Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

Correlation of nocturnal blood pressure pattern with dysautonomia in hypertensive patients with orthostatic hypotension

Codruţ Ciurea, Mariana Rădoi
[1] **Department of Cardiology, Faculty of Medicine, "Transilvania" University, Brasov, Romania.**

Abstract. The reduction of arterial baro-reflex sensitivity, evaluated by reduction of heart rate variability (HRV) indicates abnormalities in autonomous nervous system (ANS) activity, which is one of the mechanisms involved in changes of nocturnal blood pressure (BP) profile. The ANS dysfunction and its correlation with abnormal nocturnal BP pattern appear to be important in clinical practice for global cardiovascular risk stratification and therapeutic approach of hypertensive patients. Aim: Evaluation of ANS dysfunction by heart rate variability parameters in correlation with non-dipper profile of blood pressure in hypertensive patients with orthostatic hypotension. Patients and methods: We evaluated 88 patients with arterial hypertension (AH) and orthostatic hypotension (hTAO), 50 women (56.81%), 38 men (43.18%) and mean age of 68.02 ±9.02 years. The arterial hypertension profile was evaluated by 24 hours automatic ambulatory blood pressure monitoring (ABPM) and consequently 50 patients with non-dipper pattern were included in the group A (56.81%) and 38 patients with dipper pattern in the group B (43.18%). ANS dysfunction was evaluated non-invasively by heart rate variability (HRV) parameters in temporal domain - the standard deviation of the mean of all normal RR intervals 24 hours (SDNN) and in the frequency domain - high frequency spectral power (HF) and low frequency spectral power (LF), and LF/HF ratio, expression of the balance between sympathetic and parasympathetic activity. Results: Patients with non-dipper compared with those with dipper pattern of blood pressure had statistically significant lower mean values of SDNN [(63.88 ± 23.23 vs. 92.72 ± 27.41) ($p<0.001$)], illustrating an enhanced sympathetic tone. There were statistically significant differences between non-dipper and dipper pattern of BP regarding 24 hours LF/HF ratio [(1.86±0.56 vs. 2.51±0.89) ($p=0.001$]. Lower values of LF/HF ratio in nondipping versus dipping patients are determined by significant higher HF mean values in 24-hour [288.38±71.81 vs. 222.91±28.16 ($p<0.008$) which suggest an increased 24 hours parasympathetic activity. Conclusion: In hypertensive patients with orthostatic hypotension, dysautonomia is present both in patients with dipper and with non-dipper pattern of blood pressure. Non-dipping pattern present at half of hypertensive patients with orthostatic hypotension is associated with both significant HRV reduction as expression of increased of sympathetic activity and LF/HF reduction as expression of increased parasympathetic activity.

Key Words: autonomic nervous system dysfuntion, hypertension, orthostatic hypotension, non-dipper blood pressure pattern.

Corresponding Authors: C. Ciurea, e-mail: codrut_ciurea@yahoo.com

Introduction

The autonomic nervous system (ANS) has the key role in regulating blood pressure, arterial baro-reflex sensitivity being the main mechanism by which ANS influences the blood perfusion and vascular tone to adjust the changes of blood pressure. Clinical studies have shown the decrease of baroreflex sensitivity in elderly and hypertensive patients (Joyner et al 2008). The reduction of arterial baro-reflex sensitivity, evaluated by reduction of heart rate variability (HRV) indicates abnormalities in autonomous nervous system activity (Sztajzel 2004). The decreasing of HRV is associated with malignant arrhythmias and predicts the sudden cardiac death (Gerritsen et al 2001).
The reduction of arterial baro-reflex sensitivity is one of the mechanisms involved in changes of nocturnal BP profile, with the appearance of non-dipping pattern, a recognized risk factor for cardiovascular and cerebrovascular morbidity and for progression of renal disease (Routledge et al 2007; de la Sierra et al 2009; Verdecchia et al 1995).
Highlighting the autonomic dysfunction and its correlation with abnormal nocturnal blood pressure pattern appears to be important in clinical practice for global cardiovascular risk stratification and therapeutic approach of hypertensive patient.
The aim of the study was assessing of autonomic nervous system dysfunction by heart rate variability parameters in correlation with non-dipper profile of blood pressure in hypertensive patients with orthostatic hypotension.

Material and methods

The study was conducted in Brasov County Emergency Clinical Hospital from september 2013 to march 2014 and was approved by Ethics Committee of Faculty of Medicine, Brasov. Signed

informed consent was obtained from all subjects. All included patients were on anyhipertensive therapy.

In this study were included 88 patients (pts) with hypertension and orthostatic hypotension (hTAO), 50 women (56.81%), 38 men (43.18%) and mean age of 68.02±9.02 years. The diagnosis of hypertension was established according with 2013 ESH/ESC Guidelines for the management of arterial hypertension (Mancia et al 2013) and orthostatic hypotension was diagnosed on the criteria recommended by 2009 ESC update version of Guidelines for the diagnosis and management of syncope (Moya et al 2009).

The history of cardiovascular disease, smoking status and alcohol consumption (more than 21 U/week) data were collected. Patients were evaluated anthropometric [age, height, body mass index (BMI)] and by screening tests including fasting blood glucose, glycated hemoglobin A_1C, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglycerides and creatinine serum levels.

Obesity was diagnosed according to the value of BMI (≥ 30 kg/m^2) recommended by the WHO guidelines in 2012 (Jensen et al 2014). The diagnosis of diabetes was based on the 2014 American Diabetes Association criteria (ADA 2014). Chronic kidney disease was diagnosed by estimated glomerular filtration rate (EGFR) by the MDRD formula (Modification of Diet in Renal Disease) and chronic renal disease stages according to the criteria recommended by the Kidney Disease Outcome Quality Initiative ((K/DOQI) (Johnson et al 2004). Dyslipidemia was considered as controlled according to serum levels of LDL-cholesterol and total cholesterol and correlated with cardiovascular risk according with European Society of Cardiology Guidelines for the prevention of dyslipidemia 2011 (Catapano et al 2011).

The arterial hypertension profile was evaluated using information provided by 24 hours automatic ambulatory blood pressure monitoring (ABPM) and consequently 50 patients with non-dipper pattern were included in the group A (56.81%) and 38 patients with dipper pattern in the group B (43.18%) (BTL-08 ABPM II).

The diurnal and nocturnal SBP mean values and DBP mean values were appreciated considering diurnal time interval between 6: 00-22:00 hours and nocturnal time interval between 22: 00-6: 00 hours.

The autonomic nervous system dysfunction was evaluated non-invasively by heart rate variability (HRV) parameters in temporal domain - the standard deviation of the mean of all normal RR intervals 24 hours (SDNN) and in the frequency domain - high frequency spectral power (HF) and low frequency spectral power (LF), the LF/HF ratio being considerate to express the balance between sympathetic and parasympathetic nervous system activity (Holter ECG TLC 5000).

Data were analyzed using MedCalc software (v.9.2.1.0) and Statistics (v.4.7.0). Quantitative data were tested for normality of the distribution using Kolmogorov-Smirnov test. The differences of a quantitative variable between two groups were evaluated using the t test for independent variables or the Mann-Whitney test. Differences in the percentage of a nominal variable between two groups were tested using the Chi-square test. The correlation between two quantitative variables was tested using Spearman's rank correlation coefficient. Continuous variables with normal distribution were characterized by the mean ± SD. The results were interpreted as mean values±standard deviation (SD). The statistical significance threshold was chosen as p value <0.05.

Results

Clinical and laboratory data of the patients studied are shown in Table 1. Age and sex of patients did not differ significantly between the two groups.

Table 1. Clinical and laboratory data

Variable	Group A (n=50)	Group B (n=38)	p
Gender (female/male)	24F/26M	18F/20M	0.9
Age (years)	67.16±10.3	68.61±8.18	0.6
Smokers/non-smokers	19/31	15/23	0.8
Alcohol consumption yes/no	15/35	11/27	0.2
Physical activity yes/no	11/39	9/29	0.1
BMI (kg/m^2)	26.37±5.41	26.93±5.11	0.7
eGFR	67.35±16.22	78.65±31.8	0.1
Total Cholesterol (mg/dL)	201.23±27.87	178.61±24.21	0.007
LDL-Cholesterol (mg/dL)	126.61±34.11	115.34±53.42	0.3
Tryglicerides (mg/dL)	155.11±65.47	126.37±62.36	0.1
HDL-Cholesterol (mg/dL)	52.91±11.36	50.03±10.80	0.4
Glycated hemoglobin A_1C (%)	6.2±1.63	5.71±1.36	0.2

Ambulatory blood pressure monitoring values for diurnal and nocturnal BP in relation with non-dipper versus dipper pattern are shown in Tabel 2.

Tabel 2. ABPM values for diurnal and nocturnal BP

Variable	Group A (n=50)	Group 2 (n=38)	p
SBP diurnal mean (mmHg)	148.51±19.42	136.47±20.81	0.003
DBP nocturnal mean (mmHg)	126.68±16.03	113.81±14.66	0.01
SBP diurnal mean (mmHg)	92.74±16.83	86.33±13.62	0.08
DBP nocturnal mean (mmHg)	89.53±15.63	77.88±15.29	0.002

The non-dipper profile in hypertensive patients with orthostatic hypotension was associated statistically significant with very high additional cardiovascular risk, both in patients with grade 1 (p=0.04) and in those with grade 2 and 3 of arterial hypertension (p=0.009).

The ABPM recordings showed that the diurnal mean value of SBP was associated with non-dipper profile of blood pressure (p=0.001). There was a statistically significant association between nocturnal mean value of DBP and non-dipper profile of

blood pressure (p=0.002). Mean arterial pressure was statistically significantly association with non-dipper pattern of hypertension (p=0.02).
These data supports significantly higher sympathetic tone in patients with non-dipper profile of blood pressure. There was a statistically significant association between CKD (eGFR <60 ml/min/1.73m^2 BS) and SDNN <100 msec (p=0.004).
The lower LF/HF ratio in patients with non-dipper versus those with dipper profile is caused by significantly increasing in HF values which strongly suggest a higher parasympathetic activity in these patients (Table 3).

Table 3. ABPM values for 24 hr BP and HRV parameters

Variable	Group A (n=50)	Group B (n=38)	p
SBP	150.23±21.38	135.4±22.07	0.02
DBP	89.84±13.98	80.66±14.01	0.03
MAP (mmHg)	110.22±14.96	98.79±15.37	0.01
PP (mmHg)	60.38±15.33	54.5±18.95	0.2
SDNN	63.88±23.23	92.72±27.41	<0.001
LF	582.16±136.82	561.55±89.21	0.3
HF	288.38±71.81	222.91±28.16	0.008
LF/HF	1.868±0.56	2.517±0.89	0.001

MAP = mean arterial pressure, 24 hrs mean value; PP = pulse pressure, 24 hrs mean value.

Discussions

The ABPM is indicated in diagnosis of hypertension including the "white coat", masked, resistant hypertension and of orthostatic, postprandial and antihypertensive drugs induced hypotension. The ABPM is also recommended for prognosis estimation in hypertensive patients by assessing the HRV parameters and nocturnal pattern of blood pressure (Mancia et al 2013).
Nocturnal decreasing of BP is a physiological feature circadian variations of blood pressure as demonstrated by Hill since 1898. The absence of more than 10% in nocturnal decreasing of blood pressure, described as non-dipper pattern, has been reported in patients with type 2 diabetes having normal or elevated blood pressure (Poantă et al 2010), patients with obesity (Eguchi et al 2011) sleep apnea (Wolf et al 2010), chronic kidney disease (Elung-Jensen et al 2008) and orthostatic hypotension (Carmona et al 2003). Non-dipper profile was correlated with decreased renal ability to excrete sodium and autonomic dysfunction caused by the relative increase in sympathetic tone (Oded et al 2009). Non-dipper blood pressure profile was associated with serious outcomes through increased risk for left ventricular hypertrophy, cerebrovascular disease and cardiovascular events (Verdecchia et al 1992).
HRV parameters evaluation for estimating autonomic dysfunction still sparks discussion and controversy. It is estimated that LF component is sympathetic modulated, while HF component reflects parasympathetic vagal activity and LF/HF ratio expresses the balance between sympathetic and parasympathetic system, a ratio LF/HF> 3 being the expression of sympathetic hyperactivity (Circulation 1996). Among the temporal parameters: the standard deviation of the mean of all normal RR intervals of 24 hours (SDNN) estimates the global autonomic tonus, SDNN values below 70 msec being associated with an increased cardiovascular risk (La Rovere et al 1998).
Guzzetti et al showed that patients with essential hypertension had higher values of LF and lower HF values compared to normotensive patients, changes influenced by the grade of hypertension (1988). Autonomic dysfunction assessed by reducing of HRV parameters or by LF/HF ratio changes were described in elderly hypertension (Tomi et al 2004, Xiaobo et al 2014), diabetes mellitus often related to diabetic neuropathy (Koçer et al 2005), chronic renal disease (Protasov et al 2010), obesity and hyperinsulinemia (Emdin et al 2001).
In our study, half of hypertensive patients with orthostatic hypotension had non-dipper pattern, statistically significant correlated with lower SDNN values, suggesting an sympathetic activity in these patients.
In hypertensive patients with non-dipper profile versus the dipper profile, LF/HF ratio values were lower due to significant increasing of HF component, data suggesting an increased 24 hours parasympathetic activity. The increased parasympathetic activity in patients with nondipper profile of blood pressure do not have major influence the HRV that remain statistic significant lower in these patients. This aspect suggest that in hypertensive patients with orthostatic hypotension dysautonomia is characterized both by increasing sympathetic and the parasympathetic activity, with influence of sympathetic hyperactivity on HRV, which remain significantly lower in nondipper patients. It is to stress that in our study the SDNN values, characterizing the HRV reduction, were in both groups lower than 100 msec. Several clinical studies showed that SDNN value <100 msec is an important parameter of prognosis assessment of patients with myocardial infarction (Doulalas et al 2001), congestive heart failure due to ischemic or idiopathic dilated cardiomyopathy (Ponikowski et al 1997), chronic pulmonary disease (Chen et al 2006).
Our data suggest a complex dysautonomia at hypertensive patients with othostatic hypotension, which may be involved in both orthostatic hypotension and may influence the serious prognosis of these patients (Mancia et al 2009, Luukinen et al 1999).

Conclusions

In hypertensive patients with orthostatic hypotension, dysautonomia is present both in patients with dipper and with non-dipper profile of blood pressure. Non-dipper profile present at half of hypertensive patients with orthostatic hypotension is associated with significant reduction of HRV and LF-HF ratio as expression of increasing in sympathetic respectively in parasympathetic activity.

References

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37 (Suppl 1):S81-90.

Carmona J, Amado P, Vasconcelos N, et al. Does orthostatic hypotension predict the occurrence of nocturnal arterial hypertension in the elderly patient? Rev Port Cardiol 2003;22(5):607-15.

Catapano AL, Reiner Z, De Backer G, et al. European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011;217(1):3-46.

Chen WL, Chen GY, Kuo CD. Hypoxemia and autonomic nervous dysfunction in patients with chronic obstructive pulmonary disease. Respir Med 2006;100(9):1547-53.

de la Sierra A, Redon J, et al Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry Investigators. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. Hypertension 2009;53(3):466-72.

Doulalas AD, Flather MD, Pipilis A, et al. Evolutionary pattern and prognostic importance of heart rate variability during the early phase of acute myocardial infarction. Int J Cardiol 2001;77(2-3):169-79.

Eguchi K. Ambulatory blood pressure monitoring in diabetes and obesity-a review. Int J Hypertens 2011;954757.

Elung-Jensen T, Strandgaard S, Kamper AL. Longitudinal observations on circadian blood pressure variation in chronic kidney disease stages 3-5. Nephrol Dial Transplant 2008;23(9):2873-8.

Emdin M, Gastaldelli A, Muscelli E, et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: effects of weight loss. Circulation 2001;103;513–519.

Gerritsen J, Dekker JM, TenVoorde BJ, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. Diabetes Care 2001;24(10):1793-8.

Guzzetti S, Piccaluga E, Casati R, et al. Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. J Hypertens 1988;6(9):711-7.

Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93(5):1043-65.

Hill L. On rest, sleep, and work and the concomitant changes in the circulation of the blood. Lancet 1898;1:282-285.

Jensen MD, Ryan DH, et al 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014;129(25 Suppl 2):S102-38.

Johnson CA, Levey AS, Coresh J, et al. Clinical practice guidelines for chronic kidney disease in adults: Part I. Definition, disease stages, evaluation, treatment, and risk factors. Am Fam Physician 2004;70(5):869-76.

Joyner MJ, Charkoudian N, Wallin BG. A sympathetic view of the sympathetic nervous system and human blood pressure regulation. Exp Physiol 2008;93(6):715-24.

Koçer A, Aktürk Z, Maden E, et al. Orthostatic hypotension and heart rate variability as indicators of cardiac autonomic neuropathy in diabetes mellitus. Eur J Gen Med 2005;2(1):5-9.

La Rovere MT, Bigger JT Jr, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998;351(9101):478-84.

Luukinen H, Koski K, Laippala P, et al. Prognosis of diastolic and systolic orthostatic hypotension in older persons. Arch Intern Med 1999;159(3):273-80.

Mancia G, Fagard R, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31(7):1281-357.

Mancia G, Grassi G. Orthostatic hypotension and cardiovascular risk: defining the epidemiological and prognostic relevance. Eur Heart J 2010;31(1):12-4.

Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009;30(21):2631-71.

Oded Friedman, Alexander G Logan. Can nocturnal hypertension predict cardiovascular risk? Integrated Blood Pressure Control 2009:2 25–37.

Poantă L, Cerghizan A, Pop D. Blood pressure pattern and heart rate variability in normotensive patients with type 2 diabetes mellitus. Rom J Intern Med 2010;48(4):321-7.

Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1997;79(12):1645-50.

Protasov K, Dzizinsky A, Sinkevich D. Reduction in heart rate variability in Patients with hypertensive chronic kidney Disease. Journal of Hypertension 2010;28(e-Supplement A):e160.

Routledge FS, McFetridge-Durdle JA, Dean CR; Canadian Hypertension Society. Night-time blood pressure patterns and target organ damage: a review. Can J Cardiol 2007;23(2):132-8.

Sztajzel J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly 2004;134(35-36):514-22.

Tomi Laitinen, Leo Niskanen, Ghislaine Geelen, et al Age dependency of cardiovascular autonomic responses to head-up tilt in healthy subjects. J Appl Physiol 2004;96:2333–2340.

Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. Hypertension 1994;24(6):793-801. Erratum in: Hypertension 1995;25(3):462.

Verdecchia P, Schillaci G, Boldrini F, et al. Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular events. Circulation. 1992;86(suppl I):I-678.

Wolf J, Hering D, Narkiewicz K. Non-dipping pattern of hypertension and obstructive sleep apnea syndrome. Hypertens Res 2010;33(9):867-71.

Xiaobo Qin, Qin Zhang, Suping Yang, et al Blood Pressure Variability and Morning Blood Pressure Surge in Elderly Chinese Hypertensive Patients. J Clin Hypertens (Greenwich) 2014;16:511–517.

Authors

•Codruţ Ciurea, Department of Cardiology, Faculty of Medicine, "Transilvania" University, 56 Nicolae Balcescu Street, Brasov, Romania, EU, email: codrut_ciurea@yahoo.com

•Mariana Rădoi, Department of Cardiology, Faculty of Medicine, "Transilvania" University, 56 Nicolae Balcescu Street, Brasov, Romania, EU, email: mradoi_unitbv@yahoo.com

Citation	Ciurea C, Radoi M. Correlation of nocturnal blood pressure pattern with dysautonomia in hypertensive patients with orthostatic hypotension. HVM Bioflux 2015;7(1):1-5.
Editor	Ștefan C. Vesa
Received	8 December 2014
Accepted	21 December 2014
Published Online	29 December 2014
Funding	None reported
Conflicts/ Competing Interests	None reported