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Особенности вегетативной регуляции сердечного ритма и функционального состояния эндотелия у пациентов с вазоспастической стенокардией

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Обоснование. Особенности клинических проявлений вазоспастической стенокардии хорошо известны, однако ее патогенез остается предметом дискуссий. Изменения вегетативной регуляции тонуса коронарных артерий и функции эндотелия, способствующие развитию вазоспазма, недостаточно изучены. Данные опубликованных на эту тему исследований противоречивы.

Цель работы — изучить особенности вегетативной регуляции сердечного ритма и функционального состояния эндотелия у пациентов с вазоспастической стенокардией.

Материалы и методы. У 16 пациентов с доказанной вазоспастической стенокардией оценили вариабельность сердечного ритма в покое и вегетативных пробах (с глубоким дыханием, активная ортостатическая). Функциональное состояние эндотелия определили методом периферической артериальной тонометрии на аппарате Endo-PAT 2000 по величине индекса реактивной гиперемии.

Результаты. У пациентов с вазоспастической стенокардией исходный показатель общей вариабельности сердечного ритма имел пограничное с нормой значение: SDNN 50 (32,5; 50) мс. У 14 пациентов в покое выявлен дисбаланс вегетативной нервной системы с преобладанием парасимпатической активности. В пробе с глубоким дыханием у 13 больных обнаружена адекватная реакция вегетативной нервной системы в виде нарастания вагусных влияний, а в активной ортостатической пробе также у 13 пациентов — парадоксальная реакция, выраженная в усилении влияния парасимпатического воздействия на сердечный ритм. Эндотелиальная дисфункция выявлена у половины обследованных больных. При этом у всех пациентов со сниженным индексом реактивной гиперемии наблюдали сочетание эндотелиальной и вегетативной дисфункций.

Выводы. По результатам исследования у больных вазоспастической стенокардией в покое и вегетативных пробах преобладало парасимпатическое влияние на сердечный ритм, что нетипично для ишемической болезни сердца. У всех обследованных пациентов были выявлены вегетативная или эндотелиальная дисфункции, а у половины обследованных наблюдалось сочетание обоих механизмов.

Ключевые слова: вазоспастическая стенокардия; ишемическая болезнь сердца; коронарные артерии; вариабельность сердечного ритма; дисбаланс вегетативной нервной системы; вегетативная дисфункция; эндотелиальная дисфункция.

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Features of endothelial function and autonomic regulation of heart rhytm in patients with vasospastic angina

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BACKGROUND: The clinical features of vasospastic angina are well known, but pathogenesis remains a subject of discussion. Changes in the autonomic regulation of coronary artery tone and endothelial function that contribute to the development of vasospasm are not well understood. The data on the subject from the published studies are contradictory.

AIM: To evaluate features of endothelial function and autonomic regulation of heart rhythm in patients with vasospastic angina.

MATERIALS AND METHODS: The study included 16 patients with proven vasospastic angina. All the patients have been evaluated for the heart rate variability at rest and vegetative tests (deep breathing, and active standing tests). Endothelial function has been assessed in terms of reactive hyperemia index by peripheral arterial tonometry using an Endo-PAT 2000 device.

RESULTS: The baseline of the total heart rate variability was borderline with the normal parameters SDNN 50 (32.5; 50) ms in the patients with vasospastic angina. There were 14 patients who have demonstrated an imbalance of the autonomic nervous system at rest, mainly due to an increase of parasympathetic influences. The appropriate reaction of the autonomic nervous system, characterized by an increase of vagal influences, has been determined in 13 patients in the deep-breathing test. A paradoxical reaction, characterized by an increase of vagal influences on the heart rhythm, has been registered in 13 patients in the active standing tests. Endothelial dysfunction has been observed in half of the studied patients. Furthermore, a combination of both pathophysiological mechanisms, i.e., endothelial and autonomic dysfunctions have been observed in all the patients with a reduced reactive hyperemia index.

CONCLUSIONS: According to the results of our study, the parasympathetic influences of the autonomic nervous system on the heart rhythm were predominant in the patients with vasospastic angina, which is not typical for coronary heart disease. All the patients had autonomic or endothelial dysfunction. A combination of both pathophysiological mechanisms has been observed in half of the examined patients.

Keywords: vasospastic angina; coronary heart disease; coronary arteries; heart rate variability; imbalance of the autonomic nervous system; endothelial dysfunction; autonomic dysfunction.

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BACKGROUND

Vasospastic angina (VA), also called variant, spontaneous or Prinzmetal's angina, is a type of coronary heart disease (CHD). It is based on myocardial ischemia resulting from spasm of the epicardial coronary arteries, regardless of the presence of atherosclerotic lesions on the coronary bed, and causes changes in the electrocardiogram. It is registered in patients hospitalized with unstable angina, with a frequency of 2%–3% in Europe [1] and up to 40% in Japan [2].

Despite the awareness of doctors about VA clinical manifestations, the mechanisms of development of coronary spasm remain a subject for discussion. According to some authors, the pathophysiological mechanism contributing to the development of vasospasm is an imbalance of the autonomic nervous system (ANS) [1–4]. However, the published data on this subject are contradictory. On one hand, the frequent attacks at night during the minimal sympathetic activity period, the provocation of spasm by cholinomimetics and the possibility of arresting VA with atropine indicate the influence of the vagus nerve on VA development. On the other hand, the frequent occurrence of VA in the pre-dawn hours during rapid eye movement sleep and the positive results of complete sympathetic denervation of the heart in VA patients are associated with hypersympathicotonia. However, the complex mechanism of coronary spasm development, which determines the variability of its clinical manifestations through one impairment of autonomic regulation, is difficult to explain. Endothelial dysfunction, an imbalance of vasodilating and vasopressor mediators, was previously believed to be the main pathophysiological mechanism for VA development. However, recent studies show that the vasodilating function of the endothelium can be preserved in spasmodic coronary arteries [5].

The contemporary methods of functional diagnostics and clinical and laboratory studies of endothelial dysfunction have advantages, disadvantages, and certain limitations. For example, the instability and short lifetime of nitric oxide, whose activity is insufficient in VA patients, restrict the use of certain assessment methods [5–7]. Also, the determination of endothelial dysfunction using intracoronary infusion of endothelium-dependent vasodilators in patients with suspected coronary artery spasm is not available in Russia.

Understanding the pathophysiological mechanisms of VA is required to select the optimal diagnostic and therapeutic measures. It is known that the lack of adequate therapy in VA can worsen the prognosis and can lead to life-threatening arrhythmias, myocardial infarction or sudden cardiac death [2, 8, 9]. VA occurs in 28% of patients with myocardial infarction without coronary artery obstruction [10].

This work aimed to analyze the characteristics of the autonomic regulation of the heart rate and the endothelium functional state in VA patients.

MATERIALS AND METHODS

The study included 16 patients who were examined in the Cardiology Department of the Peter the Great Clinic and were diagnosed with VA based on the latest clinical guidelines (JSC, 2013; COVADIS, 2017; ESC, 2019):

1. Anginal attacks often occur at rest and are accompanied by ischemic changes in the ST segment on the electrocardiogram.
2. Attacks of retrosternal pain mainly in the morning or at night.
3. Anginal attacks can be prevented and arrested with calcium antagonists and nitrates. The effect of β-blockers is less pronounced and may even cause a proischemic effect.
4. Pain attacks are accompanied by spasm of the coronary artery during coronary angiography spontaneously or during challenge tests [2, 8, 9].

All patients included in the study met the above criteria for VA and did not have obstructive coronary artery lesions according to coronary angiography. General characteristics of the VA patients are presented in Table 1.

All patients underwent a general clinical examination and heart rate variability assessment at rest, in a deep breathing test and in an active orthostatic test using the Valenta diagnostic system [11] not earlier than one month after the emergence of myocardial infarction. Forty-eight hours before the assessment of heart rate variability and the functional state of the endothelium, the patients were recommended to temporarily stop the intake of β-blockers and calcium antagonists. Registration and computer analysis of the cardiorhythmograms were performed in accordance with accepted standards [12].

Table 1. Clinical and demographic characteristics of the patients with vasospastic angina

Таблица 1. Клинико-демографическая характеристика пациентов с вазоспастической стенокардией

Indicator	Patients (*n* = 16)
Age, years	56.5 (50; 63)
Males, *n*	8
Smoking, *n*	9
Body mass index 25–29.9, *n*	9
Type 2 diabetes mellitus, *n*	2
Arterial hypertension, *n*	15
History of myocardial infarction, *n*	5
Intake of calcium antagonists, *n*	14
Intake of β-blockers, *n*	7
Intake of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, *n*	14
Intake of statins, *n*	16

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The study took into account the parameters of R-RNN (ms) as the average value of the R-R interval duration, SDNN (ms) as the standard deviation for all R-R intervals, CV (%) as the standard deviation normalized by heart rate, TP (ms^2) as the total power of oscillations of R-R intervals, HF (ms^2) as the power of high-frequency oscillations of R-R intervals, LF (ms^2) as the power of low-frequency oscillations of R-R intervals and VLF (ms^2) as the power of very low-frequency oscillations of R-R intervals.

The vasodilatory capacity of the endothelium was assessed using peripheral arterial tonometry using the Endo-PAT 2000 device (EndoPAT 2000 Device User Manual/Itamar Medical, 2017), in accordance with the standard method. The study was conducted in a horizontal position with a blood pressure cuff put on the patient's shoulder and sensors on the index fingers of both hands, evaluating the peripheral arterial tonometry signal. The test lasted for 15 min and included three equal periods, namely stabilization, occlusion, and post-occlusion. According to the examination results, the index of reactive hyperemia was evaluated. A value less than 1.67 indicated an impairment of the endothelium functional state and its dysfunction.

Statistical data processing was performed using the Statistica 10.0 program. Mean values were presented as medians and quartiles *Me* (Q_1; Q_3). The data were compared using the Mann-Whitney *U*-test. To determine the statistical relationship between the values, the nonparametric Spearman correlation method was used. Differences were considered significant at $p \leqslant 0.05$.

RESULTS AND DISCUSSION

In modern cardiology, there are various diagnostic possibilities for the verification of obstructive CHD. However, the diagnosis of VA is still not established in clinical practice. The prognosis of this disease can be poor and the number of patients with complicated forms of VA is growing [1–3, 10]. In our work, a small sample of patients was presented since in the absence of the possibility of invasive diagnostics for VA, we carefully considered the diagnosis verification, excluding vasospastic forms of CHD associated with obstructive lesions of the coronary arteries according to coronary angiography. All patients were examined according to the protocol.

According to the literature, VA is predominantly registered in men aged 50–60 years. The gender ratio may depend on the patients in a particular country or cohort [1, 2]. We examined eight men and eight women. Their median age was consistent with epidemiological data at 56.5 (50; 63) years.

Heart rate variability in VA patients has been studied since the 1980s. However, the results of the work are ambiguous. For example, researchers from Japan were among the first to report an ANS imbalance expressed by activation of both the parasympathetic (increase in HF and CV) and sympathetic (decrease in R-R intervals) parts of the nervous system a few minutes before and during episodes of coronary spasm recorded during Holter monitoring [13]. Scientists from France indicated the activation of the sympathetic segment of the ANS, provoked by mental stress [4]. In our study, we obtained frequency and spectral indices of heart

Table 2. Parameters of the heart rate variability at rest, at deep breathing and active standing tests in the patients with vasospastic angina
Таблица 2. Показатели вариабельности сердечного ритма в покое, при выполнении пробы с глубоким дыханием и активной ортостатической пробы у пациентов с вазоспастической стенокардией

Parameter	At rest (1)	Deep breathing test (2)	Active orthostatic test (3)	*p* level
R-RNN, ms	795 (760; 872.5)	805 (775; 840)	760 (670; 940)	$p_{1-2} > 0.05$ $p_{1-3} > 0.05$
SDNN, ms	50 (32.5; 50)	45 (40; 67.5)	50 (40; 60)	$p_{1-2} > 0.05$ $p_{1-3} > 0.05$
CV, %	5.4 (4.3; 6.8)	6 (4.8; 8.3)	6.2 (3.9; 7.9)	$p_{1-2} < 0.05$ $p_{1-3} < 0.05$
TP, ms^2	946 (399; 1335)	641.5 (210.5; 1790.5)	568 (383; 1744)	$p_{1-2} > 0.05$ $p_{1-3} > 0.05$
HF, ms^2	140.5 (83.8; 277.5)	235 (94; 591)	220 (38; 476)	$p_{1-2} > 0.05$ $p_{1-3} > 0.05$
LF, ms^2	275.5 (92.5; 745.8)	136.5 (44.8; 442.3)	341 (103; 1122)	$p_{1-2} > 0.05$ $p_{1-3} > 0.05$
VLF, ms^2	124.5 (61; 222.3)	270 (71.8; 720)	74 (34; 96)	$p_{1-2} > 0.05$ $p_{1-3} > 0.05$

Note: R-RNN, average value of the R-R interval duration; SDNN, standard deviation for all R-R intervals; CV, standard deviation normalized to heart rate; TP, total power of oscillations of R-R intervals; HF, power of high-frequency oscillations of R-R intervals; LF, power of low-frequency oscillations of R-R intervals; VLF, power of very low-frequency oscillations of R-R intervals.

rate variability outside an attack of VA (at rest and during autonomic tests) (Table 2).

According to J. Camm et al., a SDNN lower than 50 ms is associated with higher mortality in cardiac patients, while a TP higher than 1000 ms^2 is registered in the healthy population [12]. In our study, the indicators of general heart rate variability at rest had borderline values with the norm (SDNN = 50 (32.5; 50) ms and TP = 946 (399; 1335) ms^2).

Based on the data of an individual program analysis of heart rate variability at rest, an imbalance of the ANS was revealed in 14 patients. In 11 patients, the parasympathetic influence on the heart rate was predominant while in 3 patients, sympathetic influences were predominant (Figure).

The results of the analysis of the heart rate variability at rest in VA patients correspond to the data of the study by T. Inazumi et al., where increased ANS vagal activity was detected with a significant increase in CV values (from 3.32% ± 0.04% to 8.15% ± 1.13%) and HF (from 90 ± 20 ms^2 to 310 ± 159 ms^2) immediately before the onset of an anginal attack, which may indicate the influence of the vagus nerve on the coronary spasm initiation [13].

Autonomic tests enable the evaluation of the nature of the reaction to a stimulus on the sympathetic and parasympathetic segments of the ANS. Normally, an increase in the frequency and depth of breathing is controlled by the vagus nerve and is accompanied by an increase in parasympathetic influence on the heart rate [11]. Parametrically, this can be expressed by an increase in SDNN and CV, a decrease in LF with an unchanged HF or an increase in HF with an unchanged LF [11]. We did not find literature on the use of cardiorhythmography with autonomic tests to study the heart rate variability in VA patients.

To clarify the nature of the reaction to stimulation of the parasympathetic division of the ANS, we conducted a test with deep breathing. When comparing heart rate variability in this sample with background values, we noted a significant increase in CV as the percentage ratio of SDNN to R-RNN increased (Table 2). An individual program analysis of heart rate variability showed that during the deep breathing test, the number of individuals with parasympathetic influence of the ANS on the rhythm increased to 13 (Figure). In most patients, the change in heart rate variability in the deep breathing test was induced by the preservation or increase in the vagal effect on the heart rate, which was an adequate response of the ANS to the autonomic test.

The ANS physiological response to an active orthostatic test is an increase in sympathetic influences on the heart rhythm. On the cardiac rhythmogram, such a reaction is displayed as a decrease in SDNN, CV, and TP, mainly due to a decrease in HF with an increase in the short-wave indicator LF. Paradoxical reactions of the ANS to the test are the rapid stabilization of the rhythm during initial vagotonia, an increase in parasympathicotonia and a pronounced increase in sympathicotonia [11]. In VA patients, in the active orthostatic test, compared with the baseline cardiorhythmogram, the R-RNN and SDNN indicators did not change significantly and the CV indicator increased ($p < 0.05$) (Table 2), which means that the parasympathetic effect on the heart rate was preserved. A detailed analysis of the spectral parameters in the active orthostatic test and their comparison with the background values and the results of the deep breathing test revealed tendencies toward an increase in LF and an increase or preservation of HF, which may indicate an increase in the influence of the ANS sympathetic division while maintaining or increase in the influence of the parasympathetic division on heartbeat. Despite the fact that the test is aimed at activating the ANS sympathetic division, an individual program analysis of the cardiorhythmogram showed the predominance of vagal influences in 13 patients (Figure). This is a paradoxical reaction of the ANS to an active orthostatic test.

We showed an unexpected predominance of parasympathetic influences on the heart rate both at rest and during autonomic tests. In patients with other forms of CHD, such as effort angina, microvascular angina pectoris and silent myocardial ischemia, the sympathetic activity of the ANS predominates with a weakening of the parasympathetic one, based on the analysis of heart rate variability [13–15].

A number of studies have shown the pathogenetic role of endothelial dysfunction in the development of cardiovascular diseases, including various forms of CHD [1, 2, 5]. Endothelial dysfunction is associated with a decrease in the production of the main vasodilator, nitric oxide, and an increase in the sensitivity of smooth muscle cells of the coronary

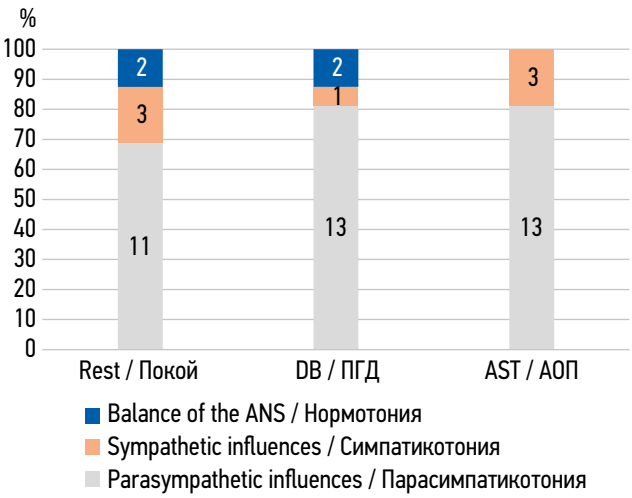

Figure. Features of autonomic regulation of the heart rhytm in the patients with vasospastic angina. DB — deep breathing; AST — active standing tests; ANS — autonomic nervous system
Рисунок. Особенности вегетативной регуляции сердечного ритма у пациентов с вазоспастической стенокардией в покое и при вегетативных пробах. ПГД — проба с глубоким дыханием; АОП — активная ортостатическая проба

arteries to vasoconstrictor mediators [1]. The ability to induce vasospasm using intracoronary challenge test and to arrest a pain attack with nitro-containing drugs indicate a possible pathophysiological role of endothelial dysfunction in the development of VA.

Endothelial vasodilatory function can be assessed using both invasive (e.g., intracoronary vasoactive testing) and non-invasive diagnostic methods. An automated non-invasive method for assessing endothelial dysfunction by peripheral arterial tonometry with the determination of the index of reactive hyperemia is simple and affordable. In addition, it correlates well with invasive methods for diagnosing endothelial dysfunction. Therefore, it is considered the most promising method, which determined our choice for its use in this study.

In patients with cardiovascular diseases, the reactive hyperemia index is known to be significantly lower compared to those without cardiac pathology [1.65 (1.49; 1.92) vs 1.73 (1.45; 2.24)] [16]. The endothelium-dependent vasodilation disorder was studied in CHD patients not only with significant atherosclerotic changes in the coronary arteries, but also with intact coronary arteries according to coronary angiography. In one of the studies in the group of patients with effort angina, a decrease in the index of reactive hyperemia was registered in 70% of cases, and in 100% of cases in the group of patients with microvascular angina [17].

The study of endothelial function using peripheral arterial tonometry in VA patients has not been previously performed. In our work in VA patients, a decrease in the vasodilating function of the endothelium was observed in five women and three men. The median index of reactive hyperemia was 1.33 (1.31; 1.44). According to the cardiorhythmograms of the patients with endothelial dysfunction, there was ANS imbalance expressed by the predominant activity of the sympathetic or parasympathetic parts, and in six patients, by vagal activity.

According to the literature, the index of reactive hyperemia may depend on the state of ANS. In patients with arterial hypertension, activation of the sympathetic division of the ANS correlated significantly with a low index of reactive hyperemia, according to cardiorhythmogram and peripheral arterial tonometry performed simultaneously [18]. Similar studies have not been performed in VA patients. In our study, correlation analysis revealed a direct strong relationship between the minimum R-RNN in the deep breathing test and the index of reactive hyperemia ($r = 0.78$, $p = 0.05$), which characterizes unidirectional changes in the autonomic and endothelial functions toward an increase in their imbalance. However, the contribution of individual parts of the ANS (parasympathetic or sympathetic) to the autonomic imbalance in this test is subject to further clarification.

Based on the study results, it can be assumed that autonomic dysfunction in the form of an increase in predominantly parasympathetic activity and endothelial dysfunction are factors contributing to VA occurrence. These disorders are interrelated, but their primacy in relation to each other remains unclear. There is also no doubt that there are a number of other mechanisms for the development of coronary spasm, which remained beyond our study. The results obtained necessitate continuation of the study.

CONCLUSIONS

1. Autonomic dysfunction in the form of parasympathicotonia was observed in majority of the VA patients examined.
2. Autonomic tests in VA patients reveal the peculiarities of the ANS reaction, expressed as the preservation of parasympathetic tone during the test with deep breathing and its paradoxical increase in the active orthostatic test.
3. Half of the patients examined had endothelial dysfunction.
4. It is necessary to continue studying the role of autonomic and endothelial dysfunctions in the development of vasospastic reactions on a larger sample size to develop additional diagnostic, treatment, and prevention methods for VA.

ADDITIONAL INFORMATION

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All authors made a significant contribution to the study and preparation of the article and read and approved the final version before its publication.

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