverse dipping status. These results are in accordance with previous researches that have shown a significant correlation between the presence of nocturnal non-dipping of BP and increased levels of urinary albumin excretion [23–25]. However, this was not the objective of our study and we did not proceed to establish further correlations with age, DM duration, or the intensity of antidiabetics and glycemic control

Limitations of study

To our knowledge, this is the first Romanian study to report the association of a higher HR with non-dipper and reverse-dipper patterns of BP in type 2 DM patients. Additionally, we only investigated the circadian BP pattern, whereas involving a larger number of patients, with a better description and identification of possible confounders and multiple ABPMs over a longer period of time, 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 frequently observed status (> 60% of patients). Most of them also have a higher resting HR than dipper patients and that may impair the long-term prognosis. ABPM should be conducted for every hypertensive diabetic patient to identify dipper/no dipper status. Moreover, it is essential to routinely include HR measurements in the clinical

assessment but further researches should clarify the importance of HR lowering in type 2 DM hypertensive patients.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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