https://doi.org/10.35336/VA-1224

CLINICAL ROLE OF TRIGGERS AND MODULATION FACTORS OF VENTRICULAR ARRHYTHMOGENESIS IN STABLE CORONARY ARTERY DISEASE

E.V.Shlyakhto, E.A.Ryngach, A.A.Tatarinova, T.V.Treshkur
FSBI «Almazov NMRC» of MH RF, Russia, Saint-Petersburg, 2 Akkuratova str.

Ventricular arrhythmias are more commonly associated with coronary artery disease. However, ventricular arrhythmogenesis can be initiated by various trigger factors against its background. The substrate of arrhythmias in various nosological forms of stable coronary heart disease is heterogeneous. The patient may have stable exertional angina without severe fibrosis or have a history of myocardial infarction with significant scarring. Therefore the predictive value and prognostic significant of ventricular arrhythmias is not always unambiguous. Thus, for the successful treatment of arrhythmias as a main component of the prevention of sudden cardiac death, an individualized pathogenetic approach is the most important. The purpose of this article is to analyze and clinically interpret the results of studies, publications for 1980-2023, in which the authors describe the etiological, pathophysiological, pathomorphological characteristics of ventricular arrhythmias and their predictive value and prognostic significant for patients with stable coronary artery disease.

Key words: ventricular arrhythmias; coronary artery disease; sudden cardiac death; chronic coronary artery disease; triggers and modulation factors of arrhythmias; substrate

Conflict of interest: none.
Funding: The study was funded by the state assignment of the Ministry of Health of the Russian Federation (registration number 123021000126-0).
Received: 23.06.2023 **Revision received:** 25.09.2023 **Accepted:** 28.09.2023
Corresponding author: Elena A. Ryngach, E-mail: panochkaru@yandex.ru

E.V.Shlyakhto - ORCID ID 0000-0003-2929-0980, E.A.Ryngach - ORCID ID 0000-0003-2795-5774, A.A.Tatarinova - ORCID ID 0000-0001-5955-2529, T.V.Treshkur - ORCID ID 0000-0002-7976-5588

For citation: Shlyakhto EV, Ryngach EA, Tatarinova AA, Treshkur TV. Clinical role of triggers and modulation factors of ventricular arrhythmogenesis in stable coronary artery disease. *Journal of Arrhythmology.* 2024;31(1):e16-e26. https://doi.org/10.35336/VA-1224.

Despite advances in prevention, diagnosis and treatment, coronary heart disease (CHD) remains one of the main causes of sudden cardiac death (SCD), and with increasing patient age its share reaches 85-90% of cases [1, 2]. It is proved that the most frequent immediate mechanism of SCD is fatal ventricular tachyarrhythmias: monomorphic ventricular tachycardia (VT) with transition to ventricular fibrillation (VF) - in 62.4% of cases, VT of «torsades de pointes» type - in 12.7%, primary VF - in 8.3% [3, 4]. The results of basic and clinical research in the pathogenesis of ventricular arrhythmias (VAs) suggest that they require a combination of several factors predisposing to myocardial electrical instability (MEI). Other things being equal, the qualitative and quantitative characteristics of VA may differ significantly in their prognostic value depending on the combination of substrate, modulating and triggering factor (Table 1).

The substrate of VA can be at the cellular and tissue level, fixed and dynamic, local and diffuse. In fact, the substrate is the pathomorphologic component of the underlying disease. Triggering factors are the immediate triggers for the development of arrhythmias. Modulating factors can be internal, developing against the background of the underlying disease, and external. They have the capacity to modulate the outcome of trigger factors in a manner that renders the same trigger capable of eliciting distinct effects on the progression of arrhythmias. The outcome of the interaction of modulating and triggering factors with the substrate always depends on the specific clinical situation, which must necessarily be taken into account. That is why VA cannot be regarded as an isolated electrocardiographic (ECG) phenomenon that implies unambiguous prognostic value and universal tactics of patient management. Since our review focuses on VA in stable CHD, the substrate, triggering and modulating factors will be considered within its possible clinical scenarios, mainly in preserved and moderately reduced left ventricular (LV) ejection fraction (EF). In the following, the most prognostically dangerous and/or frequently occurring variants of substrate, triggering and modulating factors, including their interactions, will be discussed, taking into account the risk of life-threatening arrhythmias and possible directions of influence on them.

Several classifications have been proposed for stratification of VA according to the degree of potential danger. In 1971, B.Lown and M.Wolf first developed a 5-point grading system of VA for patients with acute myocardial infarction (MI) [5]. Later M.Ryan (1975) modified it for patients with stable CHD, where 3-5 gradations were classified as «high» and considered as potentially dangerous [6]. This notion was based on studies showing that in CHD patients on cardiac electrophysiological study (EPS), VF

always developed after paired extrastimuli that contributed to shortened refractoriness and MEI formation. And further progression of arrhythmia to VT further reduced the refractoriness of the heart muscle, contributing to the development of fatal VAs.

The risk-stratification proposed by J.T.Bigger in 1984 divides VAs into non-life-threatening, potentially dangerous and dangerous depending on clinical manifestations, as well as the presence of structural heart pathology [7]. The later classification developed by R.G.Myerburg (1984, 2001) also combined only quantitative and qualitative characteristics of arrhythmias, still without taking into account the specific clinical situation of the occurrence of VA, substrate, trigger factors and modulators of arrhythmogenesis. Thus, in the absence of a comprehensive approach to the system of VA stratification, only the combination of CHD with high-grade arrhythmias was a priori considered as dangerous [8]. However, over time, studies began to appear, the results of which indicated that the isolated assessment of qualitative and quantitative characteristics of VA is not sufficient to classify arrhythmias as prognostically unfavorable [2]. Thus, it has been shown that the most unfavorable prognosis in patients with stable forms of CHD is associated directly with transient myocardial ischemia (TMI) - the incidence of SCD in such cases increased up to 20% in pro- and retrospective observations for 5-7 years [9-11]. Therefore, according to a number of authors, it is necessary, first of all, to analyze the relationship between VA and TMI.

Multifactorial contribution of myocardial ischemia to the pathogenesis of ventricular arrhythmias

Back in 1999-2002, ischemic VAs were clearly characterized as follows: exercise-induced (EI), reproducible VAs accompanied by clinical and ECG signs of TMI (angina or its equivalents, as well as reliable ischemic ST-segment changes) [10-12]. [10-12]. An important argument of ischemic origin of arrhythmias is the antiarrhythmic effect (AAE) of nitroglycerin, against the background of sublingual administration of which there is a decrease (both in quantity and complexity), up to complete disappearance of TMI-related VAs [10]. In addition, the results of successful etiopathogenetic treatment of ischemic VA are argued. Thus, it has been shown that the elimination of TMI after complete myocardial revascularization (MR) had a high AAE [13]. The authors elucidated the findings by attributing them to the ischemic nature of VA, as confirmed during the preoperative phase. This ischemic condition was further compounded by the fortuitous alignment of the arrhythmogenesis focus with the territory supplied by the stenosed coronary artery (CA), subsequently subjected to MR. The possibility of predicting AAE of MR in CHD patients based on the performance of a load test with noninvasive topical diagnostics, in which the location of arrhythmia focus (registered during physical activity) was determined with the subsequent comparison of topical diagnostics results with the zone of myocardial ischemia was proposed. If they coincide, a high AAE of MR can be predicted in patients with ischemic VA, while in case of mismatch, AAE from MR should not be expected [14].

These data echo another work performed in a group of patients with CHD who had a single-vessel lesion with hemodynamically significant CA stenosis. This study also resulted in the conclusions that stenting of CA leads to the disappearance of VA when the focus of VA coincides with the area of blood supply of the stenosed CA [15]. Thus, MR can be considered as an opportunity to influence simultaneously both the substrate and the trigger factor of ischemic VAs. These views are based on evidence that ischemia has a large multifactorial influence on MEI and can act as both a substrate and their trigger factor, as well as a powerful modulator of VA [16-18]. Thus, the development of myocardial ischemia is accompanied by inhibition of tissue respiration and simultaneously by activation of anaerobic glycolysis, retardation of fatty acids oxidation, which under normal conditions provide more than 70% of myocardial energy needs.

Adenosine triphosphate (ATP) deficiency is accompanied by impaired activity of ion pumps: sodium-potassium (Na+-K+), calcium (Ca2+), and actin-myosin pump. As a result, cardiomyocytes lose K+, intracellular Ca2+ and Na+ accumulate and, as a consequence, myocardial contractility decreases. Accumulation of Na+ and water in the cytoplasm leads to swelling of organelles, and excess Ca2+ promotes activation of lipases, phospholipases, and lipid peroxidation enzymes. All these changes lead to destabilization of lysosomes, damage to membranes and enzymes of cardiomyocytes. Decreased pH <6.0 in ischemic myocardium combined with local accumulation of catecholamines causes slowing of impulse conduction, decreased excitability with simultaneous increase in refractoriness. All this leads to cellular dissociation, a sharp decrease in the transmembrane resting potential, a decrease in the duration and amplitude of the action potential and the generation of spontaneous electrical activity. The accumulation of cell membrane degradation products and glucose reduction in the myocardium also contribute to the development of MEI and the formation of arrhythmogenesis foci [19]. Within 15 min after perfusion disruption, K+ accumulation occurs outside the ischemic cardiomyocyte. Extracellular hyperkalemia in the border zone serves as a crucial factor in conduction disturbance and conduction block in the early period of ischemia [20-22].

Against the background of acute ischemia, the resting potential of the cardiomyocyte becomes more positive. This is accompanied by slow spontaneous depolarization, including in cells that normally do not have automatism, shortening of the action potential [23]. Simultaneous prolongation of the effective refractory period, continues even after repolarization is completed, and the phenomenon of postdepolarization refractoriness develops [24]. It has been demonstrated that a series of complex and often asymptomatic changes in cardiomyocyte metabolism (the «ischemic cascade») precedes the appearance of clinical symptoms of ischemia [20-22]. In addition, due to activation of neurohumoral mechanisms, levels of norepinephrine, cytokines, endothelin, vasopressin, angiotensin II (AT II), and aldosterone increase in response to the development of acute ischemia. The increase in aldosterone synthesis is realized through activation of type 1 AT II receptors, an increase in cardiac AT II levels and aldosterone synthase

mRNA activity [22, 23]. Hyperactivation of these, initially physiological processes, in stable forms of CHD acquires pathological character. Thus, aldosterone has been found to play a major role in the formation of a number of negative clinical manifestations: sodium and fluid retention, development of endothelial dysfunction (ED), myocardial hypertrophy and fibrosis [24].

Role of endothelial dysfunction in ventricular arrhythmogenesis

It is noted that ED has an important role in the occurrence and development of MEI as a link of ventricular arrhythmogenesis in TMI. The oxidative stress that develops during ischemia promotes the production of vasoconstrictors. First of all, they include endothelin-1 (ET-1), serotonin and products of the cyclooxygenase pathway - prostaglandin H2 (PGH2) and thromboxane A2 [25, 26]. In experimental studies, it was shown that due to its pronounced vasoconstrictor properties, ET-1 can cause life-threatening VAs against the background of acute myocardial ischemia [27]. While other studies have also reliably established a direct arrhythmogenic effect of ET-1, which consists of prolongation or increase in the dispersion of the monophasic part of the action potential, prolongation of the QT interval, development of early postdepolarizations, acidosis leading to increased cellular damage. At the ionic level, the observed electrophysiologic effects of ET-1 are due to the release of Ca2+ ions from intracellular depots, formation of inositol triphosphate, inhibition of the delayed K+ current, and stimulation of the Na+/H+ pump. There is evidence that the use of endothelin receptor antagonists and endothelin-converting enzyme inhibitors by neutralizing the action of EN-1 leads to suppression of vasoconstriction and associated ischemic VA [28,29]. All this makes it possible to consider ET-1 as one of the most important «molecular targets» for treatment in vasospastic angina and primary microvascular angina.

Involvement of the autonomic nervous system in the occurrence of ventricular arrhythmias

The incidence of myocardial ischemia before the manifestation of life-threatening VT/VF has been shown to vary [30]. According to the results of the study by C.J.Pepine et al. ischemia preceded VT in 52% of cases, while in the study by Bayes de Luna et al. ischemia was detected in only 12.6% of patients with VT [3, 31]. It is possible that VA as a clinical manifestation of the «ischemic cascade» of myocardial metabolic disorders may even precede ECG and clinical signs of ischemia [16, 32]. There are indications that a higher incidence of SCD is associated with a decrease in the threshold of VF on the background of the combination of myocardial ischemia and hypersympathicotonia [9, 33]. Thus, simultaneous with ischemia, activation of the sympathetic link of the autonomic nervous system (ANS) significantly increases the concentration of adrenaline/noradrenaline both in the systemic blood flow and in the interstitial space of ischemic myocardium and in the border zone. This fact is explained by local blocking of the mechanism of reverse neuronal capture of sympathetic neurotransmitters [33, 34]. The pathological automatism formed in the distal parts of the conductive system may serve as a mechanism of arrhythmogenesis focus development, or the developing postdepolarizations at reaching the threshold potential may induce VT by the mechanism of trigger activity [31]. In experimental models, such a combination - hypersympathicotonia on the background of ischemia - often led to the development of fatal VA [22, 35].

At the same time, there are works in which no convincing data on the contribution of TMI to the development of VA in patients with stable CHD have been obtained. For example, during 24-hour ECG monitoring, the number of ventricular ectopic complexes (VECs) without signs of myocardial ischemia and against its background did not differ significantly. During stress tests in these patients, the number of VECs in pretest, during TMI episodes and during the recovery period (RP) remained without significant dynamics [36]. Presumably, such data can only suggest that patients with stable forms of CHD may have LA that are both induced by TMI and unrelated, which is not a contradiction [10, 11].

Close correlations between the ANS state, the occurrence of VA and the development of SCD have been established [33, 37, 38]. In experimental and clinical studies, it has been observed that changes in ANS function can both precede the development of VA and, thus, be a modulating factor (by changing the ANS influence on myocardium on the background of undergone MI or chronic ischemia) and directly provoke VA - exercise-induced ANS imbalance, which will already act as a trigger factor. Thus, M.Levy proposed a theory of interaction between sympathetic and parasympathetic parts of the ANS in the regulation of cardiac activity, called «accentuated antagonism», which is currently recognized as the most reasonable [39, 40]. Its essence is that the inhibitory effect of parasympathetic activity in the heart is directly proportional to the level of sympathetic activity at the pre- and postganglionic levels, but vagus action occurs only in conditions of sufficient activity of the sympathetic section of the ANS. D.P.Zipes illustrated that denervated areas of myocardium are hypersensitive to the effects of catecholamines with disproportionate shortening of refractoriness, appearance of refractoriness dispersion and formation of arrhythmogenesis focus [41]. Whereas hypersympathicotonia promotes arrhythmogenesis, the parasympathetic nervous system inhibits negative adrenergic influences on the heart and exerts a protective role against the development of VA and SCD in patients with CHD [33, 42, 43]. However, there are works that, on the contrary, show that myocardial damage can also cause parasympathetic ventricular denervation, which leads, in general, to myocardial electrical inhomogeneity and the occurrence of VA [34, 35].

It is violations of sympathovagal balance that a number of authors explain the occurrence of VA only in the RP of the stress test, especially in the first minutes [44, 45]. VAs that are registered at rest (i.e., in the pre-test period; and at the 4th minute of RP and later), decrease or disappear altogether when sympathetic activity increases (during exercise) and appear/progress in phases with predominance of parasympathetic activity are referred to vagal/vagus-dependent [10, 46]. Thus, one of the most studied, non-invasive and physiologic ways to provoke the influence of the

ANS on VA is the physical exercise tests [11, 47]. It has been shown that in one third of patients in whom VAs were not recorded during diurnal ECG monitoring, arrhythmias were detected only during the physical exercise test. Thus, it is obvious that physical exercise tests occupy an important position in the analysis of LV behavior during exercise, which largely determines the choice of further tactics of patient management and treatment [11, 48, 49].

The value of left ventricular ejection fraction for risk stratification of sudden cardiac death

Among other parameters for risk stratification of SCD, the value of LV contractility has received the most attention. Based on the results of numerous studies and registries, patients with reduced LVEF less than 40% (according to Simpson) are subject to close attention [49, 50]. However, there is an increasing return to the discussion that the isolated use of LV systolic function as a leading predictor of SCD does not fully satisfy risk stratification. This is confirmed by the results of a study in patients with reduced LVEF and implanted cardioverter-defibrillator (ICD), which showed the absence of CD activation in the majority of the observed patients [50]. Given the proven high value of reduced LVEF in the prognosis of SCD, much attention is paid to EPS with programmed ventricular stimulation, particularly in patients with postinfarction cardiosclerosis and moderately reduced LVEF (40-50%) [51, 52]. However, according to other authors, it does not make sense to perform intracardiac EPS in patients with indications for ICD implantation for the primary or secondary prevention of SCD (class III; level of evidence B-R) [53]. However, in a large percentage of cases, these patients did not develop VAs after CD implantation that would have required its triggering.

When comparing the incidence of CD triggering in patients with a history of MI and LVEF >40% with that in the group of patients with LVEF <35%, it was shown that they are comparable (22% and 21%, respectively) [54, 55]. In addition, ICD implantation is a palliative costly way to prevent SCD. In few population studies and registries with inclusion of thousands of observations it is shown that in absolute numbers among cases of SCD patients with normal LVEF predominate [56]. Thus, in a large Dutch registry (Maastricht Circulatory Arrest Registry) and a population-based American study (Oregon Sudden Unexpected Death Study), patients with normal LVEF predominated [57,5 8]. In the 2019 PRESERVE EF study, most cases of SCD were reported in normal LVEF and, according to the authors, the number of such patients will increase exponentially in the future [54]. Given the above-described limitations of LVEF in risk stratification of patients with stable CHD, it became obvious that it should be supplemented with other markers of unfavorable prognosis.

Significance of postinfarction scar in the formation of ventricular arrhythmia foci

Analyzing other pathomorphological factors predisposing to the development of MEI in CHD patients after MI, it was shown that a potential arrhythmogenic substrate in them is the zone separating necrotic and intact myocardium, where areas of fibrosis are interspersed with viable tissue. The microarchitecture of the border zone is the result of complex remodeling processes involving cardiomyocytes, fibroblasts, inflammatory cells, local autonomic innervation, vascularization, and microcirculation [59-61]. Quantitative and qualitative characteristics of myocardial fibrosis are responsible for the reduction of elastic properties of cardiac muscle and the subsequent development of diastolic dysfunction, deterioration of myocardial contractility with the formation of systolic dysfunction, and the development of cardiac rhythm disorders [61].

Statistically significant correlations have been found between myocardial fibrosis and arrhythmic complications, including SCD [62]. For example, a 3% increase in connective tissue volume in the myocardium according to magnetic resonance imaging is associated with a 50% increase in the risk of cardiovascular complications, including ventricular arrhythmias [63]. Proarrhythmic effects of myocardial fibrosis find evidence in cellular heterogeneity - different EP properties of cardiomyocytes and fibroblasts [64, 65]. Such heterogeneity of cardiac muscle leads to slowing of depolarization propagation and dispersion of refractoriness, and conditions for the formation of re-entry loops are formed. This re-

Table 1.

Links in the pathogenesis of ventricular arrhythmias in stable coronary artery disease

Substrate	Disturbance of intercellular contacts and ion homeostasis due to genetic variants; left ventricular hypertrophy; postinfarction scar with peri-scar zone (border with scar tissue) of heterogeneous myocardium; fibrosis diffuse and in the peri-scar zone of heterogeneous myocardium; left ventricular aneurysm; remodeling of cardiomyocytes and cells of the ventricular conduction system in the peri-scar zone of heterogeneous myocardium and in myocardial areas remote from the scar; myocardial changes due to chronic ischemia; zones of hibernating myocardium; endothelial dysfunction; structural pathology of the right ventricle.
Modulating factors	Violation of intercellular contacts and ion homeostasis against the background of chronic ischemia or in the pericardial zone of heterogeneous myocardium; disorders of myocardial autonomous innervation against the background of chronic ischemia or in the pericardial zone of heterogeneous myocardium; metabolic changes in cardiomyocytes against the background of chronic myocardial ischemia; postinfarction damage of intramyocardial vascular network and microcirculation; impaired left ventricular systolic function; impaired left ventricular diastolic function; medications affecting de- and repolarization processes; chronic stress.
Triggers	Transient myocardial ischemia; imbalance of the autonomous nervous system against the background of physical activity or psycho-emotional stress; electrolyte imbalance; endocrine pathology.

quires unidirectional conduction block in the myocardial area; the duration of the re-entry cycle must exceed the maximum refractory period of one of the links in this loop. Such conditions are realized due to anatomical prerequisites - presence of fibrosis/scar tissue areas or disturbance of ionic currents, which cause different refractoriness of myocardium, contributing to the occurrence of VA both by the mechanism of re-entry and pathological automatism [48, 49]. The results of the works of some authors demonstrate that it is of great clinical value to identify patients with insignificant fibrotic fields in myocardium at early stages of heart failure (with borderline reduction of LVEF). However, in routine cardiology practice, there are insufficient methods to suspect its presence in the early stages of examination.

At the molecular level, a statistically significant correlation was found between the concentration of N-terminal propeptide of procollagen type III in serum and the volume fraction of collagen III in patients with CHD and heart failure during fibrosis development [67]. The main cells of fibrogenesis in myocardium are recognized as fibroblasts, which have the highest affinity for intact tissue and are also able to form as a result of epithelial-mesenchymal transition in response to injury that stimulates the expression of factors such as ED-1, transforming growth factor 1β (TGF-1β) and angiotensin II [67-70]. Oxidative stress, the final common pathway of myocardial damage in CHD, is of great importance for fibrosis initiation [71]. However, there are a number of questions that require further study regarding the above biomarkers, which have the most convincing evidence base of diagnostic value at the present stage. An important aspect of the study of fibrosis is not only its interpretation as a typical pathologic process, but also its consideration as a systemic lesion of various organs and tissues.

Since proving the role of fibrosis in the development of myocardial dysfunction as an arrhythmogenic substrate, it has been considered as a promising therapeutic target. Moreover, fibrogenesis is regarded as a dynamic process capable of regression or significant reduction in the rate of progression under certain conditions [72]. In particular, eliminating the provoking influence is one of the main and effective therapeutic approaches. However, in current practice, the most realistic therapeutic goal is to slow the progression of fibrosis rather than its regression as a possible effect on the substrate of ventricular arrhythmogenesis [72]. For example, treatment of the underlying disease, CHD, with drugs such as angiotensin-converting enzyme inhibitors, aldosterone antagonists, and statins have antifibrotic effects. Such therapy is able to induce reverse cardiac remodeling and reduce the incidence of potentially dangerous VAs [73].

At the same time, it is impossible not to point out that in some studies it was found that in 1.2% of cases in patients with undergone MI there is an occurrence of VT, the focus of which is localized in a part of the myocardium that is not associated with either TMI or postifarction scar. It is emphasized that patients with postifarction scar may have LV-derived but non-ischemic VTs. For example, VT with focal localization in the basal regions of the LV suggests a potential nonischemic perivascular substrate [74].

Right ventricular arrhythmias in patients with stable ischemic heart disease

Arrhythmias located in the right ventricle (RV) deserve special attention; more often they are considered either as a manifestation of structural pathology of the RV (e.g., in arrhythmogenic cardiomyopathy of the RV) or as idiopathic rhythm disturbances. Only a few clinical works cover the problem of right ventricular localization in patients with CHD. As far back as 1996, J.L.Merino et al. described a case of a patient with postifarction scar in LV, in whom invasive mapping was used to verify VT, the arrhythmogenesis focus of which was localized in RV [75]. Similar results were demonstrated in 3 clinical cases of successful treatment of VA in patients with left ventricular scar after IM, the focus of which was localized in the RV [76, 77]. In another observation, it was shown that VT in patients with postifarction scar typically involves the LV endocardium and involvement of the RV in the arrhythmogenic substrate is considered uncommon but occurs in 1.8% [78]. Thus, it is necessary to emphasize once again the role of topical diagnosis of VAs and detailing the causes of their occurrence in the RV structures, which, in turn, is significant when choosing an approach to the correction of these arrhythmias.

Role of psychological factor in ventricular arrhythmogenesis in patients with stable forms of ischemic heart disease

Among the important triggers inducing VA, many authors consider the proven causal relationship of arrhythmia with anxiety, anxiety-phobic, and neurotic disorders, both in the general population and among patients with stable CHD [78]. The XXI century is characterized by a high level of personal anxiety with simultaneous oppression of social ties, which indicates the tension of the psychoemotional sphere and, in turn, is the most important link in the etiopathogenesis of the background disease - CHD [79-81]. It is shown that CHD occurs more often in people with an excitable nervous system, expressed desire for competition, constant emotional tension - behavioral type A. This personality type is characterized by elevated total blood cholesterol, low-density lipoproteins, triglycerides, and 17-hydroxycorticosteroids, which are potent modifiable risk factors for CHD. It was found that various negative emotions (despair, fear, anger, anxiety, longing) are accompanied by the same type of ANS changes, namely, an increase in the activity of the sympathoadrenal system, which leads to an increase in the secretion of catecholamines and triggers the humoral cascade that precedes the development and contributes to the progression of MEI. Such an imbalance of sympathetic and parasympathetic influence of the ANS on the heart is one of the main links in the development of arrhythmogenesis on the background of both acute and chronic stress [82]. Thus, Ch.Vega (2004) in laboratory conditions revealed that the test with reproduction of anger, as a model of acute psychological stress, caused the appearance of signs of MEI in patients with CHD and implanted CDs in comparison with the control group, and D. Magri, G. Piccirillo et al. showed that with an increase in sympathetic activity of the ANS the QT-interval variability index changed proportionally as a manifestation of temporal dispersion. Magri, G.Piccirillo et al. showed

that the QT-interval variability index, as a manifestation of temporal dispersion of myocardial repolarization, changed proportionally with increasing sympathetic activity of ANS [83]. In patients with stable forms of CHD, the QT-interval variability index did not decrease compared to baseline during the «anger playback» test. At the same time in the control group of healthy people, there was a significant and significant decrease in the QT-interval variability index. It was suggested that in healthy individuals the decrease of this index may be a manifestation of the protective effect of vagus, while in CHD patients this protective mechanism is disturbed [84]. In a number of works, when analyzing electrograms and diary data of patients with ischemic cardiomyopathy with implanted CDs, it was found that in most cases the CD discharge was preceded by anger. Such an association between stress and fatal VAs was found in patients with implanted ICD at the time of the 2001 New York City tragedy [85]. The results of EFI studies have shown that the threshold for triggering recurrent VA in acute psychological stress is lower than in MI [86]. All these data emphasize the need to develop a multidisciplinary approach in cardiology: interaction with psychologists, psychotherapists, psychiatrists, among others, to achieve success in the treatment of VA and prevention of SCD.

Other possible provoking factors of arrhythmogenesis in patients with stable forms of CHD are also described. Thus, attention is drawn to the publications that emphasize the role of a thorough collection of medical history with a detailed detailing of the time of onset of VA in relation to clinical manifestations of CHD, analysis of electrolyte imbalance, the presence or achievement of the stage of compensation in endocrine pathology, the volume of ischemia, the area and type of distribution of myocardial fibrosis, the use of antiarrhythmic drugs and basic therapy of CHD and heart failure, which, in turn, may contribute to the choice of the optimal path of patient management [2, 9, 11, 87].

CONCLUSION

Thus, the heterogeneity and multifactorial nature of the causes of VA in patients with stable forms of CHD necessitates an individualized approach to the elucidation of trigger, modulating factors and pathophysiological conditions that underlie the genesis of arrhythmias: TMI, presence of postifarction scar, psychoemotional and physical stress, ANS influence, dyselectrolyte disorders, proarrhythmic effect of drugs and others. Addressing these factors and effective treatment (medication and surgery) of the underlying heart disease are the leading conditions for success in treating VA and preventing SCD. Obviously, there is a need for a systematic approach to creating a classification of VAs and their risk stratification in relation to SCD, which would take into account all of the above factors, primarily the clinical scenarios in which arrhythmias develop.

REFERENCES

1. Ulus T, Kudaiberdieva G, Gorenek B. The onset mechanism of ventricular tachycardia. *International Journal of Cardiology*. 2013;167(3): 619-23. https://doi.org/10.1016/j.ijcard.2012.09.034.
2. ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *European Heart Journal*. 2022;43: 3997-4126. https://doi.org/10.1093/eurheartj/ehac262.
3. Bayers de Luna AB, Coumel P, Leclercq JF Curriculum in Cardiology: Ambulatory sudden cardiac death: mechanism of production of fatal arrhythmia on the basis of data 157 cases. *American Heart Journal*. 1989;117: 151-159. https://doi.org/10.1016/0002-8703(89)90670-4.
4. Bauters C, Deneve M, Tricot O, et al. Prognosis of patients with stable coronary artery disease (from the CORONOR Study). *American Heart Journal*. 2014;113: 1142-1145. https://doi.org/10.1016/j.amjcard.2013.12.019.
5. Lown B, Wolf M Approaches to Sudden Death from Coronary Heart Disease. *Circulation*.1971;44(1): 130-142. https://doi.org/10.1161/01.cir.44.1.130.
6. Ryan M, Lown B, Horn H Comparison of ventricular ectopic activity during 24-hour monitoring and exercise testing in patients with coronary heart disease. *The New England Journal of Medicine*. 1975;292: 224-229. https://doi.org/10.1056/NEJM197501302920502.
7. Bigger JT Identification of patients at high risk for sudden cardiac death. *American Jounal of Cardiology*. 1984;54: 3-8. https://doi.org/10.1016/s0002-9149(84)80277-5.
8. Myerburg RJ, Huikuri HV, Castellanos A Origins classification and significance of ventricular arrhythmias. In: Spooner PM, Rosen MR, eds. *Foundations of Cardiac Arrythmias*. New York -Basel: Marcel Dekker Inc. 2001;547-569.
9. Doshchitsin VL Sudden cardiac death and ventricular arrhythmias. *Russian journal of cardiology*. 1999;1: 46-51. (In Russ.).
10. Treshkur TV Clinical and electrocardiographic characteristics of ischemic ventricular arrhythmias. *Journal of Arrhythmology*. 2002;30: 31-38. (In Russ.).
11. Ryngach EA, Treshkur TV, Tatarinova AA, et al. Algorithm for the management of patients with stable coronary artery disease and high-grade ventricular arrhythmias. *Ter. arkhiv*. 2017;89(1): 94-102. (In Russ.). https://doi.org/10.17116/terarkh201789194-102.
12. Peters RW, Kim HJ, Buser GA, et al. Ischemically mediated sustained monomorphic ventricular tachycardia. Resolution with anti-ischemic therapy. *Chest*. 1993;104(5): 1613-1614. https://doi.org/10.1378/chest.104.5.1613.
13. Tatarinova AA, Ryngach EA, Treshkur TV Choice of ventricular arrhythmia therapy in coronary artery disease. *Russian Journal of Cardiology*. 2020;25(7): 3707. (In Russ.).https://doi.org/10.15829/1560-4071-2020-3707.
14. Treshkur TV, Tatarinova AA, Ryngach EA A method for predicting the antiarrhythmic efficacy of myocardial revascularization in patients with coronary artery disease with ventricular arrhythmias caused by myocardial ischemia. Patent for invention 27543000, C1, 08/31/2021. Application No. 2020133895 dated 10/14/2020. (In Russ.).
15. Teregulov AYU, Teregulov YUE, Phadeev VA, et al. Differential treatment of the ventricular arrhythmias induced by physical activity at patients suffering from coronary heart disease. *Practical medicine*. 2013;69(1): 117-119. (In Russ.).
16. Tatarinova AA, Ryngach EA,Treshkur TV, et al. Ventricular Tachycardia Induced by Exercise Test as a Predic-

tor of Coronary Artery Disease Development. *Rational Pharmacotherapy in Cardiology.* 2019;15(2): 198-203. (In Russ.). https://doi.org/10.20996/1819- 6446-2019-15-2-198-203.
17. Friedman PL, Shook TL, Kirshenbaum JM, et al. Value of the intracoronary electrocardiogram to monitor myocardial ischemia during percutaneous transluminal coronary angioplasty. *Therapy and prevention. Angioplasty*. 1986;2: 330-340. https://doi.org/10.1161/01.cir.74.2.330.
18. Syrensky AV, Galagudza MM, Egorova EI, et al. Effect of changes in metabolic and antioxidant status in the severity of myocardial ischemia and its reperfusion. *Russ J Physiol.* 2008;94(10): 1171-80. (In Russ.).
19. Mikhin VP, Shveynov AI, Kharchenko AV Impact of omega-3 polyunsaturated fatty acids on arrythmic activity of myocardium and characteristics of cardac rhythm in patients with unstable angina. *International Heart and Vascular Disease Journal*. 2017;5(15): 11-16. (In Russ.).
20. George AL Jr Molecular and genetic basis of sudden cardiac death. *Journal of Clinical Investigation*. 2013;123: 75-83. https://doi.org/10.1172/JCI62928.
21. Golukhova EZ, Gromova OI, Bulaeva NI, et al., Sudden Cardiac Death in Patients With Ischemic Heart Disease: From Mechanisms to Clinical Practice. *Kardiologiia*. 2017;57(12): 73-81. (In Russ.). https://doi.org/10.18087/cardio.2017.12.10069.
22. Robin M Sh, Yoram Rudy. Electrophysiologic Effects of Acute Myocardial Ischemia. *Circulation Research*. 1997;80: 124-138.
23. Rubart M., Zipes D.P. Mechanisms of sudden cardiac death. *Journal of Clinical Investigation*. 2005;115: 2305-2315.
24. Calvier L, Martinez-Martinez E, Miana M, et al. The impact of galectin-3 inhibition on aldosterone-induced cardiac and renal injuries. *JACC: Heart Failure*. 2015;3: 59-67. https://doi.org/10.1016/j.jchf.2014.08.002.
25. Jun-Yu Huo, Wan-Ying Jian, Chu Chen, et al. Effects of Angiotensin Receptor Neprilysin Inhibitors on Inducibility of Ventricular Arrhythmias in Rats with Ischemic Cardiomyopathy. *International Heart Journal*. 2019;60(5): 1168-1175. https://doi.org/10.1536/ihj.19-065.
26. Samoluk MO, Grigorieva Nyu Current Understanding Of Endothelial Dysfunction In Patients Presenting Comorbid Cardiopulmonary Pathology (Review). *Medical almanac*. 2020;1(62): 27-35. (In Russ.).
27. Szabo T, Geller L, Merkely B, et al Investigating the dual nature of endothelin-1: ischemia or direct arrhythmogenic effect? *Life Sciences*. 2000;66(26): 2527-2541. https://doi.org/10.1016/s0024-3205(00)00587-7.
28. Garjani A, Winewright CL, Zeitlin IJ, et al. Effects of endothelin-1 and the ETA-receptor antagonist, BQ123, on ischemic arrhythmias in anesthetized rats. *Journal of Cardiovascular Pharmacology*. 1995;25(4): 634-642. https://doi.org/10.1097/00005344-199504000-00018.
29. Lin L, Yuan WJ Involvement of endothelin-1 in acute ischaemic arrhythmias in cats and rats. *Clinical Science*. 2002;103(48): 228-232. https://doi.org/10.1042/CS103S228S.
30. Kimura S, Bassett AL, Cameron JS, et al. Cellular electrophysiological changes during ischemia in isolated, coronary-perfused cat ventricle with healed myocardial infarction. *Circulation*. 1988;78: 401-406. https://doi.org/10.1161/01.cir.78.2.401.
31. Pepine CJ, Morganroth J, McDonald JT, et al. Sudden death during ambulatory electrocardiographic monitoring. *The American Journal of Cardiology*. 1991;68: 785-788. https://doi.org/ 10.1016/0002-9149(91)90654-4.
32. Mehta D, Curwin J, Gomes JA, et al. Sudden Death in Coronary Artery Disease Acute Ischemia Versus Myocardial Substrate. *Circulation*. 1997; 96: 3215-322. https://doi.org/10.1161/01.cir.96.9.3215.
33. Chung WH, Lin YN, Wu MY, et al. Sympathetic Modulation in Cardiac Arrhythmias: Where We Stand and Where We Go. *Journal of Personalized Medicine*. 2023;13: 786. https://doi.org/10.3390/jpm13050786.
34. Kalla M, Herring N, Paterson DJ Cardiac sympatho-vagal balance and ventricular arrhythmia. *Autonomic Neuroscience: Basic and Clinical*. 2016;199: 29-37. https://doi.org/10.1016/j.autneu.2016.08.016.
35. Lee L, Horowitz J, Frenneaux M Metabolic manipulation in ischemic heart disease, a novel approach to treatment. *European Heart Journal*. 2004;25(8): 634-641. https://doi.org/10.1016/j.ehj.2004.02.018.
36. Bilchik KC, Stukenborg GJ, Kamath S, et al. Prediction of mortality in clinical practice for Medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. *JACC*. 2012;60: 1647-1655. https://doi.org/10.1016/j.jacc.2012.07.028.
37. Myerlurg RJ, Kessler M, Castellanos A Pathophysiology of sudden cardiac death. *PACE*. 1991;14: 935-943. https://doi.org/10.1111/j.1540-8159.1991.tb04138.
38. Inoue H, Zipes DP Results of sympathetic denervation in the canine heart: supersensitivity that may be arrhythmogenic. *Circulation*. 1987;75: 877-811. https://doi.org/10.1161/01.cir.75.4.877.
39. Levy MN, Zieske H Effect of enhanced contractility on the left ventricular response to vagus nerve stimulation in dogs. *Circulation Research*. 1969;24(3): 303-311. https://doi 10.1161/01.res.24.3.303.
40. Levy MN Sympathetic-parasympathetic interactions in the heart. *Circulation Research*. 1971;29(5): 437-445. https://doi.org/10.1161/01.res.29.5.437.
41. Zipes DP, Wellens HJ Sudden Cardiac Death. *Circulation*. 1998;98(21): 2334-2351. https://doi.org/10.1161/01.cir.98.21.2334.
42. Shlyakhto EV, Novikova IV, Rudakov MM, et al. Ventricular arrhythmias in patients with coronary artery disease: current concepts of etiopathogenesis, diagnosis and treatment. *Journal of Arrhythmology*. 2002;30: 72. (In Russ.).
43. Vanoli E, De Ferrari GM, Stramba-Badiale M, et al. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circulation Research*. 1991;68: 1471-1481. https://doi.org/10.1161/01.res.68.5.1471.
44. Brack KE, Winter J, Mechanisms underlying the autonomic modulation of ventricular fibrillation initiation - tentative prophylactic properties of vagus nerve stimulation on malignant arrhythmias in heart failure. *Heart Failure Reviews*. 2013;18: 389-408. https://doi.org/10.1007/s10741-012-9314-2
45. Brack KE, Coote JH, Ng NG Vagus nerve stimula-

tion protects against ventricular fibrillation independent of muscarinic receptor activation. *Cardiovascular Research*. 2011;91(3): 437-446. https://doi.org/10.1093/cvr/cvr105
46. Treshkur TV, Kapanadze ST, Lebedev DS, et al. A case of idiopathic ventricular fibrillation induced by vagal activity. *Journal of Arrhythmology*. 2000;20: 76-79. (In Russ.).
47. Aronov DM, Lupanov VP Functional tests in cardiology. Moscow: MED press-inform. 2003;69. (In Russ.). ISBN 978-5-98322-268-7.
48. Kushakovsky MS Arrhythmias of the heart. SPb.: Foliant. (In Russ.). ISBN 978-5-939-29-245-0.
49. Bristow MR, Saxon LA, Boehmer J, et al. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *The New England Journal of Medicine.* 2004;350: 2140-2150. https://doi.org/10.1056/NEJMoa032423
50. Sigh J, Hall W, McNitt S, et al. Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: findings from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). *JACC*. 2005;46: 1712- 1720. https://doi.org/10.1016/j.jacc.2005.05.088.
51. Goldberger JJ, Buxton AE, Cain M, et al. Risk stratification for arrhythmic sudden cardiac death: identifying the roadblocks. *Circulation*. 2011;123: 2423-2430. https://doi.org/10.1161/CIRCULATIONAHA.110.959734.
52. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *The New England Journal of Medicine*. 2005;352: 225-237. https://doi.org/10.1056/NEJMoa043399.
53. Revishvili ASh, Neminushchy NM, Batalov, et al. RE Non-invasive topical diagnosis of non-coronary ventricular arrhythmias. *Journal of Arrhythmology*. 2017;89: 2-104. (In Russ.).
54. Gatzoulis KA, Tsiachris D, Arsenos P, et al. Arrhythmic risk stratification in post-myocardial infarction patients with preserved ejection fraction: the PRESERVE EF study. *European Heart Journal*. 2019;40: 2940-2949. https://doi.org/10.1093/eurheartj/ehz260.
55. Revishvili ASh, Novikova MV, Rzaev FG, et al. Non-invasive topical diagnosis of non-coronary ventricular arrhythmias. *Journal of Arrhythmology*. 2004;35: 5-15. (In Russ.).
56. Bokeria LA, Revishvili ASh, Neminushchiy NM Sudden cardiac death. Moscow: GEOTAR-Media. 2011;266. (In Russ.). ISBN 978-5-9704-5629-3.
57. Gorgels AP, Gijsbers C, Vreede-Swagemakers J, et al. Out-of hospital cardiac arrest - the relevance of heart failure. The Maasricht Circulatory Arrest Registry. *European Heart Journal*. 2003;24: 1204-1209. https://doi.org/10.1016/s0195-668x(03)00191-x.
58. Stecker EC, Vickers C, Waltz J, et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unex- pected Death Study. *Journal of the American College of Cardiology*. 2006;47: 1161-1166. https://doi.org/10.1016/j.jacc.2005.11.045.
59. Tatli E, Alicik G, Buturak A, et al. Arrhythmias following Revascularization Procedures in the Course of Acute Myocardial Infarction: Are They Indicators of Reperfusion or Ongoing Ischemia? *Scientific World Journal*. 2013. https://doi.org/10.1155/2013/160380.
60. Schmidt A, Azevedo GF, Cheng A, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfuncion. *Circulation*. 2007;115: 2006-14. https://doi.org/10.1161/CIRCULATIONAHA.106.653568.
61. Amoni M, Dries E, Ingelaere S, et al. Ventricular Arrhythmias in Ischemic Cardiomyopathy-New Avenues for Mechanism-Guided Treatment. *Cells*. 2021;10(10): 2629. https://doi.org/10.3390/cells10102629.
62. Karetnikova VN, Kashtalap VV, Kosareva SN, et al. Myocardial fibrosis: Current aspects of the problem. *Ter-arkhiv*. 2017;89(1): 88-93. (In Russ.). https://doi.org/10.17116/terarkh201789188-93.
63. Wu KC, Weiss RG, Thiemann DR, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. *Journal of the American College of Cardiology*. 2008;51: 2414-2421.https://doi.org/10.1016/j.jacc.2008.03.018.
64. Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. *Circulation*. 2012;126: 1206-1216. https://doi.org/10.1161/Circulationaha.111.089409.
65. Spach MS, Boineau JP Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. *Pacing and Clinical Electrophysiology*. 1997;20: 397-413. https://doi.org/10.1111/j.1540-8159.1997.tb06199.x.
66. Miragoli M, Gaudesius G, Rohr S Electrotonic modulation of cardiac impulse conduction by myofibroblasts. *Circulation Research*. 2006;98: 801-810. https://doi.org/10.1161/01.res.0000214537.44195.a3.
67. Pecherina TB, Kutikhin AG Biomarkers of myocardial fibrosis and their genetic regulation in patients with heart failure. *Russian Journal of Cardiology*. 2020;25(10): 3933. (In Russ.). https://doi.org/10.15829/1560-4071-2020-3933.
68. Leask A Getting to the heart of the matter: new insights into cardiac fibrosis. *Circulation Research*. 2015;116(7): 1269-76. https://doi.org/10.1161/circresaha.116.305381.
69. Travers JG, Kamal FA, Robbins J, et al. Cardiac Fibrosis: The Fibroblast Awakens. *Circulation Research.* 2016;118(6): 1021-40. https://doi.org/10.1161/circresaha.115.306565.
70. Talman V, Ruskoaho H Cardiac fibrosis in myocardial infarction-from repair and remodeling to regeneration. *Cell and Tissue Research*. 2016;365(3): 563-81. https://doi.org/10.1007/s00441-016-2431-9.
71. Jin L, Zhang J, Deng Z, et al. Mesenchymal stem cells ameliorate myocardial fibrosis in diabetic cardiomyopathy via the secretion of prostaglandin E2. Jin et al. *Stem Cell. Research & Therapy*. 2020;11: 122. https://doi.org/10.1186/s13287-020-01633-7.
72. Rockey DC, Bell PD, Hill JA Fibrosis - a common pathway to organ injury and failure. *The New England Journal of Medicine*. 2015;372: 1138-1149. https://doi.org/10.1056/nejmra1300575.

73. Tian J, An X, Niu L Myocardial fibrosis in congenital and pediatric heart disease. *Experimental and Therapeutic Medicine*. 2017;13(5): 1660-4. https://doi.org/10.3892/etm.2017.4224.
74. Ryngach EA, Tatarinova AA, Zhabina ES, et al. Case of Successful Medical Treatment of Ventricular Tachycardia in a Patient With Ischemic Heart Disease and Heart Failure. *Rational Pharmacotherapy in Cardiology*. 2023;19(1): 89-95. (In Russ.). https://doi.org/10.20996/1819-6446- 2023-02-05.
75. Merino JL, Almendral J, Villacastín JP, et al. Radiofrequency catheter ablation of ventricular tachycardia from right ventricle late after myocardial infarction. *The American Journal of Cardiology*. 1996;77: 1261-63. https://doi.org/10.1016/s0002-9149(96)00134-8.
76. Shalganov TN, Stoyanov MK, Genova KZ Coexistence of arrhythmogenic right ventricular cardiomyopathy and coronary artery disease in a patient with ventricular tachycardia: a highly unusual combination. *Heart Asia*. 2013;5(1): 49-51. https://doi.org/10.1136/heartasia-2013-010274.
77. Yamada T, Doppalapudi H, McEderry HT, et al. Demonstration of a right ventricular substrate of ventricular tachycardia after myocardial infarction. *Europace*. 2011;13(1): 133-135. https://doi.org/10.1093/europace/euq345.
78. Yokokawa M, Good E, Crawford T, et al. Value of right ventricular mapping in patients with postinfarction ventricular tachycardia. *Heart Rhythm*. 2012;9: 938 - 942. https://doi.org/10.1016/j.hrthm.2012.02.003.
79. Oganov RG Heart disease: a guide for physicians. 2016. M.: Litterra; 118-127. (In Russ.).
80. Chazov EI Guide to cardiology. 2014. M.: MIA. (In Russ.).
81. Frank L J Visseren, François Mach, Yvo M Smulders et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), *European Heart Journal*, 2021; 42(34): 3227-3337, https://doi.org/10.1093/eurheartj/ehab484
82. Lampert R Anger and ventricular arrhythmias. *Current Opinion in Cardiology*. 2010;25(1): 46-52. https://doi.org/10.1097/hco.0b013e32833358e8.
83. Vega C, Barclay L Mental stress can induce cardiac instability. CME Released. 2004. CME Released. - 22.03.2004.
84. Lampert R, Jain D, Burg MM, et al. Destabilizing Effects of Mental Stress on Ventricular Arrhythmias in Patients with Implantable Cardioverter-Defibrillators. *Circulation*. 2000;101: 158-164. https://doi.org/10.1161/01.cir.101.2.158.
85. Steinberg JS, Arshad A, Kowalski M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Centre attack. *Journal of the American College of Cardiology*. 2004;44(6): 1261-64. https://doi.org/10.1016/j.jacc.2004.06.032.
86. Lampert R, Joska T, Burg MM, et al. Emotional and Physical Precipitants of Ventricular Arrhythmia. *Circulation*. 2002;106: 1800-05. https://doi.org/10.1161/01.cir.0000031733.51374.c1.
87. Lebedev DS, Mikhailov EN, Neminuschiy NM, et al. Ventricular arrhythmias. Ventricular tachycardias and sudden cardiac death. 2020 Clinical guidelines. *Russian Journal of Cardiology.* 2021;26(7): 4600. (In Russ.). https://doi.org/10.15829/1560-4071-2021-4600.