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The effect of nitroglycerin on cardiac extrasystoles and heart rate variability in patients with stable angina pectoris class 1 and 2

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Abstract

Aim. To study the effect of nitroglycerin on the heart rate and its variability in patients with stable angina pectoris class 1 and 2.

Methods. 85 men with stable angina pectoris class 1 and 2 pathologies were examined between 2007 and 2012 in the City Clinical Hospital No. 8 of Chelyabinsk (mean age 53.1±5.66 years). In addition to common methods, a rhythmocardiographic study was performed, which allows you to calculate heart rate variability. An electrocardiogram was recorded simultaneously with the rhythmocardiogram.

Results. After sublingual nitroglycerin, the number of ventricular extrasystoles decreased in the background test and during Valsalva maneuver, increased in the Ashner's test and an exercise stress tests and did not change in the orthostatic test. An increase in supraventricular extrasystoles after nitroglycerin administration occurred in 10.6% of patients. Nitroglycerin administration resulted in a decrease in the inter-systolic intervals, an increased in the proportion of slow low-frequency waves— statistically significant in the background and an exercise stress test. Spectral indicators of cardiac sympathetic modulation significantly increased in the Ashner's test and decreased in the background test, while spectral indicators of cardiac parasympathetic modulation decreased in all samples except in exercise stress tests.

Conclusion. Under the influence of nitroglycerin, supraventricular arrhythmias increased in all vegetative tests except for orthostatic, the number/severity of ventricular extrasystoles ambiguously changed: decreased in Valsalva manoeuvre the background test, did not change in orthostatic and increased in Aschner's and an exercise stress tests; after nitroglycerin, the proportions of sympathetic influence (in Ashner's test) and slow low-frequency waves in the spectrum of the vegetative modulation increased with a decrease in parasympathetic.

Keywords: exertional angina, heart rate variability, cardiac arrhythmias, extrasystole, rhythmocardiography, electrocardiogram.

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Background. Existing literature presents conflicting evidence on the effect of organic nitrates, specifically nitroglycerin (NG), on the heart rate (HR). In their experimental study, Baharvand et al. [1] noted a decrease in the incidence of ventricular tachycardia and ventricular fibrillation in NG-treated rats, whose hearts were subsequently subjected to 30-min ischemia and 120-min reperfusion. Assefa et al. [2] presented a clinical case of arresting an accelerated idioventricular rhythm after a spasm of the coronary artery (an episode of Prinzmetal's angina pectoris) by sublingual administration of NG. In another patient with stress cardiomyopathy, contrast administration during coronary angiography provoked spasm and ventricular tachycardia, which was resolved after intracoronary injection of NG [3].

A study [4] showed that when testing by the lean method ("head up") using the sublingual NG challenge, 29% of the cases (a total of 816 patients were examined) developed bradysystole, with pauses of more than 3 s in some patients, and tachyarrhythmia was detected in 7.9% of those examined.

Sato [5] described that bradycardia, loss of consciousness, and subsequent cardiac arrest occurred

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in a patient with preeclampsia who underwent cesarean section under spinal anesthesia, with NG intravenous drip-feed administration at a dose of 200 μg to relax the muscles of the uterus. NG was discontinued, and cardiopulmonary resuscitation was successfully performed. In light of this, a study about the effect of organic nitrates, specifically NG, on heart rhythm disorders and HR variability in patients with coronary heart disease is relevant.

This study aimed to analyze the effect of NG on cardiac rhythm and its variability in patients with stable exertional angina of grades 1 and 2.

Materials and methods. From 2007 to 2012, 85 male patients with stable angina of grades 1 and 2 (mean age 53.1 ± 5.66 years) were examined in the City Clinical Hospital No. 8 of Chelyabinsk. A cross-sectional (non-serial) study was performed on these patients.

The inclusion criteria were signs of stable angina according to the recommendations of the Society of Cardiology of Russian Federation of 2008 [6], male sex, age 40–65 years, and provision of informed consent.

The exclusion criteria were female sex, diseases that can distort the results of rhythmocardiographic studies, including anemia, infectious diseases, food and drug allergies, bradycardia (HR <50 beats per minute), diabetes mellitus, arterial hypertension, and pathology of the bone marrow, kidneys, and liver.

The average duration of ischemic heart disease was 4.43 ± 3.30 years. Three (3.53%) patients had a history of myocardial infarction. Heart failure was not more severe than stage I. Arterial hypertension was not recorded in this patient group, which was also an exclusion factor. According to echocardiography data, the average ejection fraction was 58.12 ± 4.35%.

All patients underwent instrumental examinations, including electrocardiography, 24-h electrocardiographic monitoring, and bicycle ergometry. In addition, a rhythmocardiographic study modified by Mironov and Mironova was performed using the device KAP-RK-01-Mikor, which enables calculation of the indicators of HR variability [7]. An electrocardiography data was recorded synchronously with the rhythmocardiography.

The baseline test at rest, Valsalva–Burger test with inspiration breath-hold, Aschner test (pressing on the eyeballs), orthostatic test, and power working capacity test were performed.

The power working capacity test included a dosed load on the bicycle ergometer until an *RR* interval of 0.5 s was reached with continuous recording of rhythmocardiography data before, during, and after pedaling, until 95% of the initial interval was restored. The test was intended to analyze the autonomic support of physical activity during the adaptation process which is responsible for the optimal change in the cardiac output. Changes in HR variability provide cardiac output adequate to load. The dosed load on a bicycle ergometer with a HR of 120 beats per minute serves as the average submaximal load for patients with cardiovascular pathology.

The intersystolic intervals, general HR variability, amplitude, and proportion of slow low-frequency waves, as well as sympathetic and parasympathetic influences, were assessed. KAP-RK-01-Mikor provides automatic calculation of these spectral (%) and temporal (amplitude) indicators of HR variability. The total spectral characteristics of these waves are 100%.

The slowest system of the regulation of blood circulation is humoral and metabolic. This is due to the activities of both circulating hormones in the blood and tissue hormones, which are active substances in the tissue. Its regulatory effect is associated with tissue activity, that is, one vibration per minute or less corresponds to a frequency range of less than 0.04 Hz (less than 2.4 vibrations per minute), which are so-called very slow (low-frequency) waves.

Rhythmocardiography and simultaneous electrocardiography data were recorded before and 5 min after a single sublingual administration of 0.5 mg NG. The study was performed in the morning (8–9 o'clock) before administration of the main antianginal therapy. The study duration was determined by the HR, and 300 RR intervals were recorded in each test before and after NG administration.

Statistical analysis of data was performed using IBM SPSS Statistics 19 and StatPlus 2009 Professional. Data were presented as minimum and maximum values, mean, and standard error of the mean ($M \pm m$). The maximum and minimum values were presented because the average values (M) are low. For the nominal characteristics [change in the number or severity of arrhythmias for supraventricular extrasystoles (SES) and that for ventricular extrasystoles (VES)], the absolute (number of patients) and relative (%) frequency were indicated. The nonparametric Wilcoxon test was used to assess differences between groups. Qualitative characteristics were presented as absolute and relative frequencies, and intergroup differences were assessed using the Pearson χ^2 test. For all analyses, p values of 0.05 or lower were considered statistically significant. If the significance level (p) was less than 0.001, then a p-value of <0.001 was indicated [8].

Table 1. Effects of nitroglycerin on single ventricular and supraventricular extrasystoles in patients with stable angina of grades 1 and 2.

Test	Number of extrasystoles before nitroglycerin administration				Number of extrasystoles after nitroglycerin administration				p
	n	minimum	maximum	M±m	n	minimum	maximum	M±m	
Ventricular extrasystoles									
ph	85	0	8	0.129±0.096	85	0	5	0.106±0.069	0.577
Vm	85	0	7	0.129±0.090	85	0	3	0.059±0.039	0.496
pA	85	0	5	0.071±0.060	85	0	4	0.129±0.069	0.317
Aop	85	0	2	0.094±0.043	85	0	4	0.118±0.059	0.832
PWC	85	0	12	0.212±0.146	84	0	6	0.155±0.082	0.619
Supraventricular extrasystoles									
ph	85	0	3	0.05±0.04	85	0	1	0.04±0.02	1.000
Vm	85	0	1	0.02±0.02	85	0	6	0.11±0.07	0.197
pA	85	0	2	0.07±0.03	83	0	1	0.06±0.03	0.705
Aop	85	0	3	0.08±0.04	85	0	5	0.12±0.07	0.673
PWC	84	0	1	0.06±0.03	85	0	6	0.28±0.11	0.106

Note: ph, baseline test; Vm, Valsalva–Burger test; pA, Aschner test; Aot, active orthostatic test; PWC, power working capacity test.

Table 2. Changes in the number (and/or severity) of ventricular and supraventricular heart rhythm disorders after nitroglycerin administration

Changes	ph	Vm	pA	Aop	PWC
Ventricular extrasystoles					
No changes	81 (95.3%)	80 (94.1%)	78 (91.8%)	79 (92.9%)	76 (89.4%)
Deterioration	1 (1.2%)	2 (2.4%)	5 (5.9%)	3 (3.5%)	5 (5.9%)
Improvement	3 (3.5%)	3 (3.5%)	2 (2.4%)	3 (3.5%)	4 (4.7%)
Significance	p <0.001	p <0.001	p <0.001	p >0.05	p <0.001
Supraventricular arrhythmia					
No changes	80 (94.1%)	81 (95.3%)	76 (89.4%)	79 (92.9%)	71 (83.5%)
Deterioration	3 (3.5%)	3 (3.5%)	6 (7.1%)	3 (3.5%)	9 (10.6%)
Improvement	2 (2.4%)	1 (1.2%)	3 (3.5%)	9 (10.6 %)	5 (5.9%)
Significance	p <0.001	p <0.001	p <0.001	p <0.001	p <0.001

The study protocol was approved by the Ethics Committee of the South Ural State Medical University (protocol no. 9, dated November 09, 2006, Chelyabinsk State Medical Academy). Patients provided informed consent to participate in the study.

Results. Table 1 presents data on the effect of NG on single VES and SES. In the analysis of VES using the unpaired method, no statistically significant differences were recorded. In patients with stable angina of grades 1 and 2, the maximum number of VES was recorded both before and after administration of NG in a power working capacity test. In the analysis of SES, no significant difference (using the Wilcoxon test) was found before and after NG administration, but there were more maximum values of single SES in the Valsalva–Burger test with inspiration breath-hold, orthostatic test, and power working capacity test after NG administration.

With individualized analysis, Table 2 presents the changes in SES and VES following NG administration. When the effect of NG on VES was analyzed, miscellaneous results were revealed, that is, the number of VES decreased in the baseline test and Valsalva–Burger test, did not change in the orthostatic test and Aschner test, and increased in the power working capacity test. Comparability of VES with HR was analyzed, and results revealed that in patients with increased VES, the HR tended to increase following administration of NG, that

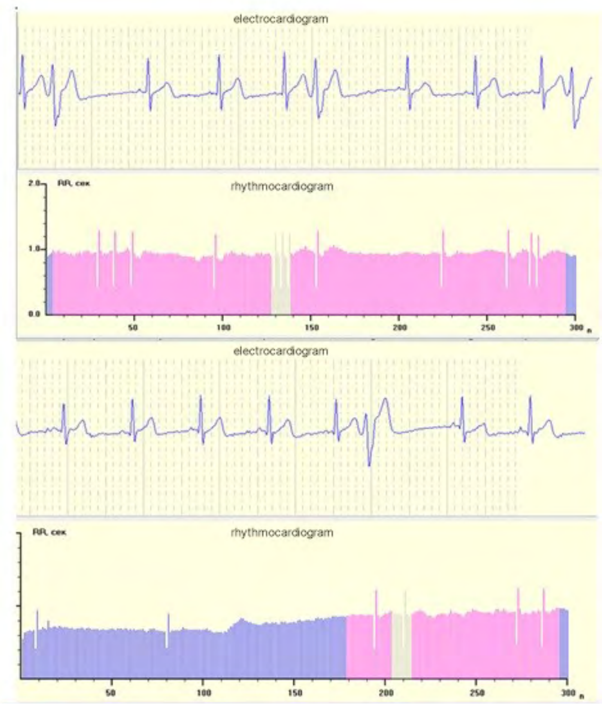

Fig. 1. Effect of nitroglycerin on single ventricular extrasystole in a power working capacity test (the upper and lower parts present data before and after nitroglycerin administration, respectively) in a 49-year-old patient.

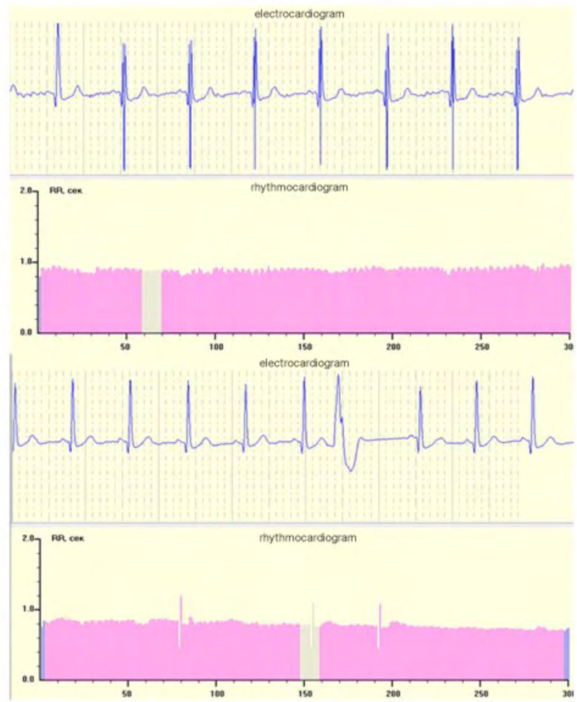

Fig. 2. Rhythmocardiogram of a 55-year-old patient in the baseline test with simultaneous electrocardiogram recording before (upper part of the figure) and after (lower part of the figure) sublingual administration of nitroglycerin.

is, from 72.20 ± 11.90 to 75.66 ± 6.96 beats per minute, while with a decrease in VES, the HR tended to decrease from 75.47 ± 11.39 to 72.46 ± 10.94 beats per minute.

In Table 2, all supraventricular arrhythmias were taken into account, including paired, group SES, and paroxysms of supraventricular tachycardia.

SES aggravated after administration of NG in all vegetative tests, except in the orthostatic test, in a maximum of 10.6% of the patients. The HR was comparable, as in patients with aggravated SES, and the HR tended to increase slightly on average from 66.30 ± 9.15 to 67.26 ± 9.13 beats per minute. Moreover, in patients with a decrease in the number of SES, the HR decreased slightly from 68.74 ± 11.87 to 66.37 ± 13.14 beats per minute. One patient had two consecutive SES (couplet) after NG administration in the Aschner test. Another patient had group SES (4 consecutive SES) and paroxysm of supraventricular tachycardia (9 consecutive SES) before NG administration in the power working capacity test, as well as paroxysm of supraventricular tachycardia (>4 consecutive SES) after NG administration in the Aschner test.

Figure 1 illustrates the decrease in the number of VES in the power working capacity test 5 min after sublingual administration of 0.5 mg NG.

Figure 2 presents the emergence of three monotopic VES after NG administration in the baseline test; no heart rhythm disorders were recorded on the initial rhythmocardiogram and electrocardiogram.

Figure 3 presents the emergence of six SES in a power working capacity test after NG administration.

According to the indicators of HR variability of the stationary rhythmocardiogram, even with a single dose of NG, the *RR* values changed in all positions with a tendency to decrease in the physiological test, Valsalva–Burger test with inspiration breath-hold, and active orthostatic test with sufficient significance, which suggests a compensatory increase in HR.

In nearly all positions, the amplitude of very low-frequency waves increased substantially in a physiological test, active orthostatic test, and power working capacity test, which indicated the reactions following the predominant participation of very low-frequency waves, which is the most influential humoral and metabolic factor.

In all positions, the proportion of humoral and metabolic effects increased, which was statistically significant in the baseline test and power working capacity test ($p < 0.01$). The sympathetic spectral characteristic (LF%) increased significantly in the

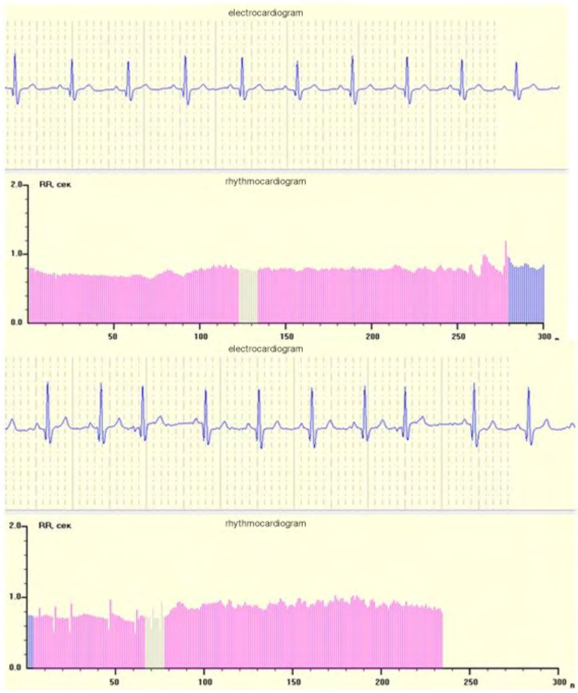

Fig. 3. Rhythmocardiogram and electrocardiogram of a 55-year-old patient before and after administration of nitroglycerin.

Aschner test ($p < 0.05$) and decreased in the baseline test ($p < 0.01$). The share of parasympathetic protective effect (HF%) decreased significantly in all tests, except in the power working capacity test [9].

Discussion. Considering the influence of NG on VES, the number of VES increased in the Aschner test and power working capacity test. This mainly occurred because we expected that NG was beneficial for the forthcoming physical activity or for subsequent angina pectoris.

In the analysis of the vegetative spectrum, the sympathetic effect increased in the Aschner test and decreased in the baseline test, which correlated with the change in VES in these tests and a decrease in the parasympathetic effect.

Aggravation of SES (an increase in the frequency, emergence of paired SES in one patient, and a paroxysm of supraventricular tachycardia in one patient) after NG administration was noted in all vegetative tests, except in the orthostatic test, in a maximum of 10.6% of the patients, which correlated with an increase in humoral and metabolic factors and a decrease in the parasympathetic effect.

The ambiguity of the effect of NG on the HR was illustrated by Efird [10] who noted an increased risk of atrial fibrillation in patients with a history of coronary artery bypass grafting with simultaneous administration of nitrates. Efremov et al. [11] registered a progressive decrease in the parasympathetic activity in patients with NG-induced syncope, which was absent in patients with a negative response to NG.

In our study [12], when using isosorbide dinitrate in patients with stable effort angina of grades 1 or 2 combined with hypertension, humoral and metabolic regulation was also increased with a decrease in the parasympathetic effect. Moreover, when isosorbide mononitrate was administered in patients with stable angina of grades 3 or 4, similar shifts in vegetative influence were found, as well as an increase in the sympathetic influence in the baseline test and Aschner test [13].

Conclusions. NG increased and/or aggravated supraventricular arrhythmias in all vegetative tests, except in the orthostatic test. After NG administration, the number of VES changed ambiguously, that is, decreased in the baseline test and Valsalva–Burger test, did not change in the orthostatic test, and increased in the Aschner test and power working capacity test in patients with stable exertional angina of grades 1 and 2. In general, in the vegetative spectrum after NG administration, a shift toward the sympathetic effect was observed in the Aschner test with a decrease in the baseline test, a change in the proportion of very low-frequency waves was recorded (significantly in the baseline test and power working capacity test), and a decrease in parasympathetic regulation was statistically significant in all tests, except in the power working capacity test.

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Conflict of interest. The authors declare no conflict of interest.

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