Analysis of arrhythmias and heart rate variability according to Holter monitoring in patients with silent myocardial ischemia

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The aim of the study was to analyze arrhythmias and heart rate variability parameters in the presence and absence of silent myocardial ischemia (SMI).

Methods. The results of Holter monitoring (HM) of 288 patients (mean age — 63.2±10.7 years), were analyzed. The following parameters were studied: ECG rhythm; heart rate (HR); ventricular extrasystoles (VE); ventricular tachycardia (VT); QT interval; ST segment displacement; T-wave; heart rate variability (HRV), standard deviation of NN interval (SDNN); root mean square of the differences in successive R-R interval (rMSSD), circadian index (CI), and circadian profile (CP).

Results. Patients with SMI more often ($p<0.00005$) had permanent atrial fibrillation (AF), while it is not a complication of myocardial infarction. The SMI group has higher mean daytime HR ($p<0.05$) and maximum HR ($p<0.00001$)

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compared to the control group (CG). SMI patients had lower minimum HR (p<0.05) and difference between maximum and minimum HR compared to CG (p<0.0000005). In the SMI group of patients with VE (p<0.005), the number of VE per day (p<0.001), the mean number of VT episodes (p<0.05) per day were significantly lower compared to CG patients. In SMI, the episodes of ST-segment depression (p<0.05) and negative T-waves (p<0.005) were significantly more frequent, and these changes were more often associated with physical activity (PA) compared to CG (p<0.05). Diurnal SDNN was significantly higher in the SMI group compared to CG (p<0.0005). Decreased CI (p<0.000005) and rigid CP (p<0.005) were less frequent in SMI patients compared to CG patients.

Conclusion. VE and VT were less frequently detected during HM in patients with SMI, indicating a milder course of coronary heart disease (CHD), where ventricular arrhythmias (VA) are one of the indicators. In patients with SMI, HRV data show normal autonomic innervation of the heart, which may be an additional reason for less severe VA along with a milder course of CHD.

Keywords: silent myocardial ischemia, heart rate variability, coronary heart disease, Holter monitoring, electrocardiography.

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Introduction

Silent myocardial ischemia (SMI) is a transient disturbance of myocardial perfusion, metabolism, function, or electrical activity that is not accompanied by angina pectoris or its equivalent [1]. The pathogenesis of SMI is thought to involve alterations in the autonomic regulation of cardiac activity accompanied by cardiac rhythm disturbances [2]. Holter monitoring (HM) allows detecting myocardial ischemia, the presence of arrhythmias and analyzing the state of autonomic regulation of the heart [3, 4]. Analysis of heart rate variability (HRV) allows to evaluate the state of autonomic regulatory influences [5]. Firstly, the activation of the sympathoadrenal system and the decrease of the parasympathetic activity raise the probability of myocardial electrical instability and fatal arrhythmias; secondly, most episodes of myocardial ischemia are accompanied by changes in the state of autonomic nervous system [6, 7]. The aim of the study was to evaluate the arrhythmias and HRV parameters in the presence and absence of SMI. The analysis of HM was aimed at clarifying the course and pathogenesis of SMI, which can be manifested not only by ST-segment dynamic changes, but also by ventricular arrhythmias (VA).

Methods

The study was retrospective, observational, analytical. The subject of the study were medical records of inpatients treated in the cardiology department of Interregional Clinical Diagnostic Center (Kazan). The medical records of 288 patients, mean age 63.2±10.7 years, were analyzed.

Inclusion criteria in the SMI group were following: patients discharged from hospital with the diagnosis of CHD, SMI confirmed during hospitalization (a combination of painless and painful myocardial ischemia was allowed); presence of VA according to HM. The control group (CG) consisted of patients discharged from hospital with the following diagnosis: CHD: angina pectoris; absence of SMI according to the HM and exercise testing; with VA according to HM. Exclusion criteria were: acute coronary syndrome; acute cerebral circulatory failure or transient ischemic attack within 3 months before the study; functional class III-IV heart failure; cardiomyopathies; inflammatory diseases of myocardium, endocardium, pericardium; heart defects; severe liver and kidney pathology; severe anemia; decompensated diabetes mellitus.

The following HM parameters were analyzed: baseline rhythm; heart rate (HR) (mean diurnal HR, mean daytime HR, mean nocturnal HR); maximum HR (relation to PA, relation to complaints); minimum HR; ventricular extrasystoles (VE) (number per day, number per hour, relation to PA), VE pairs (number per day), VE groups (number per day); ventricular tachycardia (VT) (number per day), maximum HR of VT (beats per min), maximum duration of VT; corrected QT interval (ms); ST segment displacement (number of episodes, total duration, maximum depression, minimum threshold HR, relationship to exertion); T-wave (negative, recovery to positive, at isoline, relationship to exertion); rhythm variability: standard deviation of NN interval (SDNN) diurnal (ms), SDNN daytime (ms), SDNN nocturnal (ms), root mean square of the differences in successive R-R interval (rMSSD) diurnal (ms), rMSSD daytime (ms), rMSSD nighttime (ms); circadian index (CI); circadian profile (CP) [8, 9].

Statistical analysis

The results of the study were processed using methods of parametric and non-parametric analysis using the program STATISTICA 12.0 (StatSoft). Quantitative indicators were evaluated for conformity to normal distribution using Shapiro-Wilk and Kolmogorov-Smirnov tests. For quantitative indicators with normal distribution, arithmetic mean (M) and standard deviation (SD) were calculated. For quantitative indicators with non-normal distribution, median (Me) and interquartile range (Q1-Q3) were calculated. For values in normally distributed populations, Student's t-test was used. In cases of non-normal distribution, the Mann-Whitney U-test was used. Differences were considered statistically significant at a significance level of $p<0.05$.

Results

The clinical characteristics of the patients included in the study are shown in Table 1. Patients in the SMI group were significantly older (p=0.0001) compared to CG patients. Females were significantly (p=0.04) more common in the SMI group. Myocardial infarction (MI) was detected 43% less frequently in the SMI group than in the CG (p=0.00001), silent MI was detected 15.2% more frequently in the SMI group than in the CG group (p=0.04). Coronary artery bypass grafting (CABG) (p<0.005) and coronary stenting (CS) were performed 3 times less frequently in SMI patients (p<0.00001) than in CG.

Table 2 shows the characterization of HM parameters in SMI and CG groups. Permanent atrial fibrillation (PAF) was found in 23.2% of patients in SMI and in 0.7% of cases in CG. AF occurred 33 times more frequently in SMI patients compared to CG (p=0.00001), and AF was not a complication of MI (only 6 of 35 (17.1%) patients with AF were found to have a confirmed history of MI). The SMI group had higher mean daytime HR (p=0.01) and maximum HR (p=0.000005) compared to CG patients. CG patients more often had a higher maximum HR associated with discomfort compared to SMI patients (p=0.0001). SMI patients had a lower minimum HR compared to CG (p=0.03) and a lower difference between maximum and minimum HR compared to CG (p=0.0000002).

SMI group had higher achieved maximum HR (p=0.000005) and mean daytime HR (p=0.01) compared to CG according to HM results. The SMI group also had less frequent VE (p=0.001), lower number of VE (per day) (p=0.0006), mean number of VT episodes (p=0.03) compared to CG. Patients with SMI had significantly more episodes of the diurnal ST-segment depression (p=0.03) and the negative T-wave (p=0.002); these changes were less frequently associated with VE compared to CG (p=0.04).

Diurnal SDNN was significantly higher in the SMI group compared to CG (p=0.001). When HRV parameters in SMI and CG groups were examined in patients with sinus rhythm, daily SDNN (p=0.001) was significantly higher in patients with SMI. In the SMI group, decreased CI was found less often compared to CG (p=0.00004), circadian HR profile was normal more often (p=0.001).

Table 1. **Characteristics of patients with VA according to the HM data (n=288)**

Characteristics		SMI (n=151)	CG (n=137)	p
Age, Me [IQR; 25%–75%]		66.0 [59–73]	60.0 [55–67]	0.0001
Gender	male. n (%)	106 (70.2 %)	118 (86.1 %)	0.04
	female. n (%)	45 (29.8%)	19 (13.9 %)	
Postinfarction cardiosclerosis, n (%)		49 (32.4 %)	92 (67.1 %)	0.00001
Confirmed silent MI, n (%)		16 (32.6 %)	16 (17.4 %)	0.04
CABG, n (%)		5 (3.3 %)	17 (12.4 %)	0.004
CS, n (%)		19 (12.6 %)	56 (40.9 %)	0.00001
Arterial hypertension, n (%)		126 (83.4 %)	120 (87.6 %)	0.3
Diabetes mellitus, n (%)		31 (20.5 %)	30 (21.9 %)	0.8

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Table 2. **Characteristics of HM parameters in SMI and control groups with VA (n=288)**

Characteristics		SMI (n=151)	CG (n=137)	p
Baseline rhythm	Sinus, n (%)	116 (76.8 %)	136 (99.3 %)	0.00001
	AF, n (%)	35 (23.2 %)	1 (0.7 %)	
Mean daytime HR (beats per minute), Me [IQR; 25%–75%]		78 [67–87]	72 [65–78]	0.01
Max. HR (beats per minute), Me [IQR; 25%–75%]		120 [106–142]	108 [99–123]	0.000005
Max. HR, symptomatic, n (%)		0 (0 %)	14 (10.2 %)	0.0001
Difference between max. and min. HR (beats per minute), Me [IQR; 25%–75%]		72 [57–93]	59.5 [46–72]	0.0000002
Amount of VE (per day), Me [IQR; 25–75%]		12,5 [1–81]	38 [6–268]	0.0006
VE presence, n (%)		138 (91,4 %)	135 (98.5 %)	0.001
VT (average number per day), Me [IQR; 25–75%]		1 [1–1]	1 [1–2]	0.03
Number of ST-segment depression episodes per day, Me [IQR; 25–75%]		2 [1–3]	1 [1–1]	0.03
Relationship of ST-segment depression to exercise, n (%)		67 (44,4 %)	9 (75 %)	0.04
Negative T-wave, n (%)		15 (10 %)	2 (1.5 %)	0.002
Diurnal SDNN (ms), Me [IQR; 25%–75%]		125,0 [101-148]	105.5 [79–134]	0.001
Daytime SDNN (ms), Me [IQR; 25–75%]		100,0 [91-117] n=23	85 [66.5–109.5] n=45	0.06
Nocturnal SDNN (ms), Me [IQR; 25–75%]		83,0 [64,5–106] n=23	94 [66–115] n=45	0.5
CI, Me [IQR; 25–75%]		1,19 [1,16–1,25]	1.15 [1.1- 1.21]	0.000004
Circadian profile of HR	normal, n (%)	39 (52.7 %)	37 (29.6 %)	0.001
	rigid, n (%)	35 (47.3 %)	88 (70.4 %)	

Discussion

Patients in the SMI group were older than those in the CG group. This was probably because VA occur at an earlier age in CG than in SMI. Presumably, the myocardium in SMI has a lower predisposition for this type of arrhythmia and SMI is a condition that occurs at an older age, which is supported by the literature [10]. Females were more common in the SMI group, which may be due to decreased estrogen levels, changes in levels of other hormones including increased levels of follicle-stimulating hormone, low estrogen and progesterone levels. That, among other factors, may contribute to the development or worsen the course of SMI [11].

The SMI group had a lower incidence of MI compared to CG, but silent MI was more often identified retrospectively in this group, which is due to the fact that more cases of MI are asymptomatic in SMI [12]. CABG and CS were performed less frequently in patients with SMI than in CG. This may be due to the fact that SMI patients were not admitted to the hospital with acute coronary syndrome, hemodynamic disturbances due to the absence of pain syndrome, and therefore CS and CABG were performed less frequently. PAF without MI was detected 33 times more often in patients with SMI than in CG. Myocardial ischemia, especially painless, is an independent risk factor for the development of AF, which is associated with the specific characteristics of the myocardium in such patients.

The SMI group had higher mean daytime and maximum HR compared to CG patients, which was due to the fact that SMI patients did not have clinical manifestations in the background of HR increase, which may limit its level. In CG patients, maximum HR was more often associated with discomfort, which was due to the fact that patients with SMI did not have clinical manifestations. In patients with SMI the minimum HR and the difference between maximum and minimum HR was lower compared to CG. It can be assumed that in SMI the range of sinus node capabilities is wider.

In the SMI group, HM showed higher achieved maximum HR and average daytime HR compared to CG, which was associated with the fact that SMI patients have a higher tolerance to PA, as the level of exercise is not limited by the occurrence of clinical manifestations. At the same time, AF was detected significantly more often in the SMI group. There may be a relationship between high HR and the frequency of AF detection in the SMI group, these phenomena are related to the myocardial structure in these patients. The SMI group had less frequent VE, lower number of VE (per day) and average number of VT attacks compared to CG. It is possible that the myocardial structure itself is unique in SMI, resulting in a lower predisposition to VA, ultimately indicating a more favorable prognosis in such patients. Patients with SMI were significantly more likely to have daytime episodes of ST-segment depression and negative T-wave. Patients with SMI are ECG reactive patients with unique characteristics of myocardial functional state; they have different responses to ischemia and PA.

Diurnal SDNN was significantly higher in the SMI group compared to CG. SDNN is an integral general assessment indicator of the sinus rhythm wave structure presence; its increase usually indicates a decrease in the number of monotype intervals in the intervalogram, i.e. weakening of sympathetic activity and increase of vagal effects and central regulation activity. In patients with SMI, PAF was registered more often, which means that in these patients this index does not show an obvious vegetative dependence, but determines a high adaptive corridor of rhythm fluctuations. Inverse dependence was found in the SMI and CG groups by the level of the SDNN at night and during the daytime. Daytime SDNN shows predominantly sympathetic effects, while nighttime SDNN — the parasympathetic effects. These functions are not only different, but they are opposite in 2 groups. Perhaps the balance of the autonomic nervous system is altered in SMI. In the SMI group, a decrease in CI was found less often compared to CG, and a normal CP — more often. This indicates that the total effect of autonomic regulation of blood circulation is high in SMI and its increase is associated with increased vagal activity. It means that there are no disturbances of central and autonomic connection of heart rhythm regulation, better prognosis and lower risk of fatal arrhythmias in SMI compared to CG. CG shows a certain impairment of the central and autonomic link of heart rhythm regulation and is associated with poor prognosis and high risk of sudden cardiac death. In rigid rhythm, which is significantly more common in CG, parasympathetic control of cardiac activity is reduced, and rigid rhythm is a precursor of fatal arrhythmias.

Conclusion

In patients with SMI, VE and VT are detected less frequently during the HM, indicating a milder course of CHD, where the ventricular arrhythmias are one of the indicators of its severity. In patients with SMI, HRV data show normal autonomic innervation of the heart, which may be an additional reason for the lower severity of ventricular arrhythmias along with a milder course of CHD.

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