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PREDICTIVE POTENTIAL OF BLOOD BIOMARKERS FOR SUBSEQUENT VENTRICULAR TACHYARRHYTHMIAS IN PATIENTS WITH CHRONIC HEART FAILURE AND REDUCED LEFT VENTRICULAR EJECTION FRACTION: REVIEW

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The current single-factor prognostic scale for the risk of ventricular tachyarrhythmia in patients with chronic heart failure and reduced left ventricle ejection fraction is considered by most experts to be inconsistent with modern medicine and should be modified. This position directs the efforts of researchers to search for additional prognostic factors, such as serum biomarkers. The last may reflect the state of cardiomyocytes and extracellular cardiac matrix, as well as endogenous and exogenous impacts to these structures. Such information may be important in determining the probability of the presence of myocardial pro-arrhythmic substrate and the electrophysiological conditions necessary to realize its potential.

The data presented in this review suggest that concentrations of serum biomarkers may provide additional information for the estimation of personalized arrhythmic risk, which should help to avoid the clinical underestimation of the risk of sudden cardiac death and be a determining factor in the decision to implant a cardioverter-defibrillator.

Key words: chronic heart failure; blood biomarkers; ventricular tachyarrhythmias; sudden cardiac death.

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According to the World Health Organization, diseases of the cardiovascular system are the leading cause of death. Thus, in 2016 about 18 million people died due to cardiac pathology, accounting for 30% of all deaths during this period. One of the main mechanisms for the realization of death in this category of patients is the occurrence of sudden cardiac death (SCD), usually due to the induction of fatal ventricular tachyarrhythmias (VT) [2]. In the structure of the causes predisposed to SCD, the leading is ischemic heart disease and hereditary channelopathy. Meanwhile, it has been proven that the development of chronic heart failure with a reduced left ventricle ejection fraction (HFrEF) is an important predictor of such an unfavourable outcome [3].

Conducted clinical trials MADIT and SCD-HeFT showed that the use of implanted cardioverter defibrillator (ICD) in patients with HF and left ventricle ejection fraction (LVEF) less than 35% who have a high risk of VT, enables effective prevention of SCD in both ischemic and non-ischemic causes of HF [4,5]. The promising data obtained formed the basis of the concept of preventive implantation of ICD, enshrined as the class I of current international and national clinical recommendations [6, 7]. Meanwhile, the implementation of this approach has shown that LVEF does not possess sufficient specificity and sensitivity in the selection of candidates for ICD implantation for primary prevention of SCD [8]. Thus, according to F. Merchant et al. 67% of patients with ICD (16,930 patients) did not experience shock within the first 5 years after implantation [9]. It has been shown that inappropriate ICD therapy is applied on average in 22 per cent of cases of ICD implantation for primary SCD prevention [10].

Various pathophysiological mechanisms may be at the origin of VT in patients with HFrEF including increased automaticity, trigger activity, and/or re-entry formation [11,12]. The electrophysiological conditions required to implement these scenarios arise with the progression of HF, ischemia, and hereditary myocardial diseases. The required pro-arrhythmogenic substrate appears because of the remodeling of the cardiac extracellular matrix (ECM), a connecting component that acts as an information center, accumulating and transporting signal data for all cells of the organ [13] (Fig. 1). This process is believed to be triggered by myocardial stress, ischemia, necrosis, and myocardial inflammation directly involving various biological signaling proteins [14]. Changes in the concentration of these agents in the blood may indicate anatomical and functional transformations of the cardiac ECM which

may have an arrhythmic potential [15] and for this reason may provide additional information for risk stratification of VT [16].

Given the discrepancy between the current criteria for selecting patients with HFrEF for ICD implantation and the real risk of life-threatening VT [8], the study of the predictive capabilities of such biomarkers is particularly relevant. The objective of the review was to provide accessible information on the use of blood biomarkers to predict the likelihood of VT in patients with HFrEF.

DEFINITIONS AND CLASSIFICATION OF BIOMARKERS

According to the definition proposed by the Food and Drug Administration «Biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions» [17].

Morrow and de Lemos formulated 3 criteria that determine the prospects of clinical use of a biomarker [18]. First, accurate and reproducible measurement should be available to the clinician at a reasonable cost and within a short period of laboratory analysis. Secondly, a biomarker should provide information that is not available through a thorough clinical examination. Finally, the data obtained on the level of biomarker should be relevant for clinical decision-making. Many of the biomarkers discussed in this review do not meet all three criteria. However, rapidly evolving technologies could change the way concentrations are measured soon, reducing the cost and time of analysis. Therefore, in our view, the principal criterion for the relevance of discussing an agent should be the presence of a causal link between the change in its concentration and the onset of a clinically significant event.

Although biomarkers have long attracted the attention of researchers, there is no single classification of these agents. Califf R.M. proposed that the classification be based on the possibility of using biomarkers to evaluate clinical outcomes. By this, identify diagnostic, monitoring, pharmacodynamic/response, predictive, prognostic biomarkers as well as susceptibility/risk and safety biomarkers [19]. The same agent in different situations can be referred to in different categories. Based on this position a more practical pathophysiological classification is based on the mechanism of influence on the endpoint. It emits biomarkers of inflammation, oxidative and myocardial stress, myocyte and fibrosis damage, and neurohormones [20]. From the point of view of the pathogenesis of cardiac remodeling, in our opinion, it is more convenient to use the systematization of biomarkers, based on the presence of interactions with cardiomyocytes, their micro-and macroenvironment [21].

New agents are described every year which are tested for the practical value and implementation potential of the clinic. In this regard, a common nomenclature of these agents would help to systematize existing data and help the clinician to understand the diversity of existing biomarkers.

PREDICTIVE CAPABILITIES OF BIOMARKERS IN DETERMINING THE RISK OF VT IN PATIENTS WITH HFREF

The advantage of using biomarkers is that it is possible to assess the probability of occurrence of a clinical adverse event. For the subject under discussion, it is the occurrence of stable VT. The emergence of highly sensitive biomarkers in patients with HFrEF suggested that this information could be used to calculate personalized arrhythmic risk. This should help avoid clinical underestimation of the risk of SCD and become defined in the decision to implant ICD.

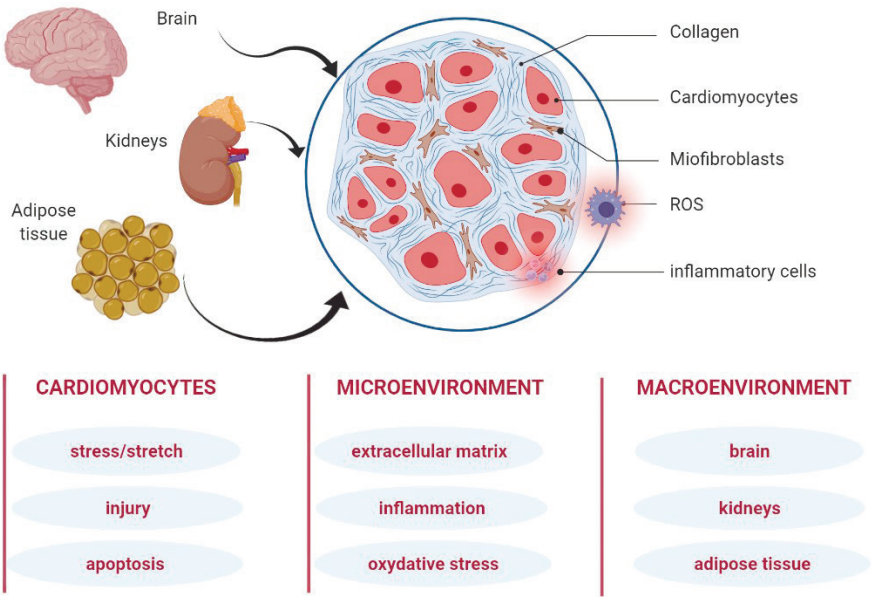

Fig. 1. Triggers that affect cardiomyocytes cause changes in myocardial structure and function (hypertrophy, apoptosis, intracellular metabolism, contraction modulation). The modification of the micro- and macroenvironment of cardiomyocytes initiates the emergence and progression of heart failure, creates ideal conditions for the implementation of the arrhythmic scenario of sudden cardiac death. ROS - active oxygen species.

Biomarkers associated with a state of cardiomyocyte

Myocyte stress/stretch

One of the first biomarkers used in HF patients were natriuretic peptides (NPs), especially the B-type natriuretic peptide (BNP). It is released in the heart ventricles in response to increased ventricular blood volume and overload in the form of prohormone (proBNP). When it is split, a biologically active aminoacid BNP and an inert N-terminal proBNP (NT-proBNP) are formed, the level of which allows not only to predict the clinical decompensation of HF, but also to stratify the risk of adverse clinical events in patients with HFrEF [22].

It is known that NPs cause a dilation of the afferent and con-

Table 1.

Main clinical studies investigating the use of blood biomarkers for VT prediction in HFrEF patients (continued)

Authors	Tested Blood Biomarkers	Population	Indications for ICD implantation	Arrhythmic endpoint	Study design	Duration of follow-up	Endpoint	Interpretation
Verma et al., 2006 [69]	CRP BNP	345 pts. (ICMP: 245 -71%; DCM: 59-11%)	Primary prevention 179 (52%)	Appropriate ICD therapy	A single-center, prospective	13±5 months.	63 (18%)	As part of the multi-factor model BNP level (above 50 centiles) predicted the risk of appropriate ICD therapy by 2.2 times (95% CI: 1.07-4.71; p =0.04)
Manios et al., 2005 [70]	NT-proBNP	35 pts. with ICMP	Primary prevention 35 (100%)	Appropriate ICD therapy	A single-center, prospective	12 months.	11 (31%)	NT-proBNP (880 ppm/l) showed positive predictive potential of 80%, negative predictive potential of 88% (73% sensitivity, 88% specificity)
Klingenberg et al., 2006 [71]	NT-proBNP	50 pts. with ICMP	Primary prevention 34 (68%)	Appropriate ICD therapy	A single-center, prospective	12 months.	16 (32%)	NT-proBNP is the only independent predictor of ICD therapy delivery (RR=7.74; 95%CI: 1.81-33.17; p=0.024)
Christ et al., 2007 [27]	BNP	123 pts.	Primary prevention 111 (31%)	Appropriate ICD therapy	A single-center, prospective	25 months.	16 (13%)	The effect of the BNP level on the probability of an endpoint was not identified.
Scott et al., 2011 [28]	NT-proBNP, sST-2 GDF-15 CRP IL-5	156 pts. (ICMP: 119 -76%; NICMP: 28-18%)	Primary prevention 58 (37%)	Appropriate ICD therapy	A single-center, prospective	15±3 months.	47 (30%)	In multi-factor analysis, NT-proBNP concentrations had a predictive potential only in a subset of pts. with secondary SCD prevention (OR=2.43; 95%CI: 1.09-5.42; p=0.03) but not primary SCD prevention (OR=1.93; 95% CE: 0.72-5.42; p=20.03).
Levine et al., 2014 [72]	BNP	- 403 pts.	Primary prevention (100%)	Appropriate ICD therapy	A dual-center, retrospective	Median 806 days	109 (27%)	The relationship between the levels of BNP, NT-proBNP (upper quartiles) and the probability of the endpoint (OR=4.74; p=0.01 and OR=12.9; p<0.001; respectively) was found.
	NT-proBNP	- 161 pts.				Median 635 days	38 (23,5%)	
Sardu et al., 2018 [73]	CRP IL-6 cTn I CK-MB BNP sST-2	206 pts. (ICMP: 135 -65,5%)	Primary prevention 206 (100%)	Appropriate ICD therapy	A multi-center, prospective	12 months.	67 (32,5%)	In the multi-factor model, predictive possibilities have been identified for ST-2 (OR=1.021; 95%CI: 1.007-1.260; p=0.001); BNP (OR=1.005; 95%CI: 1.001-1.160; p=0.028); CRP (OR=831.005; 95%CI: 1.678-1.993; p=0,028).
May B.M. et al., 2022 [34]	GDF-15	148 pts. (NICMP: 148 - 100%)	n/d	Appropriate ICD therapy; SCD	A single-center, prospective	42 months.	28 (19%)	Elevated level was associated with endpoint risk (OR=1.14, 95% CI: 1.01-1.28; p=0.03)

Table 1.

Main clinical studies investigating the use of blood biomarkers for VT prediction in HFrEF patients (continuation)

Authors	Tested Blood Biomarkers	Population	Indications for ICD implantation	Arrhythmic endpoint	Study design	Duration of follow-up	Endpoint	Interpretation
May B.M. et al., 2022 [34]	GDF-15	148 pts. (NICMP: 148 - 100%)	n/d	Appropriate ICD therapy; SCD	A single-center, prospective	42 months.	28 (19%)	Elevated level was associated with endpoint risk (OR=1.14, 95% CI: 1.01-1.28; p=0.03)
Daidoj et al., 2012 [33]	H-FABP	107 pts. (ICMP: 22 – 21%)	Primary prevention 39 (36%)	Appropriate ICD therapy; death	A single-center, prospective	Median 33,6 months	33 (30,8%)	Level above 4.3 ng/ml - independent prognostic factor for the delivery of appropriate ICD therapy and cardiac death
Zhou et al., 2019 [52]	GGT	140 pts. (ICMP: 36 - 25,7%)	Primary prevention 25 (17,9%)	VT, appropriate ICD therapy	A single-center, retrospective	44 ± 17 months.	VT - 78 (55,7%); ICD therapy - 50 (35,7%)	The GGT level of ≥ 56 U/l was associated with VT (p<0.001) and appropriate ICD therapy (p = 0.006)
Kanoupakis et al., 2010 [37]	MMP-1 TIMP-1 C-terminal telopeptide of type I collagen	70 pts. with NICMP	Primary prevention 70 (100%)	Appropriate ICD therapy	A single-center, prospective	1 year	14 (20%)	Pre-implantation levels of all studied blood biomarkers were significantly higher in pts. with appropriate ICD therapy
Akbulut et al., 2021 [44]	- galectin-3	92 pts. with NICMP	n/d	VT, VF	A single-center, prospective	n/d	n/d	Galectin-3 - independent predictor of any ventricular tachyarrhythmia

Note: CRP - C-reactive protein; BNP - brain natriuretic peptide; NT-proBNP - N-terminal fragment of prohormone natriuretic peptide B-type; sST-2 - soluble form of growth factor encoded by genome 2; GDF-15 - growth factor of differentiation; IL- interleukin; cTn - cardio-specific troponin; H-FABP - cardiac form of fatty acid binding protein; GGT - gamma-glutamyl transferase; CK-MB - creatine kinase-MB; MMP - matrix metalloproteinase; TIMP - tissue inhibitor of matrix metalloproteinase; ICMP - ischemic cardiomyopathy; NCMP - non-ischemic cardiomyopathy; DCM - dilated cardiomyopathy; VT - ventricular tachycardia; VF - ventricular fibrillation; ICD - implantable cardioverter defibrillator; RR - relative risk; OR - odds ratio; CI - confidence interval.

traction of efferent renal arterioles, an increase in kidney blood flow, and a rate of glomerular filtration, inhibition of sodium and water reabsorption. The point of NPs application about the structure of the cardiac ECM seems to be related to inhibition of renin and aldosterone secretion, and suppression of the activity of the sympathetic nervous system [23]. Thus, elevated concentrations of NPs may indicate increased activity of myocardial proliferation and hypertrophy processes which may result in the occurrence of a VT arrhythmic substrate [24].

In a study that included 521 patients with myocardial infarction, the level of NPs indicated the risk of subsequent episodes of SCD independent of clinical variables and LVEF (hazard ratio (HR) 3.39; 95% confidence interval (CI) 1.22-9.45; p-0.037) [25]. Other investigators have shown that an increase in NPs in HF patients with significant systolic dysfunction (LVEF < 20%) is associated with a high risk of SCD only at an initially prolonged QTc interval on the ECG (odds ratio (OR) 1.63; 95% CI 0.54-5.12; p<0.001). Several studies indicate both associations between high concentrations of NPs and VT occurrence including those with previously implanted ICD (Table 1) and the opposite [27, 28]. The high predictive expectations of NPs were largely overestimated, including due to the large variability in the concentration of these agents in different clinical situations. For this reason, there is now a growing view that the clinical significance of NP studies lies in the identification and assessment of myocardial stress and decompensation of HF [29].

The stimulating growth factor encoded by the gene 2 (ST-2) belongs to the interleukin receptor family and has two isoforms: soluble (sST-2) and transmembrane, embedded in the cell membrane and acting as a receptor for interleukin 33. It is believed that sST-2 is a biomarker of fibrosis, inflammation of sympathetic hyperactivation, and myocardial stress. The high concentrations of sST-2 (over 36.3 ng/ml) are associated with adverse clinical outcomes of HF. In the subanalysis of the MADIT-CRT study (Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy) increase of the soluble form of growth-stimulating factor (sST-2) more than 35 ng/ml acted as an independent predictor of SCD or sustained VT paroxysm [30]. Similar conclusions were reached in the HF-ACTION study [31].

In literature reviews of sST-2 prognostic potential in HF patients' data from Pascual-Figal et al. is often used. It has been shown that elevated levels of this biomarker lead to a 4.56-fold increase in SCD rate (95% CI 1.31-1.59; p=0.017). A combination of high levels of NT-proBNP and sST-2 were identified in 74% of examined HF patients with VT occurred [32]. However, it is not always indicated that a study included HF patients with LVEF ≤ 45%, so that the results are highly unlikely to be extended to a cohort of patients with HFrEF.

Myocyte injury

Cardiac troponins are the most used myocardial necrosis marker in the clinic. Most of the published papers suggest that a study of their concentrations in HF patients cannot provide reliable information to determine the risk of future arrhythmic events (Table 1).

Myocyte apoptosis

After the damage to cardiomyocytes, oxidized products, and ECM proteins are released into the blood and activate the inflammatory reactions. The action of proinflammatory cytokines leads to activation of fibroblasts and cardiomyocytes of the inflammation site, and initiation of mechanisms of apoptosis. Heart-type fatty acid-binding protein (H-FABP) is one of the markers of these processes. Elevated concentrations of this biomarker are associated with a high probability of adverse cardiovascular events, including VT [14]. It has been demonstrated that according to H-FABP levels risk stratification can be performed in HF patients: concentrations above 4.3 ng/ml can act as an independent prognostic factor for the delivery of appropriate ICD therapy and cardiac death [33].

Other known biomarkers of myocardial apoptosis (soluble FAS ligand; growth differentiation factor-15) are likely to be used to evaluate HF status, especially in patients with ischemic heart disease. However, the predictive value of these biomarkers for future VT reported in the literature is contradictory [21, 34].

Microenvironment biomarkers

Cardiac ECM

Studies have shown a change in the concentrations of enzymes regulating the composition of the cardiac ECM in the blood of patients with cardiovascular diseases: the normal ratio of matrix metalloproteinases (MMP) and their tissue inhibitors (TIMP) is disturbed [35], the number of proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, S-reactive protein, galectin-3) that initiate MMP synthesis increases [36]. This leads to the progression of fibrosis and the formation of an anatomic and electrophysiological substrate for VT occurrence.

A promising area for biochemical markers with predictive significance for the VT occurrence is the determination of the level of collagen exchange products (C-terminal collagen propeptide type 1, C-terminal telopeptide of type I collagen, MMP, TIMP) indicating the ECM remodeling. It has been demonstrated that the level of these markers in peripheral blood correlates with the extent of myocardial fibrosis and has an association with the probability of the delivery of appropriate ICD therapy in patients with HFrEF [37].

Known triggers that initiate myocardial fibrosis are hypoxia, chronic inflammation, and hemodynamic myocardial overstretching. Inflammatory myocardial cells begin to express several signaling proteins under the influence of these factors. That activates fibroblasts and initiates remodeling of the cardiac ECM. Galectin-3, a soluble β-galactosidase-binding glycoprotein released by activated heart macrophages, is one of such biomarkers [38].

In general, the analysis of the literature shows that the level of galectin-3 increases during inflammatory and proliferative processes. Experimental and clinical studies indicate the involvement of this biomarker in the stimulation of aldosterone-induced fibrosis and myocardial remodeling [39, 40]. Moreover, some authors point to the existence of a direct positive correlation between the concentration of galectin-3 in the blood and the presence of arrhythmic substrate in the myocardium [41], capable of manifestation in life-threatening VT [42] and causing an arrhythmic storm [43].

Russian researchers on a relatively small cohort of ischemic cardiomyopathy patients (ICMP, 40 patients) have demonstrated that an increase in the concentration of galectin-3 >10.95 ng/ml is an independent predictor of future stable VT (p=0.044) [16]. Similar results were presented by Tayyar Akbulut et al. After separating 92 patients with non-ischemic cardiomyopathy depending on the level of galectin-3 in the blood, a higher incidence of unstable VT, stable VT and ventricular fibrillation (VF) in a group with an increased level of studied biomarker was found ($p < 0,0001$; $p < 0,002$; $p < 0,026$; respectively) [44].

A group of authors from Brazil presented the opposite results, according to which the elevated level of galectin-3 in non-ischemic cardiomyopathy patients (148 patients, median of observation - 941 days), estimated immediately after inclusion in the study, did not act as a predictor of future major arrhythmic events (stable VT, appropriate ICD therapy, SCD episode), although associated with general mortality [45]. There were no galectin-3 associations at risk in another study including 1,440 HF patients [46].

Inflammation

Inflammation is a universal response to various damaging factors. In HFrEF patients' inflammatory reactions are involved in the damage of cardiomyocytes, play an important role in the implementation of their apoptosis and the reconstruction of the cardiac ECM. The severity of the inflammatory response in each case is determined by the interaction of pro-and anti-inflammatory cytokines and the change in their concentration in the blood can indicate the HF status [47].

A CAMI-GUIDE study on 300 ICD patients investigated the prognostic role of C-reactive protein in the development of SCD or VT/VF in patients with ischemic heart disease with LVEF less than 30% [48]. According to a two-year observation, the primary endpoint was 17.3%. It has been shown that an increase in C-reactive protein of more than 3 mg/l is not associated with SCD or VT/VF but this information can be used to predict HF mortality.

Another large study of PROSE-ICD (1189 patients were included, 4-year observation period): an increase in inflammation biomarkers (C-reactive protein, IL-6, tumor necrosis factor α) as well as biomarkers of neuro-humoral activation and damage of cardiac myocytes (proBNP and cardiac troponin T) was found to increase the risk of death but does not predict the delivery of ICD therapy [49].

Oxidative stress

Oxygen is an essential element of cell life, which activates many intracellular enzymes. However, during the metabolism process, a small amount of oxygen is converted to superoxide anions (highly toxic oxygen radicals). Active oxygen species (reactive oxygen species - ROS) cause the destruction of intracellular structures, triggering oxidative stress.

The experiment showed that ROS by influencing intracellular ion channels, lengthens the duration of action potential (AP), enhancing the trigger potential of arrhythmic substrate [50]. The dispersion of the AP at different sites of the myocardium creates conditions for the occurrence of VT with re-entry mechanism. In addition to the described mechanisms arrhythmic effects of oxidative stress are realized through the disruption of inter-cellular contacts and the disorganization of the cardiac ECM [51].

A gamma-glutamyl transferase may be of interest in the context of the issue under study. It is one of the markers of the ineffectiveness of antioxidant protection, its increase in the concentration in the blood indicates oxidative stress exacerbation. Zhou et al. in their prospective study concluded that gamma-glutamyl transferase concentration ≥ 56 U/L can predict a high probability of future VT and appropriate ICD therapy [52].

Macroenvironment biomarkers

Adipokins

Obesity is a known cardiovascular risk factor. The most dangerous is abdominal obesity, in which hypertrophy and hyperplasia of adipocytes lead to an increase in the number of macrophages and an increase in the secretion of hormone-like substances - adipokines. Molecular mechanisms explaining the association of obesity with increased propensity for VT occurrence are not fully disclosed. Direct effects are thought to be associated with myocardial fat infiltration, which initiates fibrotic remodeling. Increased adipokines secretion leads to autonomic dysfunction, enhances local inflammation, and oxidative stress, and stimulates cardiomyocyte apoptosis [53]. There is evidence in the literature that elevated adiponectin is associated with a pathological prolongation of the corrected QT interval on the electrocardiogram - a sign of the electrical instability of the myocardium [54]. The contribution of leptin to the occurrence and maintenance of ischemic VT was proven in the experiment [55].

Neurohormones

Progression of HF leads to hyperactivity of neurohumoral systems as a compensatory response to worsening systolic function of LV. Neurohormones secreted into the blood (adrenaline, noradrenaline, adrenomedullin, copeptin, renin, angiotensin II, aldosterone) increase myocardial contraction, but at the same time increase the heart rate and AP, lengthen the refractory period of the ventricle, change the physiological direction of repolarization propagation, forming regional electrical heterogeneity [56].

Even though in preparing this review we were not able to find a work indicating a correlation between the concentration of these biomarkers in the blood and the risk of VT in patients with HFrEF, there is the data that may indicate such a relationship. The large clinical studies available have shown neurohormonal blockade to be effective in preventing VT [57].

The experiment showed that mice having elevated angiotensin II levels exhibited pronounced myocardial hypertrophy, bradycardia due to atrioventricular conductivity disorder and increased propensity for sudden arrhythmic death [58].

Increased secretion of aldosterone in HF patients is primarily a cause of electrolytic imbalance. In addition to this, it has been proven in laboratory studies that elevated concentrations of aldosterone contribute to myocardial fibrosis, endothelium dysfunction and perivascular fibrosis, as well as increased activity of the sympathetic part of the autonomic nervous system [59].

Renal Markers

Patients with chronic kidney disease are at high risk of VT [60]. The electrical instability of the myocardium in renal dysfunction is mainly due to the stimulation of the renin-angiotensin-aldosterone system and the increased secretion of aldosterone which promotes the opening of sodium channels in collecting ducts. The triggered pathophysiological cascade forms persistent arterial hypertension and causes myocardial hypertrophy - an anatomical substrate for the VT occurrence. Deo et al. investigated the hypothesis of a link between the level of kidney markers and the risk of SCD. After analyzing the results of long-term observation (10 years), the authors found that renal dysfunction, estimated by the concentration of cystatin C (but not by the level of creatinine or the glomerular filtration rate), had a connection with an episode of SCD in the future [61].

Kidneys are an important organ involved in maintaining a constant electrolyte composition of blood. Accordingly, when impaired kidney function, the physiological balance of electrolytes is disturbed which causes depolarization of the resting membrane potential, a decrease in sodium channel activity, and shortening of the AP. However, the effective refractory period is lengthened, continuing after repolarization (post-repolarization refractoriness). Hyperkalemia and hypocalcemia developing in chronic kidney disease can manifest on ECG by lengthening the QT interval clinically manifest by bradycardia, accelerated junctional rhythm, and even VF [62].

PROSPECTS FOR THE USE OF BIOMARKERS IN BCC RISK STRATIFICATION

Undeniable interest in the new predictors of SCD, among which are often mentioned blood biomarkers, is due to the imperfection of the current system of stratification of arrhythmic risk that regulates indications for ICD implantation as the most effective mean of preventing this HF outcome. The material presented in this review gives us optimism about this perspective, especially if we use a combination of clinical, instrumental and laboratory prognostic factors to solve this problem.

For example, the well-known Seattle Heart Failure Model, created to assess the survival of HF patients and validated to predict SCD in this category of patients [63], suggests the clinician use a range of indicators, including hemoglobin levels, sodium, and cholesterol. In another predictive model, in addition to sex, race, several data and ECG features, information on the content of the biomarker NT-proBNP in the blood was added [64].

The combination of several laboratory parameters likely increases the diagnostic value of the predictive algorithm. Thus, the authors of the MUSIC study by the results have created a model that allows for calculating the individual risk of SCD in an HF patient. Creatinine clearance, NT-proBNP, and troponin were used to calculate the risk, with predicted and actual SCD rates of 91.7% and 89.6% respectively [65]. At the same time, while testing the hypothesis about possible prognostic values of potassium, sodium, creatinine, and hemoglobin levels in the blood of patients with HF, an international multi-center ATLAS study found that only the value of creatinine can act as an independent predictor of SCD ($p<0.05$) [66]. Scott et al. having investigated 5 different biomarkers at once, concluded that concentrations of NT-proBNP and sST2 may be useful in determining the probability of survival after ICD therapy [41]. However, no reliable results have been obtained on the correlation between the level of biomarkers in the blood and the risk of primary manifestation of VT (Table 1).

High expectations can be placed on the study of blood biomarkers in conjunction with the investigation of instrumental predictors of VT, the most important of which is now considered to be late gadolinium enhancement during contrast cardiac magnetic resonance imaging [67]. It has been proven that there are strong associations between N-terminal propeptide 1 and 3-type procollagen, galectin-3, ST-2 concentrations, and the presence of contrast accumulation in the myocardium which, according to researchers, points to the possibility of sharing these markers for better diagnosis of myocardial fibrosis [68].

In our view, a significant limitation of the multi-factor predictive models developed in the coming years, using data from clinical, laboratory and instrumental methods, is the relatively small number of participants. The large clinical studies presented in the literature on this subject are generally retrospective and do not allow the inclusion in the multi-factor analysis of the results of modern cardiovisualization techniques that can be performed at present. Importantly, in many of them, endpoints were recorded without the use of long-term rhythm monitoring. For this reason, on the one hand, some of the fatal episodes may have been misinterpreted as SCD, on the other hand, the VT occurring in the absence of effects on hemodynamics may have been untreated. The reasons given once again underline the urgency of carrying out research work in the context of the request to modify the existing system of stratification of arrhythmic risk of patients with HFrEF.

CONCLUSION

The primary prevention of cardiovascular diseases is based on accurate risk stratification. The current one-factor scale of prediction of VT risk in HF patients, according to most experts, does not meet the requirements of modern medicine and should be modified. The data presented in this review allow consideration of the use of blood biomarkers in future predictive algorithms.

To date, the prospect of finding a single blood biomarker that is sufficiently sensitive and specific to solve these problems seems unlikely. This directs research towards the development of diagnostic panels of biomarkers capable of assessing various pathophysiological mechanisms of VT. Information about blood biomarkers can complement the results of an instrumental search of VT substrate (ultrasound techniques, contrast magnetic resonance cardiac imaging) and increase the diagnostic value of multi-factor predictive models.

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