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SEARCH OF THE STRESS INDUSED VENTRICULAR TACHICARDIA REASONS — THE METABOLIC THERAPY OPPORTUNITIES

Abstract

A clinical case of a 56-year-old man is presented. In this case ventricular tachycardia alone (no clinical and ECG criteria of myocardial ischemia) was recorded during the exercise test. Ventricular tachycardia was the only reason for stopping the test. The case demonstrates all the difficulties in determining causes of ventricular arrhythmias induced by physical activity. The objective of the study was to show all the difficulties in determining the cause of exercise-induced ventricular arrhythmia. The literature data on exercise-induced arrhythmia differentiation is rather poor. It is only known that if a patient develops and progresses ventricular arrhythmia, a treadmill test is considered questionable. Exercise-induced ventricular arrhythmias, especially ventricular tachycardia, are the most unfavorable types of arrhytmias. Therefore, additional diagnostic methods were used to reveal the main health condition as the background of ventricular tachycardia. Results of pharmacological test with nitroglycerine were the indication of the ischemic origin of ventricular tachycardia. Coronary angiography did not reveal coronary artery stenosis. Positron emission tomography revealed coronary microcirculation disturbances and a decision about metabolic therapy with Mexicor was made. The correct choice of the drug (Mexicor) was confirmed by the results of control tests: the improvement of metabolism and antiarrhythmic effect were revealed. The choice of the exercise-induced ventricular arrhythmia treatment in patients with stable coronary artery disease should be individual and based on the pathogenesis.

Key words: *stable coronary artery disease, ventricular arrhythmias, ventricular tachycardia, Holter monitoring, exercise test*

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Ng — nitroglycerin, NO — nitric oxide, AA — antiarrhythmic, BP — blood pressure, SCD — sudden cardiac death, CE — cycle ergometry, VA — ventricular arrhythmia, FA — fatty acids, VT — ventricular tachycardia, VPC — ventricular premature complexes, CAD — coronary artery disease, CA — coronary arteries, CAG — coronary angiography, LV — left ventricle, PET — positron emission tomography, RP — radiopharmaceutical, SA — sinoatrial blockade, FFA — free fatty acids, EF — ejection fraction, PA — physical activity, HM — Holter monitoring, HR — heart rate, EMI — electric myocardial instability

The era of studying risk stratification and the factor combination influence on a given clinical outcome began in the second half of the 20th century. In the early 21st century, publications appeared, that took into account not only the clinical forms of coronary artery disease (CAD), but also other conditions that worsen the prognosis. Among them there are: postinfarction cardiosclerosis, left ventricle (LV) systolic dysfunction, permanent ventricular tachycardia (VT) with hemodynamic disorders, cardiac arrest episode or a documented sudden cardiac death (SCD) episode in the medical history [1]. However, despite the publication of study results proving the cause-effect relationship of ventricular arrhythmias (VA) with myocardial ischemia (ischemia can cause electrical myocardial

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instability (EMI) and act as an arrhythmia trigger) in patients with CAD, the necessary emphasis has not yet been made on circumstances against which arrhythmic events develop [2–4].

Based on our clinical experience and ESC guidelines, in 2017 we proposed an algorithm for managing patients with stable CAD with an intact/moderately reduced LV ejection fraction (EF) (≥ 40 % by Simpson's method) and VA taking into account their nature [5]. According to this algorithm, even based on complaints of typical anginal pains and/or equivalents of angina with the pretest probability level, the physician can presume that the patient has CAD and determine the range of necessary examinations [6]. If rhythm disorders are suspected, the examination always starts with ECG and Holter monitoring (HM). This is the class I of indications [1, 6, 7]. However, experience shows that CAD patients do not always subjectively feel arrhythmia, especially if it occurs during physical activity (PA). Therefore, in our algorithm, at the stage following HM, we recommend conducting a test with PA to identify transient myocardial ischemia, assessing tolerance to PA, and determining the angina functional class. Exercise stress ECG (cycle ergometry (CE) and treadmill), and also imaging stress-techniques (stress Echo, myocardial perfusion scintigraphy, positron emission tomography (PET), magnetic resonance imaging) were recommended. Imaging techniques, considering their higher sensitivity and specificity in comparison with ECG, are preferable in myocardial ischemia diagnosis. However, patients with VA and CAD have additional tasks for PA tests: VA "behavior" analysis during exercises (recommendations class IB) and evaluation of its temporary connection with clinical and/or ECG ischemia signs [1, 6, 7]. It should be noted that when evaluating the HM and exercise test results, the arrhythmic events reproducibility is important. It should be set forth in a medical conclusion along with other indicators (the VA number and complexity, heart rate (HR), blood pressure (BP), the appearance time of significant ST depression and/or anginal pain, tolerance to PA, etc.). Moreover, in our studies we showed that the physician's opinion on VA in a patient with stable CAD largely depends on the exercise test results [5, 8, 9]. VA "behavior" evaluation during PA is very important, since its results can be different even with a positive exercise test. A positive PA test is assessed based on clinical and ECG data, i. e. if there is an anginal attack, confirmed by a horizontal/skewed depression of the ST segment ≥ 1 mm in at least 2 ECG leads, or by the steep-rising depression of ST ≥ 2 mm.

So, **with a positive PA test** in a patient with CAD, the VA "behavior" during PA may not show any connection with myocardial ischemia signs* **(variant A):**

1) In the presence of ventricular premature complexes (VPC) at rest during PA, they can significantly decrease in number/complexity.
2) They can completely disappear at the PA peak.
3) They can remain unchanged throughout the test.

The appearance and/or buildup of VA **against the background of a positive exercise test (variant B)** allows it to be regarded as ischemic, especially if it arises and/or progresses simultaneously with anginal pain and/or with significant depression in the ST segment [2]. The increase in the number of VPCs and/or their complexity indicates the progression of VA during PA. Increased complexity is the appearance of paired (if there were only single) VPCs and an increase in their number during the VT episodes [2, 10]. During HM, it is also possible to suspect the ischemic nature of arrhythmia, additionally assessing its distribution over the day (e. g. daytime), the connection of VA to PA, the ischemia / ST segment depression episodes [11].

There is another VA "behavior" type during PA (**variant C**), which unambiguous interpretation is not very easy. The appearance and/or progression of VA at the PA peak and up to the 3rd minute of the recovery period without clinical and/or ECG myocardial ischemia signs is considered to be an

* This VA "behavior", which has no connection with myocardial ischemia, allows to conclude that it is not ischemic. Among the main causes of non-ischemic VA in patients with stable CAD are autonomic nervous system dysfunction and psychological status disorders. In addition, VA can occur long before the CAD development and can be associated with other conditions and diseases, for example, with hypertension or thyroid gland dysfunction.

arrhythmic variant of a questionable PA test [12]. Indeed, it is difficult to understand the origin of VT when it is the only criterion for stopping the test. In such cases it is very important to establish or exclude VA ischemic genesis, since it can be the first and only myocardial ischemia manifestation, and in some cases, even long before other CAD signs appear [2, 10, 13]. To explain this questionable PA test result in 2004 we patented the "Method for predicting ischemic ventricular rhythm disorders in patients with ischemic cardiac disease" [14]. The essence of the method is that with a repeated reproducible exercise test having previously taken 0.5 mg nitroglycerin (Ng) sublingually in case of a significant VPC reduction (single — by 75 %, paired — by 90 % and VT paroxysms — by 100 %), along with increasing PA tolerance, the pharmacological test is considered positive, and VA is considered ischemic [14]. In addition to the paired pharmacological stress test with Ng, an imaging stress test is recommended in case of questionable results.

In the clinical case, we want to demonstrate the complexity of differentiating the VT nature induced by PA.

In 2004, a 56-year-old patient was admitted, complaining of intermittent palpitations episodes accompanied by shortness of breath, which he associated with PA. He had previously considered himself relatively healthy, he skied, had been swimming regularly up to 1,000 m in the pool. When speaking of the concomitant diseases, he mentioned periodically high level of BP for more than 20 years with a maximum of 160/90 mm Hg (no permanent antihypertensive treatment was received). ECG showed sinus rhythm with heart rate of 62 beats per min, slightly (–) T wave in leads V1–V4; slightly (+) T wave in V5, V6. Changes in repolarization without significant dynamics in comparison to ECG of previous years were observed. Echo revealed: initial signs of LV hypertrophy, interventricular septum fibrosis signs, local contractility zones were not seen, global contractility was preserved (LV EF = 60 % by Simpson's method). Blood tests showed dyslipidemia. The results of HM showed: single VPC (with signs of parasystole) of 2 types, with one type predominance — 16,453 per day; paired mono- and polymorphic parasystoles — 172 per day; episodes of unstable VT with a ventricular contraction frequency (VCR) to 130 per minute — 295 per day (17 of them — more than 3 QRS complexes) (Fig. 1 A, B).

So, VA was observed during day-time, and physical activity was significant for the patient on the day of HM. Episodes of unstable VT were recorded only during PA (Fig. 1, A). The unstable VT of the greatest complexity coincided with the time of vigorous walking (Fig. 1, B). There were no changes in the ST segment on the ECG.

Initially (at rest) the heart rate was 60 per min without rhythm disorders (Fig. 2A). During the CE at a heart rate of 100 per minute, a reproducible unstable VT appeared, which served as the only criterion for stopping the test (Fig. 2B). Subjectively the patient complained of minor dyspnea (respiratory rate of 23 per min). At the same time, there was no typical anginal syndrome and ischemic ECG changes, BP was 170/80 mm Hg. The test was considered questionable. The next CE (Fig. 2B) was performed after taking 500 μg (1 tb) of Ng. Taking into account the increase in PA tolerance, the achievement of submaximal heart rate (136 bpm) and the absence of VA, the pharmacological test was interpreted as positive. This seemed to suggest the ischemic nature of VT.

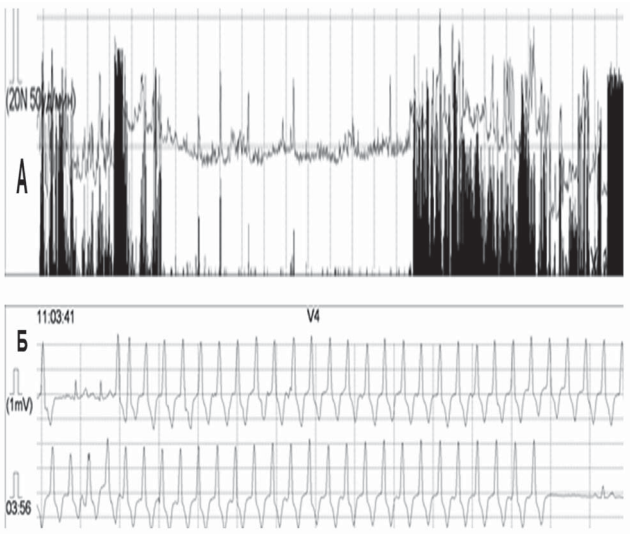

Figure 1. *A – The distribution of ventricular arrhythmias (VA) per day. B – Fragment of Holter monitoring (HM) during exercise test: unstable ventricular tachycardia. Explanation in the text*

The patient's examination was continued considering the PA-induced VT, a positive pharmacological test with Ng, and risk factors (male, 56-year-old, dyslipidemia). Stress echocardiography showed no signs of transient myocardial ischemia, and coronaroangiography (CAG) revealed no hemodynamically significant coronary arteries (CA) stenoses. Nevertheless, the stressful nature of VA was a cause for concern, since it is known that VT, arising against the background of sympathicotonia, increases the risk of developing SCD [2, 14, 15]. Therapy with β-blockers is prescribed as the first-line treatment for exercise-induced arrhythmias. Taking into account the patient's active lifestyle, it was decided to prescribe him a β-blocker. The pharmacological paired exercise test with anaprilin (60 mg) was performed to predict the effectiveness of β-blockers, and it was positive. However, during constant intake of 5 mg Betaxolol with a good antiarrhythmic (AA) effect, there was a pronounced bradycardia (40 bpm) and a transient sinoauric blockade of 2 degree (type 2) with pauses of up to 4 s (accompanied by presincope). The revealed side effect forced to discontinue betaxolol and pushed to further search for the true genesis of exercise-associated VA and the possibilities of its treatment.

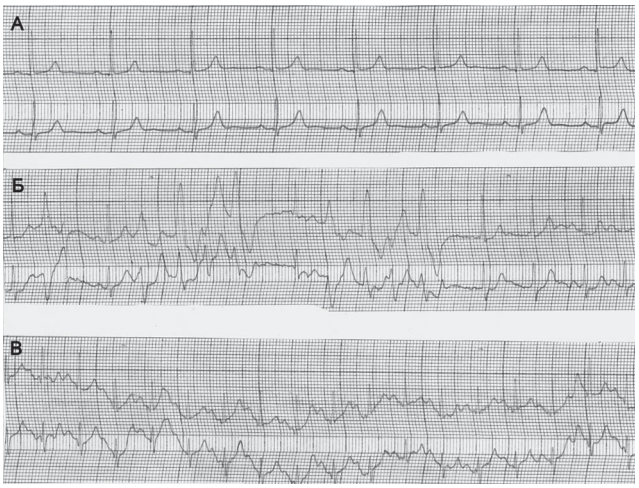

Figure 2 (A, B, C). *Fragments of the cycle ergometry (CE) (2, A – at rest, 2, B – unstable ventricular tachycardia at the peak of the test (stop test criterion); 2, C – at the peak of repeated CE after taking nitroglycerine). ECG leads: Dorsalis and Anterior. Recording speed 25 mm/sec. Explanation in the text*

The absence of hemodynamically significant CA stenoses according to CAG did not exclude the ischemic nature of arrhythmia and for visualizing the possible ischemic substrate for exercise-induced VT. In addition, PET with CE was performed to assess myocardial perfusion, which revealed transient local disorders in the anterior interventricular branch of the left CA. At the PA peak during the PET, VT was recorded with complexes of the same shape as in other exercise tests. While studying fatty acid (FA) metabolism in the myocardium with sodium ^{11}C-butyrate, there was a decrease in FA extraction mainly in the anterior LV wall. The radiopharmaceutical (RP) clearance rate was more than 40 % in all LV parts (Fig. 4). Thus, the PET results in combination with the pharmacological Ng test confirmed the ischemic nature of the exercise-induced VT. The assumed arrhythmogenic substrate could be myocardial ischemia and metabolic disorders that develop against its background, which can be described through a brief insight into the features of biochemical processes in cardiomyocytes [2]. In conditions of cardiomyocyte hypoxia, oxygen is distributed between the oxidation of free fatty acids (FFA) and glucose, while the productivity of both energy paths is reduced. With ischemia, glucose breakdown is mainly performed through anaerobic glycolysis, resulting in the formation of pyruvate. With an oxygen deficit, pyruvate turns into lactate, since it can not pass through all the oxidative decarboxylation stages in the mitochondria. Lactate, accumulating in the cytosol, leads to intracellular environment acidosis, overloading of cells with sodium, calcium and disrupts the ability of cardiomyocytes to relax and contract. In addition, an excess of calcium ions in the cell cytosol activates the phospholipase, resulting in cardiomyocyte membrane damage. In the conditions of oxygen deficit, the main part of aerobic synthesis of ATP is due to beta oxidation of FFA. Such a pathway for the formation of ATP in ischemic conditions is metabolically disadvantageous, since it requires large oxygen expenditure. In this regard, hypoxia leads to excess formation of FFA and acetyl-CoA, which inhibit the pyruvate-dehydrogenase complex, and leads to further glycolysis and oxidative decarboxylation dissociation, as well as free radical oxidation activation. Accumulation of free radical oxidation products in the cell cytoplasm also has

a damaging effect on the cardiomyocyte membrane and disrupts cardiomyocyte function [16, 17]. Thus, during hypoxia, the processes underlying the cardiac muscle dysfunction development are activated: local inflammation and peroxidation, cellular acidosis, a decrease in ATP synthesis, and ionic equilibrium disorder. All this, in turn, causes the development of EMI and arrhythmogenesis foci formation.

In a number of experimental and clinical studies, it was demonstrated that with the proven ischemic nature of VA, the treatment of stable CAD can be supplemented by metabolic drugs, as a "substrate" treatment direction [18–20]. Unlike traditional treatment methods aimed at immediately improving coronary circulation, the effect of modern cytoprotectors is based on their property to increase the myocardium ability to withstand ischemia without losing or quickly restoring its functional activity. The hypothesis that ischemic tissue protection from oxidative stress consequences and the energy balance restoration of cardiomyocytes which form arrhythmogenesis foci can lead to the normalization of its electrophysiological functions, served as the basis for prescribing ethylmethyl hydroxypyridine succinate for the patient (Mexicor) at an average daily dosage of 300 mg. The emoxipin included in its composition exhibits a powerful antioxidant and cytoprotective effect on myocardial cells. Succinate, in turn, gives the drug a pronounced antihypoxic activity. Also, Mexicor has a vasodilating effect preventing NO degeneration (due to emoxipin) [21].

After 2 months of taking the cytoprotector, according to HM there was a significant decrease in the number and complexity of VPC, namely, a 91 % reduction in the number of single polymorphic ventricular parasystoles (from 16,453 to 1,528 per day); paired polymorphic — by 90 % (from 172 to 17 per day); VTs were not registered (Fig. 3). The optimal AA effect was also confirmed by the control reproducible CE results: absence of high-complexity VA at the submaximal heart rate (123 bpm) was seen.

There was no exercise-induced VT, but a more even distribution of RP, and an increase in the rate of RP clearance from all LV parts were observed during repeated FA metabolism evaluation on the Mexicor therapy (Fig. 4 and Tab. 1).

The patient's state stabilized, dyspnea and palpitations disappeared during continued Mexicor treatment. The patient was given recommendations on antihypertensive therapy and long-term Mexicor therapy, dosing 300 mg/day. He returned to normal active lifestyle.

After 7 years, the patient complained of typical anginal pain when walking for 200 meters or walking uphill. The clinical situation was regarded as unstable angina. The patient was urgently admitted to the hospital.

Very frequent single VPC were registered during HM, mainly of one morphology — 17,308/day; paired monomorphic VPC — 1,411/day; episodes of unstable VT — 73/day maximum up to 9 QRS with VCR up to 207 per min. The VPC morphology was identical to that observed during HM during the first examination of the patient. Repeated CAG (7 years after the first) revealed hemodynamically significant anterior interventricular branch stenosis of the LCA: 70–75 % in the middle third, local stenosis at the border of the middle and distal third up to 70 %, stenosis of the mouth of the diagonal branch up to 65 %. Angioplasty and stenting of the anterior interventricular artery (2 stents) were performed with achievement of the optimal angiographic result. Mexicor (300 mg/day) was resumed. For 4 years after myocardial revascularization, anginal pain did not recur. Control HM and follow-up exercise tests demonstrated a good AA effect.

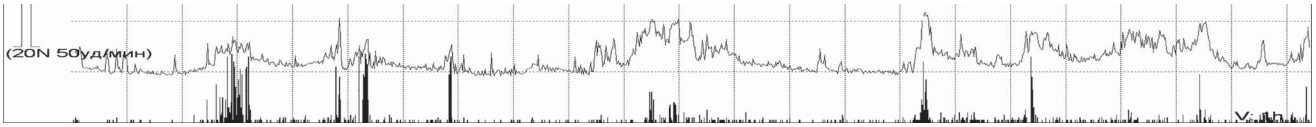

Figure 3. *The distribution of VA in a patient taking Mexicor per day according to HM. Explanation in the text*

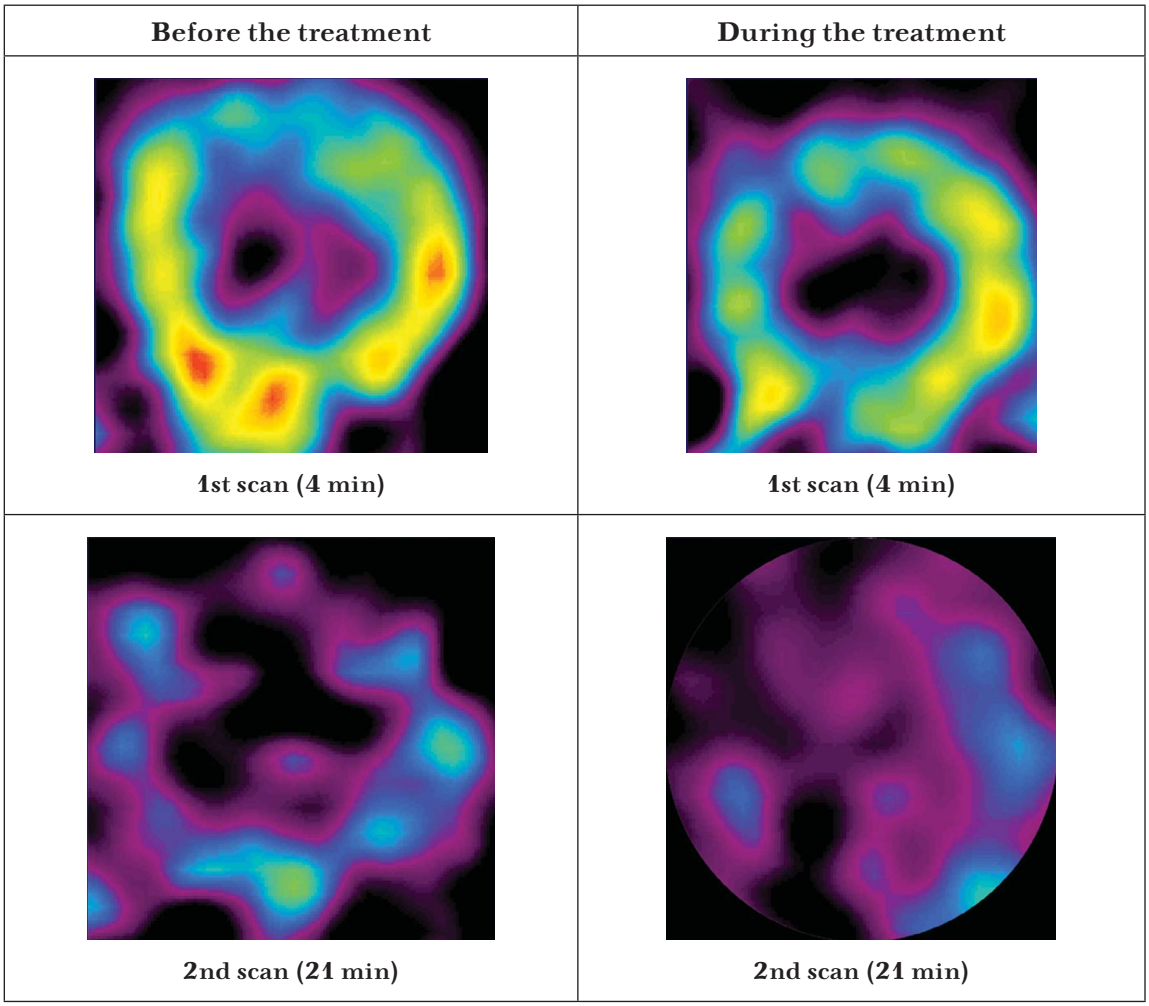

Figure 4. *Estimation of fatty acid metabolism by positron emission tomography with sodium ^{11}C-butyrate. Explanation in the text*

Table 1. *Estimation of fatty acid metabolism by positron emission tomography with sodium ^{11}C-butyrate. The excretion of the radiopharmaceutical before and during the treatment with Mexicor (explanation in the text)*

Left ventricular segments	Before Mexicor treatment (%)	During Mexicor treatment (%)
	Apical segments	
Apical anterior	59	82
Apical lateral	54	80
Apical inferior	56	70
IVS, Apical	57	76
	Mid-cavity segments	
Mid anterior	62	76
Mid lateral	58	71
Mid inferior	60	80
IVS, Mid	65	64
	Basal segments	
Basal anterior	60	70
Basal lateral	57	71
Basal inferior	56	65
IVS, Basal	61	78

Discussion

Summarizing the literature data based on the multi-centre study results and our own experience, it should be admitted that there are many unresolved issues in the VA problem in patients with CAD and choosing AA therapy. In cases where the arrhythmia locus coincides with the ischemia zone, successful myocardial revascularization has a full AA effect, contributes to the patients' survival and a decrease in SCD over a long period of follow-up [1, 22]. According to our data, ischemic VA, especially VT, is arrhythmia with the most unfavorable prognosis, and the myocardial revascularization AA effect ranges from 84 % in the early postoperative period to 65 % in 12 months [2, 9].

With the help of HM, the test with PA, the paired pharmacological exercise tests with Ng, it is possible to evaluate the VA behavior, to confirm its ischemic origin [1, 2, 5, 12]. These seemingly routine and quite accessible methods in many ways help shed light on the VA genesis and choose the correct tactics for managing patients with CAD with concomitant arrhythmia. They are especially useful in those doubtful cases, when the only criterion for stopping an exercise test is the exercise-induced VA/VT. An error in interpreting this test can have very serious consequences, SCD.

It was this type of clinical case that was presented to the readers. Its complexity was associated with both the analysis of PA-induced arrhythmia and the choice of the subsequent therapeutic tactic. There were difficulties in such VT interpretation because it was not accompanied by either clinical or electrographic myocardial ischemia signs and was not explained by the CAG results. However, we can never be convinced of the "benign" nature of exercise-induced VT. Literature contains numerous descriptions of cases of early VA detection and only after a sufficiently long time serious heart diseases were diagnosed [23, 24].

In this particular case, it could not be ruled out that the PA-induced reproducible VT was stopped by Ng, and this forced us to search for evidence of the ischemic nature of arrhythmia. As is known, sympathetic-dependent nature of VT is often associated with myocardial ischemia due to the peculiarities of myocardium innervation — ischemic changes in the anterior wall of the LV lead to an increase in the activity of sympathetic afferent nerves [25]. The assumption of the ischemic nature of VA, based on a positive pharmacological test with Ng, can be explained by the fact that the Ng action mechanism is associated with the release of nitric oxide active substance (NO) in the smooth muscles of the vessels. Subsequently, it was established that in normal physiological conditions, NO serves not only as a powerful vasodilator, but also inhibits vascular wall remodeling processes, prevents platelet adhesion and aggregation, monocyte adhesion, thus protecting the vascular wall from pathological restructuring, followed by atherosclerosis and atherothrombosis development [26]. In addition, based on the literature data, the disappearance of stress-induced myocardial hypoperfusion in intact CA when taking Ng supports vasomotor CA dysfunction as a cause of microcirculation disorder (dynamic obstruction) [27–28].

Continuing the examination of the patient, it was possible to come closer to clarifying the nature of VT. As is known, the PET method with sodium ^{11}C-butyrate determines the myocardial ischemia areas with high accuracy (before the appearance of ECG and Echo ischemia signs) [29]. The PET results in our patient were the evidence of the ischemic origin of VT and could have been caused by vasomotor CA dysfunction, which creates conditions for PA-induced ischemia, and as a result, leads to local metabolic myocardium disorders, and the development of electrical myocardium instability (EMI) manifesting by exercise-induced VT.

It is not only diagnostic difficulties that forced us to continue the examination in search for the true cause of VA. The situation with treatment was complicated by the fact that β-blockers, which are necessary in exercise-induced VT cases, were contraindicated because of the arisen symptomatic sinoatrial (SA) blockade. There was a need to look for ways to treat the patient with ischemic VT, and to prevent possible serious complications. At that time the patient categorically refused pacemaker implantation, which would allow prescribing the indicated β-blockers. We were inspired by

the current hypothesis that ischemic VA is caused by a cascade of metabolic disorders in ischemic myocardium. It made us think that restoring the cardiomyocytes metabolism can lead to the "normalization" of electrophysiological functions of the arrhythmogenesis focus. We started treating our patient with Mexicor after receiving confirmation of microcirculation impairment according to PET with sodium butyrate. That this was the right choice of tactic was proven by the positive results of the Mexicor AA efficacy, confirmed by HM, exercise test and control PET during the treatment.

In our opinion, the further course of clinical events followed this scenario. Vasomotor dysfunction of coronary arteries as a cause of myocardial ischemia at the microcirculatory level accompanied with metabolic disorders in cardiomyocytes was a pathogenetic factor in the mechanism of occurrence of ischemic VT during primary admission of the patient. Over time, developed dysfunction and endothelium microdamage, coupled with dyslipidemia, led to the gradual development and progression of CA atherosclerosis and not dynamic, but organic CA obstruction. Confirmation of this was the match of the ischemia zone detected on the PET and further CA stenosis areas.

Conclusion

So, taking into account the VA etiological and trigger factors, the background clinical situation, we emphasize the importance of determining the nature of arrhythmia in a patient with CAD: whether it is caused by myocardial ischemia or not. It is not always that arrhythmia in a patient with CAD is associated with the disease itself, as it is not always life-threatening and does not force undertake emergency measures. Such ischemic VA characteristics as reproducibility and AA response to nitrates can constitute an important link in diagnosis, choosing the treatment method and predicting its effectiveness. In addition to ischemia, there are other reasons for VA in a patient with stable CAD, which is why the search for the etiology of arrhythmia is the key to success in its elimination. The combination of standard antianginal therapy with metabolic drugs (in particular, Mexicor) in a patient with CAD with ischemic VA is not pointless and can be an important addition, especially in those patients for whom myocardial revascularization is not indicated.

Obviously, the choice of the VA treatment method in a patient with stable CAD should be individual and pathogenetically justified, since the nature of development of arrhythmia in these patients is so diverse, and the approaches to their treatment should differ.

In addition, with this report (a description of a complex clinical case), we want to draw the attention of cardiologists and physicians performing exercise tests to PA-induced ventricular rhythm disorders, even if they are not accompanied by clinical and ECG myocardial ischemia signs. PA-induced VT in patients with CAD risk factors may be its onset.

Conflict of interests

The authors declare no conflict of interests.

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