Possibilities of detecting and correcting decreased heart rate variability in patients with coronary artery disease in combination with depressive disorders in a cardiology department

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ABSTRACT

Aim. To identify the presence of decreased heart rate variability (HRV) and a method for correcting it in patients with chronic coronary artery disease (CAD) and comorbid depressive disorders (DD).

Materials and methods. 79 patients with CAD (with class II–III angina pectoris and myocardial infarction that occurred more than 6 months ago) were divided into two groups. The first group included 50 CAD patients with depression, and the second – 29 CAD patients without depression. 17 patients received agomelatine (1st subgroup), 12 patients received fluvoxamine and fluoxetine (2nd subgroup), and 21 patients refused to take antidepressants (3rd subgroup). Initially and after 6 months, the HRV parameters were evaluated using the SCHILLER MT-200 Holter-ECG apparatus (Switzerland).

Results. A significant decrease in HRV was revealed in the patients with depression compared to the patients without it: SDNN (96 [83; 117] ms vs. 110 [98; 127] ms; \( p = 0.02 \)), SDANN (80.5 [67; 94] ms vs. 91 [79; 102] ms; \( p = 0.03 \)), SDNNindex (46.5 [38; 56] ms vs. 55 [48; 66] ms; \( p = 0.006 \)), rMSSD (29 [23; 38] ms vs. 33 [29; 45] ms; \( p = 0.04 \)), pNN50% (3.9 [2.4; 5.7] vs. 5.7 [2.9; 12.6]; \( p = 0.03 \)). Initially, the 1st, 2nd, and 3rd subgroups did not differ in all HRV parameters. Against the background of antidepressant therapy, there were significant differences between the 2nd and 3rd subgroups in SDNN (110 [96; 140] ms vs. 85.5 [75; 103] ms; \( p = 0.008 \)), SDANN (93.8 ± 22.9 ms vs. 72.7 ± 21.4 ms; \( p = 0.02 \)), SDNNindex (55.8 ± 16.4 ms vs. 42.4 ± 10.8 ms; \( p = 0.01 \)) and pNN50% (7.8 ± 6.7 vs. 3.6 ± 1.8; \( p = 0.02 \)), as well as between the 1st and 3rd subgroups (SDANN (93.6 ± 28.5 ms vs. 72.7 ± 21.4 ms; \( p = 0.03 \)), rMSSD (36.5 [28.5; 51] ms vs. 26.5 [25; 32] ms; \( p = 0.02 \)).

Conclusion. In patients with CAD with comorbid DD, significant impairment of heart rhythm regulation occurs due to a pronounced decrease in HRV, which can seriously affect the course and prognosis of CAD. Prescribing modern antidepressants can be used as a method of correcting autonomic dysfunction in patients with CAD with comorbid depression.

Key words: coronary artery disease, depressive disorders, myocardial infarction, heart rate variability, antidepressants.

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Возможности выявления и коррекции сниженной вариабельности ритма сердца у больных ишемической болезнью сердца в сочетании с депрессиями в условиях кардиологического отделения

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РЕЗЮМЕ

Цель. Выявить наличие и способ коррекции сниженной вариабельности ритма сердца (ВРС) у больных с хронической ишемической болезнью сердца (ИБС) в сочетании с депрессивными расстройствами (ДР).

Материалы и методы. Больные с ИБС (n = 79, со стенокардией напряжения II–III функциональных классов и перенесенным инфарком миокарда давностью более 6 мес), распределены на две группы: 50 больных ИБС с депрессивными расстройствами (первая группа) и 29 больных ИБС без депрессивной симптоматики (вторая группа). Антидепрессант агомелатин получали 17 больных (1-я подгруппа), 12 больных – флувоксетин, флуксетин (2-я подгруппа). От приема антидепрессантов отказался 21 больной (3-я подгруппа). Исходно и через 6 мес проведена оценка параметров ВРС с помощью аппарата SCHILLER MT-200 Holter-ECG (Швейцария).

Результаты. У пациентов с депрессией в сравнении с пациентами без нее выявлено значимое снижение ВРС: SDNN (96 [83; 117] мс vs 110 [98; 127] мс, р = 0,02), SDANN (80,5 [67; 94] мс vs 91 [79; 102] мс, р = 0,03), SDNNindex (46,5 [38; 56] мс vs 55 [48; 66] мс, р = 0,006), rMSSD (29 [23; 38] мс vs 33 [29; 45] мс, р = 0,04), pNN50% (3,9 [2,4; 5,7] vs 5,7 [2,9; 12,6], р = 0,03). Исходно 1-, 2-, 3-я подгруппы по всем параметрам ВРС не различались. На фоне терапии антидепрессантами между 2-й и 3-й подгруппами появились существенные отличия по SDNN (110 [96; 140] мс vs 85,5 [75; 103] мс, р = 0,008), SDANN (93,7 ± 22,9 мс vs 72,7 ± 21,4 мс, р = 0,02), SDNNindex (55,8 ± 16,4 мс vs 42,4 ± 10,8 мс, р = 0,01) и pNN50% (7,8 ± 6,7 vs 3,6 ± 1,8, р = 0,02), а также между 1-й и 3-й подгруппами (SDANN 93,6 ± 28,5 мс vs 72,7 ± 21,4 мс, р = 0,03), rMSSD (36,5 [28,5; 51] мс vs 26,5 [25; 32] мс, р = 0,02).

Заключение. У больных ИБС при наличии ДР возникает серьезное нарушение регуляции сердечного ритма вследствие выраженного снижения показателей ВРС, что может серьезно повлиять на течение и прогноз коронарной болезни. Назначение современных антидепрессантов можно использовать в качестве способа коррекции вегетативной дисфункции у больных ИБС в сочетании с депрессией.

Ключевые слова: ишемическая болезнь сердца, депрессивные расстройства, инфаркт миокарда, вариабельность ритма сердца, антидепрессанты.

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INTRODUCTION

Currently, very high comorbidity of two such common pathologies as cardiovascular disease (CVD) and depressive disorders (DD) takes place. According to the World Health Organization (WHO) forecasts, by 2030, coronary artery disease (CAD) and depression will become the leading causes of disability in high-income countries around the world [1, 2].

On the one hand, depression is known to increase the risk of CAD. On the other hand, it is a strong predictor of poor prognosis in patients with cardiovascular diseases. Severe depressive symptoms are associated with the risk of death in patients with cardiovascular pathology [3–5]. Mortality in patients with myocardial infarction and depression is 3–6 times higher than in patients without mental disorders, while DD is detected in 35–40% of patients after myocardial infarction [4].

There has been significant deterioration in the clinical presentation of CAD against the background of DD, which is manifested by aggravation of angina pectoris, and a significant decrease in exercise tolerance; patients have a lower quality of life [6]. It should be taken into account, that only 30% of patients have complaints of psychological nature, leading to development of depressive disorders in the future, which contributes to underdiagnosis of DD and untimely administration of appropriate therapy [7, 8]. Therefore, patients more often seek medical help at a polyclinic, call an ambulance, and are more often hospitalized [9].

The most important mechanism in the effect of depression on the prognosis of CAD is activation of the sympathetic-adrenal medullary system. This causes dysfunction in the regulation of the heart rate, reducing its variability, which increases the risk of developing rhythm disturbances [10, 11]. The presented data dictate the need for timely recognition of depression, correction of psychoemotional factors [12], and administration of modern antidepressants in addition to the first-line therapy for chronic CAD. The beneficial effect of the antidepressant therapy on the clinical course of CAD has been proved [4, 5, 11]. However, there is little experience in studying the effect of antidepressants on autonomic dysfunction in patients with CAD after myocardial infarction in combination with DD. In turn, it is autonomic dysfunction that plays an important role in the prognosis of CAD.

Therefore, the aim of the study was to identify the presence of the decreased HRV and a method for its correction in patients with chronic CAD with comorbid DD.

MATERIALS AND METHODS

At the Department of Cardiology, 79 patients with chronic coronary artery disease (class II-III angina pectoris) who had had acute myocardial infarction more than 6 months prior to the experiment were examined and included in the study. All patients signed an informed consent to participate in the study. The patients were divided into two groups: 50 patients with CAD with depressive disorders (the first group) and 29 patients with CAD without depressive symptoms (the second group). The average age in the groups was (57.5 ± 6.4) years and (57.5 ± 7.4) years, respectively.

During the examination of the underlying pathology (CAD), all patients were offered to be tested with special scales for detecting depression (Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory (BDI)). When an increased level of depression was detected (more than 8 points on the HADS or more than 19 points on the BDI), the patients were referred to a psychiatrist. The diagnosis of DD was confirmed by the psychiatrist, and follow-up of the patients was also conducted by a psychiatrist as a member of a multidisciplinary team. When the diagnosis of DD was confirmed, the patients were prescribed antidepressants.

Therefore, 29 patients with DD were treated with antidepressants: 17 patients received agomelatine, an agonist of MT₁, MT₂, melatonergic receptors (1st subgroup), and 12 patients received drugs from the group of selective serotonin reuptake inhibitors (fluvoxamine, fluoxetine) (2nd subgroup) for 6 months. The dose was selected by the psychiatrist individually for each patient. For various reasons, 21 patients refused to take antidepressants (3rd subgroup). During the examination, all patients, initially and after 6 months, underwent 24-hour Holter monitoring using the SCHILLER MT-200 Holter-ECG apparatus (Switzerland).

We assessed the following HRV parameters through time domain variables: the percentage of consecutive intervals differing by more than 50 ms (pNN50, %); standard deviation of the RR interval (SDNN, ms); square root of the average sum of squares of the differences between adjacent normal RR-intervals (r-MSSD, ms); standard deviation of the average values of RR intervals for all 5-minute fragments (SDANN, ms); and mean value of standard deviations over all 5-minute sections (SDNN index, ms). HRV was determined only in sinus rhythm. For normal HRV parameters, time domain variables for healthy individuals were used (J.T. Bigger et al.,...
1995); pNN50 – 9 ± 7%, SDNN – 141 ± 38 ms, SDNN index – 54 ± 15 ms, rMSSD – 27 ± 12 ms, SDANN – 127 ± 35 ms.

Statistica for Windows v.10.0 software (StatSoft Inc., USA) was used for statistical processing of the results. The obtained data were presented in the form of $M \pm SD; n$ (%); the median and the interquartile range $Me [25\%; 75\%]$. The level of statistical significance of the differences was $p < 0.05$. The Shapiro – Wilk test was used to check the normal distribution of the actual data. With normal distribution of the sample, the significance of differences was assessed using the Student’s $t$-test. With nonparametric distribution and the number of groups equal to two, the Mann – Whitney test was used. When the number of samples was more than two, in order to avoid the effect of multiple comparisons, the nonparametric Kruskal – Wallis $H$-test was used. To compare two dependent samples for any criterion, the Student’s $t$-test (with normal distribution of the sample) and the Wilcoxon test (with abnormal distribution of the sample) were used. To check the significance of differences in the qualitative variables, analysis of contingency tables and the Pearson’s $\chi^2$ test (at low frequencies – with Yates’ correction for continuity) were used.

**RESULTS**

According to the main clinical and demographic characteristics, the functional class of angina pectoris, hemodynamic parameters, and cholesterol and triglyceride levels, the groups were comparable (Table 1).

All patients achieved the target values of blood pressure and heart rate. The patients received the main groups of drugs for treatment of stable angina pectoris without significant differences between the first and second groups (Table 2).

In the analysis of HRV parameters, significant differences were initially revealed between the first and second groups for all parameters (Table 3). In addition, in both groups in comparison with healthy individuals, a decrease in SDNN and SDANN was registered.

Initially, CAD patients with comorbid DD (1st, 2nd, 3rd subgroups) did not differ in all HRV parameters ($p > 0.05$). For 6 months, the patients were taking the selected basic therapy for CAD. In patients of the 2nd subgroup, in comparison with patients of the 3rd subgroup, a significant increase in HRV parameters (SDNN, SDANN, SDNN index and pNN50%) was observed after 6 months (Table 4).

| Parameters                  | First group | Second group | $p$  |
|-----------------------------|-------------|--------------|------|
| Average age, years, $M \pm SD$ | $57.5 \pm 6.4$ | $57.5 \pm 7.4$ | 0.4  |
| Men, abs. (%)               | 45 (90)     | 26 (90)      | 1    |
| Women, abs. (%)             | 5 (10)      | 3 (10)       | 1    |
| Anterior myocardial infarction, abs. (%) | 26 (52)     | 18 (62)      | 1    |
| Coronary artery disease, months, $Me [25\%; 75\%]$ | 48.0 [20.5; 96] | 30.0 [12; 84] | 0.2  |
| Hypertensive disease, abs. (%) | 50 (100)    | 29 (100)     | 1.0  |
| Hypertension, months, $Me [25\%; 75\%]$ | 90 [24; 162] | 90 [36; 132] | 0.8  |
| Smoking, abs. (%)           | 25 (50)     | 15 (52)      | 0.9  |
| Body mass index, (BMI), kg/m$^2$, $M \pm SD$ | 28.4 ± 4.3 | 28.5 ± 3.5 | 1.0  |
| Obesity (BMI > 29.9), abs. (%) | 17 (34)     | 11 (38)      | 0.7  |
| History of PCI, abs. (%)    | 40 (80)     | 27 (93)      | 0.1  |
| Single-vessel lesion of the coronary bed, abs. (%) | 15 (30)  | 9 (31)       | 0.9  |
| Double-vessel lesion of the coronary bed, abs. (%) | 20 (40)    | 12 (41)     | 0.9  |
| Triple-vessel lesion of the coronary bed, abs. (%) | 15 (30)    | 8 (28)       | 0.9  |
| FC of angina pectoris, abs. (%): – FC II  – FC III | 38 (76)  | 24 (83)    | 0.5  |
| – FC III                  | 12 (24)     | 5 (17)       | 0.5  |
| Total cholesterol, mmol / l, $Me [25\%; 75\%]$ | 5.3 [4.4; 6.4] | 5.3 [4.6; 6.3] | 1.0  |
| Triglycerides, mmol / l, $Me [25\%; 75\%]$ | 1.9 [1.3; 2.3] | 1.6 [1.4; 2.0] | 0.3  |
| EF, B-mode, %, $M \pm SD$ | 60.9 ± 10.4 | 61.2 ± 7.7  | 0.9  |
| EDS / ESS, mm $M \pm SD$, $Me [25\%; 75\%]$ | 48.7 ± 6.2/ 49.4 ± 4.4 | 49.4 ± 4.4/ 32.7 [29; 37] | 0.1/0.4 |
| EDV / ESV, ml, $Me [25\%; 75\%]$ | 105 [97; 137]/ 116 [100; 135]/ 44 [35; 56] | 0.4/0.5 |
| Average DBP, mm Hg, $M \pm SD$ | 121 ± 12.4 | 120.5 ± 8.43 | 1    |
| Average SBP, mm Hg $Me [25\%; 75\%]$ | 76 [70; 82] | 75 [73; 78] | 0.7  |
| Average daily HR, min, $Me [25\%; 75\%]$ | 65 [61; 71] | 64 [61; 67] | 0.3  |

Note. PCI – percutaneous coronary intervention, FC – functional class, EF – ejection fraction, EDS – end diastolic size, ESS – end systolic size, EDV – end diastolic volume, ESV – end systolic volume, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate.
We have studied one of the major mechanisms of the influence of affective disorders on the course of CAD. The study confirmed that patients with CAD and diagnosed depression have low HRV [10, 11]. The CAD patients, both with and without depression, had a decrease in SDNN and SDANN parameters in comparison with healthy people, which indicates rhythm rigidity in patients with postinfarction cardiосclerosis. A decrease in SDNN indicates a decrease in the overall HRV activity, and a decrease in SDANN reflects the activation of sympathetic tone and suppression of parasympathetic influences.

The CAD patients with depression and without a mental disorder did not differ in the main clinical and demographic parameters and concomitant therapy, which excluded their influence on the HRV parameters. When CAD was accompanied by DD, there was an increase in sympathoadrenal activity, which affected heart rate regulation and led to an even greater decrease in the main HRV parameters (SDNN, SDANN SDNNindex, rMSSD, pNN50%). Thus, the patients suffering from both CAD and DD have a worse prognosis, which was repeatedly proved in many studies [3–5].

This is determined by the fact that low HRV is a predictor of sudden death due to possible development of life-threatening arrhythmias. Of course, such patients require more attention and observation, as well as timely administration of modern antidepressants. The patients of this study received antidepressants of two groups – selective serotonin reuptake inhibitors (fluvoxamine, fluoxetine) and an agonist of MT1, MT2 melatonergic receptors (agomelatine). The choice of such antidepressants is associated with their efficacy and safety in cardiac patients according to the literature [4–6, 11].

To assess autonomic dysfunction, a temporary method of HRV analysis was used, which has high prognostic value and reproducibility of indicators. In this study, selective serotonin reuptake inhibitors had the greatest beneficial effect on autonomic dysfunction; an increase in most of the analyzed HRV parameters (SDNN, SDANN, SDNNindex and pNN50%) was observed against the background of a six-month course. The six-month course of agomelatine resulted in an increase in HRV time domain variables, such as SDNN and rMSSD. Therefore, the administration of antidepressants of both groups in addition to the first-line therapy for CAD can increase the overall autonomic tone and parasympathetic activity and suppress
sympathetic activity, which can significantly reduce the risk of heart rhythm disturbances and improve the clinical course of CAD.

CONCLUSION

The clinical presentation of CAD is accompanied by an unfavorable prognostic disorder: a decrease in HRV parameters in the presence of comorbid DD. The results of this study showed that prescription of modern antidepressants can be used as a way to correct autonomic dysfunction in patients with CAD with comorbid depression.

REFERENCES

1. Khandaker G.M., Zuber V., Rees J.M.B., Carvalho L., Mason A., Foley C.N., Gkatzionis A., Jones P.B., Burgess S. Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. Molecular Psychiatry. 2020; 25 (7): 1477–1486. DOI: 10.1038/s41380-019-0395-3.

2. Patel H., Mazur W., Williams K.A. Sr, Kalra D.K. Myocardial viability-state of the art: is it still relevant and how to best assess it with imaging? Trends Cardiovasc. Med. 2018; 28 (1): 24–37. DOI: 10.1016/j.tcm.2017.07.001.

3. Pushkarev G.S., Kuznetsov V.A., Fisher Y.A. et al. Effect of depressive symptoms on the risk of death from all causes in patients with chronic heart failure who underwent cardiac resynchronization therapy. Cardiology. 2019; 59 (1): 5–11 (in Russ.). DOI: 10.18087/cardio.2019.1.10211.

4. Lebedeva E.V., Nonka T.G., Reepin A.N., Shishneva E.V., Schastnyy E.D., Simutkin G.G., Levcuk L.A. Modern psychocardiology. Tomsk: Publishing house LLC Integral Binding, 2019: 160 (in Russ.).

5. Schastnyy E.D., Simutkin G.G., Lebedeva E.V., Yakovleva A.L., Losenkov I.S., Repin A.N., Nonka T.G. Clinical-dynamic and biological aspects of polymorphism and the efficacy of therapy of mood disorders. Siberian Medical Journal. 2018; 33 (3): 86–92 (in Russ.). DOI: 10.29001/2073-8552-2018-33-3-86-92.

6. Lebedeva E.V., Schastnyy E.D., Simutkin G.G., Repin A.N., Nonka T.G. Clinical characteristics of affective disorders and the effectiveness of antidepressant therapy in patients with chronic coronary heart disease. Bulletin of Siberian Medicine. 2018; 17 (4): 85–93 (in Russ.). DOI: 10.20538/1682-0363-2018-4-85-93.

7. Spurgeon L., James G., Sackley C. The Hospital Anxiety and Depression Scale: a pilot study to examine its latent structure and the link between psychological state and symptom severity in transient ischaemic attack patients. Psychol. Health Med. 2016; 21 (5): 632–638. DOI: 10.1080/13548506.2015.1074711.

8. Arat S., de Cock D., Moons P., Vandenbergh J., Westhovens R. Modifiable correlates of illness perceptions in adults with chronic somatic conditions: A systematic review. Res. Nurs. Health. 2018; 41 (2): 173–184. DOI: 10.1002/nur.21852.

9. Palacios J., Khondoker M., Mann A., Tylee A., Hotopf M. Depression and anxiety symptom trajectories in coronary heart disease: Associations with measures of disability and impact on 3-year health care costs. J. Psychosom. Res. 2018; 104: 1–8. DOI: 10.1016/j.jpsychoth.2017.10.015.

10. Vershuta V.A., Halilova M.A., Gognieva D.G., Bogdanova R.S., Syrkina E.A., Mesitskaja D.F., Kopylov F.Ju., Syrkin A.L. Anxiety and depressive disorders in patients with cardiac arrhythmias. Cardiology and Cardiovascular Surgery. 2019; 12 (4): 314–320 (in Russ.). DOI: 10.17116/kardio201912041314.

11. Baranov A.P., Strutynsky A.V., Oynotkinova O.Sh., Baranova A.A., Trishina V.V., Golubev Yu.Yu., Kruzhalov A.N. Treatment options for anxiety and depressive disorders in patients with chronic heart failure. Russian Journal of Cardiology. 2017; 22 (1): 128–135 (in Russ.). DOI: 10.15829/1560-4071-2017-1-128-135.

12. Kabareva M.I., Ibatov A.D. Psychosocial factors and coronary heart disease. Therapeutic Archive. 2019; 91 (12): 70–74 (in Russ.). DOI: 10.15829/1560-4071-2017-1-128-135.

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