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Predictors of the blood pressure non-dipping profile in newly diagnosed hypertensive patients

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Abstract

A non-dipping profile, assessed by 24-hour ambulatory blood pressure measurement (ABPM), is associated with a worse cardiovascular prognosis. This study assessed the impact of cardiovascular risk factors on blood pressure dipping status of newly diagnosed hypertensive patients. A 4-year prospective was performed. Cardiovascular risk factors, hypertension complications and biochemical markers were evaluated and compared on the non-dipping (ND) group (n=204) and the dipping (D) group (n=261). Old age, obesity, dyslipidemia, type 2 diabetes mellitus and chronic alcohol consumption were significantly frequent found on ND group as compared to D group. After applying multivariate logistic regression analysis, the ND profile remained strongly associated with older age (OR 1.02, 95% CI 1.008-1.048, p = 0.005), chronic ethanol consumption (OR 1.72, 95% CI 1.119-2.664, p = 0.013), obesity (OR 1.21, 95% CI 1.013-1.458, p = 0.034) and higher total cholesterol values (OR 1.007, 95% CI 1.002-1.011, p = 0.001). The results of our study sustain the correlations of the non-dipping pattern with obesity, dyslipidemias, type 2 diabetes mellitus and stroke antecedents. On the other hand, our data add the chronic alcohol consumption to other risk factors as older age, high serum values of total cholesterol and obesity to make a group of conditions that could act as independent predictors of the nocturnal BP non-dipping profile.

Keywords: blood pressure monitoring, non-dipping profile, hypertension, alcohol drinking, aging, obesity, cholesterol

Introduction

The most recent European guidelines for the management of arterial hypertension underline the reliability of out-of-office blood pressure (BP) measurement, especially emphasizing the 24 hours (24-h) ambulatory blood pressure measurement (ABPM) [1, 2]. When interpreting ABPM, the average daytime, night-time, 24-

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h BP and night-day BP ratio are the variables mostly used in clinical practice [1-4]. The 24-h BP and night-day BP ratio are two indices well correlated with target organ damage and recognized as strong predictors for future cardiovascular (CV) outcome [1-5]. A BP non-dipping profile is usually associated with increased risk of cardiovascular events and mortality in hypertensive patients [1, 6, 7]. The exact etiology of non-dipping pattern is not well established but there are certain clinical conditions associated with lack of dipping such as obesity, sleep disorders, old age or high levels of daily physical exercise or volume overload [1, 8-10]. The aim of our study was to evaluate the impact of several cardiovascular risk factors with the dipping status assessed by 24-h ABPM.

Material and Methods

Study subjects

The current 4-year prospective study included newly diagnosed hypertensive patients according to the European guidelines definitions [1]. Patients were sent from general practitioners for evaluation at the Cardiovascular Rehabilitation Department of the Rehabilitation Hospital from Iasi, Romania. Exclusion criteria were a previous diagnosis of obstructive sleep apnea, type 1 diabetes mellitus, arrhythmias (e.g. atrial fibrillation), congestive heart failure and chronic kidney disease stage 2 or higher that are already known to interfere significantly with the BP variability [2, 11].

This study was carried out in accordance with the World Medical Association Declaration of Helsinki and was approved from an ethical standpoint by the Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania.

Study design

The following cardiovascular risk factors [1, 12, 13] were assessed: age, gender, rural/ urban residence, smoking, chronic alcohol consumption, personal history of stroke and type 2 diabetes mellitus. Manual BP values evaluation with a standard manual sphygmomanometer and electrocardiogram were done in order to exclude patients for which prompt initiation of drug treatment is recommended [1, 11]. Body mass index (BMI) was evaluated and obesity was defined as BMI ≥ 30 kg/m^2. According to current guidelines [1, 11] we defined chronic alcohol consumption as an intake of more than 20 g of ethanol per day in men and more than 10 g in women and smoking as current cigarette smoking. A transthoracic echocardiogram was performed to all patients for the detection of left ventricular hypertrophy (LVH), marker of hypertension target organ damage, with a LV mass index (LVMI) threshold of 115 g/m^2 for men and 95 g/m^2 for women [1]. Blood samples were obtained in the same day and the 24-h ABPM was initiated. The following biochemical markers were analyzed: total cholesterol, HDL and LDL cholesterol, triglycerides, creatinine and fasting plasma glucose. The dyslipidaemia was evaluated and defined according with ESC/EAS Guidelines [12]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14].

518 newly diagnosed hypertensive patients were included in the study group. The 24-h ABPM was done using a device MGY-ABP1 (SunTech Medical, Inc. Morrisville, NC, U.S.A.) according to current guidelines [1, 11, 15]. The device was mounted on the nondominant arm. An appropriate cuff was selected for each patient and inflated every 15 minute intervals during the day and 30 minute overnight. More than 70% of the 24-hour blood pressures should have been accurate in order to consider and interpret properly the results. The patients were asked to engage in their normal activities during the 24-hour measurement (avoiding excessive physical activity) and data were read next day.

We defined the BP variation according to the latest guidelines [1, 16]. Dipping profile was defined [1, 16] by a decrease of nocturnal systolic and diastolic BP between 10% and 20% compared with average daytime values as determined by ABPM while non-dippers had a nocturnal systolic and/or diastolic BP fall less than 10%; we included in this category both the reduced dipping (nocturnal BP fall between 1 and 10% of daytime values) and the actual non-dipping or rising subjects (with night/day BP ratio ≥ 1). A small number of patients with extreme dipping pattern [16] were excluded from the statistical analysis. The remaining 465 patients were divided into two groups according to their BP variability. The non-dipping profile group (ND was compared with the dipping group (D) according to the cardiovascular risk factors.

Table 1. Characteristics of the study population.

Variable	Dipper (n=261)	Non dipper (n=204)	p-value
Age, years	56.7±10.3	59.3±9.6	0.007
Gender (male)	99 (37.9)	85 (41.6)	0.414
Urban/rural (urban)	166 (63.6)	133 (65.1)	0.722
SBP (by ABPM), mmHg	136.4±13.7	138.7±12.23	0.103
DBP (by ABPM), mmHg	89.63±10.96	91.16±9.31	0.126
Hypertension grade	3 (1)	3 (1)	0.205
Smoker	79 (30.2)	52 (25.4)	0.256
Chronic alcohol consumption	56 (21.4)	62 (30.3)	0.028
BMI grade	2 (1)	3 (1)	0.021
Dyslipidemia	149 (57)	145 (71)	0.002
Cholesterol, mg/dl	200.6±44.2	211.2±45.2	0.011
Triglycerides, mg/dl	141.4±76.4	160.8±143.9	0.083
Type 2 diabetes mellitus	77 (29.5)	80 (39.2)	0.028
Left ventricular hypertrophy	130 (49.8)	118 (57.8)	0.085
Stroke	21 (8)	20 (9.8)	0.507
Chronic kidney disease	2 (1)	2 (1)	0.082
Urea, mg/dl	35.8±12.9	37.2±12.5	0.243
Creatinine, mg/dl	0.91±0.18	0.93±0.22	0.138
Creatinine clearance, ml/min	80.3±16.3	78.1±17.2	0.153

Data are expressed as mean ± SD, n (%), or median (interquartile range).
SBP – systolic blood pressure; DBP – diastolic blood pressure; ABPM – ambulatory blood pressure measurement; BMI – body mass index

Statistical analysis

Data analysis was performed using SPSS 16.0 (Statistical Package for the Social Sciences, Chicago, Illinois) and MedCalc 12.7.8 (Ostend, Belgium). Continuous variables were compared using the t-test for independent samples. Categorical comparisons were performed by chi-square test. Ordinal variables were compared using Mann-Whitney U Test. Variables characterized by significant difference ($p < 0.05$) between dipping and non-dipping profiles in the univariate analysis were analyzed in the multivariate analyses, applying logistic regression. This was used to identify the independent risk factors for the non-dipping profile, investigating for potential interactions and confounders. Odds ratio (ORs) with 95% confidence interval (CI) was used to report the results. A two-sided p value < 0.05 was considered significant for all data analyses. The area under receiver-operator characteristics (ROC) curve was analyzed in order to estimate the predictive accuracy of the combined independent risk factors.

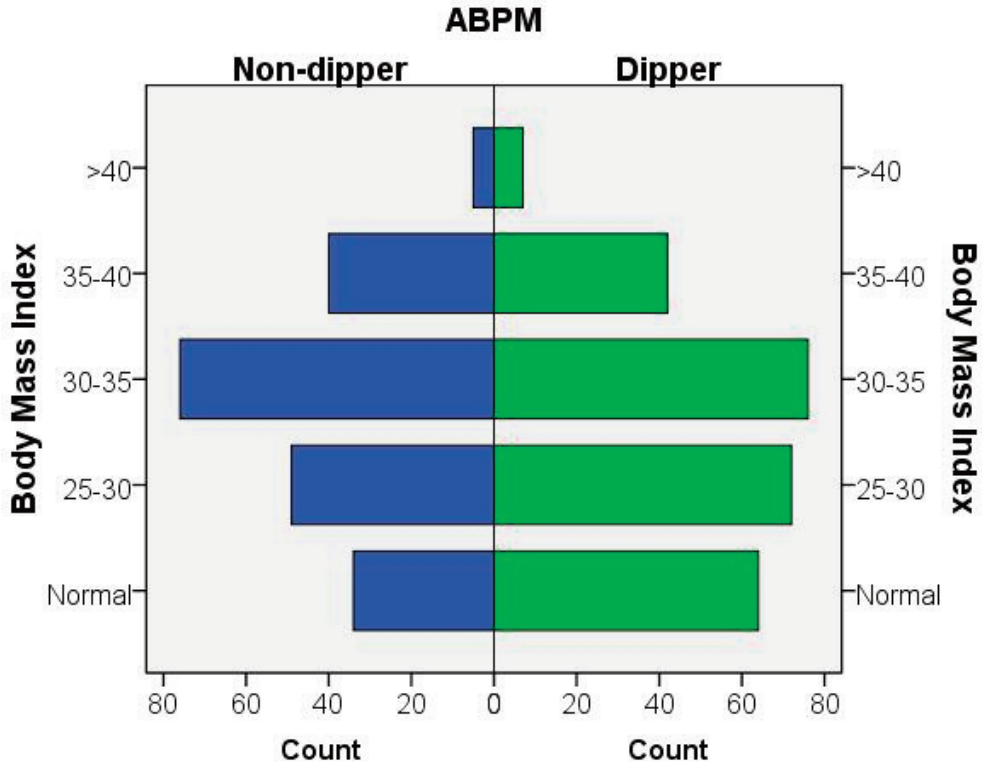

Figure 1. Obesity status in the non-dipping and dipping profiles.

Results

The study cohort included 465 hypertensive subjects, with 184 (39.5%) men. The mean age was 57.8 ± 10.1 (range 21–85) years. After reading of ABPM data, 204 (43.8%) patients were included in ND group and 261 (56.2%) were included in D group. Patients' demographics and the main risk factors were comparatively evaluated by univariate analysis (Table 1). The ND were significantly older (p = 0.007), but the gender profile was similar (p = 0.414) as compared to D. No significant differences were observed regarding urban residence (p = 0.722). Assessment of the BP before 24-h ABPM did not provide significant difference between groups of either systolic BP (SBP) (p = 0.103) or diastolic BP (DBP) (p = 0.126). Concerning cardiovascular risk factors, about ¼ of patients were smokers with no significant differences between the two groups (p = 0.256). Chronic alcohol consumption proved to be strongly associated with the ND profile (p = 0.028). As well, obesity was more frequently met in the ND patients (p = 0.019) with higher prevalence of BMI over 30 kg/m² as compared to the D group where most patients were classified as normal weight or overweight (Table 1, Figure 1). Personal history of stroke was met in less than 10% of patients in each group with no marked differences (p = 0.507). Type 2 diabetes mellitus (T2DM) was a more common pathology in the ND group (p = 0.028). Regarding the lipid values, ND group was associated with higher values only for total cholesterol (p = 0.01) and dyslipidemia presented positive correlation with the ND profile (p = 0.002). LVH was diagnosed echocardiographically in about half of patients from each group: 49.8% with dipper profile and 57.8% with non-dipper profile (p = 0.085). The renal function assessed by biochemical markers was relatively similar in the two groups with non-significant differences between groups for creatinine (p = 0.138) and estimate glomerular filtration rate (p = 0.153).

By applying the logistic regression model, age, serum cholesterol, chronic alcohol consumption and

Table 2. Independent predictors of the non-dipping profile after applying logistic regression.

Variable	Odds ratio	95% CI	p-value
Age	1.0282	1.0083 to 1.0484	0.0052
Cholesterol	1.0070	1.0027 to 1.0115	0.0016
Chronic alcohol consumption	1.7271	1.1197 to 2.6640	0.0135
Type 2 diabetes mellitus	1.4630	0.9703 to 2.2061	0.0694
Obesity	1.2159	1.0139 to 1.4580	0.0349

obesity were independently associated with the ND profile (Table 2). The ROC curves were constructed. The resulting area under ROC curve (AUC) for combined variables (Figure 2) was 0.648 with 95% confidence interval (0.602 to 0.691) indicating a moderate accuracy for detecting the ND profile. The AUC obtained for combined variables was higher than any of the four variables taken alone (Table 3).

Discussion

Our data sustain that a ND profile assessed by 24-hour ABPM is strongly associated with the presence of some easy to determine cardiovascular risk factors, especially older age, chronic alcohol consumption, obesity, hypercholesterolemia and T2DM. Some of our results prove to be consistent with those obtained in other studies

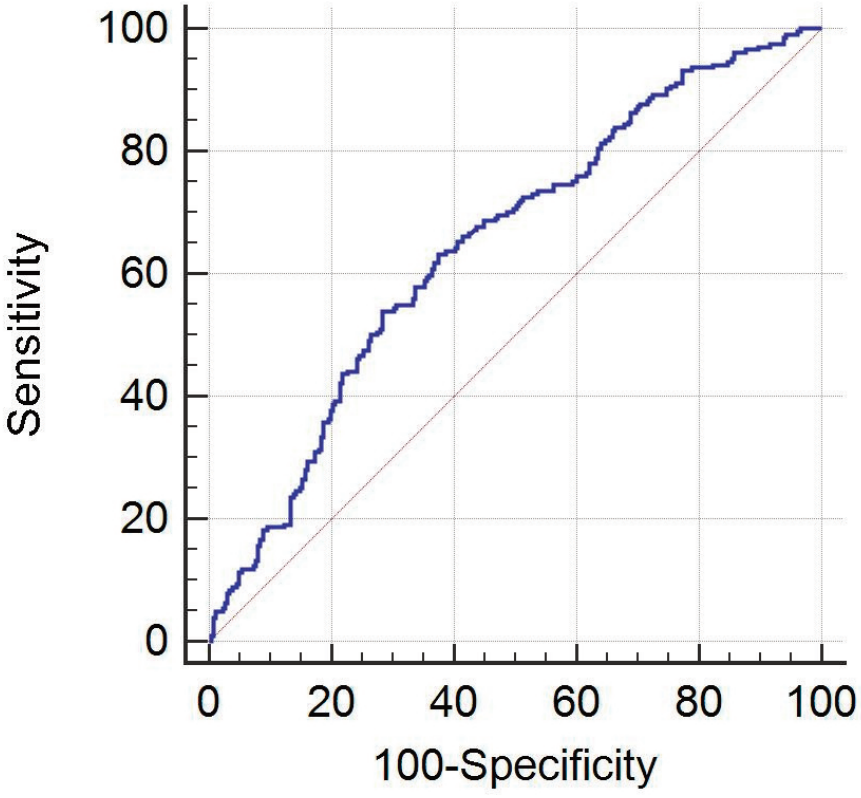

Figure 2. ROC curve of the logistic regression model obtained for predicting the non-dipping profile.

Table 3. The AUC obtained for each individual risk factor.

Variable	AUC	95% CI
Age	0.573	0.527 to 0.619
Cholesterol	0.562	0.515 to 0.608
Alcohol consumption	0.545	0.498 to 0.591
Body mass index	0.560	0.514 to 0.606

that correlate ABPM variability and its contributing factors but also point out some other cardiovascular risk factors associated with the ND profile such as chronic alcohol consumption.

The importance of a 24-hour ABPM is highlighted by all major international cardiovascular societies and the nocturnal BP variability represents an important marker of prognosis for the patients, both in hypertensive and in general population [1-3, 5, 11, 16].

Obesity and T2DM become widespread and present high prevalence rates especially in developing countries. These two pathologies are interconnected and bring an additional risk especially when they coexist with arterial hypertension and dyslipidemia and form the cardiometabolic syndrome. Our results have shown that obesity and high values of cholesterol are strongly associated to the ND profile, result that emphasizes the need for a better risk factor control in hypertensive patients. Eguchi et al. (2009) showed that night time BP variability, rather than abnormal diurnal BP values, is strongly associated with an increased risk of cardiovascular disease, especially in patients with type 2 DM [11]. One major study that used a registry comprising more than 40000 patients that performed a 24-hour BP continuous measurement concluded that a ND pattern is associated with increased age (over 60 years), presence of diabetes mellitus, obesity (BMI over 30 kg/m^2) and history of cardiovascular or renal disease emphasizing that ND patients present a higher cardiovascular risk [17]. Our data showed that T2DM correlated with the ND profile but could not be considered an independent prognostic factor ($p = 0.06$).

Older age is a well-known traditional cardiovascular risk factor. Our data indicate a significant difference in favor of a blunted BP nocturnal fall in elderly people which is consistent with the literature data. de la Sierra et al. (2009) revealed a direct correlation between advanced age and ND profile, both in untreated and treated hypertensive patients [17]. In another study comprising more than 9000 patients, an increased age was found in ND patients, with a higher prevalence both in men and women compared to younger patients (less than 50 years of age), but with no significant differences between genders [18]. Salwa et al. (2014) concluded as well that the ND pattern increased with age, resulting in a higher additional risk for elderly [19].

Hypercholesterolemia is a major cardiovascular risk factor and correlates well with future cardiovascular events [1, 12]. It is included in the 10-year risk of fatal cardiovascular disease SCORE chart, along with blood pressure values, thus representing an important target treatment in hypertensive dyslipidemic patients [12]. De la Sierra et al. proved that a ND profile is correlated with the presence of dyslipidemia, but only by analyzing the percentages of the patients (OR 1.05; 95% CI 1.01 – 1.10; $p = 0.035$) [17]. Our data showed that higher values of total cholesterol maintained the powerful relationship with the ND pattern (OR 1.007; 95% CI 1.002 – 1.011; $p = 0.0016$) suggesting that a rise with 10 mg/dl of total cholesterol could result in a plus 7% additional risk for developing a ND profile. So, total cholesterol is an independent risk factor for the ND pattern and this is, up to our knowledge, the first study that proves a direct correlation between the total cholesterol serum concentration and nocturnal BP variability.

Besides the traditional risk factors, a blunted nocturnal BP fall is associated with important target organ damage. Probably the most important cardiac structural alteration in hypertensive patients is the LVH that is recognized as a powerful predictor of cardiovascular complications and mortality [1]. In the present study, there is no significant differences regarding the presence of LVH between the two groups. However, it is well proven that the prevalence of LVH reaches higher levels in subjects with a ND profile, both in hypertensive and in normotensive patients [5, 20, 21]. Even if published articles sustain that a ND profile contributes to the renal impairment [22, 23], our data did not demonstrate any differences between D and ND groups.

Logistic regression showed that old age, high cholesterol, chronic alcohol consumption and obesity are

independently associated with the ND profile and their combination has a moderate accuracy for detecting the ND profile. However, the ROC curve (presented in figure 2) takes into account only several cardiovascular risk factors and could represent a starting point for future research in order to detect positive correlations between other risk factors and target organ damage for a better prediction of the ND profile in hypertensive patients.

Strengths and limitations

Our current study includes an important number of patients that were analyzed according to the 24-hour ABPM. Obtained results bring into perspective and emphasize the need for detection and interpretation of simple clinical parameters (age, T2DM, obesity, chronic alcohol consumption or hypercholesterolemia) that may identify the hypertensive patients that are at high risk of having a ND profile, thus commanding a more aggressive treatment and approach. On the other hand, this study has some limitations represented firstly by the sleep-related breathing disorders that could influence the 24-hour ABPM results [24]. When collecting data, we excluded the patients that have been already diagnosed with obstructive sleep apnea but the diagnosis may be underestimated in such a large hypertensive cohort. Secondly, we did not analyze other target organ damage as subclinical atherosclerotic markers [25, 26], because we focus mainly on cardiovascular risk factors routinely assessed as part of cardiovascular risk assessment in our geographic area.

Conclusions

The results of our study sustain the correlations of non-dipping pattern with age, obesity, dyslipidemias and T2DM. On the other hand, our data add the chronic alcohol consumption to other risk factors as older age, high serum values of total cholesterol and obesity to make a group of conditions that could act as independent predictors of the nocturnal BP non-dipping profile. Further studies are necessary to sustain these clinical conditions as possible indications for ambulatory BP monitoring in hypertensive patients.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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