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Mustafayeva A.H.

CHARACTERISTICS OF CHANGES IN BLOOD PRESSURE AND HEART RHYTHM DISTURBANCES IN PATIENTS WITH METABOLIC SYNDROME

AZERBAIJAN MEDICAL UNIVERSITY, BAKU, AZERBAIJAN

SUMMARY

The purpose of this work is to analyze the daily levels of blood pressure and heart rate variability in patients with signs of metabolic syndrome.

Materials and methods. In the period from 2013 to 2016, 364 patients of the age from 20 to 80 (200 men and 164 women) with newly diagnosed MS were prospectively examined. Daily ECG monitoring applying the Holter method was performed with the help of Cardiomax system (USA), in compliance with the standard method for diagnosing paroxysmal forms of arrhythmia and stress and painless forms of ischemia. V2, V5 and avF derivations were registered.

Results. The maximum daily average values of systolic and diastolic blood pressure recorded in patients of the 61 to 80 age group were the following: systolic BP – 156.9±3.5 mm Hg diastolic BP – 96.2±4.1 mm Hg

The heart rate variability analysis showed that the value of circadian index in patients of the third age group was significantly lower (1.14±0.12) than in patients of the first and second groups, amounting

to respectively 1.2±0.11 and 1.19±0.13. Besides, we noticed an increase of daytime and night Ps levels (up to 79.0±9.0 and 66.5±4.1 BPM) in patients of the second group compared to the first group, where the values of these indicators were respectively 75.4±8.4 and 60.6±6.2 BPM. Heart rate variability at different times of day depending on age indicate adverse changes in the autonomic regulation of cardiac activity alongside with increasing the age of patients with MS. With the increase of age in patients with MS, the rate of detecting cardiovascular complications risk factors steadily grows.

Conclusion. It is necessary to conduct dynamic monitoring for patients with symptoms of metabolic syndrome in order to identify signs of cardiovascular system state disturbances, blood pressure and heart rate in particular.

Keywords: *metabolic syndrome, heart rhythm, excess weight, blood pressure*

Information about the author:

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| Corresponding author: Ainur Hamlet qızı Mustafayeva | PhD, Assistant, Azerbaijan Medical University, Department of Internal Diseases. Tel. +994124657223, AZ1014, Ave. Bulbul 40, e-mail: doc-jak@mail.ru |
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✉ doc-jak@mail.ru

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About 25% or 1.7 billion people in the global population are overweight, and more than 312 million people are massively obese [1, 2]. It is commonly recognized that obesity acts as a risk factor for many diseases. [3]. It is believed that body weight is a significant factor affecting the functional state of the body, contributing, in particular, to the development of autonomic dysfunction. To a great extent, this applies to relatively young people with metabolic syndrome (MS), since it is known that neuroendocrine disorders often develop during puberty, alongside with the development of autonomic dysfunction syndrome [4-6].

Changes in blood pressure (BP) and cardiac arrhythmia are recognized as one of frequent manifestations indicating pathology of the cardiovascular system in MS, as it was demonstrated in several studies [7, 8]. Obesity has proven to be a factor predisposing to the development of atrial fibrillation (AF) [9-12].

The statements above indicate the relevance of studying the characteristics of fluctuations in blood pressure and heart rhythm disturbances in patients with excess weight. In this case, as we know, evaluation of heart rate variability (HRV) provides an

opportunity to characterize the signs of imbalance in the activity of the sympathetic and parasympathetic parts of the autonomic nervous system. Application of this approach allows to determine the adaptive reserves and stress resistance of the body, as well as identify patients with a high risk of cardiovascular complications and monitor the effectiveness and safety of the prescribed therapy.

The purpose of this work is to analyze the daily levels of blood pressure and heart rate variability in patients with signs of metabolic syndrome.

MATERIALS AND METHODS

The study was carried out at the premises of the educational and therapeutic building of Azerbaijan Medical University. In the period from 2013 to 2016, 364 patients of the age from 20 to 80 (200 men and 164 women) with newly diagnosed MS were prospectively examined. The patients were divided into groups according to their age: 104 patients – 20 to 40 years old, 131 patient – 41 to 60 years old and 129 patients at the age of 61 and older. To study the characteristics of the MS course in these categories of patients, a clinical examination was conducted including the study

of patients' complaints and anamnesis, using clinical, instrumental and laboratory examination methods.

The study included patients with various manifestations of MS: overweight and/or various degrees of obesity, abdominal obesity (AO), arterial hypertension (AH), impaired glucose tolerance (NTG) and/or type 2 diabetes mellitus (DM2), dyslipidemia (DLP). Among the criteria for patients to be excluded from the study were: symptomatic hypertension, unstable angina, atrial fibrillation, signs of heart failure, a history of cerebral circulation, myocardial infarction in history, chronic nonspecific lung diseases, kidney and liver disorders. The study also did not include patients receiving continuous drug therapy for hypertension, exertional angina or type 2 diabetes mellitus, as well as taking glucocorticoids, oral contraceptives, nonsteroidal anti-inflammatory drugs, consuming more than 50 g of alcohol daily.

The definition provided by the International Diabetes Federation (2005) was applied for diagnosing metabolic syndrome, according to this definition, abdominal obesity is considered as the main component for diagnosing MS:

- abdominal obesity: waist circumference for men >94 cm, for women >80 cm, in combination with two or more of the following components:
- arterial hypertension: the level of SBP amounts to >130 mm Hg and/or DBP is >85 mm Hg;
- hypertriglyceridemia, with a concentration of triglycerides >1.7 mmol/l;
- low cholesterol of high density lipoproteins, <1 mmol/l for men and 1.3 mmol/l for women;
- hyperglycemia, in case when the fasting plasma glucose level is >6.1 mmol/l.

In order to diagnose arrhythmias, myocardial hypertrophy of the left ventricle (LV) and left atrium (LA), the electrical instability of the myocardium was evaluated by the following parameters:

- intervals RR, PQ, QRS, QT, QTc;
- the range and polarity of peaks P, R, S and T;
- disorders in the repolarization phase of the ventricular system end segments (ST segment depression and T wave alternation).

QTc interval, corrected with heart rate (HR), was determined according to the Bazett formula:

$$QTc = QT / \text{the square root of RR (1)}$$

Daily ECG monitoring applying the Holter method was performed with the help of Cardiomax system (USA), in compliance with the standard method for diagnosing paroxysmal forms of arrhythmia and stress and painless forms of ischemia. V2, V5 and aVF derivations were registered. The average, minimum and maximum heart rate during the day, night and the day period, the circadian index, the main rhythm and rhythm disturbances were taken into account, which includes: supraventricular and ventricular ectopic activity with gradation of degrees according to Lown-Wolff, ST-T dynamics during the period of rest and during exercise, diagnostically significant changes in the ST segment of the ischemic type, episodes of painless myocardial ischemia.

The circadian index (CI) was calculated as a ratio of the average values of daytime heart rate per minute to the average value of nighttime heart rate per minute. The circadian index is a reliable prognostic indicator regarding the hemodynamics state, reflecting the influence of the sympatho-adrenal system on the heart.

Within the framework of daily ECG monitoring, heart rate variability (HRV) was studied applying the R.M. Bayevsky method of spectral analysis of variation pulsometry with creating a dynamic series of cardio-intervals (tachogram) and subsequent evaluation of the parameters of the temporal (intervalogram) and spectral analysis of HRV (spectrogram) [13].

Analysis of HRV indicators made it possible to assess the autonomic tone and the presence of the autonomic nervous system (ANS) dysfunction, since it is known that development of MS is accompanied by a decrease in vagal activity and imbalances in the ANS influence on the sinus rhythm in favor of the sympathetic section. These changes correspond to those observed in the early stages of CHD and NTG / type 2 diabetes mellitus development [14].

HRV was assessed by short 5-minute intervals on the daily record in the waking state and during sleep, while considering the following parameters:

- SDNN – standard deviation from the average duration for all sinus intervals R-R;
- PNN50 – differences between successive R-R intervals greater than 50 ms, %.

We also studied the parameters of HRV spectral analysis with calculating the power spectrum of oscillations within three frequency ranges: 0.004-0.08 Hz (very low frequencies – VLF); 0.09-0.16 Hz (low frequencies – LF); 0.17-0.5 Hz (high frequencies – HF). The range of very low frequencies reflects the functional state of the suprasympathetic structures; the low frequency range is the activity of the sympathetic section, the high frequency range is the activity of the parasympathetic section of the ANS at segmental level.

The indicators were evaluated taking into account the power density of the spectrum for each frequency range (VLF, LF, HF), their relative (normalized) values and the ratio of power spectrum for low and high frequencies ($K = LF/HF$), which characterizes the ratio of sympathetic and parasympathetic influences on sinus rhythm.

Evaluating the results of instrumental diagnostic methods, the following diagnostic criteria for heart damage were applied:

1. ECG criteria for abnormal heart rhythm and electrical myocardial instability (31):
 - HR less than 60 and more than 90 beats per minute;
 - signs of arrhythmia (disturbance of automatism, conduction, excitability);
 - disorders in the QRST ventricular system end segment repolarization phase (ST segment depression and T wave alternation).
2. Criteria for autonomic dysfunction, evaluated using daily ECG Holter monitoring and variational pulsometry:
 - changes in the parameters of time and spectral analysis, taking into account the time of day and age of the patient;
 - CI value less than 1.24 and more than 1.38.

Statistical processing of the results was performed using the STATISTICA 10 software package (USA). Determination of the significance of differences between the qualitative indicators of the compared groups was performed via the χ^2 (chi-square) test to compare the frequencies of binary feature in two unrelated groups of pairwise comparisons. To evaluate the differences in the values of quantitative indicators for independent samples after checking the distribution of characters for compliance with the law of normal distribution (Kolmogorov-Smirnov test), the non-parametric Mann-Whitney U-test was applied. The critical level when checking the statistical hypothesis was assumed to be 0.05.

RESULTS

Evaluation results of the average value of blood pressure per day in patients with MS with different ages, as well as blood pressure indicators at different times of the day are given in Table 1. The maximum daily average values of systolic and diastolic blood pressure was registered in patients of the 61-80 age group and were the following: systolic BP – 156.9±3.5 mm Hg, diastolic blood

pressure – 96.2±4.1 mm Hg The levels of these indicators were significantly higher than those of the first and second groups under survey ($p<0.01$).

A classification of MS patients with different options for blood pressure response is provided in Table 2. A total number of 71 patients (19.5%) showed a distorted BP reaction — a night increase (Night-Peakers), and the maximum number of such patients was in group 3 – wherein there were more than 61 year old patients (38.8%). The value of this indicator was significantly higher than in groups 1 – 4.8% and 2 – 12.2% ($p<0.05$).

Table 1. Blood pressure indicators in patients of various age groups M (SD) with MS (SD)

| Indicators | Age groups | | |
|-------------|--------------------------|--------------------------|--------------------------|
| | 20 – 40 years n = 104 | 41 – 60 years n = 131 | 61 – 80 years n = 129 |
| SBPP, mm Hg | 130,4±2,6 | 145,2±5,6 * | 156,9±3,5*# |
| DBP, mm Hg | 86,6±1,7 | 89,3±3,7 | 96,2±4,1*# |

Note:

* - the differences are significant (at $p<0.05$) according to the Mann-Whitney test, compared to the corresponding indicators in the group of patients aged 20-40;

- the differences are significant (at $p<0.05$) according to the Mann-Whitney test, compared to the corresponding indicators in the group of patients aged 41-60;

Other types of blood pressure disorders, such as Non-Dipper, were observed significantly more often in patients of the second group (51.9%) compared to the corresponding frequency in patients of the first and third groups, where the value of this indicator was respectively 10.6% ($p<0.05$) and 39.5% ($p<0.01$).

A normal dynamics of blood pressure, i.e. Dipper, was detected in the absolute majority of patients of the younger age group: in 74% of cases, the proportion of such patients was significantly higher than in the second and third groups, where the values of this indicator were respectively 32.0 and 21.7% ($p<0.05$).

Data analysis results for Holter ECG monitoring in patients with MS are presented in Table 3. A number of reliable differences in the values of temporal and frequency indicators depending on the age of patients was revealed. Thus, in older age groups an increase in the rhythmogram sections with a low variability of the RR interval and a decrease in the sections with normal variability of the RR intervals were observed, noted for a decrease in the PNN50 and SDNN values (reflecting the cyclic components responsible for heart rate variability during the recording period)

In older patients, the PNN50 level was 17.8±3.1%, which was significantly higher than in the second group ($p<0.05$), and the SDNN value was 50.9±18.7 ms which was significantly lower than the corresponding indicators of the first and second groups ($p<0.001$). The levels of these indicators in patients over 60 years of age were lower compared to those in patients aged 41-60 (respectively 59.3±15.5 ms and 15.9±2.6%) and in patients of the first group, respectively 61,8±19.3 ms and 17.9±3.0% ($p<0.05$). The revealed differences in HRV parameters indicate a decrease in the dominance of parasympathetic section of the autonomic nervous system over the sympathetic in older age groups of patients with MS compared to the younger patients. As we know, a significant decrease in the levels of PNN50 and SDNN indicates an unfavorable further prognosis of the disease and an increased likelihood of developing cardiovascular complications.

Table 2. Classification of patients with MS depending on blood pressure levels

| Options of circadian rhythms of blood pressure | Age groups | | | | | |
|--|------------------------|------|------------------------|-------|------------------------|--------|
| | 20-40 years n = 104 | | 41-60 years n = 131 | | 61-80 years n = 129 | |
| | abs | % | abs | % | abs | % |
| Dipper | 77 | 74,0 | 42 | 32,0* | 28 | 21,7* |
| Non-Dipper | 11 | 10,6 | 68 | 51,9* | 51 | 39,5*# |
| Night-Peakers | 5 | 4,8 | 16 | 12,2* | 50 | 38,8*# |
| Over-dippers | 11 | 10,6 | 5 | 3,8 | - | - |

Note:

* - the differences are significant (at $p<0.05$) for the χ^2 criterion compared to the corresponding indicators in the group of patients aged 20-40;

- the differences are significant (at $p<0.05$) for the χ^2 criterion compared to the corresponding indicators in the group of patients aged 41-60;

Evidence of a decrease in the parasympathetic activity of the autonomic nervous system for persons with MS in older age groups was both a decrease in the power of high-frequency waves (HF) and an increase in the “sympathetic-parasympathetic” balance (LH/HF). In patients of the third group, the HF values were significantly lower (126.0±30.2 ms²), while the LH/HF ratio was higher (3.8±0.1), than in the first and second groups ($p<0.001$), which indicated a more pronounced prevalence of the sympathetic tone of the ANS in patients aged 61-80 years compared to the younger patients. In patients of the second group with MS, the power of high-frequency waves (HF) was significantly lower (226.3±41.6 ms²), while the LH/HF ratio was higher (2.67±0.08), than in patients of the first group ($p<0.001$).

In patients of the third group, the value of the index reflecting humoral effects on the heart rate was also reduced: the power value of the spectrum of very low frequencies (VLF) (1,175±169 ms²). In these patients, the total power of the TP spectrum was significantly lower than in the first and second groups (serving as a summary criterion for distortions of HRV); its value was 1,783±170 ms². A similar tendency was observed in patients of the second group: VLF and TP values were 1,368.3±328.4 and 2,035.7±331.8 ms², respectively, and were significantly lower than those of the younger patients – of the first group, where their values were, respectively, 1,332.6±198 and 2,422.4±252.9 ms² ($p<0.001$).

Estimation of the pulse average value in the daytime and at night showed higher figures of these indicators in the third group observed, making Ps during the day – 80.0±7.9 BPM and Ps at night – 70.0±10.5 BPM, which there were reliably higher indicators in patients of the first and second groups ($p<0.001$).

We know that an observed decrease in the CI value for this indicator, if it goes below 1.2, is interpreted as an unfavorable change for diseases associated with autonomic heart denervation, and is associated with a poor prognosis, especially in the risk group patients, including MS, prolonged QT syndrome, progressing heart failure, diabetic vegetopathy, etc. Boosting the circadian profile of the heart rhythm (raising the circadian index above 1.5) is associated with increased heart rate sensitivity to sympathetic stimulation and is noted in patients with idiopathic supraventricular and ventricular tachycardia, with primary pulmonary hypertension and a number of other diseases.

Table 3. Data of Holter ECG monitoring for patients with MS in different age groups M (SD)

| Indicators | Age groups | | |
|------------------------|------------------------|------------------------|------------------------|
| | 20-40 years n = 104 | 41-60 years n = 131 | 61-80 years n = 129 |
| Ps in the daytime, BPM | 75,4±8,4 | 79,0±9,0 * | 82,7± 6,3 *# |
| Ps at night, BPM | 60,6±6,2 | 66,5±4,1 * | 69,1±10,8 *# |
| Circadian index (CI) | 1,20±0,11 | 1,19±0,13 | 1,15± 0,14 *# |
| VLF, ms ² | 1332,6±198,0 | 1368,3±328,4 | 1210,4±250 *# |
| LF, ms ² | 643,7±97,5 | 581,9±63,6* | 479±70,4 *# |
| HF, ms ² | 395,9±61,9 | 226,3±41,6* | 129,8±35,3 *# |
| TP, ms ² | 2422,4±252,9 | 2035,7±331,8* | 1836,5±185,8 *# |
| LF/HF | 1,76±0,06 | 2,67±0,08* | 2,97±0,5 *# |
| NLF,% | 28,6±1,3 | 27,9±4,9 | 29,4±0,5 |
| NHF,% | 16,4±1,9 | 10,5±1,2* | 7,1±1,2 *# |
| SDNN, ms | 61,8±19,3 | 59,3 ±15,5 | 50,9±18,7 # |
| PNN 50,% | 17,9±3,0 | 15,9±2,6* | 17,8±3,1 # |

Note:

* - the differences are significant (at $p<0.05$) according to the Mann-Whitney test, compared to the corresponding indicators in the group of patients aged 20-40;

* - the differences are significant (at $p<0.05$) according to the Mann-Whitney test, compared to the corresponding indicators in the group of patients aged 41-60;

The analysis showed that the value of circadian index in patients of the third age group was significantly lower (1.14 ± 0.12) than in patients of the first and second groups, amounting to respectively 1.2 ± 0.11 and 1.19 ± 0.13 ($p<0.001$). Comparing CI values in surveyed groups 1 and 2 did not reveal any significant differences. Besides, we noticed an increase of daytime and night Ps levels (up to 79.0 ± 9.0 and 66.5 ± 4.1 BPM) in patients of the second group compared to the first surveyed group, where the values of these indicators were, respectively, 75.4 ± 8.4 and 60.6 ± 6.2 BPM ($p<0.001$). The revealed alteration in the cardiac rhythm of patients with MS indicates adverse changes in the autonomic regulation of cardiac activity with the increase in their age.

It is noted that a considerable number of patients with MS have extrasystoles, especially ventricular ones. Evaluation of their nature and frequency showed a statistically significant increase in the frequency of both atrial and ventricular extrasystoles in the second and third groups compared to corresponding indicators in patients of the first group ($p<0.001$). At the same time, in the third group examined, the frequency of ventricular extrasystoles was higher than in the second group, while the indicator values amounted to 122.0 ± 94.5 and 85.0 ± 64.9 , respectively, ($p<0.001$).

It should be noted that, with ageing, the patients an increased frequency of prognostically unfavorable ventricular extrasystoles was observed. So, in the third group, the relative number of ventricular extrasystoles of third and fourth gradations (L-W III and L-W-IV) was 11 (8.5%) and 7 (5.4%) of all cases, respectively (Table 4). In patients of the second group, the above mentioned extrasystoles were detected in 7 (5.3%) and 1 (0.8%) of all cases, respectively. In the first group no extrasystoles of high gradations were observed in any case. Extrasystoles of low gradations (L-W I

Table 4. Classification of patients with MS in different age groups by the sort of deviations of Holter ECG monitoring indicators

| Варианты ВРС | Age groups | | | | | |
|--------------------------|------------------------|------|------------------------|-------|------------------------|--------|
| | 20-40 years n = 104 | | 41-60 years n = 131 | | 61-80 years n = 129 | |
| | abs | % | abs | % | abs | % |
| Es/п | 33 | 50,1 | 86 | 65,6* | 95 | 73,6* |
| Es/ж | 9 | 8,6 | 85 | 64,9* | 122 | 94,5*# |
| L-W I | 7 | 6,7 | 48 | 36,6* | 51 | 39,5* |
| L-W II | 2 | 1,9 | 29 | 22,1* | 53 | 41,1*# |
| L-W III | - | - | 7 | 5,2* | 11 | 8,5* |
| L-W IV | - | - | 1 | 0,8 | 7 | 5,4 |
| ST seq. 1.5 mm Decrease. | 4 | 3,8 | 54 | 41,2* | 97 | 75,2*# |

Note:

* - the differences are significant (at $p<0.05$) for the χ^2 criterion compared to the corresponding indicators in the group of patients aged 20-40;

- the differences are significant (at $p<0.05$) for the χ^2 criterion compared to the corresponding indicators in the group of patients aged 41-60;

and L-W II) were more frequently detected in older age groups. In the third group the relative frequency of ventricular extrasystoles L-W I and L-W II amounted to 39.5% and 41.1%, respectively, and these values were significantly higher than in patients of the first group, where we had 6.7 and 1.9%, respectively, ($p<0.01$). At the same time, in the second group patients the frequency of this kind of extrasystoles (L-W I and L-W II) was higher than in the first group ($p<0.05$).

Another peculiarity of the data obtained during daily ECG monitoring of the patients with MS was the frequency of ST segment depression cases over 1.5 mm. In the third group we noticed 97 such cases (75.2%), which was significantly higher than in patients of the second and first groups, where the value of this parameter was 54 (41.2%) and 4 (3.8%) of all cases, respectively, ($p<0.05$).

Thus, when evaluating the daily ECG monitoring indicators in patients under survey, we can draw a conclusion that with ageing of MS patients the frequency of identifying risk factors for cardiovascular complications steadily increases.

DISCUSSION

The prevalence of metabolic syndrome in many countries in the world has become an epidemic [15]. We see a high probability of developing structural heart changes in patients with MS [6]. It is known that in such patients with a high frequency HRV disorders are observed, and by studying them we have a chance to evaluate the activity of various parts of the autonomic nervous system. Changes in HRV act as a prognostic marker of lethal outcomes in patients with diseases of the cardiovascular system [16-19]. At the same time, the debated issue is: changes in which type of activity (sympathetic or parasympathetic) act as a determining factor in the development of ANS dysfunction in MS.

Analysis of the daily ECG monitoring results in patients with MS conducted in our study showed that with ageing of patients, the frequency of detecting risk factors for cardiovascular complications, including heart rhythm disturbances, increases. The data we obtained are consistent with the results of a number of other authors. Thus, A. Ye. Kratnov et al. in their survey studied

heart rate variability in 131 men with MS at the age of 29 to 60 without coronary heart disease. The authors showed that the presence of metabolic syndrome in men comes amid dysfunction of the autonomic nervous system with a decrease in sympathetic effects on the heart (decrease in LF and VLF) [6].

The survey carried out by Ye. N. Kazidayeva and Yu. L. Venevtseva include 103 young people, 16-27 years old (average age 18.5 ± 0.3), of whom 49.5% had normal body weight, 21.4% increased BW, and 14.6% obesity. In the group with obesity, the circadian index of heart rate was significantly lower against the background of a decrease in heart rate variability due to the waves of all three ranges, with more frequent disorders of repolarization processes and sleep apnea [5].

In general, researchers agree that today the availability of new bioinformatics methods allows to use a systematic approach in identifying disorders of the neurovegetative regulation of cardiac activity, which fully applies to patients with manifestations of the metabolic syndrome. Integrative characteristics of HRV indicate the presence of a number of pronounced disorders of the vegetative regulation in these patients, while HRV TP, VLF, LF indicators are interpreted as markers of changes.

CONCLUSION

The obtained results indicate the need for dynamic monitoring of patients with signs of metabolic syndrome conducting regular surveys to identify signs of cardiovascular system disorders, such as blood pressure and heart rate. The above confirms the need for further in-depth studies in order to identify factors that affect heart rhythm changes in overweight patients.

Disclosure of conflicts of interest. The author declares no financial or other potential conflicts of interest.

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Abbreviations

- HR – heart rate or the number of heartbeats
HRV – heart rate variability
LF – low frequencies
VLF – very low frequencies
HF – high frequencies
Es/a – Extrasystoles, atrial
Es/v – Extrasystoles, ventricular
L-W – Lown-Wolff (Lown-Wolff classification of rhythm disorders)
CI – Circadian index
Dipper – Normal (optimal) degree of nightly fall in blood pressure
Non-Dipper – Insufficient nightly fall in blood pressure
Night-Peakers – Sustainable rise in night blood pressure («Night Peak»)
Over-dippers – Increased night-time fall in blood pressure («over-dip»)
TP-TP (Total Power) – the total power of all waves with a frequency ranging from 0,0033 Hz to 0.40 Hz
N-N – gaps between normal contractions
NLF – normal LF indicator [(LF/(LF+HF)]
NHF – normal HF indicator [HF/(LF+HF)]
SDNN – standard deviation from the average duration for all sinus intervals;
R-R PNN50 – The percentage of differences between successive R-R intervals greater than 50 ms

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