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Non-Dipping Phenomenon; is it Reversible in Diabetic Hypertensive Cases?

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Abstract

Objectives: To detect reversibility of non-dipping phenomenon in diabetic hypertensive patients.

Materials and methods: This study enrolled 60 patients who were diabetic with uncontrolled hypertension with non-dipper pattern proved from the first ABPM. Then after office BP control, we classified the cases according to the second ABPM data regarding reversibility of non-dipping status into two groups:

Group (I): Irreversible cases: included 56 patients, still having non-dipping pattern.

Group (II): Reversible cases: only four cases who returned back into dipper status.

Results: Mean age was 54.36 ± 5.62 years; and 73% of the study population was male. Also, 70 of the patients had LVH. There was no significant difference between both groups concerning demographic data p value was more than 0.05. Concerning ABPM data after BP control there was a highly significant difference between both groups regarding: Dipping % of SBP, Dipping % of DBP and Nocturnal SBP (p value<0.001). In addition, there was a significant difference between the two groups regarding: SBP in 24 h, Nocturnal DBP (p value<0.05). Also, there was highly significant difference between both groups regarding nighttime doses of antihypertensive medications (p value<0.001).

Conclusion: Non-dipping phenomenon in diabetic hypertensive patients can be reversible. As such identifying non-dippers can be accomplished by conventional 24 h ABPM.

Keywords: ABPM; Blood pressure; Diabetes; Non-dipper pattern

Introduction

The prevalence of diabetes mellitus is estimated to increase in the future decades. Cardiovascular diseases may be the first cause of mortality in diabetic patients. The prevalence of arterial hypertension in diabetic patients is twice as high as general population [1]. ABPM is particularly useful in diabetic patients for characterizing the nocturnal profile, because a non-dipping or hypertensive nocturnal BP pattern is more common in diabetic patients and is a strong predictor of future cardiovascular events [2].

Because adequate BP control is especially important in diabetic patients, it becomes essential to verify the appropriateness of antihypertensive treatment with ABPM. ABPM allows for assessment of the efficacy of treatment on particularly important periods of the circadian cycle, such as the night-time and morning [3].

Many studies using ABPM in diabetic patients treated for hypertension have shown that restoring nocturnal BP fall in diabetic non-dippers may be a difficult task with conventional antihypertensive therapy [3].

The practice of pharmacological chronotherapy may increase in coming years given increasing interest in this approach. Chronotherapy involves "the timing of hypertension medications to endogenous circadian rhythm determinants of the 24 h [blood pressure] pattern" [4].

The aim of this study is to evaluate reversibility of non-dipping phenomenon in diabetic hypertensive patients.

Methods

Study population

This cross-sectional study enrolled 60 diabetic hypertensive patients had non-dipper pattern including 16 women and 44 men with age 54.36 ± 5.62 years (mean ± SD) at cardiology department, faculty of Medicine, Zagazig University from January 2016 to February 2017.

Diabetic patients with thyroid and parathyroid diseases, chronic kidney diseases, metabolic syndrome, sleep apnea, secondary causes of hypertension or dipper hypertensive patients were excluded. The local ethical committee of Zagazig University of Medical Sciences approved the study and all the patients gave written informed consent.

Data collection

The baseline characteristics age, gender, smoking, hypertension, duration of diabetes mellitus, dyslipidemia, body weight, height, body mass index, waist circumference, together with the results of para clinical evaluation blood chemistry analysis, echocardiogram, electrocardiogram, and 24 h ambulatory blood pressure monitoring were recorded.

Diabetes mellitus was diagnosed on basis listed by American Diabetes Association (2004) as: fasting blood sugar ≥ 126 mg% or 2 h post-prandial blood sugar ≥ 200 mg% or symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl.

Hypertension is defined as values ≥ 140 mmHg SBP and/or ≥ 90 mmHg DBP or on anti-hypertensive therapy according to ESH/ESC Guidelines for the management of arterial hypertension (2013).

Dyslipidemia was considered according to recommendation of Third Report of the National Cholesterol Education Program (NCEP), 2002, when any of the following was present after 9-12 h fast; serum LDL-cholesterol ≥ 130 mg/dl, HDL < 40 mg/dl.

The Body Mass Index (BMI) was calculated as body weight/height^2 (kg/m^2).

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) is the method for obtaining automated brachial blood pressure measurements, at fixed time intervals during a 24 h period away from a medical environment. It provides multiple readings with minimal interference with the patients' activities. The 24 h ABPM was performed using an automated oscillometric device (Contec ABP50), and data were analyzed using ABPM50software. The device was calibrated before start of the study. Also, for each patient, the same device was used. ABPM was placed on the arm with higher BP value and patients recommended keeping their habitual routine. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean BP, and heart rate (HR) were recorded every 15 min throughout the day and every 30 min at night. Daytime and nighttime were determined individually, depending upon the patient's sleep-wake times.

SBP, DBP and HR were average for the day and the night. The normal dip was defined as a 10% or more reduction in BP during the night compared with the day. Percent dipping for systolic BP and diastolic BP is calculated from the mean values for daytime and nighttime blood pressure as follows:

[(daytime BP-nighttime BP)/daytime BP] × 100.

Statistical analysis

Data management and analysis were performed using SPSS program; version 20. The numerical data were statistically presented in items of mean and standard deviation. Categorical data were summarized as percentages. Comparisons between numerical variables were done by unpaired student's t-test. Comparing categorical variables was done by Chi-square test or fisher exact test for small sample size. A probability value $p<0.05$ was considered statistically significant, a P value<0.001 was considered highly significant and P value>0.05 was considered non-significant (SPSS INC. Chicago, IL).

Results

First, all patients who were included in this study were diabetic with uncontrolled hypertension (on medical treatment or not) with non-dipper pattern proved from the first ABPM. Then after office BP control, we classified the cases according to the second ABPM data regarding reversibility of non-dipping status into two groups:

Group (I): Irreversible cases: included 56 patients, still having non-dipping pattern.

Group (II): Reversible cases: only four cases who returned back into dipper status.

Demographic data

Basic demographic data and risk factors of the study population (Table 1)

Collectively, the age of the patients was 54.36 ± 5.62 years old. 44 (73.3%) patients were males. Body mass index (BMI) was 30.15 ± 3.01 kg/m^2. Duration of diabetes and hypertension were 11.06 ± 3.59 years, 11.23 ± 3.54 years respectively. 32 (53.33%) patients were current smokers and 41 (68.33%) patients had dyslipidemia.

Parameters		N=60
Sex	Male	44 (73.33%)
Age, years old		54.36 ± 5.62
BMI, kg/m^2		30.15 ± 3.01
HTN duration, years		11.23 ± 3.54
DM duration, years		11.06 ± 3.59
Smoker	Yes	32 (53.33%)
Dyslipidemia	Yes	41 (68.33%)

Table 1: Basic demographic data and risk factors.

Echocardiographic data of the study population (Table 2)

Interventricular septum thickness, posterior wall thickness and LV mass index (LVMI) were 11.36 ± 1.51 mm, 10.90 ± 1.43 mm and 109.15 ± 18.03 g/m^2 respectively. Number of females who had LVH (F>95 g/kg^2) was 11 (18.33%) while; number of males who had LVH (M>105 g/kg^2) was 32 (53.33%).

Parameters		N=60
IVS thickness mm		11.36 ± 1.51
PW thickness mm		10.90 ± 1.43
LV mass index (g/m^2)		109.15 ± 18.03
LVH	Males (>105 g/m^2)	32 (53.33%)
	Females (>95 g/m^2)	11 (18.33%)

Table 2: Echocardiographic data.

Comparison between Group I and II regarding the demographic and clinical data (Table 3)

Concerning age; in-group I, it was 54.32 ± 5.6 years old; while it was 55 ± 6.2 years old in group II. This difference is non-significant (t=-0.23, p>0.05).

Concerning gender; there were 42 males (75%) in-group I versus two males (50%) in-group II, This difference is non-significant (t=1.19, p>0.05).

Body Mass Index; it was 30.12 ± 3.06 kg/m^2 in-group I versus 30.50 ± 2.51 kg/m^2 in-group II. This difference is non-significant (t=-0.23, p>0.05).

Regarding the duration of HTN and DM, It was 11.42 ± 3.56 years, 11.14 ± 3.59 years in-group I respectively, while it was 8.50 ± 1.73 years, 10.00 ± 3.91 years in-group II respectively. This difference is non-significant (t=1.61, p>0.05), (t=0.61, p>0.05).

Regarding dyslipidemia and smoking; 37 patients (66%) had dyslipidemia and 31 patients (55.66%) were smoker's in-group I, while four patients (100%) had dyslipidemia and 1 patient (25%) was smoker in group II. There was no significant difference between the two groups regarding dyslipidemia, smoking (X=1.98, p>0.05), (X=1.38, p>0.05) respectively.

Parameters		Group (I)	Group (II)	Test	
		N=56	N=4	χ^2/t^*	P-value
Sex	Male	42 (75.0%)	2 (50.0%)	1.19	>0.05
Age, years		54.32 ± 5.6	55 ± 6.2	-0.23	>0.05
BMI, Kg/m^2		30.12 ± 3.06	30.50 ± 2.51	-0.24	>0.05
HTN duration, years		11.42 ± 3.56	8.50 ± 1.73	1.62	>0.05
DM duration, years		11.14 ± 3.59	10.00 ± 3.91	0.61	>0.05
Smoker	Yes	31 (55.4%)	1 (25.0%)	1.38	>0.05
Dyslipidemia	Yes	37 (66.1%)	4 (100.0%)	1.99	>0.05

Table 3: Comparison between group I and II regarding demographic and clinical data.

Comparison between group I and II regarding the echocardiographic data (Table 4)

IVS thickness: It was 11.42 ± 1.53 mm in group I while it was 10.50 ± 1 mm in group II, this difference is non-significant (t=1.18, p >0.05).

PW thickness: It was 10.92 ± 1.45 mm in group I while it was 10.50 ± 1.29 mm in group II, this difference is non-significant (t=0.57, p >0.05).

LV mass index: It was 110.26 ± 18.10 g/m^2 in group I while it was 93.5 ± 6.40 g/m^2 in group II, this difference is significant (t=4.18, p <0.05).

LVH: There were 10 females in group I (17.8%) who had LVH while there was one female in group II (25.0%) who had LVH (F>95 g/kg^2). In addition there were 31 males in group I (55.4%) who had LVH while there was one male in group II (25.0%) who had LVH (M>105 g/kg^2). This difference is non-significant (X =0.99, p >0.05).

Parameters		Group (I)	Group (II)	Independent t-test	
		N=56	N=4	t/χ^{2*}	P-value
IVS thickness, mm		11.42 ± 1.53	10.50 ± 1.00	1.19	>0.05
PW thickness, mm		10.92 ± 1.45	10.50 ± 1.29	0.57	>0.05
LV mass index,(g/m^2)		110.26 ± 18.10	93.5 ± 6.40	4.18	<0.05
LVH	Males(>105 g/m^2)	31 (55.4%)	1 (25.0%)	0.99	>0.05
	Females(>95 g/m^2)	10 (17.8%)	1 (25.0%)		

Table 4: Comparison between group I and II regarding echocardiographic data.

Comparison between group I and II regarding the electrocardiographic data (Table 5)

Sokolow-Lyon: It was 32.50 ± 3.41 mm in group I while it was 32.00 ± 1.41 mm in group II, This difference is non-significant (t=0.29, p >0.05).

LV strain pattern: It was found in 12 cases of group I (21.4%) while no one in-group II had strain pattern (0%). This difference is non-significant (t=1.07, p>0.05).

Parameters		Group (I)	Group (II)	test	
		N=56	N=4	t/χ^{2*}	p-value
Sokolow-Lyon		32.50 ± 3.41	32.00 ± 1.41	0.29	>0.05
LV strain pattern	Yes	12 (21.4%)	0 (0.0%)	1.07	>0.05

Table 5: Comparison between group I and II regarding electrocardiographic data.

Comparison between group I and II regarding the prescribed medication data (after BP control) (Table 6)

There were no significant difference regarding different categories of antihypertensive medications after BP control between group I and group II (p >0.05). Whereas there was highly significant difference between both groups regarding night time doses of short acting medications (p<0.001).

Medication after controlling BP		Group (I)		Group (II)		Chi-square test	
		56		4			
		No.	%	No.	%	χ^2	P-value
Diuretics [n (%)]	Yes	0	0.00%	0	0.00%	NA	NA
ACEI [n (%)]	Yes	12	21.43%	4	100.00%	0.58	>0.05

ARBS [n (%)]	Yes	13	23.21%	0	0.00%	1.01	>0.05
BB [n (%)]	Yes	4	7.10%	0	0.00%	0.31	>0.05
CCB [n (%)]	Yes	7	12.50%	0	0.00%	0.57	>0.05
Combination [n (%)]	Yes	20	35.71%	0	0.00%	1.62	>0.05
Short acting medication (Nighttime doses) [n (%)]	Yes	0	0.00%	4	100.00%	60	<0.001

Table 6: Comparison between group I and II regarding the prescribed medication data.

Comparison between group I and II regarding the ABPM data before BP control (Table 7)

There were no significant difference regarding all ABPM parameters before BP control between group I and group II (p>0.05).

ABPM before BP Control		Group (I)	Group (II)	Chi-square test	
		N=56	N=4	χ^2/t^*	P-value
SBP in all day, mmHg		141.30 ± 4.87	141.75 ± 8.88	-0.17	>0.05
DBP in all day, mmHg		86.48 ± 3.40	87.75 ± 1.70	-0.73	>0.05
SBP in wake time, mmHg		152.73 ± 6.08	156.50 ± 4.04	-1.2	>0.05
DBP in wake time, mmHg		88.44 ± 3.10	88.50 ± 1.91	-0.03	>0.05
SBP in night time, mmHg		142.55 ± 8.84	138.00 ± 8.04	1	>0.05
DBP in night time, mmHg		83.19 ± 3.31	81.75 ± 3.20	0.85	>0.05
Percent dipping for SBP		6.12 ± 1.58	7.50 ± 0.70	-1.7	>0.05
Percent dipping for DBP		6.01 ± 1.26	6.87 ± 0.94	-1.3	>0.05
Morning surge [n (%)]	Yes	18 (32.1%)	2 (50.0%)	0.54	>0.05

Table 7: Comparison between group I and II regarding the ABPM data before BP control.

Comparison between group I and II regarding the ABPM data after BP control (Table 8)

There was a highly significant difference between the two groups regarding:

Dipping % of SBP: It was 4.33 ± 1.53% in group I while it was 12.37 ± 1.60% in group II, this difference is highly significant (t=-1.01, p<0.001).

Dipping % of DBP: It was 4.44 ± 1.68% in group I while it was 12.00 ± 1.47% in group II, this difference is highly significant (t=-8.71, p<0.001).

Nocturnal SBP: It was 125.60 ± 2.84 mmHg in-group I while it was 116.00 ± 3.16 mmHg in-group II, this difference is highly significant (t=6.48, p<0.001).

In addition, there was a significant difference between the two groups regarding:

SBP in 24 h: It was 128.96 ± 3.05 mmHg in-group I while it was 125.25 ± 3.09 mmHg in-group II, this difference is significant (t=2.35, p<0.05).

Nocturnal DBP: It was 74.41 ± 3.26 mmHg in-group I while it was 70.50 ± 2.51 mmHg in-group II, this difference is significant (t=2.34, p<0.05).

While there were no significant difference regarding other ABPM parameters after BP control (p>0.05).

Parameters	Group (I)	Group (II)	Chi-square test	
	No=56	N=4	χ^2/t^*	P-value
SBP in all day, mmHg	128.96 ± 3.05	125.25 ± 3.09	2.34	<0.05
DBP in all day, mmHg	77.12 ± 4.09	75.75 ± 1.50	0.66	>0.05
SBP in wake time, mmHg	131.91 ± 2.65	132.50 ± 2.38	-0.43	>0.05
DBP in wake time, mmHg	78.53 ± 3.45	80.25 ± 3.86	-0.95	>0.05
SBP in night time, mmHg	125.60 ± 2.84	116.00 ± 3.16	6.48	<0.001
DBP in night time, mmHg	74.41 ± 3.26	70.50 ± 2.51	2.34	<0.05
Percent dipping for SBP	4.33 ± 1.53	12.37 ± 1.60	-1.01	<0.001
Percent dipping for DBP	4.44 ± 1.68	12.00 ± 1.47	-8.7	<0.001

Table 8: Comparison between group I and II regarding the ABPM data after BP control.

Discussion

The diagnostic criteria for hypertension based upon in-clinic cuff measurements have evolved over time, being adjusted downward markedly and with special consideration given to high-risk (complicated) patients, such as those with diabetes, renal disease, or previous CVD events [5].

The increasing application of ABPM has revealed a more complex picture of BP and its 24 h patterning, suggesting new and clinically important targets and goals of therapy, e.g. control of morning BP rise and daytime and nighttime SBP/DBP means plus normalization of the atypical non-dipping 24 h SBP/DBP profile [6].

Some studies have shown that the reproducibility of BP values in diabetic patients is better with ABPM than with office BP; in particular,

the reproducibility of non-dipping is higher in diabetic patients than in the general population (International ABPM Registry ARTEMIS).

ABPM provides a number of other relevant parameters, over and above average SBP and DBP values, which can be useful in diabetic patients. These include a rough estimate of heart rate variability, which when decreased may indicate diabetic neuropathy; pulse pressure which when increased, may be an alternative marker of arterial wall stiffening; and the AASI (Ambulatory Arterial Stiffness Index), which predicts cardiovascular events and organ damage [7].

Concerning risk factors; our study revealed that patients who had non dipping phenomenon closely related to high risk categories such as those older, smokers, DM, obese (BMI ≥ 30 kg/m^2), dyslipidemia and long duration of HTN and DM. This agrees with The Spanish ABPM Registry in which they found that patients with blunted nocturnal dip frequently belong to high- or very high-risk categories and specifically are often older, obese, diabetics or with overt cardiovascular or renal disease.

There was high prevalence of LVH (70%) in our study population and this result was consistent with pioneering study, Verdecchia and colleagues in which left ventricular hypertrophy was more closely associated with non-dipping pattern. As well as, there were numerous studies on the issue, many of which supported this finding [8].

As regard the patients who were on ACE I medication; in our study, there was no reversion from non-dipper to dipper pattern in-group (I) who ingested long acting ACE I medication in the morning. On contrary, in-group (II) they ingested short acting ACE I medication (one of the doses in the night). These results are concordant with results conducted by Hermida and Ayala who evaluated 115 untreated essential hypertension patients who were randomized to upon-awakening ramipril. Consequently, the sleep-time relative BP decline was attenuated toward a more non-dipping pattern when ramipril was ingested upon awakening while, the other group who significantly potentiated towards a more dipping pattern when ingested at bedtime and this explained by bedtime ACEI administration significantly reduced nighttime BP and restored normal dipping pattern [9].

As well as previous study, our study results were concordant with Qiu study where non-dipper hypertensive patients were assigned to evening 12.5 mg captopril or placebo treatment. The finding that the ACEI restored the normal dipping circadian BP rhythm in 70% of the patients. Which can be explained by bedtime captopril administration significantly reduced nighttime BP and restored the normal dipping status [10].

In our study, concerning conventional morning dose of ARBS, BB, Diuretics and combined medications had no effect on non-dipper pattern. These results are consistent with results that conducted by Hermida study who investigated the treatment-time-dependent effects of different types of antihypertensive medications on non-dipper subjects. There were attenuation of the sleep-time relative BP decline when these medications were ingested upon awakening, which resulted in no changing in the BP non-dipper pattern While the BP non-dipper pattern significantly potentiated towards a more dipping pattern when these medications were ingested at bedtime. This discrepancy explained by bedtime combination treatment significantly reduced nighttime BP and restored normal dipping pattern [11].

Multiple studies have confirmed that it is possible to achieve a dipping pattern by administering antihypertensive in the night. Chronotherapy of hypertension is a new therapeutic option and benefits have been established in long-term studies with clinical outcomes as end points [12].

Conclusion

Identifying non-dippers can be accomplished by conventional 24-h ABPM. A non-dipping pattern and nocturnal hypertension are strongly associated with increased cardiovascular morbidity and mortality.

Non-dipping phenomenon in diabetic hypertensive patients can be reversible. It can be occurred more with subjects who ingested some doses of antihypertensive medications in the night. While restoring dipping pattern in diabetic non-dippers may be a difficult task with conventional antihypertensive therapy.

Non-dipping phenomenon closely related to high-risk categories such as those older, smokers, DM, obese, dyslipidemia and long duration of HTN and DM.

Limitations of the Study

The relatively limited number of patients included could limit the strength of results and conclusion obtained from this study.

Follow up period was relatively short in comparison with other studies.

Recommendation

Treatment based on dipper/no dipper status is a new concept for identifying high risk hypertensive patients who would derive maximum benefit with antihypertensive medication. Antihypertensive medication administered in the night significantly improves the dipping pattern [12].

There is a need to simplify the method for nocturnal BP recording. Simpler methods are evolving to document the basal BP at night, which would help in greater use of the concept of dipper/non-dipper in managing hypertension at the primary care level [12].

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