

# Vegetative and electrical disorders in women with chronic coronary syndrome depending on the state of bone mineral density

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

## Key words:

chronic coronary syndrome, osteopenia, osteoporosis, disorders of the autonomic nervous system, arrhythmia.

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**Aim:** to determine the features of heart rate variability and electrical changes in the myocardium in women with chronic coronary syndrome, depending on the state of the bone mineral density (BMD).

**Materials and methods.** 121 women with chronic coronary syndrome (CCS): stable exertional angina of II–III functional class (FC) (mean age 68.0 (60.0; 75.0) years) were examined and divided into 3 groups: group 1 – 30 women with CCS and normal BMD; group 2 – 33 women with CCS and osteopenia (OPe); group 3 – 58 women with CCS and osteoporosis (OP). All patients underwent daily ECG monitoring and ultrasound osteodensitometry.

**Results.** In women with CCS and OP, increase in the frequency (by 2.9 times;  $P < 0.05$ ) and duration (by 2.3 times;  $P < 0.05$ ) of tachycardia episodes, the frequency of registration of ventricular and supraventricular extrasystole episodes (by 8.1 time and 1.2 times, respectively;  $P < 0.05$ ) if compared to patients without BMD disorders was found. In women with CCS and OPe there was a tendency to increase in these indicators, which did not reach the level of statistical significance. The presence of BMD disorders in patients with CCS was accompanied with decrease in total HRV activity (RMSSD and HRVT), the development of the predominance of ANS sympathetic domain activity, as evidenced by an increase in LF by 44.3 % at the daytime and 44.0 % at night, decrease in HF 2.3 times during the day and 2.1 times at night in patients with OPe and OP, respectively. According to the correlation analysis data, the presence of correlations between the state of BMD and indicators of electrical and autonomic activity of the myocardium was established.

**Conclusions.** In postmenopausal women with CCS, the severity of autonomic and electrical disorders is associated with the degree of bone disorders and is maximal in osteoporosis.

## Ключові слова:

хронічний коронарний синдром, остеопенія, остеопороз, розлади вегетативної нервової системи, порушення ритму.

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## Вегетативні й електричні порушення в жінок із хронічним коронарним синдромом залежно від стану мінеральної щільності кісткової тканини

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**Мета роботи** – визначити особливості варіабельності серцевого ритму й електричні зміни міокарда в жінок із хронічним коронарним синдромом (ХКС) залежно від мінеральної щільності кісткової тканини (МЩКТ).

**Матеріали та методи.** Обстежили 121 жінку з ХКС: стабільною стенокардією напруження II–III функціонального класу віком 68,0 (60,0; 75,0) року. Пацієток поділили на 3 групи: 1 – 30 жінок із ХКС і нормальними показниками МЩКТ; 2 – 33 особи з ХКС та остеопенією (ОПе); 3 – 58 хворих на ХКС та остеопороз (ОП). Усім обстеженим виконали добовий моніторинг ЕКГ, а також ультразвукову остеоденситометрію.

**Результати.** У жінок із ХКС та ОП виявили збільшення частоти (у 2,9 раза;  $p < 0,05$ ) та тривалості (у 2,3 раза;  $p < 0,05$ ) епізодів тахікардії, частоти реєстрації шлуночкової та надшлуночкової екстрасистолії (у 8,1 раза та 1,2 раза відповідно;  $p < 0,05$ ) порівняно з пацієнтами без порушень МЩКТ. У жінок із ХКС та ОПе визначили тенденцію до підвищення названих показників, що не досягла статистичної значущості. Порушення МЩКТ у хворих на ХКС супроводжувалися зменшенням загальної активності ВСР (RMSSD і HRVT), а також переважанням активності симпатичного домену ВНС, підтвержене збільшенням LF на 44,3 % вдень і на 44,0 % вночі, зниженням HF в 2,3 раза вдень і в 2,1 раза вночі у пацієнтів з ОПе та ОП відповідно. У результаті кореляційного аналізу виявили зв'язок стану МЩКТ з індикаторами електричної та вегетативної активності міокарда.

**Висновки.** У жінок із ХКС у постменопаузальному періоді вираженість вегетативних та електричних порушень асоціюється зі ступенем кісткових порушень та є максимальною при остеопорозі.

Chronic coronary syndrome (CCS) is one of the main causes of high mortality and disability in Ukraine and many industrialized countries and one of the most common diseases of the cardiovascular system [1,2].

Today, the pathogenetic factors that contribute to the development and progression of CCS include disorders of the autonomic nervous system (ANS) [3]. Chronic activation of the sympathetic nervous system with elements

of its depletion (“sympathetic overdrive”) leads to a number of adverse consequences at the cardiovascular system, causes cardiac hypertrophy, vascular remodeling, endothelial dysfunction and thus increases the cardiovascular risk profile in patients with CCS [3].

In addition, sympathetic nervous factors may be responsible for the development and/or progression of metabolic disorders, as it is confirmed by a number of

studies in the last decade [4–7]. One of the most common metabolic diseases associated with CCS in postmenopausal women is osteoporosis (OP) – a pathology of bone tissue characterized by decreased bone mass and impaired microarchitectonics of the bones, which leads to its increased fragility and risk of fractures [6].

Adrenoreceptors on the cell surface are involved in the regulation of osteoblast function by the sympathetic nervous system (SNS). Catecholamines, such as epinephrine, norepinephrine and dopamine, increase bone morphogenetic protein and induce bone formation [8]. However, according to S. Athimulam et al., activation of the sympathetic nervous system and elevated levels of catecholamines, in contrast, lead to bone loss and increased risk of osteoporotic fractures [9]. According to the research of German scientists,  $\beta_1$ -adrenoreceptors provide a stimulating effect on bone formation due to the dominance of  $\beta_1$ -adrenergic effect over  $\beta_2$ -adrenergic [10]. According to the study of Japanese scientists in mice, the effect of SNS on bone morphogenesis can be explained by the effect on  $\alpha_2a$ - and  $\alpha_2c$ -adrenoreceptors, acting as a regulator of osteoclastogenesis [11].

Scientific data indicate that the course of CCS on the background of osteopenic syndrome is characterized by development of sympatho-parasympathetic imbalance, which leads to a violation of the myocardium electrical properties and the unfavorable course of cardiovascular pathology. However, the reference literature data on this issue are quite contradictory, as there are other studies that refute the idea of the relationship between autonomic imbalance in CCS patients with the development of bone mineral density disorders (BMD) [12]. Therefore, it is extremely important to study changes in heart rate variability (HRV) in CCS women for primary screening of patients at the increased risk of arrhythmic disorders in various cohorts of patients, including postmenopausal osteoporosis (PMOP).

## Aim

To determine the features of heart rate variability and electrical changes in the myocardium in women with CCS, depending on the state of the BMD.

## Materials and methods

121 postmenopausal women with chronic coronary syndrome (CCS): stable exertional angina of II–III functional class (FC) (mean age 68.0 (60.0; 75.0) years) were examined and divided into 3 groups: group 1 – 30 women with CCS and normal BMD; group 2 – 33 women with CCS and osteopenia (OPe); group 3 – 58 women with CCS and OP.

The inclusion criteria: presence of CCS; presence of postmenopausal period, written informed consent of a patient. The exclusion criteria: decompensated diseases of the internal organs, as well as conditions that lead to the development of secondary OP.

CCS was diagnosed in accordance with 2019 ESC Guidelines for the diagnosing and management of chronic coronary syndromes. Postmenopausal period was stated based on the results of consultation with a gynecologist in accordance with generally accepted criteria.

The BMD state was assessed with the help of the ultrasound osteodensitometry on the Omnisense 7000 apparatus (Israel) according to the criteria specified in our previous works [13–15]. Electrical and ischemic parameters were investigated using Holter ECG daily monitoring with the use of a Cardiosens K instrument (KhAI MEDICA, Ukraine) according to the recommendations of the European Society of Cardiologists, and the Ukrainian Association of Cardiologists.

The design of the study was agreed with the local commission on bioethics.

Statistical data processing was carried out with the help of software package Statistica 13.0 (StatSoft Inc., No. JPZ8041382130ARCN10-J). Probability of differences in the compared groups was performed using one-way analysis of variance Kruskal–Wallis (Kruskal–Wallis ANOVA) followed by pairwise comparison. The research of the directionality and strength of relationships between indicators was carried out using correlation analysis with the calculation of Pearson's  $r$  correlation coefficients (under normal distribution) and Spearman (under conditions of deviation from normal distribution). The type of data distribution was determined using the Shapiro–Wilk test. Data were represented as  $M \pm m$  (arithmetic mean  $\pm$  standard error of arithmetic mean) or  $Me$  (Q25; Q75) (median, 25 and 75 distribution quartiles). Differences were considered statistically significant at  $P < 0.05$ .

## Results

Indicators of the heart electrical activity according to the results of daily Holter ECG monitoring in women with CCS are shown in *Table 1*.

According to the study results, significant increase in heart rate both during the day period (by 11 %;  $P < 0.05$ ) and during the night period (by 13.62 %;  $P < 0.05$ ) in postmenopausal women with CCS and OP was found, if compared to patients with CCS without BMD changes.

In patients with CCS comorbid with OP, there was significant increase in the number of tachycardia episodes per day (by 2.9 times;  $P < 0.05$ ) and significant increase in the total duration of tachycardia episodes per day (by 2.3 times;  $P < 0.05$ ) if compared to women with CCS without BMD disorders. In women with OPe and CCS, there was only a tendency to increase in these indicators.

Women with CCS and BMD disorders (OPe and OP) had significant and reliable arrhythmias by the type of supraventricular and ventricular arrhythmias if compared to women with CCS and normal BMD. Thus, in patients with OPe the number of episodes of high-grade ventricular arrhythmias was 2.9 times higher, and the number of episodes of supraventricular arrhythmias was 1.2 times higher ( $P < 0.05$ ), in women with OP – 8.1 times and 1.2 times higher, respectively ( $P < 0.05$ ).

According to the indicators characterizing ischemic changes of the myocardium (ST segment depression, duration of ST depression, episode of maximum duration of ST segment depression and maximum ST depression), no significant difference was found between the studied groups of patients.

**Table 1.** Indicators of the heart electrical activity in CCS patients depending on the BMD state, M ± m, Me (Q25; Q75)

Indicator, units of measurement	Group 1 CCS (n = 30)	Group 2 CCS + OPe (n = 33)	Group 3 CCS + OP (n = 58)
Average HR throughout the period, bpm	63.56 ± 2.59	66.35 ± 2.47	68.03 ± 2.00
Average HR per day, bpm	64.43 ± 2.92	69.67 ± 2.74	71.45 ± 2.31*
Average HR at night, bpm	54.57 ± 2.34	59.33 ± 2.23	62.00 ± 1.87*
Minimum HR throughout the period, bpm	46.78 ± 2.92	49.30 ± 2.29	50.29 ± 1.88
Maximum HR throughout the period, bpm	104.50 ± 6.81	107.05 ± 3.95	110.48 ± 4.70
Circadian index	1.18 ± 0.03	1.19 ± 0.02	1.17 ± 0.01
Number of episodes of tachycardia, ep/24 h	15 (13; 41)	44 (19; 135)	43 (7; 70)*
Tachycardia, min	22 (9; 48)	49 (26; 123)	51 (9; 102)*
Ventricular arrhythmia, ep/24 h	20.5 (3.0; 36.0)	60.0 (3.0; 2242.0)*	167.5 (14.5; 1202.0)*
Supraventricular arrhythmia, ep/24 h	57 (14; 174)	67 (13; 212)*	70 (18; 162)*

\*: the probability of indexes difference if compared to the CCS patients and normal BMD state (P < 0.05).

**Table 2.** Indicators of heart rate variability in patients with CCS depending on the BMD state, Me (Q25; Q75)

Indicator, units of measurement	Group 1 CCS (n = 30)	Group 2 CCS + OPe (n = 33)	Group 3 CCS + OP (n = 58)
<b>Active period</b>			
mRR day period, ms	882.00 (847.00; 1043.00)	840.00 (768.00; 1028.00)*	830.00 (765.00; 990.50)*
SDNNi, ms	61.10 (54.20; 84.00)	50.10 (43.60; 62.00)	51.95 (39.20; 81.00)
RMSSD, ms	26.00 (18.00; 29.00)	25.00 (17.50; 32.50)*	24.50 (16.00; 36.00)*
RMSSD, %	8.50 (3.50; 11.00)	3.90 (0.70; 9.30)	2.55 (0.85; 9.85)*
HRVT, c. u.	28.50 (23.00; 38.30)	27.40 (19.50; 32.70)*	24.20 (19.00; 29.40)*
VLF, ms <sup>2</sup>	893.00 (330.00; 1239.50)	898.00 (513.50; 1677.50)	996.00 (530.00; 1273.00)
LF, ms <sup>2</sup>	305.00 (134.20; 564.00)	400.50 (224.50; 696.50)	444.00 (254.00; 1007.00)*
HF, ms <sup>2</sup>	318.00 (155.00; 473.30)	203.60 (93.00; 320.50)*	140.00 (73.50; 373.00)*
LF/HF	2.20 (1.80; 2.40)	2.50 (1.85; 3.20)	2.50 (2.10; 4.00)
<b>Passive period</b>			
mRR night period, ms	1086.50 (1010.00; 1189.00)	977.00 (924.00; 1117.00)	976.50 (893.50; 1097.50)
SDNNi, ms	68.95 (62.70; 74.20)	57.50 (45.30; 70.00)	51.80 (43.80; 83.60)
RMSSD, ms	41.50 (35.00; 164.50)	39.00 (20.00; 49.00)*	33.50 (24.00; 48.00)*
RMSSD, %	23.05 (12.65; 29.20)	12.95 (2.10; 19.50)	7.50 (2.85; 13.95)
HRVT, c. u.	23.30 (18.30; 23.40)	21.10 (16.30; 25.70)	19.55 (16.10; 24.35)*
VLF, ms <sup>2</sup>	1312.00 (712.00; 1938.50)	1490.50 (1099.00; 1927.00)	1282.00 (1112.00; 2054.00)
LF, ms <sup>2</sup>	501.50 (203.50; 815.50)	725.00 (448.00; 1067.00)	722.00 (433.00; 2167.00)*
HF, ms <sup>2</sup>	555.00 (207.00; 605.00)	471.50 (132.00; 581.00)*	265.50 (147.50; 541.50)*
LF/HF	1.40 (1.30; 1.80)	1.70 (1.30; 3.10)	1.80 (1.12; 2.50)

\*: the probability of indexes difference if compared to women with CCS and without BMD changes (P < 0.05).

Indicators of heart rate variability, according to the results of daily Holter ECG monitoring, in patients with CCS, depending on the presence of BMD disorders are given in *Table 2*.

Comparative analysis of temporal indicators of HRV revealed decrease in overall HRV according to RMSSD in both active and passive periods – by 4.0 % and 6.4 %, respectively (P < 0.05) in CCS women with OPe if compared to CCS patients without BMD disorders. In CCS patients with OP, a greater number of changes in HRV was found: a probable decrease in total activity by the average duration of the RR interval (mRR) by 6.2 % in the active period (P < 0.05); by the standard deviation of the difference of successive intervals NN (RMSSD) by 6.1 % in the active period and by 23.9 % in the passive period; by RMSSD index, expressed as a percentage, the significant difference was 3.3 times in the active period (P < 0.05); by the triangular index (HRVT) – by 17.8 % in the active period and by 19.2 % in the passive period (P < 0.05) if compared to patients with CCS without BMD disorders.

When comparing CCS patients with OPe and OP, more pronounced violations of autonomic regulation of cardiac

activity were observed in women with CCS and PMOP, but this difference did not reach the level of statistical significance.

The noticed features of the vegetative status of CCS patients with low BMD may have an unfavorable prognostic value in this category of patients, as it has been proven that low HRV is associated with the high risk of arrhythmias and sudden cardiac death [7].

According to the results of spectral analysis of HRV in patients with CCS and OPe, there was only a tendency to increase in low-frequency indicators (VLF and LF) and significant decrease in HF in both active and passive periods (by 1.6 times and 1.2 times respectively, P < 0.05). Whereas in patients with CCS and OP there was significant increase in low frequency (LF) by 44.3 % during the day and 44.0 % at night period (P < 0.05), which reflects the activation of the sympathetic part of the autonomic nervous system, and a tendency to increase in very low frequencies (VLF). There was also decrease in HF by 2.3 times in the active period and 2.1 times in the passive period (P < 0.05), which indicates the suppression of parasympathetic effects on cardiac activity.

In addition, in patients with comorbid pathology there was a tendency to increase the LF/HF ratio – the most sensitive indicator of autonomic balance, indicating autonomic imbalance due to suppression of the parasympathetic system and compensatory activation of the sympathetic link of autonomic regulation.

The results of correlation analysis are shown in Fig. 1, 2.

## Discussion

According to our results, changes in women with BMD on the background of CCS in the postmenopausal period are characterized with a significant increase in heart rate (both day and night period), as well as increase in tachycardia episodes per day, increasing the total duration of tachycardia episodes per day in comparison to women with CCS without BMD disorders. Increased heart rate as a direct consequence of hypersympathictonia, is an important risk factor at all stages of the cardiovascular continuum. According to the Framingham study, “sympathetic overdrive” is a key factor in increasing heart rate and causes increase in CVD mortality regardless of age [16]. In our study, women with CCS and BMD disorders (OPe and OP) were significantly more likely to have arrhythmias by type of supraventricular and ventricular arrhythmias if compared to women with CCS and normal BMD. The results obtained can be explained by activation of the sympathetic domene of the ANS, which also coincides with the results of Yu. V. Zharikova, that hypersympathictonia is an independent factor in the abdominal obesity, depression, dyslipidemia, osteoporosis occurrence [17].

Comparative analysis of temporal indicators of HRV revealed decrease in overall HRV in the RMSSD, mRR, HRVT indices. According to the results of spectral analysis in patients with CCS and OP, there was a significant increase in LF during the day and night, which reflects the activation of the sympathetic part of the autonomic nervous system, and a tendency to increase in very low frequencies (VLF). There was also decrease in HF both in the active and passive periods, which indicates the suppression of parasympathetic effects on cardiac activity. Our results on increase of the tone of the sympathetic ANS in CCS patients coincide with the data of other researchers. Thus, according to the research of E. Kh. Zaremba in the HRV study in CCS patients increase in sympathetic tone of the autonomic nervous system was found, namely: significant decrease in SDNN, pNN 50 %, high frequency spectrum, increased low frequency spectrum and sympatho-parasympathetic balance [18]. Our results also coincide with the results of the study conducted by P. K. Stein and co-authors, which included 1299 examined individuals with increased cardiovascular risk: a statistically significant relationship between very low frequency power and hip fracture in women was found [19].

In addition, in patients with concomitant course of CCS and OP there was a tendency to increase in the LF/HF ratio, which indicates autonomic imbalance due to suppression of the parasympathetic system and compensatory activation of the sympathetic link of autonomic regulation. According to A. R. Kiselev et al. in adult men the frequency indices

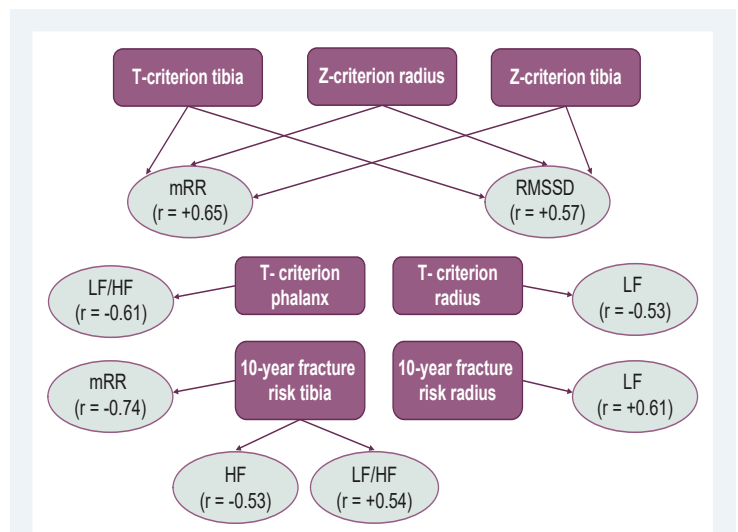


Fig. 1. Correlative interrelationships fixed in the group of patients with CCS and OPe ( $P < 0.05$ ).

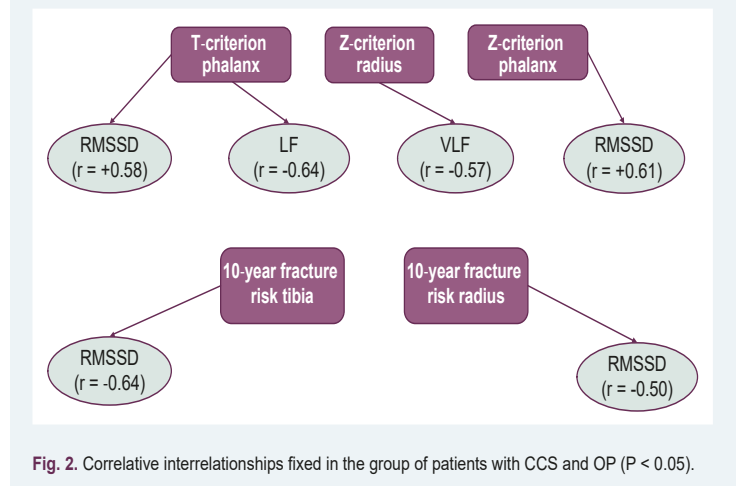


Fig. 2. Correlative interrelationships fixed in the group of patients with CCS and OP ( $P < 0.05$ ).

of variability (in particular, HF %, LF %, LF/HF) are quite sensitive and specific markers of arterial hypertension and CCS [20]. According to the results of M. Abdelnaby et al., there is a state of autonomic imbalance with the sympathetic activity predominance in CCS patients. Authors also associate autonomic dysfunction with an increased risk of cardiovascular morbidity and mortality [21].

In addition, study by F. Elefteriou found out a significant reduction in the 24-hour high-frequency rate, as well as a significantly higher LF/HF ratio during daily ECG monitoring in the group of patients with OP than in the control group with normal BMD [22].

The established by us interrelationships between temporal, spectral parameters of HRV and BMD indicators determine the presence of common mechanisms of development and progression of bone disorders and autonomic imbalance provoked by elevation of proinflammatory and bone biomarkers in the early stages of bone resorption [23].

## Conclusions

1. The course of CCS on the background of osteopenic syndrome in postmenopausal women is characterized by

increase in the frequency and duration of episodes of tachycardia, increased frequency of episodes of ventricular and supraventricular arrhythmias, which is the most pronounced in patients with OP.

2. The presence of BMD disorders in patients with CCS is accompanied by decrease in total HRV activity (RMSSD and HRVT), the development of sympathoparasympathetic imbalance of the ANS in the direction of sympathetic link activation, the severity of which depends on the degree of bone loss, confirmed by the results of correlation analysis.

**Prospects for further research:** study of the prognostic value of HRV in women with CCS and OP is the prospect of further research.

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