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Research Article

Comparison of Heart Rate Variability Parameters in Patients with Cardiovascular Diseases and Concomitant Phenomenon of Heart Rate Turbulence wih the Indicators of Apparently Healthy Individuals

A.I. Vytryhovskyy

Abstract
The objective of the research was to develop new approaches to the prognosis, prevention and treatment of complications in patients at high and very high total cardiovascular risk based on the assessment of the state and effect on heart rate variability and heart rate turbulence.
Materials and methods. There were examined 319 patients; they underwent a 24-hour monitoring of their heart rate variability and heart rate turbulence. All the patients were divided into three groups: Group 1 included patients with coronary heart disease (post-infarction cardiosclerosis) without concomitant risk factors such as smoking, obesity, metabolic syndrome; Group 2 consisted of patients smoking tobacco for more than 2 years; Group 3 included patients with metabolic syndrome and arterial hypertension; the control group.
Results. In patients with coronary heart disease and concomitant phenomenon of heart rate turbulence, the activity of the parasympathetic nervous system was significantly higher in the active period of the day, while the passive period of the day was associated with the elevated level of stress. Due to this, among patients of this group, there was a decrease in the tension value of the total body regulation in the passive period of the day, while in healthy individuals, its increase was observed. In patients at high and very high cardiovascular risk according to the SCORE charts with the phenomenon of heart rate turbulence, the stress index was significantly higher throughout the day as compared to apparently healthy individuals. In patients at high cardiovascular risk and concomitant phenomenon of heart rate turbulence, the parameters of heart rate turbulence acceleration were significantly higher as compared to those of apparently healthy individuals.
Conclusions. In patients at high and very high cardiovascular risk according to the SCORE charts with coronary heart disease and concomitant phenomenon of heart rate turbulence, the occurrence of ventricular extrasystole had a vagal nature; they were characterized by a higher level of stress in the passive period of the day as compared to the active one.

Keywords
cardiovascular risk; coronary heart disease; arrhythmia; sudden cardiac death; heart rate variability

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine
Ivano-Frankivsk Regional Clinical Cardiology Dispensary, Ivano-Frankivsk, Ukraine
Corresponding author: vytryhovskiy@yahoo.com

Problem statement and analysis of the recent research

The study of the electrocardiogram (ECG) measurements is closely related to ventricular ectopy, and the analysis of their relationships with the autonomic regulation provides the basis for new methods of diagnosing risk stratification markers of sudden cardiac death [5, 7]. Nowadays, one of the methods to predict sudden cardiac death is the evaluation of heart rate turbulence (HRT) [4]. Literature data show that the sensitivity and predictive accuracy of HRT parameters are higher as compared to other non-invasive tests (heart rate variability (HRV), ventricular late potentials) [3, 7]. In the European Myocardial Infarction Amiodarone Trial (EMIAT) and the Multicenter Post-Infarction Program (MRIR) studies, in case of the combination of pathological values of turbulence onset (TO) and turbulence slope (TS), the sensitivity was 30%, the specificity was 90% and positive predictive ability was 32%. In other words, by establishing TO and TS within 2.5 ms/RR and 0%, it is possible to detect 30% of patients who will suffer from cardiac arrest. However, the predictive accuracy of other risk factors such as advanced age, past myocardial infarction, low HRV, arrhythmia, low ejection fraction (EF) values was within 18-24% in the EMIAT and 16-30% in the MRIR studies [1]. According to the MRIR study, the predictive accuracy of EF corresponded to 30% being close to the value of predictive ability of the combination of TS and TO. EF value had better sensitivity (43%) and predictive ability (85%) than HRT parameters. According to the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI)

study, the predictive accuracy of the value of TS is equal to 12.5% at 40% sensitivity, thus, being more significantly important than the values of baroreflex sensitivity (7.8%). The predictive capacity can be increased when considering HRT in combination with other risk factors [6]. At 40% sensitivity, the pathological value of TS in combination with low HRV gives 20.3% of positive predictive accuracy and in combination with low EF - 17.3% [4]. In previous scientific studies, HRT was studied in patients with acute myocardial infarction only, and the study of HRT among healthy individuals, individuals with early manifestations of atherosclerosis, or the initial stages of the cardiovascular disease was not performed. On this basis, patients were selected for this study [7, 8].

1. Materials and methods

During 2007-2013, there were examined 319 patients (198 men and 121 women) at the age of 35-85 years who underwent a 24-hour monitoring of HRV and HRT. The average age of patients was 63.3 $\pm$ 9.11 years. There were no gender- or age-related differences between groups. All the patients were divided into three groups: Group 1 included 72 (38 men and 34 women) patients with coronary heart disease (CHD) (post-infarction cardiosclerosis) without concomitant risk factors such as smoking, obesity, metabolic syndrome; Group 2 consisted of 69 (67 men and 2 women) patients smoking tobacco for more than 2 years; Group 3 included 138 (68 men and 70 women) patients with metabolic syndrome and arterial hypertension without CHD. The control group included 50 (25 men and 25 women) individuals. The study excluded patients with concomitant myocardial injury (acute coronary syndrome with the presence or absence of ST segment elevation, secondary arterial hypertension, permanent atrial fibrillation or atrial flutter), autoimmune, hematological diseases, mental disorders, endocrine disorders (except for patients with diabetes mellitus), acute renal and hepatic failure, cancer, pregnant women, and athletes.

The spectral method of HRV analysis which is based on the formation of spectral sequence of the cardiac cycle duration was used in the research. The analysis of the spectral density of the fluctuations allowed us to quantify various frequency components of cardiac rhythm as well as a correlation between different components of cardiac rhythm, which represent the activity of certain components of regulative mechanism. In the literature, spectral components are known as a high-frequency (HF) component, a low-frequency (LF) component and a very low-frequency (VLF) component [5]. According to the spectral analysis, the following indices were calculated: a) the centralization index (CI) = (HF+LF) /VLF), and the vagosympathetic interaction index (LF/HF). The power of the VLF zone allows evaluating the effects of neurohumoral factors. The size and correlation between different waves of cardiac rhythm of the LF and HF zones were identified by sympathetic and parasympathetic balance and parasympathetic regulation, respectively. In addition to the determination of component amplitude, there were measured the index of total power (TP) - the total power of the spectrum which represents the total activity of autonomic influences on heart rate and LF/HF ratio which indicates the balance between sympathetic and parasympathetic influences. The stress index (SI) characterizes the degree of predominance of the activity of central mechanisms over autonomic ones [6]. This index is very sensitive to the increase in the sympathetic activity. The analysis of HRT was based on two indices - TO and TS. TO is a value of sinus rhythm acceleration immediately after ventricular extrasystole (VES) and TS is the intensity of sinus rhythm deceleration, which occurs after its acceleration. TO is calculated as the ratio of differences between both the sum of values of the first two sinus RR intervals occurring immediately after VES and the next two sinus RR intervals occurring before VES to the sum of two sinus RR intervals to VES, expressed as a percentage.

To calculate TO, the following formula was used:

TO (%) = 100*RR [1] +RR [2]) - (RR [-3] +RR [-2]) / RR [-3] +RR [-2]),

where RR-2 and RR-3 are the first and second sinus RR intervals that precede the ectopic complex; RR1 and RR2 are the first and second sinus RR intervals, which occur immediately after the compensatory pause. To determine TS (mc/RR), the tilt of the RR interval changes was calculated using straight lines of regression for each 5 RR intervals among the next 20 after the compensatory pause RR [1] +RR [5]), RR [2] +RR [6])... RR [16] +RR [20]). The value of TS is defined as the maximum positive regression slope. The parameters of acceleration (TO$\leq$-1.5) and deceleration (TS$\geq$2.5) of the sinus cycle which occur immediately after premature ventricular contraction are normal. The parameters of acceleration (TO$<$0.0 and TO$\geq$-1.5) or deceleration (TS$>$0.5) and (TS$<$2.5) are considered pathological. If the parameter of acceleration (TO$>$0.0) or deceleration (TS$<$0.5) is significantly less than normal level - the risk of fatal ventricular ectopy is very high [9]. The acceleration of sinus rhythm followed by short-lasting slowdown is considered as the physiological response to VES [2].

All the data were processed using statistical software STATISTICA 10. The arithmetic mean (M), its variance and average error (m) were calculated for all parameters. To determine the reliability of differences between research results, the Student's t-test was used and, then, the probability of differences between samples (p) was determined; confidence interval was calculated using Student's t distribution. The values for which p$<$0.05 were considered statistically significant. The determination of HRT and HRV was performed using the Holter monitoring system "CardioSens 2008", "CardioSens+V3.0" and "CardioSens CS" ("Medica-Khai", Kharkiv, Ukraine).

2. Results

The comparative characteristics of HRV indices with HRT phenomenon between the control group and Group 1 are presented in Table 1. In patients of Group 1, the TP index was significantly higher as compared to apparently healthy individ-

uals due to the absolute value of HRV spectra. The activity of the parasympathetic nervous system was significantly higher in the active period of the day ($p < 0.01$) as compared to the control group. In the passive period of the day, the absolute value of the SI in patients with postinfarction cardiosclerosis and HRT increased being significantly higher ($p < 0.01$) as compared to apparently healthy individuals; however, the TP index decreased. The absolute value of the parameters of HRT acceleration and deceleration was higher as compared to apparently healthy individuals.

The comparative characteristics of HRV indices with HRT phenomenon between the control group and Group 2 are presented in Table 2. When comparing HRV parameters of patients at high and very high cardiovascular risk according to the SCORE charts with concomitant phenomenon of HRT with HRV parameters of apparently healthy individuals, it was found that in patients of Group 2, QT interval was longer than its absolute value, and the adjusted index ($p<0.01$). The SI was significantly higher throughout the day ($p<0.01$). HF spectrum which is responsible for regulating the parasympathetic autonomic system was significantly higher ($p < 0.01$). The value of TP was higher in Group 2; however, no significant difference was observed. In the active period of the day, the relative activity of the subcortical sympathetic nerve center was lower, while in the passive period of the day, it was higher than in the control group. Similar changes were observed in the CI; however, they were not statistically significant.

The comparative characteristics of HRV indices with HRT phenomenon between the control group and Group 3 are presented in Table 3. When comparing HRT parameters of patients of Group 3 with the phenomenon of HRT with HRV parameters of apparently healthy individuals, a significantly higher SI was found in the both active and passive period of the day ($p<0.01$). The activity of the parasympathetic division of the autonomic nervous system, i.e. its absolute and relative value ($p < 0.01$) was significantly higher. In the passive period of the day, the indicator was significantly lower as compared to healthy individuals ($p<0.01$). The analysis of HRT indices revealed that the parameter of HRT acceleration was significantly ($p<0.01$) higher in patients of Group 3, while the parameter of HRT deceleration was not significantly lower.

3. Discussion

On the basis of the obtained data, we can assert that in patients with CHD, namely postinfarction cardiosclerosis and the phenomenon of HRT, in contrast to apparently healthy individuals, the activity of the parasympathetic division of the autonomic nervous system was significantly higher in the active period of the day, while the passive period of the day was associated with the elevated level of stress which proves the fact that the occurrence of life-threatening arrhythmia increases in the passive period of the day. Due to this, among patients of this group, there was a decrease in the tension value of the total body regulation in the passive period of the day, while in healthy individuals, its increase was observed. In patients with CHD, the occurrence of VES and the phenomenon of HRT had more vagal nature. In patients at very high cardiovascular risk according to the SCORE charts with the phenomenon of HRT, the SI was significantly higher throughout the day as compared to apparently healthy individuals. In patients at high cardiovascular risk and concomitant phenomenon of HRT, the SI was significantly higher throughout the day as compared to apparently healthy individuals. There was observed high activity of the parasympathetic system of body regulation. In patients with such risk of developing cardiovascular events, the parameter of HRT acceleration was significantly higher, while the parameter of HRT deceleration was not significantly lower.

4. Conclusions

In patients at high and very high cardiovascular risk according to the SCORE charts with CHD and concomitant phenomenon of HRT, the occurrence of VES had a vagal nature; they were characterized by a higher level of stress in the passive period of the day as compared to the active one..

5. Prospects for further research

An important task is to improve the existing criteria and to search for new ones for primary prevention of sudden cardiac death and the detection of patients at high risk of sudden cardiac death. Further determination of HRT and HRV can be quite simple, non-invasive, affordable screening method for early detection of patients with a predisposition to sudden cardiac death among the general population.

Conflict of interests

None.

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Table 1. Comparative characteristics of HRV parameters in patients with CHD (postinfarction cardiosclerosis) (Group 1) and the control group, (M ± m)

	QT, mc	QTc, mc	SI	TP, mc^2	HF%	LF%	HF, mc^2	LF, mc^2	VLF, mc^2	LF/HF	CI	TO, %	TS, mc/bit
Control group (the active period of the day)	389.70 ± 3.91	421.94 ± 3.29	40.45 ± 4.06	3484.72 ± 324.42	28.02 ± 1.32	71.83 ± 1.3	343.11 ± 45.41	858.41 ± 89.79	1424.00 ± 139.10	3.03 ± 0.19	8.65 ± 0.08	-2.53 ± 0.33	8.39 ± 0.75
Group 1 (the active period of the day)	379.82 ± 6.68	408.61 ± 6.93	47.18 ± 4.63	4366.98 ± 471.52	32.01 ± 2.35	74.44 ± 5.02	707.58 ± 124.01 1	1006.50 ± 142.05	1594.11 ± 156.60	3.01 ± 0.21	9.71 ± 0.85	-2.23 ± 0.33	9.23 ± 1.06
Control group (the passive period of the day)	389.70 ± 3.91	421.94 ± 3.29	32.76 ± 3.14	4094.76 ± 405.44	31.53 ± 1.36	68.33 ± 1.35	606.25 ± 105.94	1124.41 ± 118.76	1749.42 ± 175.53	2.47 ± 0.15	6.91 ± 0.55	-2.53 ± 0.33	8.39 ± 0.75
Group 1 (the passive period of the day)	379.82 ± 6.68	408.61 ± 6.93	50.78 ± 6.351	3660.08 ± 329.76	31.13 ± 1.30	68.27 ± 1.43	543.14 ± 94.22	1015.38 ± 112.63	1577.08 ± 139.20	2.59 ± 0.14	7.84 ± 0.50	-2.23 ± 0.33	9.23 ± 1.06

Table 2. Comparative characteristics of HRV parameters in patients at high cardiovascular risk according to the SCORE charts (Group 2) and the control group, (M ± m)

	QT, mc	QTc, mc	SI	TP, mc^2	HF%	LF%	HF, mc^2	LF, mc^2	VLF, mc^2	LF/HF	CI	TO, %	TS, mc/bit
Control group (the active period of the day)	389.70 ± 3.91	421.94 ± 3.29	40.45 ± 4.06	3484.72 ± 324.42	28.02 ± 1.32	71.83 ± 1.3	343.11 ± 45.41	858.41 ± 89.79	1424.00 ± 139.10	3.03 ± 0.19	8.65 ± 0.08	-2.53 ± 0.33	8.39 ± 0.75
Group 2 (the active period of the day)	370.72 ± 4.62[1]	408.51 ± 4.33[1]	58.61 ± 6.96[1]	3915.75 ± 389.2	33.63 ± 1.50[1]	65.91 ± 6.29	703.99 ± 131.82[1]	1101.57 ± 163.85	1496.67 ± 158.68	2.77 ± 0.24	8.05 ± 0.66	-2.37 ± 0.28	8.42 ± 0.67
Control group (the passive period of the day)	389.70 ± 3.91	421.94 ± 3.29	32.76 ± 3.14	4094.76 ± 405.44	31.53 ± 1.36	68.33 ± 1.35	606.25 ± 105.94	1124.41 ± 118.76	1749.42 ± 175.53	2.47 ± 0.15	6.91 ± 0.55	-2.53 ± 0.33	8.39 ± 0.75
Group 2 (the passive period of the day)	370.72 ± 4.62[1]	408.51 ± 4.33[1]	51.87 ± 6.37[1]	4783.60 ± 493.55	33.63 ± 1.37	66.58 ± 2.46	937.34 ± 197.70	1383.17 ± 200.13	1808.48 ± 139.17	2.51 ± 0.16	7.74 ± 0.63	-2.37 ± 0.28	8.42 ± 0.67

Notes: [1] - the difference between the control group and Group 2, $p<0.01$

Table 3. Comparative characteristics of HRV parameters in patients at high cardiovascular risk according to the SCORE charts (Group 3) and the control group, (M ± m)

	QT, mc	QTc, mc	SI	TP, mc2	HF%	LF%	HF, mc^2	LF, mc^2	VLF, mc^2	LF/HF	CI	TO, %	TS, mc/bit
Control group (the active period of the day)	389.70 ± 3.91	421.94 ± 3.29	40.45 ± 4.06	3484.72 ± 324.42	28.02 ± 1.32	71.83 ± 1.3	343.11 ± 45.41	858.41 ± 89.79	1424.00 ± 139.10	3.03 ± 0.19	8.65 ± 0.08	-2.53 ± 0.33	8.39 ± 0.75
Group 3 (the active period of the day)	381.85 ± 3.96	417.57 ± 3.48	67.36 ± 6.59[1]	3299.92 ± 314.31	33.83 ± 1.91	70.49 ± 3.97	609.03 ± 86.87[1]	686.33 ± 75.29	1171.30 ± 81.28	2.72 ± 0.15	9.44 ± 0.76	-1.34 ± 0.26[1]	9.44 ± 0.56
Control group (the passive period of the day)	389.70 ± 3.91	421.94 ± 3.29	32.76 ± 3.14	4094.76 ± 405.44	31.53 ± 1.36	68.33 ± 1.35	606.25 ± 105.94	1124.41 ± 118.76	1749.42 ± 175.53	2.47 ± 0.15	6.91 ± 0.55	-2.53 ± 0.33	8.39 ± 0.75
Group 3 (the passive period of the day)	381.85 ± 3.96	417.57 ± 3.48	69.79 ± 9.59[1]	3880.03 ± 486.71	34.17 ± 1.24	65.82 ± 1.24	741.67 ± 93.82	1027.38 ± 162.25	1509.83 ± 131.93	2.38 ± 0.13	7.75 ± 0.53	-1.34 ± 0.26	9.44 ± 0.56

Notes: [1] - the difference between the control group and Group 3, $p<0.01$