ORIGINAL ARTICLE

CONTENTS

Features of complex medicamental therapy in patients with silent myocardial ischemia of high risk after myocardial infarction

Tetiana V. Merhel, Tetiana V. Naluzhna, Khrystyna V. Levandovska
IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: To determine the peculiarities of the course of silent myocardial ischemia (SMI) in patients with post-infarction cardiosclerosis depending on the risk factors (RFs); to reveal the interdependence between the presence of pathological turbulence of the heart rhythm and the peculiarities of the course of SMI in patients with post-infarction cardiosclerosis and the effectiveness of treatment applying S-amlodipine and enalapril in complex therapy.

Materials and Methods: There were observed 154 patients with SMI with a history of myocardial infarction, having received anti-anginal therapy. The diagnosis of SMI was made according to Holter ECG monitoring data. Among the additional indices of the severity of the patient's condition, the maximum value of the ST segment deviation amplitude was evaluated.

Results: It was determined that in patients with SMI with post-infarction cardiosclerosis, there is a positive correlation between the presence of RFs and Holter ECG monitoring indices, in particular, the average daily values of the number of ischemic episodes, the total daily duration of ST segment depression and the average duration of one ischemic episode. Enalapril and S-amlodipine are the effective means of pharmacotherapy in the SMI.

Conclusions: The silent myocardial ischemia, which is associated with the presence of such Rfs as arterial hypertension, diabetes melitus, dyslipidemia or their combination, is characterized by a severe course of the disease, which is manifested by a worsening of the clinical condition, a decrease in tolerance to physical exertion, significant changes in hemodynamics.

KEY WORDS: heart rate turbulance, heart rate variability, anti-ischemic therapy, post-infarction cardiosclerosis

Wiad Lek. 2025;78(2):328-335. doi: 10.36740/WLek/201337 DOI

INTRODUCTION

SMI – is a special form of coronary artery disease (CAD), which is characterized by atherosclerotic damage to the coronary arteries and the occurrence of myocardial ischemia, in which the intensity of efferent nociceptive stimulation does not reach a level sufficient to cause pain [1]. In the SMI pathogenesis, at the same time, a lower degree of severity of ischemic and atherosclerotic changes is noted, compared to stable angina pectoris. The presence of SMI for a long time is the cause of local or diffuse damage to the heart muscle, disturbances in the kinetics of the left ventricle, and leads to the progression of heart failure. This is the reason why patients with SMI should be included into the group with a complicated course of CAD [2].

One of the most prognostically unfavourable complications of CAD, including its silent form, is sudden cardiac death (SCD) [3]. The fight against the emergence of life-threatening arrhythmias and SCD is one of the most important tasks of the modern health care system of Ukraine and the world in general. The importance of this problem is due to high mortality, especially among young and working-aged people [4]. Current selection criteria for primary prevention of SCD in patients with SMI are insufficiently effective. In many cases, SCD is the first, but at the same time, it is the fatal manifestation of the disease [5]. Therefore, the main direction of modern research in medicine is to identify the silent form of myocardial ischemia, followed by the search for early risk markers and ways to effectively prevent SCD [6].

Research over the past three decades suggests a probable relationship between autonomic regulation and mortality from cardiovascular diseases (CVD), including SCD. There is experimental evidence [7] of a correlation between the frequency of occurrence of fatal arrhythmias and destabilization of the balance of the sympathetic and parasympathetic parts of the autonomic nervous system (ANS) [8]. This led to the discovery of quantitative markers of autonomic regulation – heart rate variability (HRV), the analysis of which is one of the main quantitative methods of assessing the mechanisms of neurohumoral regulation of the heart,

which allows establishing the relationship between the sympathetic and parasympathetic divisions of the ANS in temporal and spectral dimensions and quantitatively characterize the activity of different departments of the ANS. An imbalance of the ANS, which leads to a decrease in HRV, causes an increased risk of severe cardiovascular complications and death [9].

The lack of clear criteria for the detection of SMI, assessment of the risk of life-threatening arrhythmias and SCD provoked by modified (smoking, dyslipidemia, arterial hypertension (AH), etc.) and unmodified risk factors (RFs) of CVD, differentiated approaches to the application of basic methods of early diagnosis and treatment, do not allow in many cases achieve the desired clinical effect during the treatment of patients with cardiovascular pathology. Thus, in-depth elucidation of the factors, mechanisms of their occurrence, formation and progression, and complications of SMI constitute an actual and important scientific problem for practical medicine [10,11].

One of the most relevant aspects of the study of CAD is the issue of effective and adequate anti-anginal therapy [12]. The choice of therapeutic tactics for each patient with CAD should be based on the clinical-pathogenetic peculiarities of the course of the disease, the presence of concomitant pathology, and the individual effectiveness of the therapeutic regimen. At the same time, CAD should be considered as a multifactorial disease, in the development and course of which the patient's lifestyle and environmental factors play a significant role. A number of scientific works prove the importance of these modified factors for assessing the prognosis of the course of CAD and determining the risk of its complications [13, 14].

AIM

To study and determine the peculiarities of the course of SMI in patients with post-infarction cardiosclerosis depending on the RFs. To reveal the interdependence between the presence of pathological turbulence of the heart rhythm and the peculiarities of the course of SMI in patients with post-infarction cardiosclerosis and their prognostic value for assessing the severity of the disease course and the effectiveness of treatment applying S-amlodipine and enalapril in complex therapy.

MATERIALS AND METHODS

The study was conducted on the basis of Regional Clinical Cardiology Center.

The members of the Ethics Commission at the Ivano-Frankivsk National Medical University decided that this study would not contradict the main provisions of the GCP, Convention Council of Europe on human rights and biomedicine, the Helsinki Declaration of the World Medical Association on ethical principles for the conduct of scientific medical research with the participation of man and the Law of Ukraine «On Medicines». All patients signed an informed consent to participate in a clinical trial.

There were observed 154 patients with SMI with a history of myocardial infarction (MI), having received anti-anginal therapy. Among the examined patients there were 112 men – it was 72.7%, and 42 women – it was 27.3%. The average age of the patients was (53.5±2.82) years: men – (51.2±1.2), women – (56.9±1.5) years old. The most numerous was the age group of patients aged 30-44 and 50-59 years, respectively – 37.0% and 42.9% of the examined. During the clinical-functional examination of the above-mentioned patients, 30 healthy persons were also examined in order to form a control group. The homogeneity of the patients included into the study, was established by age and gender.

For a detailed study of the clinical-functional and laboratory peculiarities of SMI at different stages of its course and the influence of the medicines selected on the course of the disease, all the examined were divided into the following groups: I) – patients with SMI receiving basic therapy: metoprolol succinate 25 mg/day, clopidogrel 75 mg/day and atorvastatin at a dose of 20 mg/day (n=39) – BT; II) – patients with SMI, who in addition to the BT were prescribed enalapril at a dose of 2.5-10 mg per day (n=37) – BT+ E; III) – patients with SMI, who against the background of BT were prescribed S-amlodipine 2.5-5 mg per day (n=40)– BT+sA; IV) – patients with SMI receiving combined treatment with medicines of BT together with enalapril 2.5-10 mg/day and S-amlodipine at a dose of 2.5-5 mg/day (n=38) – BT+E+sA.

The diagnostic criteria were: episodes of SMI verified with the help of Holter ECG monitoring and a test with dosed physical load. The diagnosis of SMI was made according to Holter ECG monitoring data, using the rule of "three units": deviation of the ST segment with an amplitude of 1 mm or more, lasting at least 0.08 s from point j, for 1 min or more, with an interval between episodes of at least 1 min.

Among the additional indices of the severity of the patient's condition, the maximum value of the ST segment deviation amplitude was evaluated. In addition, the occurrence of accompanying rhythm disturbances during myocardial ischemia was noted, which is important not only for the diagnosis of SMI, but also makes it possible to differentiate arrhythmogenic ST segment shift. The total number of supraventricular and ventricular extrasystoles

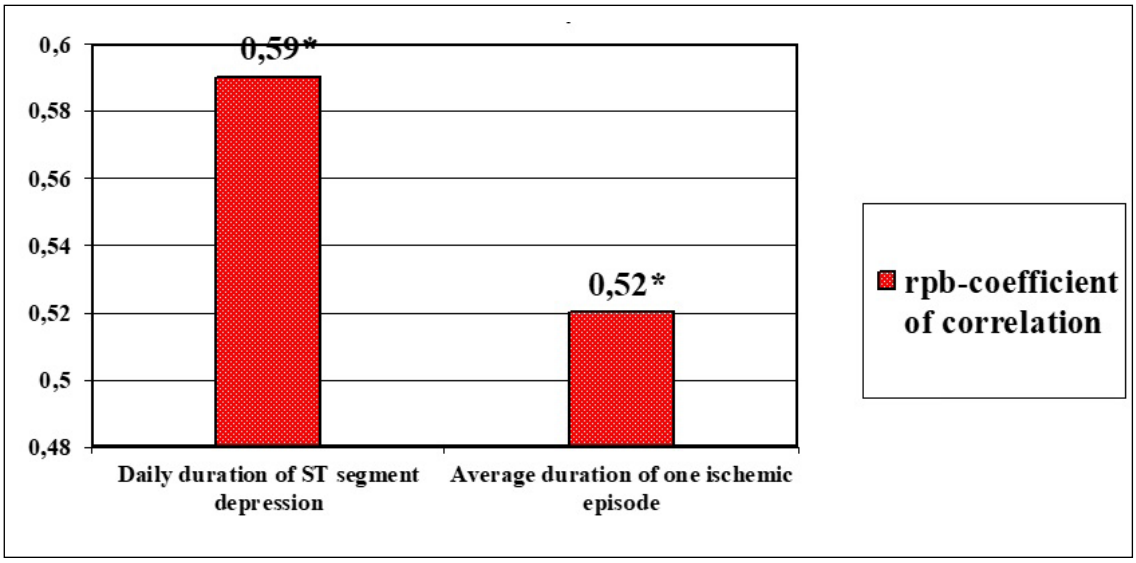

Fig. 1. A point-biserial correlation analysis between the presence of RFs and indices of Holter ECG monitoring in patients with SMI. Note. The probability of a difference in average values is *p<0.05.

(VE) was calculated, and the class of VE according to V. Lown was determined. The analysis of heart rate turbulence (HRT) parameters was carried out according to the criteria offered by G. Schmidt and co-authors [12] with the determination of indices of the "start" of HRT and the "slope" of HRT.

Determination of HRTO (%) and HRTS (ms/RR) was performed as follows. The HRTO index – is the ratio between the sum of the values of the first two RR sinus intervals occuring after extrasystole and the two RR sinus intervals preceding extrasystole to the sum of the two RR sinus intervals before extrasystole:

HRTO (%) = $((RR_1 + RR_2) - (RR_{-3} + RR_{-2}))/(RR_{-3} + RR_{-2})$;

where RR_1, RR_2 – are the intervals that come after the compensatory pause; RR_{-3}, RR_{-2} – are the intervals that precede the VE.

To determine HRTS (ms/RR), the slope of the change in RR intervals was calculated using straight regression lines for every 5 RR intervals out of 20 occurring after a compensatory pause. The HRTS value was taken as the maximum regression slope. Values of HRTO < 0% and HRTS > 2.5 ms/RR were considered normal, and HRTO > 0% and HRTS < 2.5 ms/RR – pathological ones.

Daily monitoring of heart rate variability (HRV) was carried out using the system of daily monitoring and analysis of HRV. Among daily HRV indices, statistical (SDNN-i, SDNN, rMSSD, pNN50), total power of heart rate fluctuations (TP) and spectral indices (LF, HF) were studied, and the LF/HF ratio was calculated. Indices were calculated automatically for every 5 minutes of recording. Five-minute intervals, which included non-stationary processes, artifacts and frequent extrasystoles, were excluded from the calculation in direct recording analysis.

For temporal analysis of HRV, the following indices were calculated: SDNN – standard deviation (SD) of values of normal NN intervals during 24 hours; SDANN – standard deviation of the average values of NN intervals for every 5 minutes of continuous ECG recording; and iSDNN – index – average of standard deviations of N-N intervals for every 5 minutes; rMSSD – standard deviation of the difference of N-N consecutive intervals; pNN50 – the percentage of consecutive N-N intervals, the difference between them exceeds 50 ms.

Spectral analysis made it possible to detect periodic changes in the frequency of the sinus rhythm using special mathematical methods, while the sequence of sinus contractions is transformed into a sequence of frequencies (in Hz), each of which corresponds to the amplitude of the oscillations. Thus, high frequencies (High Frequency – HF) – 0.15-0.40 Hz are the markers of the activity of the parasympathetic part of the ANS; low frequencies (Low Frequency-LF) – 0.04-0.15 Hz – sympathetic department. The ratio of sympathetic and parasympathetic effects on HRV was characterized by the LF/HF ratio (norm 1.5-2.0).

Spectral analysis of HRV was performed based on the study of the following indices: HF – high-frequency component of the spectrum (0.15-0.40 Hz), index of the activity of the parasympathetic part of the ANS; LF – a low-frequency component of the spectrum (0.04-0.15 Hz), which reflects slow heart rate fluctuations, closely related to the heart's response to vegetative influences; LF/HF – the coefficient of sympatho-parasympathetic balance, reflecting the balance of activity of the sympathetic and parasympathetic divisions of the ANS; VLF – the power of very low-frequency waves (0.0033-0.04 Hz), reflecting the activity of the humoral mechanisms of slow-acting heart rhythm regulation; TP – the total power of the spectrum, is an analogue of the SDNN index.

All the data of the work were processed using the package of applied and statistical programs STATISTICA 10. For all indices, the value of the average arithmetic sample (M), its dispersion and the average error (m) were calculated. To identify the probability of differences in research results, the Student's

Table 1. The influence of the studied schemes of anti-ischemic therapy on the dynamics of heart rate variability analysis indices according to Holter ECG monitoring in patients with SMI

Indices	Norm n=30	Basic therapy (I group), n=39		Basic therapy + enalapril (II group), n=40		Basic therapy + S-amlodipine (III group), n=37		Basic therapy + enalapril + S-amlodipine (IV group), n=38	
		before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p
SDNN, ms	155,6± 7,95	107,4± 5,61 p<0,001	123,32± 5,24* Δ+14,8	103,7± 5,34 p<0,001	125,7± 7,1* Δ+21,2	111,6± 5,5 p<0,001	139,7± 5,68** Δ+25,2	105,2± 6,02 p<0,001	147,1± 8,16*** Δ+39,8
RMSSD, ms	38,2± 2,25	21,4 ±1,18 p<0,001	25,3 ±1,16* Δ+18,2	23,5 ±1,21 p<0,001	29,3 ±1,64** Δ+24,7	22,9 ±1,09 p<0,001	34,7 ±1,51*** Δ+51,5	20,8± 1,27 p<0,001	36,5 ±1,38 *** Δ+75,5
pNN50, %	20,3± 0,93	23,6 ±1,37 p<0,05	18,3± 1,58 *	24,1± 1,75 p<0,05	18,2± 1,39 *	22,9± 1,57 p<0,05	16,9 ±0,64 **	23,5± 1,93 p<0,05	17,1± 0,82 **
TP, ms^2	4120,6± 194,34	2289,15± 147 p<0,001	2730,09± 161* Δ+19,3	2179,27± 183 p<0,001	3174,3± 132*** Δ+45,65	2301,64± 113 p<0,001	3300,01± 155*** Δ+43,4	2259,35± 101 p<0,001	3645,85± 179 *** Δ+61,4
ln ULF	10,8± 0,49	11,92± 0,67	11,6± 0,53 p_1>0,05	11,98± 0,78	11,57± 0,42 p_1>0,05	11,91± 0,71	11,26± 0,68 p_1>0,05	11,89± 0,92	11,04± 0,59 p_1>0,05
ln VLF	8,04± 0,33	8,34± 0,51	8,1± 0,38 p_1>0,05	8,39± 0,47	8,1± 0,29 p_1>0,05	8,34± 0,45	7,85± 0,31 p_1>0,05	8,32± 0,69	7,73± 0,4 p_1>0,05
LF, ms^2 Δ %	1103,9± 67	1820,14± 112 p<0,001	1512,56± 89 p_1<0,05	1901,92± 125 p<0,001	1470,23± 81 **	1813,35± 94 p<0,001	1205,28 ± 69 ***	1793,03± 138 p<0,001	1050,48± 61 ***
HF, ms^2, Δ %	631,7± 28	674,1± 53	657,4± 46 p_1>0,05	678,9± 39	653,4± 32 p_1>0,05	636,4± 48	602,5± 29 p_1>0,05	649,6± 36	617,6± 31 p_1>0,05
LF/HF	1,75±0,1	2,7±0,16	2,3±0,1 *Δ-14,8	2,8± 0,15	2,25± 0,14 *Δ-19,6	2,83± 0,19	2,0± 0,07 ***Δ-29,3	2,74±0,17	1,7±0,09 ***Δ-37,95

Note. P – the probability of changes in relation to norm indices, the probability of a difference compared to the indices before treatment: *- p<0,05, **- p<0,01, *** – p<0,001.

coefficient (t) was determined, after which the probability of sample differences (p) and the confidence interval of the average were determined according to Student's distribution tables. Values with p<0.05 were considered probable. To determine the relationship between parametric indices, the correlation coefficient was determined.

RESULTS

In our study, the frequency of occurrence of the SMI was analyzed, taking into account the presence of RFs. It was found that in patients with dyslipidemia, AH, diabetes mellitus (DM) and the presence of two or more RFs, the formation of asymptomatic variants of MI was observed more often compared to patients without RFs. At the same time, it should be noted that the frequency of ventricular tachycardia (VT), syncopal conditions did not depend on the presence of RFs. The results obtained can be explained by the different degree of sensitivity of individuals to efferent nociceptive stimulation, which is partly determined by the individual characteristics of the patient and his/her lifestyle. The interrelationship of the RFs of CAD and the probability of the formation of asymptomatic MI indicate a significant influence of external factors on susceptibility to myocardial ischemia. An important aspect of the study was the investigation of lifestyle peculiarities of patients that increase the risk of dyslipidemia or carbohydrate metabolism disorders. It has been determined that DM is more often observed in people with hypodynamia and excess body weight.

A clinical-instrumental analysis was performed in patients with SMI with post-infarction cardiosclerosis. The evaluation of the data obtained of the ECG-study in 12 standard leads showed that in patients with SMI, in comparison with the subjects studied in the control group, rhythm disorder according to the type of supraventricular and VE, as well as sinus tachycardia, were more often detected. The peculiarities of the course of the SMI in patients with post-infarction cardiosclerosis, depending on the RFs, were analyzed. When performing an ECG in people with dyslipidemia, compared to patients without RFs, focal cicatricial changes were detected more often (76.5% vs. 9.1%; p<0.001), in studied with type II DM, VE (48.3% vs. 9.1%; p<0.05), and in patients with 2 or more RFs had LV hypertrophy (73.8% vs. 9.1%; p<0.001) and focal cardiosclerosis (88.1% vs. 18 .2%; p<0.001).

The results of the standard ECG study provided the necessity for the performance of a Holter ECG monitoring. When analyzing Holter ECG monitoring indices, it was

determined that patients with SMI with RFs such as AH, DM and dyslipidemia have higher average daily values of the number of ischemic episodes per day, total daily duration of ST segment depression, total ST depression amplitude, average duration of one ischemic episode in comparison with individuals without RFs ($p<0.05$). When analyzing the dynamics of the indices of the average value of maximum ST segment depression, the average depth of ST segment depression, the average heart rate during ST segment depression, the heart rate at the maximum depth of ST shift, no significant differences were found in various groups of studied patients ($p>0.05$). The frequency of SMI episodes is proportionally related to the RFs number of the complicated course of CAD.

A point-biserial correlation analysis was performed between the presence of RFs and the duration of myocardial ischemia in patients with SMI.

As one can see from fig.1, a direct correlation of average strength was established between the daily duration of the ST segment and the presence of FRs. The point-biserial correlation coefficient (rpb) was +0.59 ($p<0.05$). When analyzing the correlation interrelationship between the average duration of one ischemic episode and the presence of FRs, a statistically significant correlation of the average strength was found. The point-biserial correlation coefficient was equal to +0.52 ($p<0.05$).

The obtained results proved that such RFs as AH, type II DM, dyslipidemia can negatively affect the condition of myocardial perfusion and provoke ischemia of the heart muscle in patients with SMI. This is manifested by more intense manifestations of ischemic changes detected during Holter ECG monitoring.

Analysis of the prevalence of VT and other ventricular rhythm disturbances did not reveal significant differences between the study groups ($p>0.05$). A significantly higher frequency of VE was noted in patients with concomitant type II DM, AH, lipid metabolism disorders, and the presence of two or more RFs, compared to patients without RFs ($p<0.05$). When analyzing the dynamics of indices of the average value of heart rate, P-Q and Q-T intervals, no differences in these indices were found in different groups of the studied patients ($p>0.05$). The results of the echocardiographic study proved that the course of SMI in patients with dyslipidemia, DM and AH is accompanied by more pronounced hypertrophy of the LV and lower indices of its systolic function in comparison with patients with the absence of RFs. It was determined that when at least one RF was identified, higher indices of the volumes and sizes of the LV into systole and diastole were observed ($p<0.01$), as well as a decrease in LV ejection fraction ($p<0.05$).

It is noteworthy that higher values of LV myocardial mass were recorded in patients with concomitant AH; they are characterized by a more intensive development of LV hypertensive remodeling processes compared to patients of other studied groups. The results obtained in this group may be due to a higher blood pressure and a higher value of the aortic stiffness index. It was found that for patients with SMI in the presence of concomitant hypertension, DM, two or more RFs, the average diastolic value of the thickness of the back wall of the LV and the interventricular septum was significantly higher ($p<0.001$) compared to the group of patients with no RFs.

Evaluating the effectiveness of the used treatment regimens for six months, the advantages of the combined use of S-amlodipine and enalapril against the background of BT were proven.

The study analyzed the dynamic indices of complaints in the examined patients under the influence of anti-anginal therapy. It was noted that in all studied groups during the treatment, a positive dynamics of decreasing the frequency of manifestation of subjective clinical signs of the disease course was observed. A significant reduction in heart rate and the feeling of interruptions in the work of the heart during physical exertion and at rest was already observed after 3 months of medicinal treatment. Changes in tolerance to physical exertion in patients with SMI after treatment were studied. It was noted that the complex use of BT medicines in combination with S-amlodipine and enalapril in patients with SMI was accompanied by the most pronounced increase in tolerance to physical exertion compared to other groups.

The results of Holter ECG monitoring proved that the investigated treatment regimens were effective in reducing ischemia indices. The total duration of ischemia, the number of ischemic episodes, and the mean and maximum depth of ST segment depression decreased in all four groups. A statistically significant decrease in the frequency of episodes of myocardial ischemia during the day under the influence of BT and enalapril, as well as when using BT in combination with S-amlodipine, was noted.

It was determined that the most intense anti-anginal effect was observed in the combined treatment with enalapril and S-amlodipine. The index of the average daily number of ischemic episodes before the start of the study in the group I decreased at 30.7% after the end of the treatment course ($p<0.001$). The average number of episodes of myocardial ischemia during the day in the group II decreased at 37.94% and amounted to (3.19 ± 0.15) after therapy ($p<0.001$). It was proved that the addition of S-amlodipine to the basic therapy in patients of the group

III was accompanied by a more pronounced anti-anginal effect, reducing the average daily number of ischemic episodes at 49.2% ($p<0.001$). It should be noted that anti-anginal treatment of the group IV patients using a combination of BT, enalapril and S-amlodipine led to the most statistically significant change in this index in the studied patients, namely at 59.5% ($p<0.001$).

The dynamics of HRT in patients with SMI during their treatment was evaluated using the offered medicinal regimens. In the group of patients with pathological values of turbulence onset (TO), there was no trend towards pathological values of turbulence slope (TS), only 5 (3.2%) patients of all studied groups were registered both pathological parameters of HRT before the start of anti-anginal treatment.

Normalization of HRT indices was established as a result of the use of BT and when using a combination of BT with S-amlodipine and enalapril. The analysis of the dynamics of HRT indices showed that under the influence of the studied treatment regimens, the degree of detection of the pathological value of HRT decreased in all groups of patients ($p<0.05$). In particular, in the BT group, the frequency of registration of the pathological value of the onset of turbulence after therapy was 10.3%, against 23.1%, in patients receiving BT with enalapril – 8.1%, against 18.9% ($p<0.05$), in patients treated with BT in combination with S-amlodipine – 5.0%, against 20.0% ($p<0.05$), and in patients of the group of combined therapy – 2.6%, against 23.7% ($p<0.05$). Therefore, the most effective for the normalization of HRT was the therapy based on the combination of BT with S-amlodipine and enalapril. The higher effectiveness of anti-anginal therapy with S-amlodipine and enalapril when added to BT for the elimination of pathological HRT has been proven.

HRV is an important index for evaluating the therapeutic effectiveness of the studied medicines. Analysis of HRV makes it possible to evaluate the effect of pharmacotherapy on the activity of the ANS, and is also important for predicting the course of the disease. Patients with SMI were characterized by a significant decrease in daily HRV compared to practically healthy individuals. The dynamics of HRV parameters is shown in table 1.

They were observed a statistically significant decrease in the time indices of the total HRV: SDNNi, SDNN, rMSSD, pNN50 ($p<0.05$). A decrease in total HRV may be associated not only with an increase in sympathetic activity, but also with a decrease in all autonomic influences on the heart, which is confirmed by a decrease in the total power spectrum (TP). A decrease in high-frequency oscillations of the heart rhythm (RMSSD, pNN50) in patients of the study group indicates a decrease in parasympathetic influence.

It is known that a significant decrease in HRV increases the risk of developing acute cardiovascular disease. Analyzing the indices of the total HRV, it was found that almost all time indices characterizing the total HRV in patients with SMI compared to patients without ischemia, were reduced, however, significant differences between the groups were found only in relation to the index of total power (2263.15 ± 126.05) ms^2 and (4120.6 ± 194.34) ms^2 ($p<0.05$).

The rate of SDNN in patients with SMI was low before the start of anti-anginal therapy and probably increased in all groups of patients after 6 months of treatment ($p<0.05$). Characterizing the parameters of the spectral analysis of HRV, it was established that the LF level, which reflects the low-frequency component of HRV and characterizes the sympathetic tone, was significantly higher in patients with SMI than in the control group ($p<0.05$). The LF/HF index (sympathovagal index) in patients with SMI was significantly ($p<0.05$) higher compared to the group of healthy individuals, which characterizes a shift in the sympathetic-parasympathetic balance towards the predominance of the sympathetic division of the ANS. The absolute values of the HF index did not change significantly under the influence of anti-anginal treatment in all groups ($p>0.05$).

Thus, the investigated schemes of anti-anginal treatment had a positive effect on HRV, which was confirmed by the dynamics of indices of time and frequency analyzes of Holter ECG monitoring. In the course of treatment with S-amlodipine and when combining this medicine with enalapril against the background of BT, sympathetic-parasympathetic dynamic balance was restored.

DISCUSSION

Our study proved the importance of the influence of modified RFs on the characteristics of the clinical picture and on certain pathogenetic aspects in patients with CAD.

In the absence of clinically-manifest symptoms, SMI, nevertheless, is characterized by a complex of clinical-pathogenetic signs inherent in other forms of CAD. The study of SMI, the study of the peculiarities of its course allows to some extent deny the erroneous statement about the easier development of this disease in comparison with ischemic pathology, which is characterized by the pronounced anginal symptoms.

These research data allow us to consider SMI as a disease leading to a decrease in the electrical stability of the myocardium, the development of LV hypertrophy, and an increase in the thickness of its walls. The described processes are accompanied by the pronounced phenomena of myocardial ischemia. Thus, in the ab-

sence of clinically-manifest symptoms, SMI is nevertheless characterized by a complex of clinical-pathogenetic signs inherent in other forms of CAD [5]. The study of SMI and of the peculiarities of its course allows to some extent deny the false statement about the easier development of this disease in comparison with ischemic pathology, which is characterized by pronounced anginal symptoms. The evaluation of the results of the Holter ECG monitoring showed that the presence of such RFs as AH, violation of carbohydrate and lipid metabolism in patients with SMI with a history of MI, is associated with a probable decrease in the electrical stability of cardiomyocytes and is capable ofinducing rhythm disturbances according to the type of supraventricular and VE. Thus, in the absence of clinically-manifest symptoms, SMI is nevertheless characterized by a complex of clinical-pathogenetic signs inherent in other forms of CAD. The study of SMI and of the peculiarities of its course allows to some extent deny the false statement about the easier development of this disease in comparison with ischemic pathology, which is characterized by pronounced anginal symptoms.

A more pronounced intensive anti-ischemic effect was determined when using against the background of BT, combined adequate therapy with enalapril and amlodipine in comparison with the performed BT in a separate combination with each of these medicines [10]. The high anti-ischemic efficiency of the studied medicines makes their use justified in the therapeutic algorithm of management of patients with SMI. In the course of this work, the effectiveness of the studied schemes of antianginal therapy for the normalization of HRT and HRV indices was proven. The results of the study could be a fundamental step towards the development of a clinical protocol for the SMI treatment.

CONCLUSIONS

The SMI, which is associated with the presence of such RFs as AH, DM, dyslipidemia or their combination, is characterized by a severe course of the disease, which is manifested by a worsening of the clinical condition, a decrease in tolerance to physical exertion, significant changes in hemodynamics and autonomic regulation, more intense manifestations of myocardial ischemia, pronounced remodeling of the LV ($p<0.05$), compared to individuals without RFs ($p<0.05$).

It was determined that in patients with SMI with post-infarction cardiosclerosis, there is a positive correlation of medium strength between the presence of RFs and Holter ECG monitoring indices, in particular, the average daily values of the number of ischemic episodes, the total daily duration of ST segment depression and the average duration of one ischemic episode.

In patients with SMI with post-infarction cardiosclerosis and LV systolic dysfunction, chronic HF, in the presence of heart rhythm disorders, additional information obtained with the help of Holter ECG monitoring can be of significant importance in choosing the strategy and tactics of patient management.

Enalapril and S-amlodipine are the effective means of pharmacotherapy in the SMI. The combined use of these drugs with BT in the studied patients allows the reduction of daily myocardial ischemia at 55.1% ($p<0.001$), to normalize indices of HRT and HRV. Therefore, the study of symptoms, as well as possible causes and circumstances contributing to the occurrence of SMI in patients with post-infarction cardiosclerosis, is still an urgent task, the solution of which would allow us to identify such patients, and modern anti-ischemic therapy would help to improve the prognosis.

REFERENCES

1. Kumar A, Avishay DM, Jones CR et al. Sudden cardiac death: epidemiology, pathogenesis and management. Rev Cardiovasc Med. 2021;22(1):147- 158. doi: 10.31083/j.rcm.2021.01.207. DOI
2. Marijon E, Garcia R, Narayanan K et al. Fighting against sudden cardiac death: need for a paradigm shift–Adding near-term prevention and pre-emptive action to long-term prevention. Eur Heart J. 2022;43:1467-1464. doi:10.1093/eurheartj/ehab903. DOI
3. Severino P, D'Amato A, Netti L et al. Diabetes mellitus and ischemic heart disease: the role of ion channels. Int J Mol Sci. 2018;19(3):802. doi:10.3390/ijms19030802. DOI
4. Kovalchuk V, Svechnikova O, Bulavin L. Multifractal Analysis of Cardiac Series and Predictors of Sudden Cardiac Death. Ukr J Phys. 2021;66(10):879. doi:10.15407/ujpe66.10.879. DOI
5. Valensi P, Meune C. Congestive heart failure caused by silent ischemia and silent myocardial infarction. Herz. 2019;44:210-217. doi: 10.1007/s00059-019-4798-3. DOI
6. Dongmo Fokoua-Maxime Ch, Lontchi-Yimagou E, Erwan Cheuffa-Karel T et al. Prevalence of asymptomatic or "silent" myocardial ischemia in diabetic patients: Protocol for a systematic review and meta-analysis. PLoS ONE. 2021;16(6):e0252511. doi:10.1371/journal.pone.0252511. DOI
7. Indolfi C, Polimeni A, Mongiardo A et al. Old unsolved problems: when and how to treat silent ischaemia. Eur Heart J Suppl. 2020;22(L): L82-L85. doi:10.1093/eurheartj/suaa141. DOI

8. Ivanov VP, Mezhievska IA, Maslovskyi VYu. Characteristics of anatomic injury of coronary arteries in patients with acute myocardial infarction without ST elevation depending on plasma level of gene 2 growth stimulating factor and risk of adverse events. Acta Med Leopoliensia. 2020;26(1):20-25. doi:10.25040/aml2020.01.020. DOI
9. Prasad DS, Kabir Z, Devi KR et al. Prevalence and risk factors for silent myocardial ischemia (PRISM): A clinico-observational study in patients of type 2 diabetes. Indian Heart J. 2019;71:400-405. doi: 10.1016/j.ihj.2019.12.002. DOI
10. Dongmo Fokoua-Maxime C, Lontchi-Yimagou E, Erwan Cheuffa-Karel T et al. Prevalence of asymptomatic or "silent" myocardial ischemia in diabetic patients: Protocol for a systematic review and meta-analysis. PLoS One. 2024;19(11):e0314301. doi: 10.1371/journal.pone.0314301. DOI
11. Polimeni CIA, Mongiardo A, De Rosa S, Spaccarotella C. Old unsolved problems: when and how to treat silent ischaemia. Eur Heart J. 2020;22:L82–L85. doi:10.1093/eurheartj/suaa141. DOI
12. Prasad DS, Kabir Z, Devi KR et al. Prevalence and Risk factors for Silent Myocardial ischemia (PRISM): A clinico observational study in patients of type 2 diabetes. Indian Heart J. 2019;71:400–405. doi: 10.1016/j.ihj.2019.12.002. DOI
13. Bullock-Palmer RP, Shaw LJ, Gulati M. Emerging misunderstood presentations of cardiovascular disease in young women. Clin Cardiol. 2019;42:476-483. doi: 10.1002/clc.23165. DOI
14. Sullivan S, Hammadah M, Al Mheid I et al. Sex Differences in Hemodynamic and Microvascular Mechanisms of Myocardial Ischemia Induced by Mental Stress. Arterioscler Thromb Vasc Biol. 2018;38:473-80. 11. doi: 10.1161/ATVBAHA.117.309535. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Khrystyna V. Levandovska
Ivano-Frankivsk National Medical University
24 Serpnia St, Ivano-Frankivsk 76000, Ukraine
e-mail: levandovska87@ukr.net

ORCID AND CONTRIBUTIONSHIP

Tetiana V. Merhel: 000-0002-8017-3475 A B C D
Tetiana V. Naluzhna: 000-0003-0840-5355 B C D E
Khrystyna V. Levandovska: 0000-0003-3259-7940 B D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 12.08.2024
ACCEPTED: 24.01.2025