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Indentify a High-Risk Group of Cardiovascular Complications in Hypertensive Patients by Analyzing Heart Rate Variability and Heart Rate Turbulence Parameters

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Abstract: Background: Low heart rate variability (HRV) in patients with arterial hypertension (AH) is a prognostic factor that increases the risk of adverse cardiovascular outcomes. There are extreme HRV values (so called "cut-points"), beyond which there is a poor prognosis and a high risk of fatal outcomes: SDNN < 50 ms; SDANNi < 40 ms; SDNNi < 20-30 ms; RMSSD < 15 ms; pNN50 (%) < 0.17. Abnormal heart rate turbulence (HRT), as a baroreflex-mediated short-term oscillation of sinus rhythm cycle length after spontaneous ventricular extrasystoles, also has a high predictive value as a cardiovascular risk factor. The aim of our study was to evaluate HRV parameters by the "cut-points" criteria and to analyze HRT in the patients with AH. Materials and Methods: We have analyzed HRV and HRT parameters in 214 patients with AH of the II-nd degree aged 35 to 70 (57.7 ± 7.6) years: 121 women (56.5%) and 93 men (43.5%). To study changes in HRV and HRT, all patients underwent Holter monitoring (HM). The obtained data were processed using the analytical paskage "Statistics 10.0". Results: The maximum output of HRV parameters beyond the critical values (17.39%—male, 6.58%—female) was registered at the age of 50-59 years, mainly in male with a reduction of the TS parameter. Conclusions: The analysis of HRV and HRT parameters makes it possible to identify hypertensive patients with a high risk of developing cardiovascular complications and an increased risk of fatal outcomes that should be used for timely modification of treatment measures.

Key words: AH, HM, HRV, "cut-points", HRT.

Abbreviations

HRV	heart rate variability;
AH	arterial hypertension;
SDNN	standard deviation of NN intervals;
SDANNi	standard deviation of the means of all NN intervals for all 5-minute segments of the entire recording;
SDNNi	mean of the standard deviations of all filtered NN intervals for all 5-minutesegments of the analysis;
RMSSD	square root of the mean squared differences of successive NN intervals;
pNN50	percentage of differences between adjacent filtered NN intervals that are greater than 50 ms for the whole analysis;
HRT	heart rate turbulence;
TO	turbulence onset
TS	turbulence slope;
HM	Holter monitoring.

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1. Introduction

Heart rate variability (HRV) has a great predictive value in hypertensive patients, as a method for evaluation of the relationship between the sympathetic and parasympathetic parts of the autonomic nervous system. Vegetative tone of the patients with arterial hypertension is characterized by pronounced sympathicotonia at all levels of regulation of the autonomic nervous system [1, 2]. This will be manifested by low "time domain" HRV parameters. There are extreme values of "time domain" HRV parameters (so-called "cut-points"), which are associated with a poor prognosis and a high risk of the fatal outcomes in the population or in

persons with cardiovascular diseases. Bounds of "time domain" HRV parameters according to the "cut-points" values are follows: SDNN < 50 ms; SDANNi < 40 ms; SDNNi < 20-30 ms; RMSSD < 15 ms; pNN50 < 0.17% [3].

HRV studies show that in the male population, the relative risk of overall mortality in middle-aged patients during 5 years of follow-up was 2.1 times higher in cases where the SDNN was less than 20 ms (compared to persons of comparable age, in whom the SDNN was 20-39 ms). A decrease in SDNN of less than 50 ms is a highly specific feature in predicting of fatal outcomes in individuals who have suffered a myocardial infarction. Additionally, reduced SDNN is an independent predictor of cardiovascular complications after ischemic stroke. Threshold values of the SDNN index (= 71 ms) have been established, below which the risk of cerebral and cardiac disorders significantly increases [4, 5]. In addition, correlations with high statistical significance between HRV and heart rate turbulence (HRT) parameters were established [6, 7].

HRT, as a brief heart rate acceleration followed by a gradual heart rate deceleration after ventricular extrasystole, has a high predictive value as a cardiovascular risk factor. There are two parameters of HRT: the beginning of turbulence—(turbulence onset—TO, %) and the slope of turbulence—(turbulence slope—TS, ms/RR). TO—the value of the sinus rhythm increase after the ventricular extrasystole and TS—the intensity of the sinus rhythm deceleration following its increase. The values TO < 0% and TS > 2.5 ms/RR are considered as normal, TO > 0% and TS < 2.5 ms/RR—pathological. HRT values are usually classified into 3 categories: (1) HRT category 0 means TO and TS are normal; (2) HRT category 1 means that one of TO or TS is abnormal; (3) HRT category 2 means both TO and TS are abnormal [8, 9].

In hypertensive patients aged 60-69 and 70-74 years, compared with the age group of 50-59 years, the number of ventricular extrasystoles increases, the amount of pathological meanings of TO increases 2.7 times, and the average TS values decrease by 1.3 times. The values of TO and TS correlate with AH: in normotensive patients, TO = -1.64% ± 2.85% compared to 1.21% ± 1.95% in individuals with hypertension; the TS value was 4.29 ± 3.18 ms/RR compared to 2.27 ± 0.93 ms/RR in hypertensive patients. There is an association between AH and HRT disorders ($p = 0.02$) [10].

The aim of our study was to estimate "time domain" HRV parameters by the "cut-points" criteria and to analyze HRT in hypertensive patients finally to create the group of the patients with increased risk of possible cardiovascular complications and fatal outcomes.

2. Materials and Methods

The study included 214 patients with AH of the II-nd degree: 121 women (56.5%) and 93 men (43.5%) aged 35 to 70 (57.7 ± 7.6) years. The patients agreed to all diagnostic and treatment procedures and were informed of their participation in the study. All of them had the sinus rhythm on ECG.

To analyze HRV and HRT changes, all patients underwent Holter monitoring (HM). During the study, HM was performed repeatedly without discontinuing antihypertensive therapy. "Time domain" HRV parameters, based on the "cut-points" criteria, were evaluated. For calculating HRT parameters (TO and TS), a sufficient number of ventricular arrhythmias was registrated in 173 (80.8%) hypertensive patients. The category type for estimating HRT parameters in hypertensive patients was clarified.

In the group of the patients with AH of the II-nd degree 24 myocardial infarctions, 3 strokes, 9 paroxysms of atrial fibrillation, 20 episodes of unstable angina and 4 fatal outcomes were registered during the entire follow-up period (2.6 ± 1.3 years).

The obtained data were processed with help of the software Statistics 10.0 and presented as M ± σ, where M is the arithmetic mean value and σ is the standard

deviation. The significance level of $p < 0.05$ was considered reliable.

3. Results and Discussion

All the patients with AH of the II-nd degree were divided into four age subgroups. The "time domain" HRV parameters were evaluated in relation to the "cut-points", which are associated with a poor prognosis and a high risk of the fatal outcomes (Table 1).

In 35-39 years old patients, exceeding the limits of the "cut-points" values of two parameters (RMSSD and pNN50) was registered in 0.47% of cases (1 female). The HRT parameters (TO and TS) were within normal values, which corresponds to the 0 turbulence rating category.

In 40-49 years old patients, exceeding the limits of the "cut-points" values of three parameters (SDNN, SDNNi, pNN50) in combination with the 2 category of HRT assessment (total parameters reduction) was registered in 0.94% of cases (2 males). Exceeding the limits of the "cut-points" values of two parameters (RMSSD and pNN50) in combination with the 0 category of HRT assessment was registered in 0.47% of cases (1 female). Exceeding the limits of the "cut-points" values of one parameter—pNN50 in combination with 0 category of HRT assessment was registered in 0.47% of cases (1 female).

At the age of 50-59 years, exceeding the limits of SDNNi "cut-points" values was registered in 3.29% of cases (5 males; 2 females), critical values of pNN50 were detected in 7.52% of cases (12 males; 4 females). The combination of exceeding "cut-points" values of SDNN and SDNNi was registered in 0.47% cases (1 male), RMSSD and pNN50—4.7% (7 males; 3 females). Exceeding the limits of SDNNi, RMSSD and pNN50 "cut-points" values was recorded in 1.41% of cases (2 males; 1 female). Mainly 1 category of HRT assessment (one parameter reduction) was registrated. It should be noted that pathological changes of HRT are represented by TS parameter reduction.

At the age of 60-70 years exceeding the limits of the extreme (less than "cut-points") values of all the analyzed "time domain" HRV parameters was detected in 0.47% of cases (1 male). The combination of critical values of SDNNi, RMSSD and pNN50 was registered in 1.88% of cases (3 females; 1 male), SDNNi and pNN50—in 1.41% of cases (2 females; 1 male); RMSSD and pNN50—0.47% (1 female). Generally, in 60-70 years old patients, critical values of SDNNi were registered in 4.23% of cases (5 females; 4 males); RMSSD—in 2.82% of cases (4 females; 2 males); pNN50—7.52% (7 females; 9 males). At that, pathological changes in HRT are represented by reduction of the TS parameter (1 category of turbulence estimation).

The association between HRV and HRT parameters with the probability of fatal outcomes development was revealed (Table 2).

Also, significant correlations between the left ventricular ejection fraction (LV EF) ($p = 0.00022$), development of myocardial infarctions and strokes ($p < 0.0001$) during the follow-up period (2.6 ± 1.3 years) and the probability of the fatal outcomes development were found. In patients with AH of the II-nd degree

Table 1 "Time domain" HRV parameters in relation to the "cut-points" values.

"Cut-points"	SDNN < 50 ms		SDANNi < 40 ms		SDNNi < 30; < 20 ms		RMSSD < 15 ms		pNN50 < 0.17%	
Age	Gender; detectability of parameters in age subgroups (%)									
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
35-39	0	0	0	0	0	0	0	0.47	0	0.47
40-49	0.94	0	0	0	0.94	0	0	0.47	0.94	0.94
50-59	0.47	0	0	0	2.82	0.94	4.23	1.88	9.87	3.76
60-70	0.47	0	0.47	0	1.88	2.35	0.94	1.88	4.23	3.29

Table data on the detectability of the "time domain" HRV parameters in relation to the "cut-points" values are summarized.

Table 2 The association of HRV and HRT parameters with fatal outcomes.

Parameters	M ± σ	γ-correlations	p-levels
SDNN, ms	140.55 ± 45.85	-0.7773	0.00119
SDANNi, ms	121.35 ± 39.43	-0.7026	0.0034
SDNNi, ms	57.9 ± 30.2	-0.9354	0.000088
RMSSD, ms	49.97 ± 53.5	-0.59903	0.01289
pNN50, %	8.4 ± 12.27	-1.0000	0.0003
TS, ms/RR	7.82 ± 7.03	-0.9046	0.00017

Table 3 HRV and HRT values, associated with an increased risk of fatal outcomes.

Parameters	AH without an increased risk of fatal outcomes	AH with an increased risk of fatal outcomes	p
SDNN, ms	140.55 ± 45.85	76.4 ± 35.4	0.0082*
SDANNi, ms	121.35 ± 39.43	70.6 ± 34.45	0.0169*
SDNNi, ms	57.9 ± 30.2	24.6 ± 5.4	0.0014*
RMSSD, ms	49.97 ± 53.5	16.0 ± 7.8	0.0432*
pNN50, %	8.4 ± 12.27	0.14 ± 0.38	0.0037*
TO, %	-0.8 ± 3.5	-0.24 ± 3.04	0.1235
TS, ms/RR	7.82 ± 7.03	1.1 ± 0.97	0.0022*

* The difference is significant at $p < 0.05$.

we have identified an association of HRT parameters with the probability of myocardial infarctions (MI) development (for TO $p = 0.0144$; for TS $p = 0.0164$) [6].

So, in the group of the patients with AH of the II-nd degree, we identified individuals with an increased risk of developing cardiovascular complications and fatal outcomes and determined the values of HRV and HRT parameters associated with an increased risk (Table 3).

4. Discussion

Thus, in the group of examined individuals with AH of the II-nd degree, we have identified patients with an increased risk of possible adverse outcomes, who have one or more "time domain" HRV parameters, which go beyond the critical values (less than "cut-points") in combination with a reduction of one or two HRT parameters (TO and TS). Pathological TO values are more associated with the MI development, while pathological TS is associated not only with MI, but also with the probability of fatal outcomes.

To sum up, it can be noted that exceeding the "cut-points" limits of one or more "time domain" HRV parameters was registered in 16.45% of cases in female and 27.73% in male with AH of the II degree. The maximum output of HRV parameters beyond the critical values (17.39% in male, 6.58% in female) was registered at the age of 50-59 years, mainly in males with 1 category of HRT assessment, represented by TS parameter reduction.

5. Conclusions

To prevent the development of adverse cardiovascular outcomes, hypertensive patients with critical values of "time domain" HRV parameters (less than "cut-points") in the combination of TO or TS reduction, or total reduction of HRT, especially in connection with a low LV EF, should be modified treatment and prevention measures.

References

[1] Hering, D., Lachowska, K., and Schlaich, M. 2015. "Role of the Sympathetic Nervous System in Stress-Mediated Cardiovascular Disease." *Current Hypertension Reports* 17 (10): 1-9. doi: 10.1007/s11906-015-0594-5.

[2] Drenjancevic, I., Grizelj, I., Harsanji-Drenjancevic, I., Cavka, A., and Selthofer-Relatic, K. 2014. "The Interplay between Sympathetic Overactivity, Hypertension and Heart Rate Variability (Review)." *Acta Physiologica*

Hungarica 101 (2): 129-42. doi: 10.1556/APhysiol.101.2014.2.1.

[3] Makarov, L. M., Komolyatova, V. N., Kupriyanova, O. A., et al. 2014. “National Russian Guidelines on Application of the Methods of Holter Monitoring in Clinical Practice.” *Russ J Cardiol* 2 (106): 6-71. (in Russian)

[4] Xhyheri, B., Manfrini, O., Mazzolini, M., Pizzi, C., and Bugiardini, R. 2012. “Heart Rate Variability Today.” *Progress in Cardiovascular Diseases* 55 (3): 321-31. doi: http://dx.doi.org/10.1016/j.pcad.2012.09.001.

[5] Katan, M., and Lubitz, S. A. 2019. “ECG Monitoring after Acute Ischemic Stroke.” *Neurology* 92 (2): 65-6. doi: https://doi.org/10.1212/WNL.0000000000006719.

[6] Aleynikova, T. V. 2018. “Assessment of Heart Rate Variability and Heart Rate Turbulence Parameters in the Patients with Arterial Hypertension of the II Degree.” *Journal of Pharmacy and Pharmacology* 6: 935-39. doi: 10.17265/2328-2150/2018.10.006.

[7] Yu, Y., Xu, Y., Zhang, M., Wang, Y., Zou, W., and Gu, Y. 2018. “Value of Assessing Autonomic Nervous Function by Heart Rate Variability and Heart Rate Turbulence in Hypertensive Patients.” *International Journal of Hypertension* 2: 1-9. doi: 10.1155/2018/4067601.

[8] Tuyzarova, I. A., Kozlov, V. A., and Shukanov, A. A. 2018. “Analysis of Baroreflex under Essential Hypertension in Clinical Practice.” *Human Sport Medicine* 18 (1): 74-81. doi: 10.14529/hsm180106. (in Russian)

[9] Disertori, M., Masè, M., Rigoni, M., Nollo, G., and Ravelli, F. 2016. “Heart Rate Turbulence Is a Powerful Predictor of Cardiac Death and Ventricular Arrhythmias in Postmyocardial Infarction and Heart Failure Patients. A Systematic Review and Meta-Analysis.” *Circulation: Arrhythmia and Electrophysiology* 9 (12): 1-11. doi: 10.1161/CIRCEP.116.004610.

[10] Kossaify, A., Garcia, A., and Ziade, F. 2014. “Assessment of Heart Rate Turbulence in Hypertensive Patients: Rationale, Perspectives, and Insight into Autonomic Nervous System Dysfunction.” *Heart Views* 15 (3): 68-73. doi: 10.4103/1995-705X.144790.