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Research Article

Optimization of Life-Threatening Ventricular Ectopy and Sudden Cardiac Death Prevention in Patients with Postinfarction Cardiosclerosis

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Abstract

The objective of the research was to optimize treatment of patients with ischemic heart disease (postinfarction cardiosclerosis) and concomitant phenomenon of heart rate turbulence based on the study of heart rate turbulence and heart rate variability.

Materials and methods. The study included 100 patients with ischemic heart disease and postinfarction cardiosclerosis complicated by cardiac rhythm disorder (ventricular ectopic beats). Patients were divided into 2 groups according to the type of prophylaxis: Group I received bisoprolol; Group II received quercetin in addition to bisoprolol. A daily dose of bisoprolol was 0.07 mg/kg body weight while a daily dose of quercetin was 1g for 7 days. The control of therapy effectiveness was performed using Holter monitoring of heart rate turbulence and heart rate variability.

Results. Bisoprolol intake by patients with ischemic heart disease and concomitant heart rate turbulence led to significant increase in the stress index as well as the decrease in the overall tension of body regulation, either parasympathetic or sympathetic divisions of the autonomic nervous system and the vasomotor center. Drug intake did not lead to the abnormal physiological correlation between the activity of the subcortical and peripheral components of the nervous systems. While analyzing the changes in the indices of heart rate turbulence and heart rate variability, there was found, that during combination treatment of patients with ischemic heart disease using bisoprolol and quercetin, positive changes appeared in the regulatory parts of the body.

Conclusions. Combination treatment of post-myocardial infarction patients with bisoprolol and quercetin allows us: a) to achieve complete reduction in ventricular ectopic activity in more than half of patients; b) to reduce the number of patients with life-threatening ventricular ectopic beats significantly; c) to maintain the physiological value and the activity of the autonomic nervous system as well as the vasomotor center of the body; d) to decrease the level of turbulence onset and maintain the value of turbulence slope.

Keywords

postinfarction cardiosclerosis; ventricular fibrillation; sudden cardiac death; heart rate turbulence; heart rate variability

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Problem statement and analysis of the recent research

Abnormal cardiac rhythms, either in the early or late postinfarction periods, is not a rare phenomenon [1]. In many cases, sudden cardiac death is the first but at the same time the fatal manifestation of heart disease; therefore, the main direction of many recent studies in cardiology is the search for new risk markers and effective ways of sudden cardiac death prevention [2-4]. Well-studied ectopic parameters such as quantity, gradation and morphology of ventricular ectopies and variability of QT interval duration being recorded by Holter monitoring remain to be useful predictors of high risk when deciding the necessity of cardioverter-defibrillator implantation or antiarrhythmic therapy [5]. Currently existing selection criteria for primary prevention of cardiac death are not effective [1].The study of the measurements on the electrocardiogram (ECG) is closely connected with ventricular ectopy; the analysis of their relationships with autonomic regulation provides the basis for new methods of diagnostics and treatment of risk-stratified markers of sudden cardiac death. When selecting an antiarrhythmic drug, a doctor should always consider the state of the autonomic regulation of cardiac activity [6]. For instance, reduced indices of heart rate variability (HRT) indicate imbalance of autonomic regulation of cardiac rhythm alongside with weakened activity of the parasympathetic part of the autonomic nervous system resulting in decreased threshold of developing ventricular disorders of cardiac rhythm of high gradations [7].

The objective of the research was to optimize treatment of patients with ischemic heart disease (IHD) (postinfarction cardiosclerosis) and concomitant heart rate turbulence (HRT) based on the study of HRT and HRV using β1-selective adrenoblocker (bisoprolol) and quercetin.

1. Materials and methods

The study included 100 patients with IHD and postinfarction cardiosclerosis complicated by cardiac rhythm disorder (ventricular ectopic beats (VEBSs). Patients were divided into 2 groups according to the type of prophylaxis: Group I received bisoprolol; Group II received quercetin in addition to bisoprolol. A daily dose of bisoprolol was 0.07 mg/kg body weight while a daily dose of quercetin was 1g for 7 days.

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).

The spectral analysis of HRT, which is based on the construction of spectra of cardiac cycle length, was used in the research. The analysis of the power 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 world scientific literature, the corresponding spectral components are known as high-frequency (HF), low-frequency (LF) and very low-frequency (VLF). According to the data of the spectral analysis the following indices were calculated: a) the centralization index (CI) = (HF+LF)/VLF), and the vago-sympathetic 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 are 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. This index is calculated on the basis of analyzing the graph of cardiac interval distribution – variational pulsogram. The activation of the central contour as well as the increase in the sympathetic regulation during psychic and physical stress manifests itself as cardiac rhythm stabilization, the decrease in cardiac interval amplitude. This index is very sensitive to the increase in the sympathetic activity [8]. The analysis of HRT was performed based on two indices – turbulence onset (TO) and turbulence slope (TS). TO is a value of sinus rhythm acceleration immediately after VEBs and TS is the intensity of sinus rhythm deceleration, which comes 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 VEBs and the next two sinus RR intervals occurring before VEBs to the sum of two sinus RR intervals to VEBs, expressed as a percentage.

To calculate TO the following formula was used:

$$TO(\%) = 100 * \frac{(RR[1] + RR[2]) - (RR[-3] + RR[-2])}{RR[-3] + RR[-2]} \quad (1)$$

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 follow 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 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 (TST $>$0.5) and (TS$<$2.5) are considered pathological. If the parameter of acceleration (TO$>$0.0) or deceleration (TS$<$0.5) is significantly less than normal leves the risk of fatal ventricular ectopy is very high. The acceleration of sinus rhythm, followed by short-lasting slowdown, is considered as the physiological response to VEBs [9-12].

All 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.

2. Results

Table 1 presents changes in the prevalence of VEBs among patients with IHD according to our observations. The group of patients who underwent combination treatment with bisoprolol and quercetin included people with more severe condition - 59.08% of patients had life-threatening premature ventricular contractions, in 11.11% of patients early VEBs (Class V according to the Lown classification) were recorded. In the group of patients who received bisoprolol only the proportion of patients with life-threatening extrasystole was 49.95%. The number of patients with Lown Class I ventricular extrasystole was almost identical between the groups; there were more patients with Lown Class II ventricular extrasystole in the group of patients who received bisoprolol only; the relative number of patients with Lown Class III ventricular extrasystole was almost identical between the groups; there were no patients with Lown Class IV ventricular extrasystole in the group of patients who received bisoprolol + quercetin. On the background of treatment in individuals receiving bisoprolol only, in 11.11% of patients with ventricular extrasystole there was complete reduction in clinic and symptoms of arrhythmia;

the number of patients with life-threatening extrasystole increased from 49.95% to 58.98%. The number of patients with Lown Class II did not change while the number of patients with Lown Class I reduced twofold. On the background of quercetin inclusion, in 54.54% of patients complete reduction in ventricular extrasystole was achieved. The number of patients with life-threatening extrasystole reduced from 59.08% to 31.8%. The number of patients with Lown Class I reduced twofold; there were no patients with Lown Class II ventricular extrasystole; the number of patients with Lown Class I reduced from 40.9% to 22.72%.

Table 2 presents the comparative characteristics of changes in the parameters of HRV and HRT secondary to bisoprolol intake. In patients receiving bisoprolol, a significant reduction in the duration of the QT interval throughout the day ($p<0.01$) which reduced cardiac electric systole ($p<0.01$) was observed. In the active period of the day, in patients receiving bisoprolol the SI increased twofold ($p<0.01$). The value of the total tension of HRV reduced significantly by 56.82% ($p<0.01$), and it occurred owing to all components ($p<0.01$). The absolute value of HRV spectra after treatment with bisoprolol decreased. Thus, HF spectrum decreased by 56.73%; LF spectrum decreased by 58.36%, VLF spectrum decreased by 34.25% ($p<0.01$). The relative activity of subcortical sympathetic centers remained unchanged being within the range of 2.8. The CI in the active period of the day in patients receiving bisoprolol increased by 17.72%. In the passive period of the day, on the background of treatment the SI increased by 58.72% which was a significant difference ($p<0.01$). The value of TS was significantly lower after treatment - by 61.37% ($p<0.01$). In this case, only the values of LF and VLF spectra were significantly lower – by 51.44 and 39.96% ($p<0.01$), respectively. The HF parameters reduced by 19.22%, however, this difference was not significant. In patients receiving bisoprolol the relative activity of subcortical sympathetic center increased by 18.11% while the CI increased by 74.23%. On the background of treatment with bisoprolol only - the parameter of TO increased significantly ($p<0.01$). Before treatment it was within normal range, after treatment it was low. TS decreased by 19.5% on the background of treatment, however, it was not a significant decrease in this indicator.

The next step was to determine change in HRT on the background of ccombination treatment with beta-blockers (bisoprol) and quercetin. Combination therapy with bisoprolol and quercetin led to insignificant reduction in the duration of the QT interval (Table 3). In the active period of the day, the SI decreased by 16.68%, which was not a significant difference. The total tension of HRV reduced significantly - by 4.19%. The analysis of the value of individual HRV spectra found that HF spectrum increased by 35.03%, LF spectrum increased by 36.87% and the activity of the sympathetic nervous system (VLF spectrum) decreased by 13.57%. The relative activity of subcortical sympathetic center increased insignificantly by 14.0%. The CI increased insignificantly as well - by 6.1%. In the passive period of the day, the SI decreased on the background of combination treatment being lower in contrast to that prior to treatment - by 14.89%. The value of the total tension of body regulation was not significantly lower compared to that before treatment and the difference was 3.19%.

After combination treatment with bisoprolol and quercetin, the activity of the parasympathetic nervous system increased by 11.13%; the activity of the vasomotor center reduced by 35.55%; the activity of the sympathetic nervous system did not decrease significantly - by 2.84%. The relative activity of subcortical sympathetic center decreased by 4.18%. The CI decreased by 0.02% only. During treatment with bisoprolol and quercetin, positive dynamics was observed in changing the parameters of HRT. Thus, TO decreased by 21.98% and TS decreased by 8.95%.

3. Discussion

Half of patients with IHD die suddenly due to life-treatening arrhythmias, especially ventricular tachycardias and irreversible ventricular fibrillation. There are primary and secondary prevention of sudden cardiac death. The last is applied in patients who were saved from sudden cardiac death. In case of coexistence of pathology and frequent ventricular extresytole of high gradation the appropriate antiarrhythmic therapy is chosen. The drugs of choice are ß-blockers, especially if additional indications are present, namely IHD, hypertension, sinus arrhythmia. ß-blockers are the only group of drugs used for non-surgical prevention of sudden cardiac death in patients with acute myocardial infarction. High efficiency of these drugs is associated with antiarrhythmic and bradicardial action [6]. On the basis of the study results, we can state that namely bisoprolol is the drug, which can prevent the development of life-threatening ventricular ectopies including sudden cardiac death. Bisoprolol intake by patients with IHD and concomitant HRT phenomenon leads to significant increase in the SI as well as the decrease in the overall tension of body regulation, either parasympathetic or sympathetic divisions of the autonomic nervous system and the vasomotor center. Drug intake did not lead to the abnormal physiological correlation between the activity of the subcortical and peripheral components of the nervous systems. Bisoprolol intake increases the CI, especially in the passive period of the day. This drug does not increase the value of TO in patients with IHD; the value of TS reduces insignificantly being within physiologically acceptable limits. While analyzing the changes in the indices of HRT and HRV, we can state, that during combination treatment of IHD with co-existent HRT phenomenon there were no significant changes in the indices of HRT and HRV. The inclusion of quercetin allowed us to maintain the physiological value and the activity of the autonomic nervous system as well as the vasomotor center of the body and to decrease the level of TO and maintain the value of TS. Considering the resulting dynamics, we can state that combination treatment of patients with myocardial infarction using bisoprolol and quercetin allows us to achieve complete reduction in ventric-

Table 1. Prevalence of VEBs on the background of treatment (the Lown classification)

	I	II	III	IV	V	No arrhythmia
Bisoprolol before treatment	6 (33.3%)	3 (16.6%)	8 (44.4%)	1 (5.55%)	0	-
Bisoprolol after treatment	3 (16.6%)	3 (16.6%)	9 (50%)	1 (5.55%)	0	2 (11.11%)
Bisoprolol + quercetin before treatment	8 (36.36%)	1 (4.54%)	9 (40.9%)	0 (0%)	4 (18.18%)	-
Bisoprolol + quercetin after treatment	4 (18.18%)	0 (0%)	5 (22.72%)	1 (4.54%)	1 (4.54%)	12 (54.54%)

Table 2. Dynamics of changes in the parameters of HRV and HRT in patients with IHD on the background of bisoprolol intake, (M±m)

	QT, mc	QTc, mc	SI	TP, mc^2	HF, %	LF, %	HF, mc^2	LF, mc^2	VLF, mc^2	LF/HF	IC	TO, %	Ts, mc/bit
Before treatment (day)	384.25 ±4.77	405.95 ±4.54	26.25 ±2.8	5111.2 ±910.88	30.08 ±2.49	69.91 ±2.49	834.9 ±274.74	1504.0 ±355.32	1677.25 ±215.24	2.8 ± 0.34	8.35 ±1.39	-2.35 ±0.49	9.65 ±1.78
After treatment (day)	369.61 ±6.75[1]	407.13 ±6.15	52.52 ±8.49[1]	2904.26 ±437.78[1]	29.19 ±2.36	70.81 ±2.36	360.95 ±175.59[1]	626.39 ±132.12[1]	1102.74 ±130.35[1]	2.82 ±0.23	9.83 ±1.16	-1.14 ±0.33[1]	7.77 ±1.63
Before treatment (night)	384.25 ±4.77	405.95 ±4.54	32.95 ±3.66	6238.76 ±981.04	30.33 ±2.1	69.65 ±2.1	1033.2 ±219.54	2396.65 ±529.29	2058.8 ±263.86	2.65 ±0.27	6.56 ±1.01	-2.35 ±0.49	9.65 ±1.78
After treatment (night)	369.61 ±6.75[1]	407.13 ±6.15	52.30 ±10.21[1]	3828.04 ±486.35[1]	29.48 ±2.54	70.52 ±2.54	827.30 ±194.22	1163.56 ±112.63[1]	1235.56 ±191.16[1]	3.13 ±0.44	11.43 ±2.22	-1.14 ±0.33[1]	7.77 ±1.63

Notes.

[1] - difference $p<0.01$ before, during and after treatment

Table 3. Dynamics of changes in the parameters of HRV and HRT in patients with IHD on the background of quercetin intake, (M±m)

	QT, mc	QTc, mc	SI	TP, mc^2	HF, %	LF, %	HF, mc^2	LF, mc^2	VLF, mc^2	LF/HF	IC	TO, %	Ts, mc/bit
Before treatment (day)	381.94 ±11.57	412.29 ±6.45	76.64 ±4.89	4831.76 ±1110.08	31.34 ±2.66	68.64 ±2.66	754.41 ±346.93	1184.12 ±370.28	1672.52 ±265.87	2.57 ±0.3	8.03 ±1.28	-2.82 ±0.7	9.95 ±2.04
After treatment (day)	376.35 ±4.81	419.35 ±5.89	63.94 ±16.8	4633.65 ±1035.83	30.84 ±3.86	69.17 ±3.86	1018.17 ±577.15	1620.65 ±523.15	1445.17 ±238.58	2.93 ±0.39	8.52 ±1.18	-3.44 ±0.64	9.06 ±1.32
Before treatment (night)	381.94 ±11.57	412.29 ±6.45	38.70 ±12.23	5736.23 ±1185.72	31.38 ±2.26	68.61 ±2.26	1171.94 ±456.12	1882.70 ±522.62	2046.76 ±310.99	2.45 ±0.23	7.41 ±0.96	-2.82 ±0.7	9.95 ±2.04
After treatment (night)	376.35 ±4.81	419.35 ±5.89	32.94 ±5.36	5553.23 ±1159.73	34.22 ±3.38	66.35 ±3.41	1301.35 ±660.24	1401.29 ±292.41	1988.05 ±315.73	2.35 ±0.28	7.44 ±2.22	-3.44 ±1.04	9.06 ±1.32

ular ectopic activity in more than half of patients as well as to reduce the number of patients with life-threatening VEBs significantly.

4. Conclusions

Combination treatment of post-myocardial infarction patients using bisoprolol and quercetin allows us: a) to achieve complete reduction in ventricular ectopic activity in more than half of patients; b) to reduce the number of patients with life-threatening VEBs significantly; c) to maintain the physiological value and the activity of the autonomic nervous system as well as the vasomotor center of the body; d) to decrease the level of TO and maintain the value of TS.

5. Prospects for further research

The aforementioned data point to a promising combination of a beta-blocker bisoprolol and quercetin when treating patients with impaired cardiac rhythm secondary to myocardial ischemia.

6. Conflict of interest

None

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