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Prognostic Role of Melatonin in the Assessment of the Hypertension Clinical Course

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Abstract

Background: Sleep disorders are one of the most common problems in patients with arterial hypertension (AH). Circadian blood pressure (BP) cycles are most likely associated with the regulatory influence of melatonin. However, in patients with hypertension, if melatonin production decreases there is no adequate decrease of BP during sleep. The purpose of this study was to analyze the quality of sleep, chronotypes, and clinical, instrumental and laboratory parameters depending on urinary melatonin level (UML) to determine a prognosis for the course of AH in patients with insomnia.

***Methods and Results*:** We examined 178 patients with AH and insomnia aged from 30 to 70 years (mean age of 61.3±0.92 years). The AH diagnosis was based on 2018 ESC/ESH Guidelines for the management of arterial hypertension and Russian Society of Cardiology Clinical guidelines – Arterial hypertension in adults (2020). The insomnia diagnosis was based on the international classification of sleep disorders (2005). Using Multiple Regression Analysis, we determined the factors that influence the levels of systolic BP (SBP) and diastolic BP (DBP) in AH patients with insomnia.

AH patients with insomnia have a more severe clinical course of the disease, with frequent requests for medical help, a*ltered* BP variability, high anxiety level, high depression level and low level of the quality of life. The patients with AH and insomnia have low UML, which correlated with hypertension grade, chronotypes, high systolic and diastolic BP, BMI, high depression level, and low level of the quality of life in the physical and psychological domains.

Conclusion: The developed methods for calculating the levels of SBP and DBP, depending on UML, body mass index, depression level, and PSQI, allow reliably evaluating and controlling the BP level in AH patients with insomnia. (**International Journal of Biomedicine. 2020;10(3):231-234.**)

Key Words: arterial hypertension • insomnia • chronotype • quality of life

Abbreviations

AH, arterial hypertension; **BP**, blood pressure; **BoP**, bodily pain; **BMI**, body mass index; **DBP**, diastolic BP; **DL**, depression level; **GH**, general health; **MEQ**, Morningness-Eveningness Questionnaire; **MH**, mental health; **PF**, physical functioning; **PSQI**, The Pittsburgh Sleep Quality Index; **QL**, the quality of life**; RP**, role-physical functioning; **RE**, role emotional; **SF-36**, the 36-Item Short-Form Health Survey; **SF**, social functioning; **SBP**, systolic BP; **STAI**, State-Trait Anxiety Inventory; **UML**, urinary melatonin level; **VAS**, the 10-point Visual Analogue Scale; **VC**, vital capacity; **VT**, vitality; **WC**, waist circumference.

Introduction

According to the latest data from the World Health Organization, the Russian Federation established itself as a leader among developed countries in terms of cardiovascular mortality.[1] In addition, diseases of the cardiovascular system are the main cause of disability in Russia. One such disease, AH, is associated with severe complications, with temporary incapacity and permanent disability.[2] AH is one of the most common precursors of chronic heart failure. In 70.0% of cases, AH forecasts chronic heart failure.[3]

Sleep disorders are one of the most common problems in cardiovascular diseases, including AH.[4] According to various studies from European countries, the prevalence of chronic

insomnia is from 5.7% to 19.0% of the population.[5] Sleep is the main modulator of the pulmonary and cardiovascular systems, both in norm and in pathology.[6-8]

Melatonin is a hormone that is synthesized by the pineal gland cells and regulates the sleep-wake cycle. Melatonin also has significant antioxidant properties and carries out hormonal regulation of the circadian rhythm of the peripheral organs through appropriate receptors. Normally, BP during sleep is significantly lower than during the wakefulness period. Circadian BP cycles are most likely associated with the regulatory influence of melatonin.[9]

However, in patients with hypertension, if melatonin production decreases there is no adequate decrease of BP during sleep. In addition, melatonin can play the role of an adaptogen in weather-sensitive persons.[10]

To indicate the individual characteristics of the organization of circadian rhythms, the term «chronotype» is proposed. Neurophysiologist N. Kleitman, Swedish psychologist O. Okvist, as well as J. Horn and O. Ostberg, actively studied various aspects of the rhythmic functions of human organs and systems, including human chronotypes.[11]

Three varieties of chronotype were identified: morning ("Larks"), intermediate ("Dove") and evening ("Owl"). However, there are no pronounced boundaries between these three chronotypes.[12] Therefore, for research purposes, a more detailed gradation is used, for example, five chronotypes: definitely a morning type ("Lark"), moderate morning type, indifferent type ("Dove"), moderate evening type, and definitely an evening type ("Owl").[13]

The purpose of this study was to analyze the quality of sleep, chronotypes, and clinical, instrumental and laboratory parameters depending on UML to determine a prognosis for the course of AH in patients with insomnia.

Materials and Methods

We examined 178 patients (98/55.1% men and 80/44.9% women) with AH and insomnia aged from 30 to 70 years (mean age of 61.3±0.92 years). The AH diagnosis was based on 2018 ESC/ESH Guidelines for the management of arterial hypertension and Russian Society of Cardiology Clinical guidelines – Arterial hypertension in adults.[14,15] The insomnia diagnosis was based on the international classification of sleep disorders.[16]

The study was approved by the Ethics Committee of Voronezh State Medical University named after N.N. Burdenko. Written informed consent was obtained from each patient.

A comprehensive clinical examination and laboratory tests included the following procedures:

•Assessment of AH severity (visits to the general practice doctor, calls to emergency service, and hospital admissions for the past 12 months)

•Quantity assessment of arterial hypertension symptoms (headache, vertigo, seeing spots, general weakness) by VAS

•Anthopometrical reference data: BMI was calculated using Quetelet's formula (in kg/cm^2). WC was measured using centimetric tape at the navel level on a horizontal line (in cm).

•Assessment of individual chronotype by MEQ[17]

•Assessment of insomnia by PSQI

•Functional test: 24-hour BP monitoring.

•Laboratory test: UML(ng/ml)

•Assessment of psychosomatic disorders (anxiety level, depression level) by STAI and Zung Self-Rating Depression Scale

•Assessment of QL by SF-36

All data was evaluated with STATGRAPHICS Plus 5.1. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SD for continuous variables. Student's unpaired t-test was used to compare two groups for data with normal distribution. A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

According to clinical examination results, AH Grades 1, 2 and 3 had 15/8.4%, 110/61.8%, and 53/29.8% patients, respectively.

Assessment of AH severity demonstrated that the number of visits to the general practice doctor was 2.67±0.11 per year, calls to emergency service – 1.0±0.32 per year, and hospital admissions – 0.7±0.11 per year.

Results of quantity assessment of AH symptoms by VAS: headache - 5.1±0.10, vertigo - 3.32±0.15, seeing spots - 2.2±0.09, and general weakness - 7.01±0.16.

According to anthopometrical reference data, 30/16.8% patients had normal weight; 90/50.6% patients were overweight; 49/27.5% patients had first-degree obesity; 9/5.1% patients had second-degree obesity.

According to MEQ, there were five chronotypes: definitely a morning type ("Lark") in 14/7.9% patients, moderate morning type in 17/9.5% patients, indifferent type ("Dove") in 100/56.2% patients, moderate evening type in 22/12.4% patients, and definitely an evening type ("Owl") in 25/14.0% patients.

In patients with AH and insomnia, PSQI was 8.61±0.31, which demonstrates poor sleep quality.

According to 24-hour BP monitoring, average daily BP (SBD/DBP) was 153±4.2/83±3.2mmHg, average daytime BP was 160±3.2/92±2.9mmHg, and average nighttime BP was 141±2.9/79±3.1mmHg. According to SBP night decrease, 6/3.4% patients were dippers, 80/44.9% patients were non-dippers, 89/50.0% patients were night-dippers, and 3/1.7% patients were over-dippers.

According to DBP night decrease, 5/2.8% patients were dippers, 79/44.4% patients were non-dippers, 88/49.4% patients were night-dippers, and 6/3.4% patients were over-dippers.

UML was 11.49±1.56 ng/ml.

According to STAI, there were patents with high and medium state and trait anxiety (Table 1). According to the Zung Self-Rating Depression Scale, there were patients without depression, with mild (neurotic) depression, and masked depression. There were not patients with true depression (Table 2).

Table 1.

The State-Trait Anxiety Inventory

Variable	Patients in with AH and insomnia, n=178			
	State anxiety		Trait anxiety	
	n	%	n	%
High Medium Low	120 58 -	67.4 32.6 -	103 75 -	57.9 42.1 -
The average values	47.43±1.02		46.88±0.73	

Table 2.

Zung Self-Rating Depression Scale

Variable	Patients in with AH and insomnia, n=178	
	absolute	%
No depression Mild (neurotic) depression Masked depression True depression	40 83 55 -	22.5 46.6 30.1 -
The average values	57.41±1.08	

Patients with AH and insomnia demonstrated a low level of QL in the physical and psychological domains, according to SF-36 (Table 3).

Table 3.

SF-36 parameters in patients with AH and insomnia, n=178

Variable	Average values	Variable	Average values
PF	45.56±1.11	VT	52.05±1.13
RP	42.25±1.02	SF	49.16±1.14
BoP	41.97±1.35	RE	41.89±1.21
GH	53.15±1.27	MH	52.78±1.07

The performed correlation analysis between UML and the indicators characterizing the clinical course of AH, BP levels, AH symptoms, chronotypes, PSQI, anxiety level, DL, and the QL revealed statistically significant values of correlations. UML correlated with hypertension grade (r=-0.102258433; $P<0.05$) and significant differed depending on hypertension grade: 32.56±1.64 in Grade 1, 13.14±1.02 in Grade 2, and 3.05±0.11 in Grade 3 (F=77.44; $P=0.0003$).

UML also correlated with chronotypes (r=-0.108763549; $P<0.05$) and significantly differed depending on chronotypes: 29.18±1.04 in definitely a morning type, 21.11±0.89 in moderate morning type, 15.13±1.02 in indifferent type, 9.14±0.23 in moderate evening type, and 2.17±0.22 in definitely an evening type (F=38.49; $P=0.0001$).

Low UML correlated with high SBP (r=-0.205125635; $P<0.05$), high DBP (r=-0.104202288; $P<0.05$), BMI (r=0.041247740; $P<0.05$), high PSQI (r=-0.289759602; $P<0.05$), high state anxiety level (r=-0.213676388; $P<0.05$), high trait anxiety level (r=-0.177919008; $P<0.05$), high depression level (r=-0.283007396; $P<0.05$), and low level of QL in the domains PF (r=0.123196233; $P<0.05$), GH (r=0.152036746; $P<0.05$), VT (r=0.233206665; $P<0.05$), SF (r=0.118219426; $P<0.05$), RE (r=0.121586436; $P<0.05$), and MH (r=0.145305371; $P<0.05$).

Using Multiple Regression Analysis, we determined the factors that influence the levels of SBP and DBP in AH patients with insomnia. We calculated regression models, where the levels of SBP and DBP were chosen as the dependent variable.

The regression model for SBP level:

SBP=79.1142–0.487361×UML+2.10585×BMI+0.570448×DL–1.52905×PSQI.

The regression model for DBP level:

DBP=84.7495–0.585358×UML+1.84045×PSQI.

There was a statistically significant relationship between the variables at the 99% confidence level (P<0.05).

The models we developed allow reliably evaluating and controlling the BP level in AH patients with insomnia.

Example 1

A 52-year-old patient with AH Grade 1, moderate evening chronotype, UML–13.12, BMI–24.4, DL–59, and PSQI–6.

The levels of SBP and DBP by regression model were 148.58483568 and 92.11230304, respectively. Thus, the patient's BP was 149/92 mmHg, which corresponded to AH Grade 1 and confirmed the correctness of the calculation.

Example 2

A 63-year-old patient with AH Grade 3, definitely an evening chronotype ("Owl"), UML–1.56, BMI–37.18, DL–65, and PSQI–15.

The levels of SBP and DBP by regression model were 170.79266984 and 111.44309152, respectively. Thus, the patient's BP was 170/111 mmHg, which corresponded to AH Grade 3 and confirmed the correctness of the calculation.

In conclusion, AH patients with insomnia have a more severe clinical course of the disease, with frequent requests for medical help, altered BP variability, insufficient decrease of BP at night, high anxiety level, high DL and low level of QL. The patients with AH and insomnia have low UML, which correlated with hypertension grade, chronotypes, high systolic and diastolic BP, BMI, high DL, and low level of QL in the physical and psychological domains. The methods we developed for calculating the levels of SBP and DBP, depending on UML, BMI, DL, and PSQI, allow reliably evaluating and controlling the BP level in AH patients with insomnia.

Competing Interests

The authors declare that they have no competing interests.

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