PRINZMETAL'S STENOCARDIA. PATHOGENESIS. DIAGNOSTICS

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Abstract. *In 1959, Myron Prinzmetal first described attacks of chest pain occurring in particularin stable angina pectoris predominantly at rest and accompanied with temporary ST-segment elevation above isolation. He noted that this form can be combined with CHD and coronary artery (CA) atherosclerosis.*
Keywords: *prostacyclin, sympathicotonia, pathogenesis, coronary angiography.*

M. Prinzmetal called this form of angina "variant" [1]. In the literature it is known as angiospastic, spontaneous angina, angina pectoris.The exact incidence of variant angina pectoris (AS) has not been established, but it is known to occur significantly less frequently. It is known to be significantly less common and other forms of unstable angina (UA). In the U.S., ICH is diagnosed in 2-3% of all patients undergoing diagnostic coronary angiography. Ultrasound (CAG) for chest pain [5]. In the European population, of all forms of HC, Prinzmetal's stenocardia accounts for ~2% [6,7]. In Japan In our country, the prevalence of MCV is higher than in Europe [8].

Pathogenesis.

As pathophysiological and CAG studies have shown , the basis of pain attacks that occur in VSC is a CA spasm [1,8-10,14]. The narrowing of the CA lumen to 70-75% leads to a decrease in blood flow in the myocardium and ischemia [2]. Spasm can occur as in atherosclerosis-affected CA, so it is in intact vessels [15]. However, it is known that KA spasm plays an important role not only in the pathogenesis of VSC, but also in the development of other forms of SSN and NS, acute myocardial infarction (AMI), sudden cardiac death (SCD) [5,8]. There is a combination of SSN and vasospastic angina [5,16]. Such patients, as a rule, develop seizures of SSN during the day, provoked by physical exertion (FN), emotional overstrain , and an increase in blood pressure (blood pressure), characteristic changes on the electrocardiogram (ECG); while at night, VSC attacks occur without provoking factors and signs of previous increased myocardial oxygen demand [16]. Studies in recent years have shown that even normal ones according to CAG data, with a more thorough study, may have minimal- signs of atherosclerosis. Using intravascular ultrasound, it was demonstrated that areas of arteries unchanged according to CAG data may have signs of moderate atherosclerosis [17]. The pathogenesis of KA spasm is very complex and has not been studied to the end. In recent years, great importance has been attached to the endothelial dysfunction (ED) of CA in VSC [18]. The endothelium is a highly active cellular layer with multiple metabolic functions, which plays an important role in the regulation of vascular tone, platelet function, coagulation , as well as proliferation and migration of CSF- distal smooth muscle cells (MMC). ED lead to disturbances in the local regulation of vascular tone and blood coagulation and is an important component of the pathogenesis of KA diseases [19-20]. In order to study ED as an independent factor in the development of vasospastic angina, a study of 30 patients with confirmed vasospastic angina was conducted 30 patients with angiographically

confirmed absence of CA lesion were taken as a control group. Flow-dependent dila was used as the main indicator of endothelial function- (flow-mediated dilatation) of the pulmonary artery (LA). The study showed that the value of flow- dependent dilatation was significantly lower in patients with vasospastic angina compared with the control group with the same thickness of the intima-media complex in both groups , which indicated ED as an independent risk factor (FR) of coronary spasm [21,22]. An important role in the pathogenesis of CA spasm is played by the disbalance between constrictor and dilating factors produced by the endothelium. Vasodilating substances are endothelial relaxing factor - nitric oxide (NO), prostacyclin and hyperpolarization factor [23, 24]. The main importance in the regulation of vascular tone is given to NO [24]. In the lumen of the vessel, this chemically unstable compound is rapidly inactivate by dissolved oxygen and bisuperoxide anions, in erythrocytes by hemoglobin, which prevents the action of NO at a distance from its place it explains its local regulating effect on vascular tone. This is the reason why it is impossible to compensate for the disruption of the production of endothelial relaxing factor in ED by releasing it by healthy endothelial cells of the border region [24,25]. In a study of Japanese population patients with coronary vasospasm, the following were found 3 various mutations of the NO-synthetase gene, leading to a significant decrease in production NO and arterial spasm [26]. It is the mutations of the gene NO-synthetases are the most reliable causes of the development of vasospastic angin [26,27]. It has been shown that individuals homozygous for the mutant NO-synthetase allele suffer from more severe forms of vasospastic stenocardia, and some of them suffer from IT in the absence of organic stenosis according to CAG data [26].

These mutations may affect not only the coronary blood flow, but also cause similar vasospastic changes in other tissues. This is probably why many researchers have noted that Raynaud's phenomenon, migraines and spasm of the ocular arteries quite often occur in patients with VSC [26,27]. All this indicates a general altered endothelial function and vascular reactivity of the body [27]. The role of ED was demonstrated in a study of women with VSC in the premenopausal period, in whom the frequency of seizures varied depending on the phase of the cycle and the level of estrogen in the blood. Episodes of angina pectoris more often occurred against the background of low estrogen levels at the end of the luteal -the beginning of the menstrual phase. This is probably due to the ability of estrogens to block Ca2+ channels [28]. The spasm of the CA is associated not only with an imbalance of hormonal factors, but also with increased sensitivity of the CA to vasoconstrictor agents. First of all, this can be explained by the excessive sensitivity of alpha-adrenergic receptors of the KA to catecholamines , which can lead to the development of spasm even in the absence of an imbalance between vasoconstrictor and vasodilator factor . In vasospastic angin , a combination of an imbalance between vasoconstrictor and vasodilator factors and increase vascular sensitivity to vasoconstrictor is likel agents [6,29]. Nevertheless, the issue hypersensitivity of α-adrenoreceptors in vasospastic angina remains controversial, since the use of α-adrenoreceptor blockers in such patient does not always have a positive effect [29]. Hypersensitivity of the spacecraft t vasoconstrictors may be associated with an increase in overall tone of the autonomic nervous system (VNS in patients with VSC [30,31]. There is no consensus on thi issue. From the point of view of a numbe of authors, the most important mechanism for the development of spas KA serves increased activity sympathetic who is the VNS link, others refute this theor [29-31]. On the one hand, the frequent occurrence of seizures at night and in the early morning hours, during minimal sympathetic activity, as well as the possibility of causing spasm with the use of cholinomimetics, indicate a significant role of the

vagus nerve in the development of coronary spasm [30-32]. On the other hand, the excess of the physiological concentration of vasoconstrictors in the vessels is necessary for the drug provocation of the spasm of the CA . Nocturnal attacks of VSC usually occur in the REM phase of sleep, during which sympathicotonia is observed [33]. The role of hypersympathicotonia in the development of spasm is also evidence by the positive results of treatment withcomplete sympathetic denervation of the heart in patients with VSC, refractory to drugs [30,31]. Thus, the question of the influence of the ANS on the development of a spasm of the SC in VSC requires further study. The idea of the pathogenesis of coronarospasm in patients with VSC changed after the discovery in 1996 Rho kinase enzyme [34,35]. Rho kinase is a enzyme of the serine tyrosine kinase group that reduces the activity of myosin phosphatase. By phosphorylating the myosin-bound subunit of this enzyme, it leads to an increase in the contractility of smooth myocytes and an increase in their sensitivity to ions Ca2+ [34]. Based on this, among the cellular an molecular mechanisms of spasm development in VSC The most important is currently considered to be the increased content of the Rho kinase enzyme in such patients [36]. Molecular studies have shown that the phenomenon of up-regulation of Rho kinase (an increase in the number of Rho kinase receptors) is observed directly in the area of the spasm, which causes inhibition of myosin light chain phosphatase and, as a consequence, vessel spasm [37,38]. There is a proposal to consider an elevated level of the Rho kinase enzyme as one of the main triggers of the development of KA spasm [14]. A certain value in the development of vasoconstrictions also have increased activity of Na+- H+ channels, which are the main regulators of intracellular pH [39]. The increased activity of the isoform-1 of the Na+-H+ pump in the MMC leads to the alkalinization of the intracellular medium and an increase in the concentration of Ca2+, which contributes to vasoconstriction.

Elevated endothelin-1 levels may lead to an increase in the number of Na+-H+ channels in the cell membrane, aggravating spasm [39,40]. It has previously been shown that the peroxidation of low-density lipoproteins (LDL) contributes to increased vascular reactivity and vascular sensitivity to vasoconstrictor factors. This suggested that the spasm KA may also be associated with the insufficiency of the main physiological antioxidant – vitamin E [41]. Repeated episodes of ischemia and subsequent myocardial reperfusion lead to the production of free radicals and depletion of vitamin E reserves. Studies have shown that the level of vitamin E in blood plasma in patients with VSC is significantly lower than in healthy people [42]. However, the role of vitamin E deficiency in the development of KA spasm remains unclear. Among other important factors contributing to the development of spasm, it is necessary to note smoking. In a 1993 study involving 351 patients (175 patients with confirmed CAH spasm and 176 control group patients with other CA diseases). In all patients of the main group, CA spasm was observed with narrowing of the vessel lumen not < 75% and with fixed atherosclerotic stenosis not > 25%. Differences between body mass index (BMI), content cholesterol (HC), LDL and high density lipoproteins (HDL), blood glucose , and blood pressure (BP) were absent in the main and control groups. FR analysis showed that 91% of patients in the main group smoked compared to 51% in the control group [43]. The adverse effect of smoking on the prognosis in patients with VSC is also known [44]. However, the effect of nicotine and the mechanism of development of KA spasm during smoking require further study.

Diagnostics.

Currently, there is no single algorithm for the diagnosis of VSC in Russian cardiology. Physical examination methods for vasospastic angina are not informative enough and in

the absence of a combined pathology, as a rule, do not reveal any changes. Some researchers note that during an anginal attack, the fourth cardiac tone and systolic murmur of mitral regurgitation can be heard [47]. Instrumental examination of VSC patients begins with an ECG analysis. In the intercalary period, it remains unchanged in 50% of patients. By if there are changes on the ECG, it should be remembered that they are not specific and can be observed in other diseases, in particular with SSN. An ECG recorded during an attack of VSC often has characteristic signs important for diagnosis, but in practice ECG registration during an attack is not always possible [2,48]. The most characteristic ECG sign of VSC is the rise of the ST segment above the isoline, indicating the presence of pronounced transmural myocardial ischemia caused by transient dynamic occlusion of a large CA [2,47,48]. In in more rare cases, ischemic depression of the ST segment below the isoline is observed, which indicates the occurrence of subendocardial ischemia associated with incomplete overlap of a large CA or spasm of smaller intramural CA – small arteries and arterioles, with good development of collaterals. After the arrest of the VSC attack, the ST segment returns to the isoelectric line [2,48]. In the process of establishing a diagnosis, it is necessary to clearly distinguish between SSN and spontaneous angina pectoris.

This is quite a difficult task for several reasons [45]: most patients have a combination of SSN, caused by atherosclerotic lesion of the CA, and vasospastic angina; in one third of patients, attacks of vasospastic angina can be provoked by FN in the morning; not all seizures are accompanied by changes on the ECG in the form of a transient ST segment elevation; in patients with SSN of functional classes III-IV (FC) according to the classification of the Canadian Association of Cardiologists and severe atherosclerosis of the CA, anginal attacks often occur at rest; during ECG examination in the conditions of samples with dosed FN in women, mainly young age (30-45 years), in 24% of cases false positive test results are manifested, which may be due to hyperventilation, electrolyte disturbances, smoking, eating, menopausal cardiopathy and the fact that women tolerate worse FN and can't always master it to get reliable test results. In men, the frequency of false positive results does not exceed 5-10% [45,46]. Differentiation of patients with SSN and VSC is of great importance, because it affects the choice of treatment tactics and prognosis. A more informative diagnostic method VSK is a method of Holter monitoring (XM) ECG. Characteristic features of daily ECG monitoring (CM) in VSC are: the development of seizures at rest, more often at night or in the early morning hours; seizures are not accompanied by an increase in heart rate (HR) > 5 beats / min., which distinguishes VSC from SSN due to increased myocardial oxygen demand; the displacement of the ST segment at the beginning of the attack occurs very quickly and disappears just as quickly after the end of the spastic reaction [2,48]. XM is a convenient, safe, informative method, but the changes on the ECG are not specific, which makes it difficult to diagnose VSC only based on the results of CM ECG [2,48]. CAG serves as the gold standard for the diagnosis of VSC [49-51]. It is carried out primarily to exclude atherosclerotic lesions of the spacecraft, as well as to detect local spasm. The detection of atherosclerotic lesions of the CA with an existing VSC clinic indicates for a mixed form of angina pectoris [47]. In the absence of changes in the tone of the spacecraft at rest, provocative tests have been used to diagnose coronary spasm since the 80s of the last century [48-50]. In Russia, hyperventilation tests, cold tests, as well as tests with FN performed in the early morning hours are most widely used in everyday cardiological practice in patients with suspected VSC to provoke coronary spasm [41]. These provocative tests are quite safe, but they are not sensitive enough for the purpose of diagnosing coronary spasm [52]. Currently , pharmacological tests with vasospastic

substances are used in Europe, America and Japan . The most sensitive for the diagnosis of angiospastic angina is considered to be a test with intravenous (IV) administration of lysergic acid derivatives or a test with intracoronary administration of acetylcholine. From lysergic acid derivatives to The USA uses ergonovine more often, in Europe – ergometrine [50-52]. In response to the administration of ergonovine to healthy people, there is a gradual moderate spasm of all CS. Patients with VSC have a rapid development of local spasm [54].

The test with intravenous administration of ergonovine (ergometrine) is characterized by high sensitivity and specificity for provocation of coronary spasm [50]. However , it cannot be considered safe enough: with the intravenous administration of ergonovine (ergometrine) it can cause simultaneous spasm of several SC and lead to severe ischemia up to the development of MI [49]. The development of multiple spasm is especially dangerous in patients with multivessel damage to the coronary bed. Insecurity tests with ergonovine forced to narrow the indications for its use [45,48]. Absolute contraindications to the administration of methylergonovine include pregnancy, severe hypertension, severe aortic stenosis, high-grade left stenosis [48]. Relative contraindications include other forms of NS, ventricular arrhythmias, recent MI, progressive atherosclerosis of the CA. Currently , a test with ergonovine is prescribed mainly for the diagnosis of coronary spasm only in cases when a patient with anginal chest pain is not detected with CAH stenosing atherosclerosis of CA [48]. If there are contraindications, it is recommended to perform a test with acentilcholine (AH) [43]. The test with intracoronary administration of AH is characterized by the same high sensitivity as the test with ergonovine (~ 70%), but it is superior in specificity (99%) [39]. In addition, the test with AH is safer, since with intracoronary administration of AH, an isolated coronary spasm of the left or right CA can be caused [43,49]. Thus, the most reliable and acceptable method in the diagnosis of VSC is CAG with functional tests.

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