https://doi.org/10.35336/VA-1213

ECG-BASED RISK STRATIFICATION OF SUDDEN CARDIAC DEATH AND LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

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Risk stratification of sudden cardiac death and life-threatening ventricular arrhythmias remains an unsolved problem of modern cardiology. Technological progress in the field of electrocardiography and cardiac monitoring enables discovering and researching potential ECG risk predictors based on novel methods of ECG data analysis.

Key words: sudden cardiac death; ventricular arrhythmias; ECG predictors; QRST angle; fragmented QRS; ventricular late potentials; T-wave alternans; heart rate variability; heart rate turbulence; novel ECG markers

Conflict of interest: none.
Funding: The study was funded by government contract of the Ministry of Health of the Russian Federation (registration number 123021000126-0)
Received: 16.05.2023 **Revision received:** 26.09.2023 **Accepted:** 23.09.2023
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This work was presented as part of the competition for young scientists of the X All-Russian Congress of Arrhythmologists, held on June 8-10, 2023 in Moscow

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For citation: Stepanov DA, Tatarinova AA. ECG-based risk stratification of sudden cardiac death and life-threatening ventricular arrhythmias. *Journal of Arrhythmology*. 2024;31(1): e1-e15. https://doi.org/10.35336/VA-1213.

Holter monitoring (HM) electrocardiogram (ECG) data reveal that sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) constitute the predominant cause of sudden cardiac death (SCD) in the majority of cases (80%) [1]. Consequently, these ventricular arrhythmias (VAs) are categorized as «life-threatening» (LTAs) in research papers addressing SCD, and their documentation is frequently regarded as a research endpoint, parallel to the occurrence of sudden death itself.

Ventricular arrhythmias (VA) are indicative of myocardial electrical instability (EMI), but not all of them pose a life-threatening risk. Hence, the contemporary approach to the study of VA is multifaceted. It considers the arrhythmia substrate, which is influenced by the underlying disease, its clinical-electrocardiographic and electrophysiological (EP) characteristics (including the connection with provoking factors), and VA indicators of EMI. This approach aims to enhance the prediction of the potential transformation of various forms of VA into LTA (see Fig. 1).

The substrate for the development of LTA involves pathological changes in the heart at the tissue and cellular levels, leading to disruptions in the electrical stability of the myocardium. These changes encompass areas of fibrosis and scar tissue, alterations in the conductive system (e.g., ventricular tachycardia with circulation along the left bundle branch, more common in patients with structural heart disease, interfascicular ventricular tachycardia, and fascicular ventricular tachycardia, presumably associated with abnormal electrophysiological properties of the Purkinje fiber section), as well as channelopathies (such as Brugada syndromes, prolonged QT (LQTS), short QT (SQTS), and catecholaminergic polymorphic ventricular tachycardia). Triggering factors of VA are myocardial ischemia,

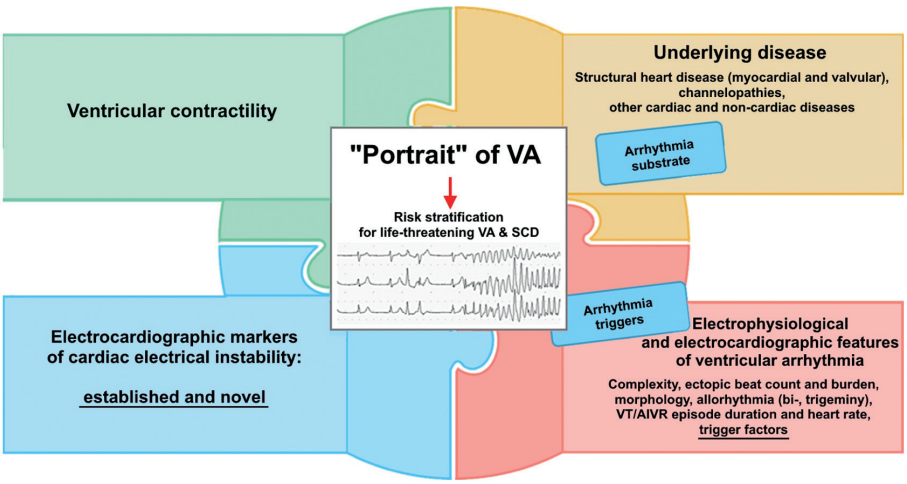

Fig. 1. A comprehensive approach to the study of arrhythmogenesis of ventricular arrhythmias (VA), hereinafter referred to as SCD - sudden cardiac death, VT - ventricular tachycardia, AIR - accelerated idioventricular rhythm.

inflammation, impaired sympathovagal or electrolyte balance, and psychogenic factors.

Researchers employ various categorizations of ECG markers for EMI, considering ECG cycle phases (depolarization and repolarization), the component of arrhythmogenesis (substrate and trigger), and evaluation methodology (morphology of cardiac signal elements and integral assessments requiring the accumulation of ECG data with subsequent processing).

The review aims to assess the current state of foreign and domestic research on the use of ECG indicators of EMI for predicting and stratifying the risk of LTA and SCD. Additionally, it aims to explore new directions in the study of this problem. The review considers the results of large studies and meta-analyses from 2010-2023 and reflects the representation of indicators in current clinical guidelines. The basic search strategy is summarized in Table 1. The comparative analysis of search results reveals a significant quantitative predominance of foreign studies. Foreign studies typically involve larger sample sizes, often consisting of thousands of patients, and exhibit a multicenter nature, contributing to increased result reliability. Based on the results of the review, an integrative Table 2 was generated to summarize the ECG parameters and thresholds associated with increased risk of SCD.

PR interval duration

Alterations in the duration of the PR interval, indicative of fluctuations in atrioventricular (AV) conduction speed, have been recognized as potential markers associated with an elevated risk of cardiovascular mortality, encompassing instances of SCD. Increased PR interval duration (AV blockade of the 1st degree) in young individuals without significant concomitant pathology is usually associated with the influence of the parasympathetic nervous system, whereas in older individuals it is more likely to be a symptom of structural heart disease. This explains the association identified by some researchers with increased mortality in these patients. In general, the results of the studies are contradictory. Thus, R.Crisel et al. (2011) in a study of the PR interval in patients with stable coronary heart disease (CHD) (n = 938) found an association of its prolongation with a 2.33-fold increase in cardiovascular mortality (p = 0.005), regardless of HR, therapy taken and the average daily duration of ischemia episodes [9].

On the other hand, large cohort studies by J. Magnani et al. - NHANES (2011, n = 7486) and Health-ABC (2013, n = 2722) showed no association of PR interval prolongation with increased total and cardiovascular mortality, including in patients with CHD [10, 11]. A study by F.Holmqvist et al. (2015, n = 9637) also found no association of PR prolongation with increased mortality, including SCD [12]. C.Kwok et al. (2016) in a meta-analysis that included 14 studies (n = 400750) found an association of 1st degree AV blockade with increased overall mortality (relative risk (RR) = 1.31) and increased risk of AF (RR = 1.47), but differences in mortality from cardiovascular causes were not significant. The authors of the meta-analysis refrained from categorical conclusions, explaining the inconsistency of the available studies by the heterogeneity of samples and research methods, and stating the need for additional study of the problem [13]. It is worth noting that the differences in the results obtained in the studies may be due to a different cause of PR interval prolongation. The study by E. Soliman et al. (2014, n = 7501) found no significant increase in mortality in individuals with PR duration >200 ms; however, within this group, significantly higher mortality (RR = 2.00) was observed in individuals with a higher value of the ratio of P wave duration to PR interval duration. According to the authors, this correlates with the results of earlier studies linking the risk of adverse cardiovascular events with P wave duration, i.e., intra-atrial conduction disturbance - including the previously mentioned NHANES [14].

There are few studies investigating PR prolongation as a predictor of risk for direct VA and SCD. Of interest is the work of Y.Li et al. (2019), who found an association of increased corrected PR interval (calculated as PR/RR ratio) with increased risk of VA (RR 2.230, $p < 0.001$) and SCD (RR = 2.105, p = 0.024) in patients with implanted cardioverter-defibrillators (ICDs)/cardiac resynchronization therapy (CRT) devices. The authors note that in addition to the association of PR prolongation with the presence of structural myocardial damage that increases the risk of VA, the association may be due to the use of PR duration cor-

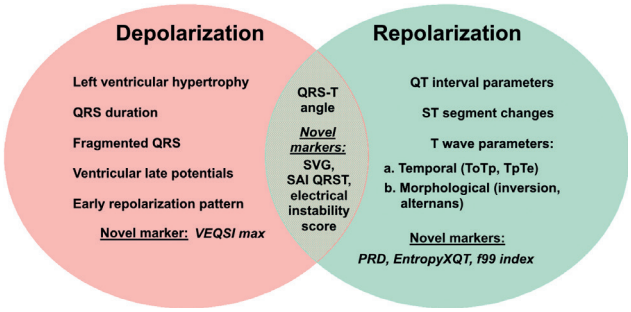

Fig. 2. Categorization of EMI markers according to the phases of the ECG cycle, hereinafter, LVH - left ventricular hypertrophy, EntropyXQT - repolarization entropy, f99 - repolarization fragmentation index, PRD - periodic repolarization dynamics, SAI - area under the QRST curve, SVG - spatial gradient vector, VEQSI max - maximum duration of ventricular ectopic complex.

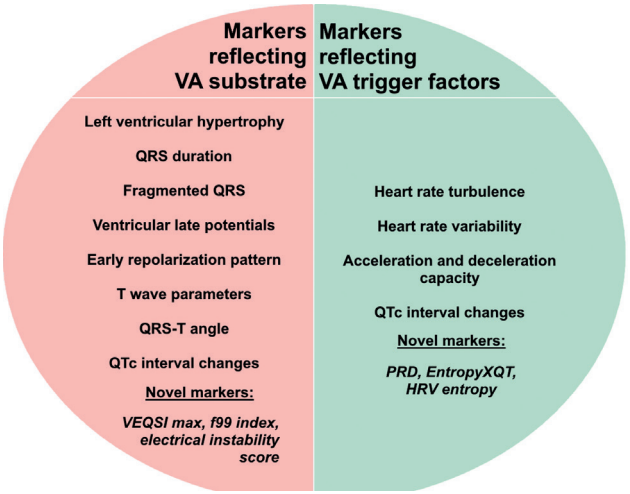

Fig. 3. Categorization of EMI markers according to the reflected component of LV arrhythmogenesis, hereinafter EMI - electrical myocardial instability.

rection for HR, since resting tachycardia is also associated with an increased risk of VA and SCD [15].

In contrast to prolongation, shortening of the PR interval has long been recognized as a marker of increased risk of SCD. This ECG phenomenon is characteristic of the preexcitation syndromes: Wolff-Parkinson-White (WPW) and Laun-Ganong-Levin (LGL; the existence is not recognized by all investigators). The typical arrhythmia in these syndromes, AV reciprocal tachycardia, is usually not fatal. However, the development of AF in these patients can be life-threatening because of the potential for 1:1 conduction through additional pathways, causing extremely high rates of ventricular contractions, which could potentially progress to AF. Although patients with WPW syndrome have a higher incidence of AF than the population average of up to 30%, their associated increased risk of SCD is small, at about 0.6% per year. Researchers investigating the problem of SCD in patients with WPW syndrome are attempting to increase the detection of higher-risk patients. The short (<250 ms) effective refractory period of an additional conduction pathway, the presence of multiple additional pathways or their septal localization, and the possibility of induction of any supraventricular tachycardia during EP study are considered as additional predictors [16].

The strategic approach in managing individuals with pre-excitation syndromes and AF, including decisions regarding cardioversion, selection of antiarrhythmic agents, and the consideration of ablation for additional rapid conduction pathways, holds critical implications for patient well-being. This significance is duly addressed in both domestic and international guidelines specifically focused on AF [17-19]. Thus, it can be argued that PQ interval shortening is a recognized marker of increased risk of SCD, but scientific consensus has not yet been reached regarding prolongation (1st degree AV blockade).

QRS complex duration

The duration of the QRS complex reflects the time of coverage of the ventricular myocardium by the depolarization wave. Its increase is associated with a disruption of this process due to structural or functional heterogeneity of the myocardium. According to the results of the study performed by D.Morin et al (2009) on the basis of the LIFE study (including patients with arterial hypertension, n = 9193), an increase in QRS duration for every 10 ms was associated with a 22% increase in the risk of SCD regardless of the presence of left bundle branch blockade (LBBB) [20].

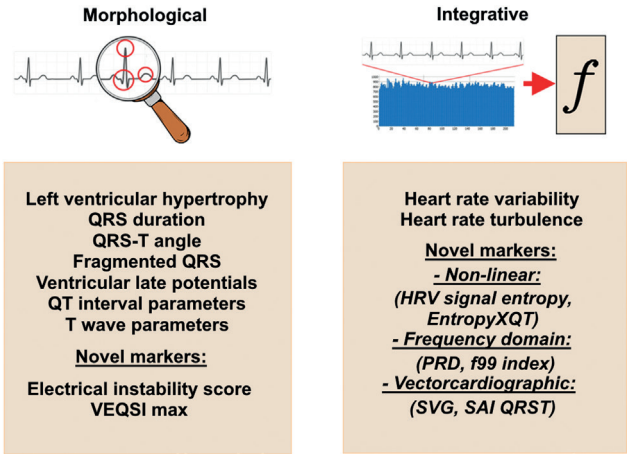

Fig. 4. Categorization of EMI markers according to the assessment methodology, hereafter HRV - heart rate variability.

In a retrospective study by H.Terho et al. (2018, n=9511) in individuals without documented cardiac pathology, QRS prolongation>110 ms was a significant risk factor for SCD. In the 10-year follow-up period, QRS prolongation was associated with a 3.09-fold (p=0.013) increased risk of SCD when analyzed with clinical and anamnestic data and cardiovascular disease (CVD) risk factors. However, at 30 years, QRS prolongation was associated with an increased risk of SCD (2.2-fold) only in univariate analysis (p = 0.003) [21].

Similar data were obtained in a study by A.Holkeri et al (2020, n=6830) on the prediction of the risk of SCD in the general population based on ECG markers. QRS prolongation >110 ms in univariate analysis was associated with a 2.05-fold (p=0.006) increase in 10-year risk of SCD (p=0.006) in multivariate analysis considering other ECG markers. QRS prolongation was among the top five most significant ECG markers, based on which a risk-stratification model was developed [22].

In the current clinical guidelines on VA, SCD, CHD, and implantable devices, QRS complex dilation is considered only from the position of patient selection for CRT: QRS >150 ms and >130 ms (for MoH RF and ESC recommendations [23, 24]) or >120 ms (for AHA/ACC recommendations [25]) is one of the criteria evaluated when deciding on implantation of CRT and CRT-D in patients with CHS, with recommendation class I in patients with LBBB and II without it.

Signs of left ventricular hypertrophy (LVH)

In a study by D.Morin et al (2009), the presence of left ventricle hypertrophy (LVH) was associated with an increased risk of SCD: in a multivariate analysis taking into account clinical and anamnestic data, SCD risk factors, and the presence of LBBB when assessed by the Sokolov-Layon criterion, a 1 mm increase in the criterion value was associated with a 32% increased risk of SCD (p<0.001). In this case, the Cornell voltaic criterion of LVH and the Cornell product did not reach statistical significance of differences [20].

A study by H.Terho et al (2018) also established the value of ECG signs of LVH as a marker of SCD risk: when assessed by the Sokolow-Layon or Romhilt-Estes criterion, the presence of LVH was associated with a 2.67-fold increase in 10-year SCD risk in multivariate analysis (p=0.002). At 30 years, the associated increased risk of SCD was 1.5 times for multivariate analysis (p=0.007) [21].

According to the results of A.Holkeri et al. (2020), signs of LVH by Sokolow-Lyon criteria were also associated with a 1.73-fold increased risk of SCD (p=0.009) in multivariate analysis. Signs of LVH, as well as QRS prolongation, were among the top five most significant ECG markers of increased risk of SCD. However, the authors suggest that in the future a combined criterion based on several indices of LVH should still be used [22].

Domestic and foreign clinical guidelines on VA and SCD mention the assessment of ECG signs of LV hypertro-

phy as a simple and accessible screening method for identifying patients at high risk of SCD (hypertrophic cardiomyopathy (HCMP), Fabry disease, etc.) for further in-depth examination [23, 26, 28].

QRS-T angle

This index reflects the absolute value of the difference between the direction of depolarization and repolarization vectors. A distinction is made between the spatial QRS-T angle, determined from a vectorcardiogram, and the frontal angle, calculated from a normal ECG recording. A case-control study by K.Chua et al (2016) based on the Oregon SUDS database found a strong correlation between frontal QRS-T angle widening and risk of SCD: an angle >97° was associated with a 2.5-fold higher risk of SCD, and a QRS-T angle >90° was also associated with an increased risk of SCD regardless of the presence of intraventricular conduction abnormalities and after adjustment for clinical and anamnestic CV risk factors. According to the authors' findings, the frontal QRS-T angle is an acceptable substitute for the spatial angle and shows prognostic value (PV) with respect to SCD even with electrical axis deviation associated with intraventricular blockades [27].

A study by H.Terho et al (2018) also demonstrated an association of QRS-T angle widening >100° with increased risk of SCD. In a 10-year multivariate analysis, the risk of SCD was 3.4 times higher in patients with a wide QRS-T angle (p=0.009). At 30 years, the associated increased risk of SCD was 1.5 times for multivariate analysis (p=0.007) [21]. In the study of A.Holkeri et al. (2020), QRS-T frontal angle >90° was associated with a 3.14-fold increase in the risk of SCD in univariate analysis (p<0.001), but in multivariate analysis with other ECG markers, the differences in the risk of SCD did not reach statistical significance, so this indicator was not included in the risk stratification model [22]. In domestic and foreign clinical guidelines on VA and SCD, the determination of the QRS-T angle is not mentioned.

Fragmentation of the QRS complex (fQRS)

FQRS, manifested as jagged or extra R' teeth, has been known to researchers since the 1960s. This index reflects impaired depolarization wave propagation and, according to the original theory, is a sign of postinfarction cardiosclerosis or myocardial fibrosis. Subsequently, an alternative theory of fQRS origin was proposed, according to which not only structural but also functional heterogeneity of myocardial electrical properties associated with channelopathies and disorders of autonomous regulation plays a role [30].

The fQRS criteria were formulated by M.Das et al. in 2006 for a narrow QRS complex as the presence in two adjacent leads of one or more additional R' teeth, serrations of the ascending knee of the R wave or the descending knee of the S wave [31]. In 2008, M.Das et al. also proposed criteria for a wide QRS complex: the presence of more than two additional R' or jagged R or S teeth in two adjacent leads, or two additional R' teeth more than 40 ms apart [32]. These studies confirmed the applicability of fQRS as a marker of sustained myocardial infarction (MI) and correlated the presence of fQRS with increased mortality in patients with wide QRS. Subsequently, this indicator has been extensively studied in patient populations with different clinical and anamnestic characteristics, and several meta-analyses and reviews have been performed on the results.

For example, a meta-analysis by G. Luo et al. (2020), which included 19 studies (n = 6914), found that in patients with MI, the presence of fQRS was associated with an increased risk of a serious adverse cardiovascular event, i.e. death from cardiovascular causes or development of non-fatal MI or acute cerebrovascular accident (odds ratio (OR) = 2.48, $p < 0.0001$ for hospitalization period, OR = 3.81, $p < 0.00001$ for distant period) and development of LTA (OR = 2.76, $p < 0.0001$) [33].

A meta-analysis by N. Engstrom et al. (2022, 10 studies, n = 3885) found that in patients with CHF with a background of CHD or non-ischemic cardiomyopathies (CMP) and an indication for an ICD for primary prevention of SCD, the presence of fQRS was associated with increased risk of LTA, discharge and antitachycardic ICD stimulation (OR = 1.51, p=0.04) and increased all-cause mortality (OR = 1.68, p=0.01). The authors note the significant heterogeneity of the samples of studies included in the meta-analysis, which explains the low reliability values [34].

Table 1.

Strategy for searching for publications in scientometric databases

Language	Search means	Keyword combinations	
English	PubMed, Google Scholar, Scopus scientific databases	Basic	(SCD OR Sudden cardiac death OR Sudden arrhythmic death) AND (ECG OR Electrocardiography OR Electrocardiographic) AND (Markers OR Predictors)
		Clarifying	(Ventricular AND (Arrhythmia OR Dysrhythmia)) AND (ECG OR Electrocardiography OR Electrocardiographic) AND (Markers OR Predictors)
		Clarifying	(Name of disease) AND (Name of ECG marker)
Russian	Google Scholar, eLibrary, Cyberleninka electronic library.	Basic	SCD OR Sudden cardiac death OR Sudden arrhythmic death) AND (ECG OR Electrocardiographic) AND (Markers OR Predictors)
		Clarifying	(Ventricular AND (Arrhythmias OR Rhythm disorders)) AND (ECG OR Electrocardiographic) AND (Markers OR Predictors))
		Clarifying	(Name of disease) AND (Name of ECG marker)

Several meta-analyses have further explored the value of fQRS as a marker of SCD risk in patients with CMP. For example, a meta-analysis by J.Goldberger et al. (2014, 45 studies, n=6088) found that in patients with dilated CMP (DCMP), the presence of fQRS was associated with a greater than sixfold increased risk of SCD, development of LTA, and justified ICD activations (OR = 6.73, p <0.001) [35]. And a meta-analysis by P.Rattanawong et al. (2018, 5 studies, n=673) found that in patients with HCMP, the presence of fQRS was also associated with a significant increase in the risk of SCD and sustained VT (OR = 7.29, p<0.01) [36].

The FQRS is mentioned in the European clinical guidelines on VA and SCD as a risk marker in patients undergoing surgery for tetrad of Fallot and as one of the indicators to suspect the presence of CHD when examining a patient with first-onset sustained VT [26]. The fQRS is not represented in the domestic and US guidelines. Overall, fQRS may be considered a valuable marker of high risk for overall mortality, SCD, and development of LTA in patients with CHD, CHF, and non-ischemic CMP. Further study of this ECG parameter in groups of patients with ICD and canalopathies seems relevant.

Ventricular late potentials (VLPs)

VLPs were first described in the 1980s as a marker for the presence of areas of non-excitable tissue that disrupt the propagation of the depolarization wave. According to modern concepts, VLPs may reflect not only organic but also functional heterogeneity of myocardial electrical properties - like fQRS described above. The signal-averaged ECG technique with measurement of time and amplitude parameters of the signal of the averaged filtered QRS complex is used for the assessment of VLPs The parameters and criteria for the diagnosis of VLPs are presented in Fig. 5.

Early studies of VLPs after MI found them to be associated with milder inducibility of VT on EMI and an increased risk of LTA and SCD [37]. With the spread of the use of revascularization and rational pharmacotherapy for MI, studies of VLPs in patients with MI have demonstrated mixed results: some have reported a reduction [38] or absence of PC [39, 40], while others have found no significant reduction in the sensitivity and specificity of this index with respect to dangerous VA and SCD [41]. On this basis, the authors J.Waks and A.Buxton (2018) in a review including more than 100 studies concluded that the results of early studies of VLPs cannot be extrapolated to the current population of patients with MI. On average, the sensitivity of VLPs in relation to VA and SCD in this group of patients is about 60%, the assessment of specificity is difficult due to the small number of works differentiating sudden and non-sudden cardiac death. The characteristic feature of VLPs remains the low prognostic value of a positive result (PR PV) and the extremely high (>90%) prognostic value of a negative result (NR PV), i.e., the potential applicability of VLPs for identifying patients at low risk of VA can be argued [42]. In patients with chronic CHD, the most reliable predictor of arrhythmic and CV mortality is the combination of VLPs and left ventricular ejection fraction (LVEF) <30% [43].

Table 2.

ECG parameters are potential predictors of the risk of SCD

ECG parameter	Parameter values associated with increased risk of SCD
PQ interval duration	<120 ms, >200 ms
QRS complex duration	>110 ms
ECG signs of LVH	SV1 + RV5/6 >35 mm according to Sokolov-Layon criterion >5 points on the Romhilt-Estes scale
QRS-T angle	>90-100°
fQRS	Presence of fQRS according to the criteria of Das et al
Late ventricular potentials	Presence of VLP on signal-averaged ECG
QTc interval duration	<330 ms, >500 ms
Duration of QTc components	Increase in rise and fall time of T
Alternation of the t-tine	Presence of macro- and micro alternation of T wave
T-wave inversion	Presence of T-wave inversion in survivors of MI, CMP, Brugada syndrome, LQTS, as part of the pattern of LV systolic overload. Isolated T-wave inversion in the general population.
Heart rate turbulence	Anomalous onset (TO ≥0%) and slope (TS <2.5ms) of turbulence.
Rate of pacing (DC) ≤4.5 ms	Снижение SDNN и LF
Heart rate variability	SDNN and LF reduction
"New" ECG parameters	Increased information entropy of ECG-signal, periodic repolarization dynamics, pathological values of global myocardial electrical heterogeneity parameters, shift of the frequency pattern of repolarization processes to the region of high frequencies.

Note: SCD, sudden cardiac death; LVH, left ventricular hypertrophy; fQRS, fragmentation of QRS; MI, myocardial infarction; CMP, cardiomyopathy; LV, left ventricle; SDNN, standard deviation of R-R intervals; LF, low frequency spectrum complexes.

VLPs PV studies have also been performed in patients with non-ischemic CMPs. A meta-analysis by G.Bazoukis et al. (2019, 7 studies in arrhythmogenic cardiomyopathy (ACMP), n = 672) found a significantly higher risk of VA and SCD in patients with VLPs (OR = 2.38, p=0.002) [44]. Despite the increased incidence of VLPs in HCMP, studies have not demonstrated the value of VLPs as a risk-marker of VA and SCD and in general had contradictory results: while T.Gavaghan et al. (1986) noted no significant differences in the occurrence of VLPs in patients with and without episodes of VT detected during HM [45], T.Cripps et al. (1990) found a significant correlation between the presence of VLPs and episodes of unstable VT during HM, but not with a history of syncope and family history of SCD [46]. There are few more recent studies of this issue. A study by Â.Chaves-Markman et al. (2020) found no significant correlation of the presence of VLPs with syncopal states, VA and family history of SCD in patients with familial HCMP [47]. Patients with DCMP have also been found to have a frequent occurrence of this phenomenon; however, overall, the PC of VLPs was insufficient for use in risk-stratification [48].

The assessment of VLPs is reflected in domestic and European recommendations as a criterion for improving the diagnosis of ACMP in patients with VA (class IB) [23, 26]. In 2020, during the revision of ACMP diagnostic criteria by an international group of experts (D.Corrado et al.), this indicator was not included in the criteria due to its low diagnostic value [29].

Duration of the QT interval and its components

The association of abnormal QT interval prolongation with increased risk of VA and SCD is well established. In the 1960s, authors A.Jervell and F.Lange-Nielsen, later C.Romano et al. and O.Ward described hereditary syndromes including syncopal states at physical or emotional load, high risk of early sudden death and QT interval prolongation [49, 50, 51]. These studies initiated the study of LQTS.

I.Gussak et al. (2000) described for the first time the opposite case - idiopathic short QT syndrome [52]. The hereditary nature, arrhythmogenic potential of SQTS and its association with SCD were described in more detail in 2003. F.Gaita et al [53]. SQTS is much less common than LQTS.

Not only the QT interval but also its constituent components are studied as ECG markers of the risk of SCD, as presented in Fig. 5. A large prospective cohort study by W.O'Neal et al. (2017), based on the ARIC study database (n = 12241), analyzed the relationship between the duration of QT interval components (ST segment duration, rise (ToTp) and fall (TpTe) of the T wave) and the risk of SCD. The interval from the end of the R wave to the apex of the T wave (ReTp) was also analyzed because of the frequent difficulty in determining the onset of the T wave. The model used included known SCD risk factors in addition to ECG parameters. Despite the significant and known association of QT prolongation with risk of SCD, only ToTp duration retained statistical significance after including all constituent components of the QT interval in the model. Prolongation of the ReTp interval also correlated with increased risk of SCD, suggesting that this interval should be used instead of the more difficult to measure T-wave rise time. The authors conclude that in their study, the association of prolonged QT with risk of SCD was due to only one component of this interval, the duration of ToTp, and that a shift from assessment of the entire QT interval to its components (temporal characteristics of the T wave) may improve the accuracy of SCD risk stratification. The authors attribute the results of earlier studies in which TpTe duration (reflecting transmural dispersion of repolarization) was associated with risk of SCD to possible differences in sampling and study design. Changes in TpTe duration are more common in individuals with congenital LQTS and HCMP and may be a valuable marker of SCD risk in this group, whereas increased ToTp duration (reflecting delayed repolarization of subepicardial layers) may be a more prognostically important marker in individuals without canalopathies and myocardial hypertrophy, but this hypothesis requires testing [54].

Assessment of QT interval duration during standard ECG is an important diagnostic method (class I) in patients with registered VA or suspected of it, and the study of QT duration and dynamics during provocation tests is necessary in patients with suspected LQTS, which is reflected in domestic and foreign clinical recommendations [23, 26, 28]. Evaluation of individual QT interval components (ToTp, TpTe, ReTp, etc.) is not presented in the guidelines.

Microvolt alternation of the T-wave (MVAW)

The early development of a methodology for the assessment of MVAW dates back to 1988, when the alternative ECG morphology index (AEMI) proposed by J.Smith et al. reflecting the spectral power of microvolt oscillations of the cardiac signal showed a correlation with the risk of induction of VT in patients during EMI [55]. Subsequently, the method of calculating this index, modified by D.Rosenbaum et al. (1994), demonstrated a significant correlation with the risk of VT during EMI (sensitivity 81%, specificity 84%) regardless of the pres-

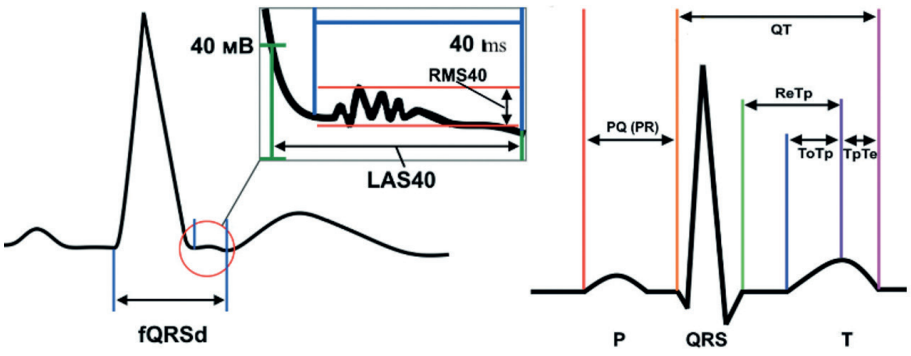

Fig. 5. Assessment of ventricular late potentials (A) and QT interval components (B), where fQRSd is the duration of the averaged QRS, LAS40 is the duration of terminal oscillations with amplitude <40 mV, and RMS40 is the RMS amplitude of terminal oscillations during the last 40 ms of the QRS complex. VLP criteria: fQRS >114 ms, LAS40 >38 ms, RMS40 <20 mV.

ence of structural heart disease [56]. The algorithm for estimation of MVAW using spectral analysis of differences between 128 consecutive T teeth was the first most widely used method of estimation of this index; its essence is shown in Fig. 6. 6. In 2002, B.Nearing and R.Verrier proposed a new method of MVAW estimation based on the calculation of differences between averaged T teeth in even and odd cardiac cycles, called modified moving average (MMA), also presented in Fig. 7. The method was tested in an in vivo experimental model of myocardial ischemization and reperfusion. MVAW indices calculated by the MMA method were significantly higher in animals with FJ developed on the background of ischemia [57].

Numerous studies, including those in patients with CHD and MI, have been devoted to MVAW as a predictor of LTA and SCD. In a series of studies performed in 2000-2010 in patients with MI, T.Ikeda et al. showed high sensitivity (93%) and CI of OR (98%), but low PR PV (28%) of MVAW in relation to the development of VA in them, and also established the association of MVAW presence in the acute stage of MI with a 6-fold increase in the risk of SCD or AF in patients with reduced or preserved LVEF [58-60]. However, other large studies have shown opposite results. Thus, in the studies of M.Gold et al. (2008, SCD-HeFT) and H.Huikuri et al. (2009, CARISMA), no significant differences were obtained in terms of CSD, ICD activation and event-free survival between groups with and without MVAT, regardless of the presence of CHD [61, 62]. The MASTER study performed by T.Chow et al. (2008) on a sample of patients with a history of MI and CHF with low ejection fraction (LVEF) also showed no significant differences between groups with and without MVAW in the annual probability of developing SCD or ICD activation, but patients with MVAW had significantly higher all-cause mortality [63].

A meta-analysis by S. Hohnloser et al. (2009) explored the reason for the differences in outcomes between the MVAW studies. According to the authors' hypothesis, MVAW has value as a predictor of dangerous VAs in patients with an indication for ICD implantation for primary prevention of SCD, but cannot reliably predict the risk of device activation in patients with an already implanted ICD. After reviewing data from the ABCD, MASTER, MADIT-II, and SCD-HeFT trials, the authors found that the number of patients with justified ICD triggering was significantly higher than the number of patients in whom this triggering prevented the development of SCD, with these «excess» triggering events occurring about equally in patients with and without MVAT, reducing the PV of MVAT, i.e., ICD triggering cannot be considered analogous to SCD. In patients without MVAT, ICD implantation has no effect on mortality, whereas in patients with CHD, LVEF <35%, and a positive or indeterminate MVAW test, ICD implantation can achieve a meaningful reduction in mortality. The authors propose to consider the result of the MVAW test when deciding on ICD implantation in patients with LVEF <35% and when referring patients with LVEF >35% but with a history of MI or episodes of unstable VT for advanced arrhythmologic evaluation [64].

In 2011, an expert panel of the International Society of Chem and Noninvasive Electrocardiology issued consensus recommendations on MVAT. According to the authors, the methods of MVAW estimation have been tested and demonstrated their value in risk stratification of VA development in more than 12000 patients, and

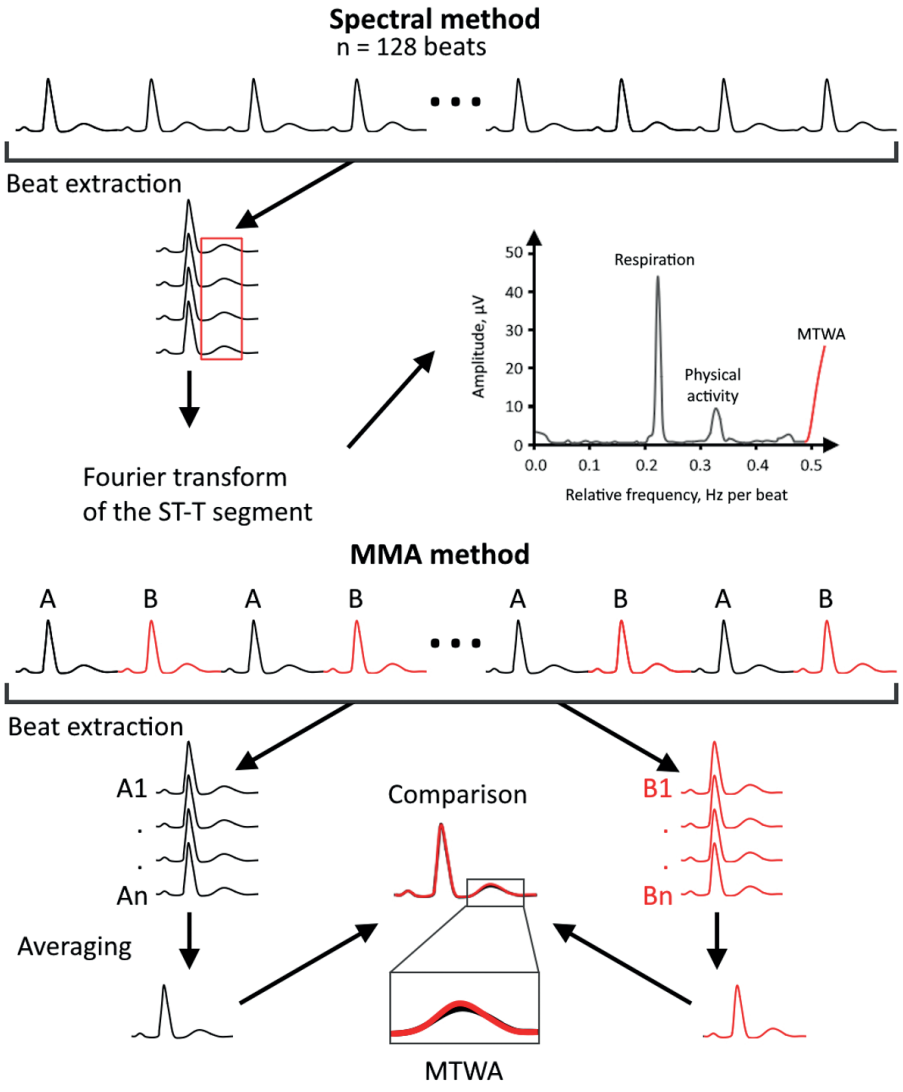

Fig. 6. Techniques for assessing microvolt alternans of the T wave, where the unit "Hz/cardiac cycle (CC)" means that oscillations with a frequency of N Hz/CC occur every 1/N cardiac cycles. Thus, the MTWA has a frequency of 0.5 Hz/CC, between 2 neighboring T waves.

promising directions for further study of this index are its evaluation as a predictor of arrhythmia risk in patients with preserved LVEF and as an index for the choice and direction of therapy [65].

The variability of PP MVAT, which depends on the characteristics of the study population, was the reason for performing a meta-analysis by A.Gupta et al. (2012). In contrast to most previous studies, instead of estimating the PV of PR/RR, which strongly depend on the prevalence of the disease in the study population, the authors performed the likelihood ratio/LR test, which as well as its components (sensitivity and specificity) do not have this feature. The objective of the meta-analysis was to determine the ability of the MVAW test to improve risk-stratification of LTA and SCD. An analysis of 20 studies (n = 5945), including the «MADIT-II-like» (MI survivor and LVEF <30%) and «SCD-HeFT-like» (NYHA class II and III CHF and LVEF <35%) patient populations, yielded rather modest results from the MVAW LR test. Thus, the considered significant LR PR >5 was not achieved (only 1 study achieved an LR PV >3). For LR PV, the results were slightly better: a value <0.2 was achieved in 8 of 17 studies, which is broadly similar to the high zlr pv characteristic of MVAT. The risk-stratifying ability of MVAW was also low in additionally studied populations. Among «MADIT-II-like» patients with a 6% annual risk of SCD, a negative MVAW test distinguished a group with a 4.3% annual risk of SCD, and a positive or indeterminate test distinguished a group with a 7.1% annual risk of SCD. In a population of «SCD-HeFT-like» patients with an annual risk of SCD of 2.95%, the high-risk group identified by the test had a risk of SCD of 3.9% and a low-risk group had a risk of 2.6%. No significant differences in stratification were obtained when the end point with SCD was replaced by the development of ventricular tachyarrhythmias. According to the authors' conclusions, this poor improvement in stratification by the MVAW test is unlikely to significantly improve the selection of patients referred for prophylactic ICD implantation [66].

Thus, the contradictions in the results of studies and meta-analyses support the interest in studying MVAW : both in terms of its potential for clinical application in different patient populations and in terms of the underlying EF mechanisms [67].

The 2017 American Heart Association clinical guidelines dedicated to VA and SCD state that there is no scientific consensus on this ECG indicator [28]. In the domestic and European recommendations, MVAW does not appear, but macroAT is mentioned among the diagnostic criteria for LQTS [23, 26].

T-wave inversion (TTI)

TTI, i.e., change of the T wave polarity normal for the lead in question to the opposite one, is a nonspecific ECG phenomenon and can be both a variant of norm (for example, in the right thoracic leads in children) and a pathologic sign. Pathologic TTI is seen in ventricular hypertrophy (including HCMP), ACMP, takotsubo CMP, LBB blockade, Brugada syndrome and some variants of LQTS, electrolyte disturbances, overdose of cardiac glycosides and psychostimulants, myocardial ischemia, pulmonary embolism., and intracranial hypertension. Cardiomyopathies represent an important cause of sudden death, particularly in young adults, and as a consequence, a large number of studies have focused on TTI in cardiomyopathies. TTI has also been studied in postinfarction patients, as part of the systolic overload pattern in LV hypertrophy, and simply as an isolated ECG phenomenon in the general population.

In a study by B. Milovanović et al. (2006), performed on a sample of 881 MI patients, the presence of TTI in the orthogonal X lead was one of the significant predictors of increased risk of total mortality and SCD (RR 1.9, p = 0.012) [68]. A randomized study by P.Okin et al (2014), which included 7409 patients with arterial hypertension from the LIFE study sample, aimed to evaluate the PV dynamics of the systolic overload pattern. The results of the study were expected: the appearance of ECG signs of systolic overload on antihypertensive therapy was associated with a worse prognosis, including in relation to SCD (OR = 2.19, p = 0.035) [69].

Large cohort studies by Finnish authors have been devoted to the study of TTI as a predictor of risk of SCD in the general population. Thus, J.Laukkanen et al (2014) performed a cohort study of 1951 men (mean age 55.6 years) in which isolated STEMI in the absence of ST-segment depression or NPY blockade was studied. The presence of such TTI was associated with a 3.3-fold (p < 0.001) increased risk of SCD at 20-year follow-up in univariate analysis and improved reclassification by the IDI method (I index 0.014, p = 0.036) when added to a model based on clinical-anamnestic factors [70]. In another already mentioned population-based study by A.Holkeri et al. (2020), TTI was one of the most significant ECG markers of SCD risk (zrR = 2.29, p = 0.005) and was included in the final combined risk-stratification model [22].

TTI has been studied quite closely as a predictor of the risk of SCD in patients with ACMP. T.Agbaedeng et al (2022), based on the results of a meta-analysis of 52 studies on this topic (n = 5485 people), found that TTI in such patients was associated with a 1.12-fold increase in the risk of SCD (p < 0.05). Other important factors were male sex (RR = 2.08), right ventricular dysfunction (RR = 6.99) and fQRS (RR 6.55) [71].

TTI is mentioned in current recommendations on VA and SCD. In the European guidelines, evaluation of STEMI is included in the algorithm for the evaluation of a patient

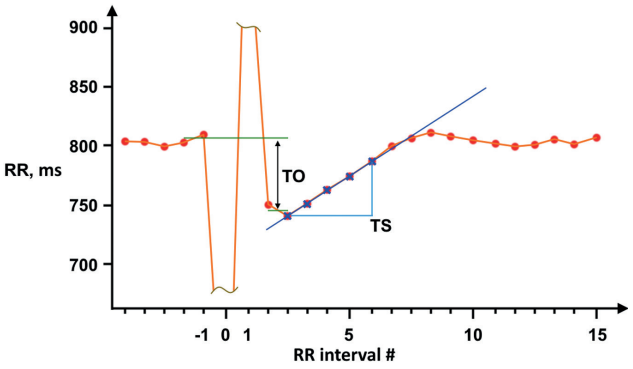

Fig. 7. Heart rate turbulence parameters, where TO is the onset of turbulence (reflecting the acceleration of the rhythm after VE), TS is the slope of turbulence (reflecting the rate of deceleration of the rhythm after initial acceleration). Normal TO <0%, TS >2.5 ms/RR.

with first-onset persistent VT. It has been claimed to be promising for the application of this marker in risk-stratification models [26]. The American Heart Association guidelines present CHF as a diagnostic sign of Brugada syndrome associated with an increased risk of SCD in young individuals [28]. Domestic guidelines do not mention TTI as a «separate» ECG phenomenon [23].

Heart rate turbulence (HRT)

The phenomenon of short-term fluctuations in RR-interval durations after ventricular extrasystole was first described by G. Schmidt et al. (1999) in patients undergoing MI, and subsequently formed the basis of the concept of HRT [72]. HRT is characterized by the parameters of turbulence onset (TO) and turbulence slope (TS), reflecting the severity of HR change after VE and its recovery rate. These parameters are presented in Fig. 7.

It is reasonable to present a large systematic review and meta-analysis by M.Disertori et al. (2016) evaluating abnormal HRT as a predictor of the development of LTA and SCD in MI patients and in patients with CHF (20 studies, n =12832) [73]. In addition to the study of standard HRT parameters, works devoted to the deceleration capacity (DC) index were included. This marker, calculated on the basis of a series of RR-intervals, reflects the average «severity» of episodes of heart rate slowing during a long ECG recording and, according to the authors of the methodology, characterizes the activity of the parasympathetic part of the autonomous nervous system (ANS). Abnormal HRT had high specificity (70-90%) for total mortality, cardiovascular mortality, and development of arrhythmic events in both patients with CHF (SCD RR = 3.73, VA RR = 2.51) and patients after MI (SCD RR = 4.82, VA RR = 4.48), with the presence of reduced DC further increasing risk. No meta-analysis of the data was performed in the study of HRT impairment in combination with MVAW because of the significant heterogeneity of the data. The authors note the value of abnormal HRT as a predictor of cardiovascular and arrhythmic death risk (PR similarity ratio 4.1 and 2.7, respectively) in postinfarct patients and suggest that HRT assessment should be considered as an additional method of identifying a high-risk group of patients for ICD implantation, but point out the lack of data for postinfarct patients with LVEF <30% and lower PV in the group of patients with CHF. The authors also suggest that the combination of HRT and MVAW should be looked at as improving prognostic value. There is no mention of HRT in the current domestic and foreign clinical guidelines on VA and SCD.

Heart rate variability (HRV)

Systematic study of HRV began in the 1960s of the 20th century and was associated with the development of ECG signal processing techniques and the invention of the HM. Abnormal HRV, reflecting violations of autonomous regulation of physiological processes, is a predictor of increased mortality in populations of patients with cardiologic (MI, CHD) and other diseases.

S.C.Fang et al (2019) performed a meta-analysis of HRV studies in patients with CVD (28 papers, n=3094). The correlation of HRV time and frequency parameters with all-cause mortality and cardiovascular events (including LTA and SCD) was assessed. In patients with MI, low HRV was found to be associated with increased all-cause mortality (RR = 2.27, $p < 0.01$) and risk of CV events including SCD (zrR = 1.41, $p < 0.01$), whereas in patients with stable CHD and CHF, the differences did not reach significance. Among HRV indices, the most significant were low SDNN and power of the low-frequency part of the spectrum (LF). The authors note that their findings do not contradict the results of a previous meta-analysis from 2009 that demonstrated a correlation of reduced SDNN with high mortality in postinfarction patients. The authors explain the absence of reliable correlation between HRV parameters and risk of CV events in patients with stable CHD and CHF by the complexity of hemodynamic and autonomous cardiac regulation disorders in chronic course of the disease, which makes it difficult to unambiguously identify specific markers.

On the other hand, according to the authors' conclusion, the study of HRV parameters in patients with CHD can be considered from the side of tracking the progression of disorders of autonomous regulation of cardiac activity [74]. It also remains promising to study the applicability of HRV assessment for the prediction and risk stratification of CHD in the general population and in patients without severe CVD and comorbidities: there are relatively few studies devoted to this issue.

Domestic and foreign clinical guidelines on VA and SCD do not yet regulate the use of HRV for SCD risk stratification, but the European guidelines of 2022 state the potential promising results of the conducted studies [26].

Risk-stratification models based on combinations of ECG parameters

In addition to analytical search for new ECG markers with high sensitivity, specificity, and PV, a number of authors use a synthetic approach, i.e., identification of combinations of different indices associated with the greatest increase in RR and PV.

A landmark in this direction was the REFINE study by authors D.Exner et al. (2007), which focused on the combined assessment of the substrate of VA and the impact of ANS. In a study of ECG markers in surviving MI patients (n = 322), HRT and MVAW were identified as associated with the highest RR and having the best classification values in ROC (receiver operating curve) analysis. LVEF was also included in the model as a recognized marker of SCD risk. The combined model showed a sensitivity of 62%, specificity of 74%, PR PV of 19% and PR PV of 95%. This low PR PV is a characteristic feature of HRT and MVAW [75].

The mentioned study by A.Holkeri et al. (2019) developed a combined model based on the most reliable ECG markers of SCD risk. It included HR >80/min, PR duration >220 ms, QRS duration >110 ms, signs of LVH, and T-wave inversion. Having a score of 3 or more was associated with a 10-fold increase in the risk of SCD (OR 10.23, $p < 0.001$). The use of an ECG model in addition to the standard one based on clinical-anamnestic and laboratory parameters resulted in an improvement in PC; when assessed by Harrell's C-index (0.028 increase, $p < 0.05$), NRI (0.397, $p < 0.001$) and IDI-statistics (0.037, $p < 0.001$). The combined application of both models reasonably reclassi-

fied 21.1% of SCD cases into the high-risk group and 4.0% of non-SCD cases into the low-risk group [22]

A. Frolov et al. (2019) proposed a new combined ECG-based combined model for risk stratification of LTA based on the EMI index. The index was calculated using a regression model accounting for the presence of fQRS, QRST angle >105°, QT duration >394 ms, and MVAW >23 μV with individual component weights. The indicators were selected according to the highest level of reliability of differences. The «balanced» index reflects the depolarization and repolarization phases and includes indices characterizing the substrate and triggers of VA. The results of the study in patients with CV disease (n = 1014) showed a sensitivity of 75%, specificity of 78%, PR PV of 77%, and RR PV of 76%. Also, the standardized calculation formula makes the EMI index convenient for automated evaluation [76].

N. Ilov et al. (2021) presented the first results of an ongoing prospective Russian study on the prediction of the risk of LTA in patients with HFrEF (n = 165). A regression model was constructed by analyzing several ECG markers of EMI, which included the duration of the P wave, the TpTe interval, and the Cornell product value. The model showed a sensitivity of 61.1%, specificity of 59.6% and diagnostic efficiency of 60%. A feature of this model is the inclusion of the P waveform parameter because the association of atrial remodeling with the risk of SCD is also being studied. The authors note the low level of significance of the differences and expect to increase it in the process of accumulating data of the ongoing study [77].

Despite the promising results of the studies performed, clinical guidelines on VA and SCD have not yet presented scales and calculators of SCD risk based on combined ECG patterns.

New ECG markers of myocardial electrical instability

New approaches to the study of ECG data with the use of information theory, nonlinear dynamics and new methods of signal analysis allowed to develop indices and criteria reflecting the features of the frequency pattern, dynamics, self-similarity, and randomness of the processes of electrical activity of the heart and autonomic regulation of cardiac activity. This group includes HRV entropy parameters [78], periodic repolarization dynamics (PRD) [79, 80, 81], global electrical heterogeneity (GEH) parameters [82], QT interval entropy [83], and f99 index [84, 85]. In studies, these indices have demonstrated potential applicability as risk markers for overall and cardiovascular mortality and the development of LTA, including in patients with CHD, MI, and HFrEF. Entropic HRV parameters have also been studied for short-term (within minutes and hours) prediction of SCD and have shown potential promise.

A peculiarity of many new integral ECG indices is their non-obvious and complex explainability, including clinical explanations. Despite the demonstrated PV, the author's methodology of parameter estimation is often a «black box», and the supposed connection with physiological mechanisms is based on unusual or new theories (fractal dynamics of myocardial electrical processes, connection of periodic volley activity by the sympathetic nervous system with repolarization vector oscillations, etc.). New ECG markers are still to be actively studied, but they may be the ones that can help to further understand the pathogenesis of life-threatening arrhythmias and make significant steps toward addressing the problem of primary prevention of SCD.

CONCLUSION

The development of ECG models for risk-stratification of SCD remains an important unresolved problem in modern medicine. In addition to the search for new ECG markers, comparative analysis of PV of long studied, but not studied definitively, «generally recognized» indicators and synthesis of the results of studies is also of interest, but this task is extremely complicated by the heterogeneity of the studied populations and the methods used (endpoints of studies, selected threshold values for ECG markers). Thus, various meta-analyses have demonstrated that the value of ECG predictors significantly depends on the underlying disease, and therefore their study for the assessment of the risk of SCD may be more promising not in the general population, but in relation to specific neologies and considering clinical and anamnestic risk factors of CVD. In addition, the often-observed contradictory results of studies of individual ECG markers may indicate the prospect of studying and evaluating not so much individual parameters as their combinations associated with the strongest increase in the risk of SCD and reflecting different «facets» of VA pathogenesis (substrate and trigger, depolarization and repolarization disorders) and developing risk-stratification models on this basis.

Standardization of approaches to test performance and interpretation of results, validation of new methods and models in prospective randomized trials are important tasks.

A specific trend in modern scientific works on this problem is the synthesis of medical, mathematical knowledge and information technologies, requiring a multidisciplinary approach, since many new ECG indicators require the use of complex, «science-intensive» methods and evaluation algorithms.

The vastness and heterogeneity of the population with risk factors for SCD, the complex multifactorial nature of arrhythmogenesis, and the huge clinical potential of the results of the studies give reason to name the problem of ECG-stratification of SCD risk one of the «holy grails» of cardiology.

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