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NOVEL ELECTROCARDIOGRAPHIC RISK PREDICTORS OF SUDDEN CARDIAC DEATH

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Among studies addressing ECG-based risk stratification for sudden cardiac death and life-threatening ventricular arrhythmias, novel approaches to ECG data analysis and derived markers of myocardial electrical instability are of particular interest. Notably, metrics obtained through vector-based, frequency-domain, and nonlinear ECG analysis have demonstrated significant value as predictors of high-risk ventricular arrhythmias and sudden cardiac death.

Key words: electrocardiography; sudden cardiac death; ventricular tachycardia; ventricular fibrillation; heart rate variability; global electric heterogeneity; periodic repolarization dynamics; entropy of repolarization

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Sudden cardiac death (SCD) remains one of the most pressing challenges in contemporary healthcare. According to current understanding, its most common cause is the occurrence of life-threatening ventricular arrhythmias (VA), including sustained ventricular tachycardia (VT) and ventricular fibrillation (VF).

The modern approach to VA research considers a comprehensive "arrhythmic profile" comprising the arrhythmic substrate, determined by the underlying cardiac disease, clinical, electrocardiographic, and electrophysiological characteristics (including the precipitating (trigger) factors), and ECG-derived markers of myocardial electrical instability (MEI). ECG-based MEI markers can reflect various mechanisms of arrhythmogenesis - both substrate-related and trigger-related, and are intended to improve the prediction of life-threatening VA.

A recent review dedicated to ECG MEI markers proposed their classification into two groups: established and novel markers. The first group markers are widely recognized by researchers and clinicians, have been extensively studied (including meta-analyses), and in some cases incorporated into clinical guidelines [1]. Meanwhile, novel markers enabled by advances in information technologies and computational power allow extraction of previously inaccessible ECG information. As such, novel ECG markers warrant further investigation to evaluate their clinical applicability.

The aim of the present review is to analyze studies focusing on selected novel ECG MEI markers as predictors of life-threatening VA and SCD, examining the underlying hypotheses, methodological aspects of their assessment, and nuances in clinical interpretation.

Table 1.

Strategy for searching publications in scientometric databases for the period 2014-2025

Language	Search tools	Keyword combinations	
English	PubMed, Google Scholar, Scopus	Main	(SCD OR Sudden cardiac death OR Sudden arrhythmic death) AND (ECG OR Electrocardiography OR Electrocardiographic) AND (New OR Novel) AND (Markers OR Predictors)
		Clarifying	(Ventricular AND (Arrhythmia OR Dysrhythmia)) AND (ECG OR Electrocardiography OR Electrocardiographic) AND (New OR Novel) AND (Markers OR Predictors)
		Clarifying	(SCD OR Sudden cardiac death OR Sudden arrhythmic death) AND (Entropy OR Nonlinear dynamics OR Frequency OR Transform OR <дополнительные уточняющие ключевые слова>)
		Clarifying	<Название заболевания> AND <Название нового ЭКГ-маркера>

This review covers research published between 2015 and 2025. Core search strategy is presented in Table 1. Within the scope of this work, the novel ECG MEI markers are categorized into three groups based on their approach to analysis of recorded ECG signal and derived data:

Analysis of diagnostically relevant parameters directly measured from the ECG. Here, the temporal dynamics of quantitative indices are evaluated and correlated with VA/SCD risk. Of particular interest is a set of novel vectorcardiographic (VCG) parameters collectively termed Global Electrical Heterogeneity (GEH) [5-12]:

- Spatial QRST angle - the 3D angle between the depolarization and repolarization vector loops, analogous to the well-known frontal QRST angle, a recognized MEI marker.
- Spatial ventricular gradient (SVG) vector magnitude and sum absolute QRST integral (SAI QRST) - indices reflecting heterogeneity in myocardial depolarization and repolarization.

Frequency-domain analysis of ECG parameters related to ventricular repolarization. This includes time-frequency transformation of time series of angles between successive T-wave axes, or direct analysis of T-wave frequency content. Parameters are assessed both relative to threshold values and as trends. Two frequency-based ECG markers are of particular interest:

- Periodic Repolarization Dynamics (PRD) - low-frequency (<0.1 Hz) power spectral density of a time series of angles between successive T-wave axes, evaluated from a 20-minute ECG recording [13-15].
- f99 index - the frequency at which the normalized spectral energy of the T wave reaches 99% [16, 18, 19].

Nonlinear analysis of ECG parameters (RR, QT intervals). This approach assesses the presence and degree of nonlinear components against deterministic and stochastic components of a time series. Notable nonlinear ECG markers include entropy-based measures (e.g., heart rate variability (HRV) entropy, repolarization entropy) and fractal methods such as detrended fluctuation analysis (DFA):

- Combinations of linear (statistical and frequency-domain) and nonlinear (entropy-based, fractal) HRV indices, analyzed using machine learning algorithms (e.g., k-nearest neighbors, support vector machines) for risk stratification or prediction of VA/SCD [27-36].
- Nonlinear indices of the repolarization phase calculated from sequences of selected ECG intervals [37, 42].

PROPERTIES OF LINEAR AND NONLINEAR SYSTEMS

Key properties of linear systems include additivity (the system's response to a composite input equals the sum of its responses to each component), homogeneity (the system's response is proportional to the input magnitude), and invariance (temporal changes in the input produce corresponding temporal changes in the output). These properties significantly simplify the study, modeling, and prediction of linear system behavior.

In contrast, the defining feature of nonlinear systems, as the name implies, is the absence of these properties, enabling the emergence of phenomena such as chaotic behavior (high sensitivity to initial conditions), multistability (presence of multiple stable states), emergence (appearance of properties absent in individual elements), scale invariance and self-similarity (retention or repetition of structural patterns across scales), temporal evolution of states, self-organization, and adaptability.

Such properties complicate the investigation and prediction of nonlinear system behavior considerably. However, by employing numerical measures of chaoticity - such as entropy, Lyapunov exponents, fractal dimension, phase portraits, and others - it is possible to assess certain properties of a dynamic system from its time series, obtaining important prognostic parameters.

NONLINEAR AND FRACTAL PROPERTIES OF THE CARDIOVASCULAR SYSTEM

Multiple levels of organization and richness of component interactions that inherently confer nonlinear behavior characterize biological systems. The cardiovascular (CV) system is no exception, exhibiting nonlinear properties at all organizational levels: from the single myocardiocyte (dependence of response to a stimulus on the current phase of the action potential), to the heart as an organ (loss of Frank-Starling law linearity in pathologically elevated preload), to the CV system as a whole (complex neurohor-

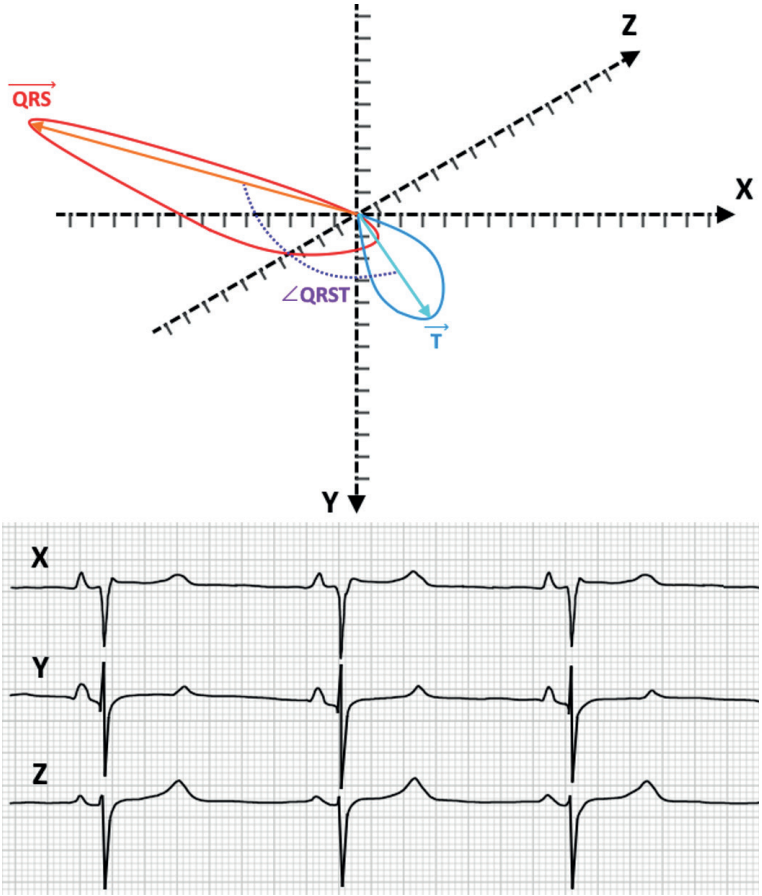

Fig. 1. GEH parameters: spatial QRST angle between QRS and T wave loops in three-dimensional space.

monal regulation of blood pressure and heart rate mediated by feedback loops).

Another important property of many biological systems is fractality - self-similarity and recurrence across different scales. In the CV system, this property manifests both structurally and functionally. Examples include fractal-like branching of the conduction system and the hierarchically interconnected operation of feedback control loops from cellular to systemic level.

CV biosignals (ECG, HRV and others) under certain conditions can be viewed as generated by deterministic chaos, where apparently irregular fluctuations conceal deterministic nonlinear components [2, 3].

The dynamic system generating these signals evolves over time in such a way that current-state analysis enables forecasting of future state, such behavior known as iterative. This forms the basis for studying and predicting physiological system dynamics using a set of nonlinear parameters measured at the present or prior time points.

It can therefore be assumed that the nonlinear, dynamic, iterative and fractal nature of processes within the CV system determines the properties of the biosignals it generates. While nonlinear system behavior can be described using linear methods in a process known as linearization, this requires the system to be near an equilibrium point - for example, the analysis of resting ECG recordings. These constraints support the rationale for exploring novel MEI markers obtained via nonlinear analysis. Nonlinear indices offer greater precision and reliability in extracting information from signals originating from inherently chaotic, dynamic sources, despite their increased computational complexity.

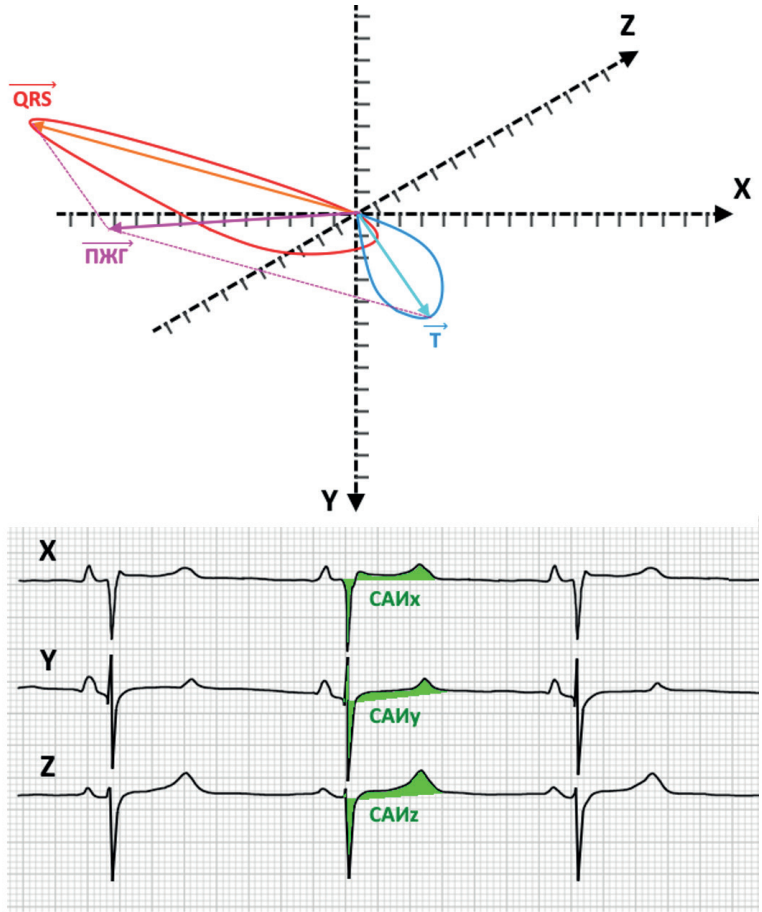

Fig. 2. GEH parameters: SVG vector (sum of QRS and T vectors in three-dimensional space) and its scalar analog SAI (total area under QRST curve).

ANALYSIS OF DIRECTLY MEASURED ECG PARAMETERS

Numerous temporal and amplitude-based parameters can be directly measured from the raw ECG signal. This group includes various intervals, many of which are already recognized as established markers of myocardial electrical instability, as well as VCG features (vectors, angles, areas) that have yielded several novel MEI markers.

The assessment of myocardial electrical activity and its spatiotemporal dynamics in normal and pathological states is of particular interest for stratifying the risk of life-threatening VA and SCD. These dynamics can be described geometrically in terms of vectors, angles, and areas. Well-known examples of such descriptors include the electrical axes of the QRS complex, P and T waves. Differences in vector orientations are quantitatively expressed as angles, the most familiar being the frontal QRST angle. While these vectors and angles can be readily calculated in the frontal plane from a standard 12-lead ECG, their three-dimensional assessment is more feasible using ECG recorded in a VCG system (most commonly Frank leads system) or transformed into such system, as reflected in the calculation methods for this group of indices.

Global electrical heterogeneity parameters

in the 1930s, Wilson et al. introduced the concept of the SVG - a vector directed toward the myocardial region with the shortest action potential duration. This index reflects the axis of maximal electrical heterogeneity in the heart, but its calculation complexity historically limited its clinical adoption [4]. In 2010, Tereshchenko et al. expanded this concept by introducing the SAI QRST parameter. This parameter is calculated as the sum of the absolute values of areas under QRST curve, averaged over 5 minutes, in three orthogonal leads. The authors hypothesized that changes in SAI QRST reflect the spatiotemporal heterogeneity of myocardial electrical activity. In a healthy heart, synchronous depolarization wave propagation ensures mutual cancellation of opposing electrical fields in different myocardial regions, whereas electrical heterogeneity - such as that arising from ischemia or fibrosis - leads to uncompensated potentials, altering the SAI of the QRS complex. Similarly, heterogeneity of repolarization (e.g., due to ischemia or electrolyte imbalances) manifests as differences in the temporal and amplitude characteristics of repolarization among myocardial segments, producing changes in the SAI of the T wave. Integrating over the entire QRST interval allows assessment of heterogeneity contributions from both depolarization and repolarization.

In a pilot study, a low SAI QRST was associated with a more than threefold increase in the risk of life-threatening VA; however, this finding was not replicated in a subsequent

study in which elevated, not reduced, SAI emerged as the risk marker. These contradictory results were likely attributable to differences in the clinical characteristics of the study populations [5-7].

Subsequently, the group of VCG parameters comprising the spatial QRST angle [8], SVG vector magnitude, and SAI QRST became collectively known as GEH parameters (Figs 1 and 2).

In a large, long-term population-based study based on the ARIC database, Perez-Alday et al. (2019) investigated the prognostic value of GEH parameters for SCD over a mean follow-up of 24,4 years. Based on the analysis of 577 SCD events recorded (3,7% of the cohort), the authors proposed a biphasic model of SCD risk stratification: in the short term, the significant predictor was an SVG vector directed toward the ventricular outflow tracts, indicating the presence of myocardial regions with a short refractory period - a potential VA substrate; in the long term, greater predictive value was found for an SVG vector directed toward the LV and a wide QRS-T angle, reflecting LV remodeling as a chronic arrhythmic substrate [9].

Further work focused on developing an SCD risk score based on GEH indices. Waks et al. (2016) conducted a study combining cohorts from the ARIC and CHS studies. Over a median follow-up of 14 years, 486 SCD events occurred (7,56%). Proportional (PR) and competing risk (CR) models were constructed, incorporating demographic characteristics, cardiovascular history and risk factors, established ECG indices (heart rate, QTc duration, QRS width, LV hypertrophy, intraventricular conduction abnormalities), and longitudinal changes in the GEH parameters. Across all models, GEH indices retained independent prognostic value; inclusion of LVEF did not significantly alter the correlations. The most robust predictors were the spatial QRS-T angle, SAI QRST, and SVG vector magnitude. A risk calculator based on these findings was made available in the supplementary materials of the original article [10].

Subsequently, Waks et al. investigated the prognostic utility of GEH parameters in patients with structural heart disease in the multicenter retrospective GEHCO study [11]. The primary endpoint was appropriate ICD therapy delivery for sustained VT. Over a median follow-up of 4 years, 541 patients (≈5% annually) reached the endpoint. Four CR models were developed: model 1 including demographic variables only, model 2 adding cardiovascular risk factors, model 3 adding device characteristics and model 4 additionally incorporating established ECG markers (heart rate, QRS width, QTc duration).

Given the previously observed inconsistent association of SAI QRST with arrhythmic risk, additional analysis was performed for subgroups by IHD status. After full adjustment (model 4), the spatial QRS-T angle, SVG vector direction, and SVG magnitude were significantly associated with the primary endpoint. Notably, arrhythmic risk correlated directly with QRST angle and SVG direction, and inversely with SVG magnitude. In IHD patients, elevated SAI QRST correlated with increased risk, whereas in non-IHD patients, lower SAI QRST was the risk marker. These findings were consistent with earlier observations that a superior-posterior SVG direction and wide QRS-T angle indicate elevated arrhythmic risk. The authors hypothesized that nonuniform SAI-VA risk correlation was caused by the underlying substrate for electrical heterogeneity. In IHD, electrical heterogeneity is driven by localized ischemia - manifesting as increased SAI, higher SVG magnitude, and vector orientation toward the arrhythmogenic substrate, whereas in non-ischemic etiologies, diffuse myocardial remodeling and fibrosis dominate, replacing electrically active myocardium and thus decreasing both SAI and SVG magnitude, without specific directional changes (described as the vector pointing «toward the entire LV»).

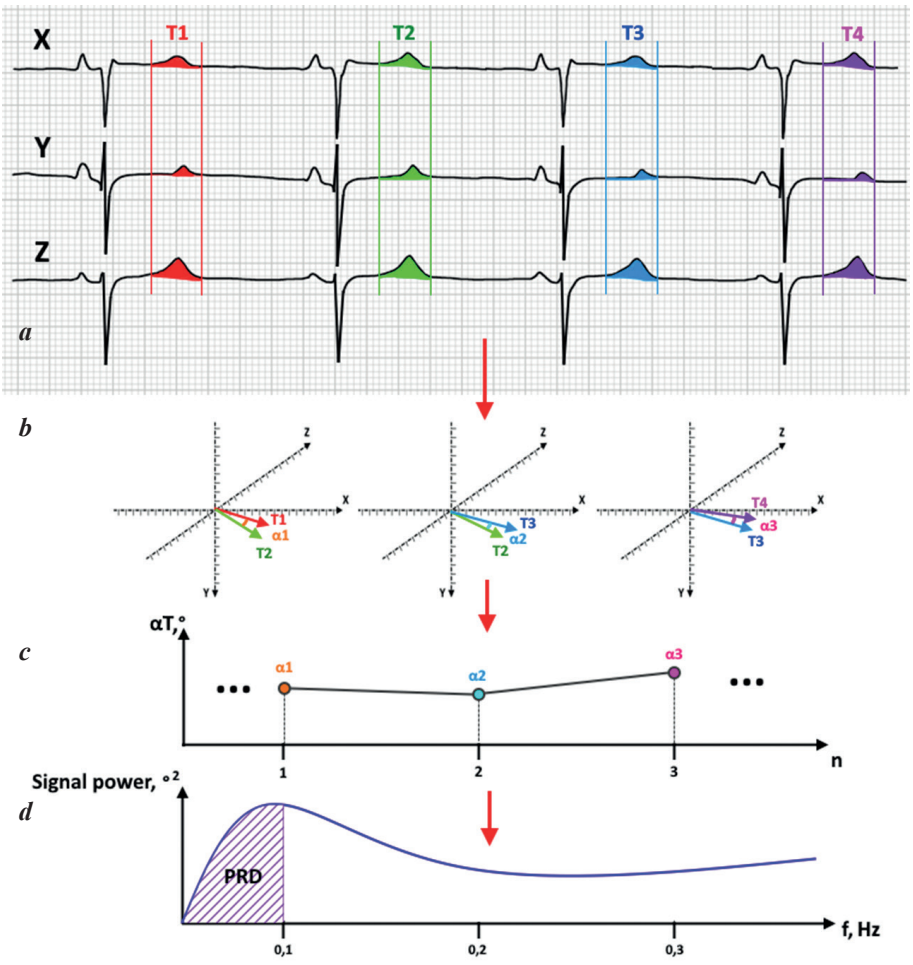

Fig. 3. PRD calculation: a - ECG in orthogonal lead system and T wave extraction; b - T wave electrical axis vectors and angles between them; c - time series of angles between T wave vectors (αT); d - power spectrum obtained by Fourier transform of angle time series. PRD is defined as power below 0,1 Hz.

These observations emphasize the necessity of accounting for myocardial disease etiology when developing GEH-based risk models. Study limitations included the lack of standardized ICD programming protocols, absence of postmortem ICD analysis in deceased patients to determine arrhythmic events immediately preceding death, and the debated validity of using ICD therapy delivery as a surrogate endpoint for SCD - concerns also noted in earlier studies [12].

VCG markers exemplify a concept discovered ahead of its time: introduced in the 1930s, they remained largely unused in clinical practice due to calculation complexity, but modern advances in automated ECG analysis have revived scientific interest in these parameters.

FREQUENCY-DOMAIN ANALYSIS OF REPOLARIZATION PHASE ECG PARAMETERS

Frequency is a fundamental characteristic of oscillatory processes ubiquitous in biological systems. Physiological homeostasis is maintained through numerous feedback loops, whose operation is accompanied by characteristic oscillations in the parameters under their control. Consequently, alterations in the frequency characteristics of biosignals can reflect disturbances in homeostatic regulation. Periodicity in regulatory influences, as manifested in the heart's electrical activity, can be investigated using frequency-domain analysis of ECG and HRV signals. In addition, intrinsic oscillatory patterns of cardiac electrical processes, including impulse conduction, excitation, and myocardial repolarization, are of considerable interest.

Some frequency-domain indices are already established risk markers (e.g., frequency domain parameters of HRV), whereas others remain under investigation for clinical applicability.

Periodic repolarization dynamics (PRD)

In 2014, Rizas et al. proposed a novel risk stratification method for post-myocardial infarction (MI) patients, grounded in three key premises:

- The influence of sympathetic overactivity on myocardial repolarization process.
- Proven role of sympathetic stimulation in the pathogenesis of life-threatening arrhythmias.
- Experimentally proven pattern of sympathetic nerve activity manifesting as low-frequency «bursts».

The authors hypothesized that sympathetic modulation of repolarization should manifest as low-frequency periodic oscillations of the T-wave axis, termed PRD. PRD assessment was based on 20-minute high-resolution ECG recordings. A time series of angles between the electrical axes of successive T waves - reflecting instantaneous instability of the repolarization vector - was computed, followed by frequency transform to quantify low-frequency (<0.1 Hz) spectral power (Fig. 3).

Potential confounders were systematically excluded. Possible relationship between PRD and HRV was ruled out experimentally via fixed-rate atrial pacing in volunteers, which abolished HRV while leaving PRD unaffected. The effect of spontaneous respiration was excluded in an animal model (anesthetized pigs) using fixed-rate mechanical ventilation, which preserved PRD. The link between PRD and sympathetic activity was further supported by observations of PRD elevation during tilt-table testing and exercise, and PRD reduction following β-adrenergic blockade. In the ART study cohort, PRD demonstrated prognostic value for 5-year mortality. A threshold of 5,75°² (upper quartile) was associated with a nearly threefold increase in all-cause and cardiovascular mortality risk after adjustment for clinical history and cardiovascular risk factors. PRD was also evaluated alongside T-wave alternans (TWA) in the FINCAVAS study, showing independent predictive value for cardiovascular mortality, including among patients without detected TWA. Combined use of PRD and TWA improved prediction of 6-year all-cause mortality

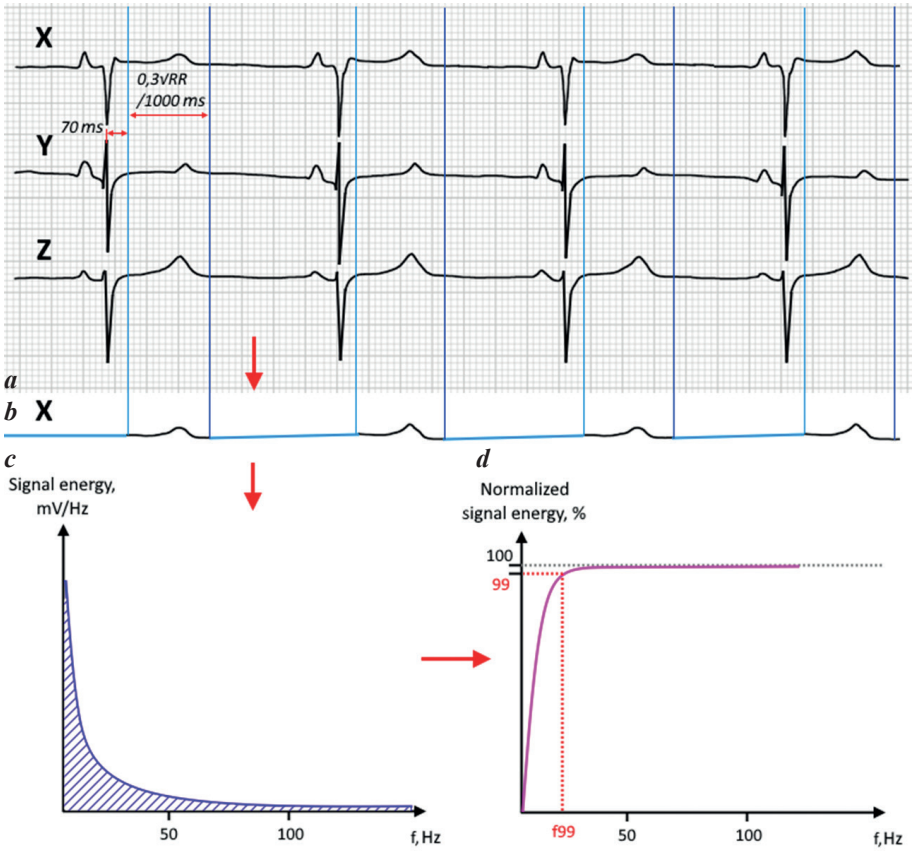

Fig. 4. f99 calculation: a - ECG in orthogonal leads and borders of «repolarization window», b - repolarization signal (ECG with QRS complexes and P waves removed and replaced by zeros), c - repolarization signal energy spectrum, d - normalized signal energy curve (0 to 100%). F99 is defined as frequency where normalized signal energy reaches 99%.

[13]. It is worth noting that the pilot study did not directly evaluate mortality from fatal VA.

Rizas et al. (2017) conducted the first dedicated investigation of PRD as an SCD risk marker in the MADIT-II cohort. Of 854 patients, 506 received ICDs and 348 received medical therapy. Given that in CHF elevated sympathetic tone is associated with both arrhythmic death and pump failure death (non-sudden cardiac death, non-SCD), the study endpoints included all-cause mortality, SCD and non-SCD. Over a median follow-up of 20,4 months, 53 SCD cases occurred. After adjustment for clinical history, cardiovascular risk factors, therapy, QRS width and LVEF, PRD was a significant predictor of SCD across the entire cohort. Among medically treated patients, PRD predicted SCD, whereas in ICD recipients, it predicted both appropriate ICD therapy and non-SCD. The authors noted the potential utility of PRD for identifying post-MI patients with reduced LVEF who may benefit from prophylactic ICD implantation. Study limitations included variability in ECG acquisition methods, exclusion of atrial fibrillation patients, changes in patient management protocols since MADIT-II, and a relatively small sample size [14].

Palacios et al. (2021) obtained further data on the prognostic role of PRD in the MUSIC cohort of CHF patients. Endpoints included SCD and non-SCD. Over the follow-up period, there were 53 SCD and 53 non-SCD events. PRD thresholds were established at 1,33°² for SCD and 1,31°² for non-SCD. SCD cases were significantly more common in patients with elevated PRD, whereas no significant difference in non-SCD cases was found between elevated and normal PRD groups. After adjusting for demographics, clinical history, laboratory parameters, HRV, HRT, TWA and Holter monitor findings (non-sustained VT and frequent PVCs), elevated PRD remained an independent predictor of a nearly twofold higher SCD risk. The combination of elevated PRD with abnormal turbulence slope or TWA further increased SCD risk two- to threefold.

In the discussion, the authors emphasized PRD's reliability for differentiating high- and low-risk patients, its prognostic relevance for both SCD and pump failure death, and its potential for combination with other MEI markers. Notably, HRV parameters showed no clinically significant prognostic value in this cohort, and overall among traditional risk factors, the most influential were CHF functional class and LVEF <35% [15].

Fragmentation of repolarization (f99 index)

In 2013, Burattini and Giuliani proposed an alternative approach to analyzing the frequency structure of repolarization. A comparative study of T-wave frequency content in healthy individuals and post-MI patients revealed significant differences. In the latter group, an increased number of harmonics was observed in the 10-35 Hz range, which the authors interpreted as reflecting fragmentation of the repolarization process - the appearance of additional electrical oscillations. This can be compared to the high-frequency notching and slurring in the QRS complex caused by depolarization heterogeneity in structurally abnormal myocardium, visible as QRS fragmentation on standard ECG or detectable via spectral analysis [17]. Given the intrinsic coupling between depolarization and repolarization, the similarity of these abnormal patterns supports the proposed hypothesis.

On this theoretical basis, Giuliani et al. (2014) introduced the f99 index, defined as the frequency (in Hz) at which the normalized T-wave spectral energy reaches 99% (Fig. 4). Their study included 108 post-MI patients and 47 clinically healthy controls (mean age 45 ± 15 years, 82% male). On average, f99 values were higher in post-MI patients. The best sensitivity and specificity for prior MI detection were achieved in leads I (threshold 15 Hz; sensitivity 80%, specificity 77%) and aVL (threshold 17,8 Hz; sensitivity 84%, specificity 74%), with the lowest performance in leads III and aVF. Averaging f99 across precordial leads yielded better results (sensitivity 81%, specificity 74%) than averaging across all 12 leads (sensitivity 69%, specificity 74%). The authors noted that f99 was robust to random fluctuations in T-wave end detection, independent of heart rate, and unaffected by spatial dispersion of repolarization, making the index promising for evaluating repolarization abnormality [18]. However, the pilot study did not examine f99 specifically as an arrhythmic risk marker.

Giuliani et al. later evaluated f99's prognostic value for life-threatening VA using the Leiden University database of 170 CHF patients (LVEF <35%) with ICDs. Over four years of follow-up from ICD implantation, patients underwent exercise testing with ECG recording. Based

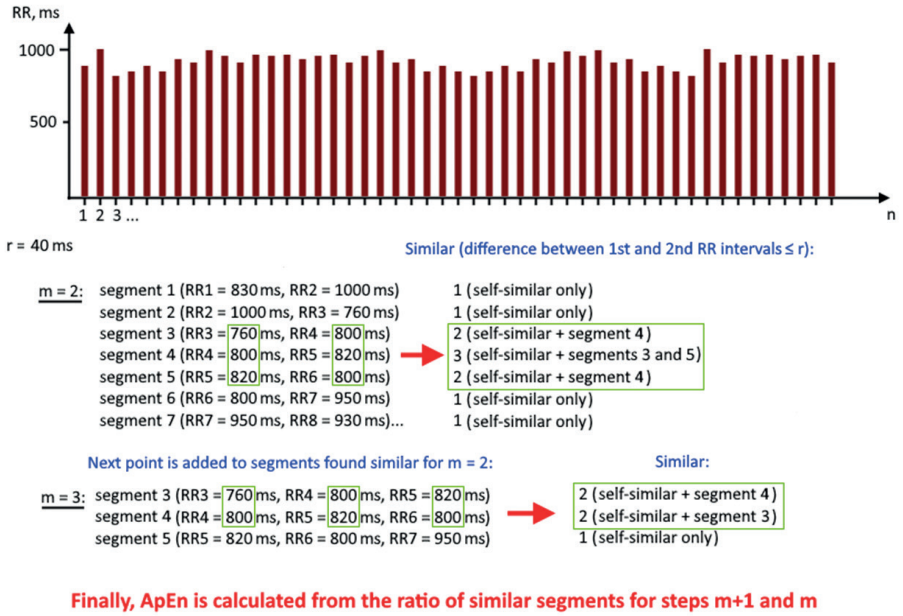

Fig. 5. Calculation of approximate entropy (ApEn) for HRV time series. If pairs of neighboring RR intervals (m = 2) are similar and adding next RR interval (m = 3) gives similar triplets, ApEn is low (system behavior is predictable); conversely, if increasing segment length (m = 2 → m = 3) drastically reduces the number of similar RR segments, ApEn is high and system behavior is more chaotic.

on whether ICD therapy occurred during follow-up, patients were classified into ICD-positive and ICD-negative groups, which were similar in clinical characteristics but differed in LVEF (31% ± 12% in ICD-positive vs. 39% ± 13% in ICD-negative). f99 was calculated from the first minute of exercise ECG using the previously described method. Maximum f99 values (maxF99) were computed for 6 precordial, 12 standard, and 3 orthogonal leads, and classification performance was assessed via ROC analysis. The highest AUC (0,68), comparable to that of LVEF (0,70) in this study, was obtained for orthogonal leads. Cross-correlation analysis showed independence between maxF99 and LVEF. The authors highlighted f99's reproducibility, robustness to spatial repolarization dispersion, and prognostic value comparable to LVEF - an established risk stratification marker [19].

Frequency-domain ECG markers emphasize the importance of a deep physiological understanding for work in electrophysiology. The approaches discussed - both the hypothesis linking PRD to burst-like sympathetic activity and the concept of repolarization fragmentation reflected in the spectral characteristics of the T wave - require investigators not only to possess comprehensive knowledge of cardiovascular regulation, myocardial electrophysiology and mechanisms of arrhythmogenesis, but also to engage in interdisciplinary collaboration with specialists in medical informatics and biosignal analysis.

NONLINEAR ANALYSIS OF ECG PARAMETERS

Among nonlinear indices derived from ECG and HRV signals and studied as MEI markers, particular interest lies in those reflecting chaoticity and fractality - properties directly linked both to the structure and function of the cardiac conduction system and myocardium, and to the autonomic regulation of the CV system.

A key quantitative measure of chaoticity, estimable from finite-length datasets, is entropy. In practice, several entropy measures are employed, differing in calculation methods and interpretative focus, including Shannon entropy (ShanEn), approximate entropy (ApEn), sample entropy (SampEn), fuzzy entropy (FuEn), Rényi entropy (RenEn), multiscale entropy (MSE), permutation entropy (PE), multiscale permutation entropy (MPE), and others.

For assessing fractal properties of a time series, the Hurst exponent is widely used, calculated using methods such as rescaled range (R/S) analysis, detrended fluctuation analysis (DFA), or frequency-domain approaches. For biomedical signals - which are typically nonstationary and noisy - DFA is a preferred method, as it removes the influence of local trends. Limitations of DFA include the assumption of monofractality (self-similarity at a single scaling factor) and the requirement for relatively long data series (several hundred points). For shorter segments, frequency-domain methods or DFA with modified detrending can be applied. Moreover, multiscale entropy methods (MSE and related) are also capable of incorporating the fractal properties of the analyzed signals.

Entropy and fractal properties of HRV

The pioneering application of entropy estimation in electrocardiology is attributed to S. Pincus, developer of the ApEn method [20] (Fig. 5), who described its use in cardiovascular disease diagnostics [21]; J. Richman and J. Moorman, who developed the improved SampEn method [22]; and A. Goldberger, M. Costa, and C.-K. Peng, who created the MSE method [23].

Concurrently, the concept of the fractal nature of CV system activity was being established. T. Musha and M. Kobayashi first described the HRV signal spectrum characteristic of fractal systems - the so-called pink noise [24]. A. Goldberger et al. identified the relationship between conduction system architecture and fractal spectral properties of the depolarization process (Fig. 6) [25]. C.-K. Peng and A. Goldberger developed DFA as a key tool for fractal analysis (Fig. 7) [26].

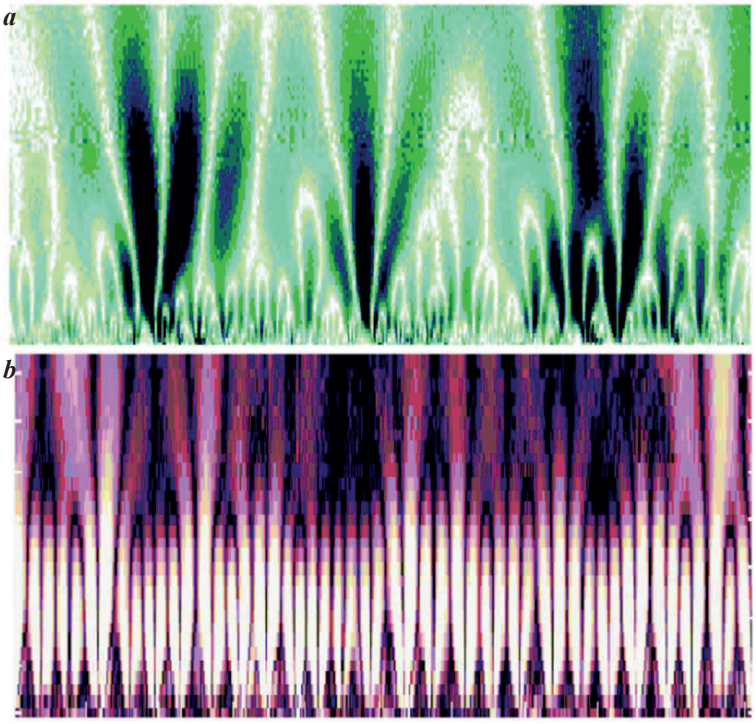

Fig. 6. a - fractal (self-similar) patterns in a spectrum obtained by wavelet analysis of RR time series of a healthy person. b - loss of fractality, increased rigidity and periodicity in a patient with obstructive sleep apnea. Adapted from [44].

Studies of nonlinear HRV analysis in the context of SCD can be broadly categorized into those addressing long-term risk stratification (identifying high-risk patients in specific cohorts, e.g., post-MI) and those addressing short-term prediction (anticipating life-threatening VA episodes before their onset). These two settings differ substantially in the temporal dynamics of nonlinear indices.

Long-term prognostic studies date back to the 1990s-2000s. In an early study by Voss et al. (1996; n = 26 post-MI patients, 16 with prior life-threatening VA or SCD), entropy indices were lower in the high-risk group, with predictive accuracy around 75%. In the DIAMOND-MI cohort study by Huikuri et al. (2000; 446 post-MI patients with LVEF <35%, mean follow-up 685 days, 75 SCD events), a reduced short-term fractal scaling exponent α_1

< 0,75, reflecting short-range RR interval correlation, was a significant SCD risk predictor (hazard ratio (HR) 2,5 in univariate analysis and 1,4 after clinical adjustment), outperforming established HRV measures (SDNN, LF, HF) [27]. Similarly, in a prospective study by Mäkikallio et al. (2001; random sample of 325 subjects > 65 years from a social insurance registry, 10-year follow-up, 29 SCD events), α_1 < 1,0 was the strongest predictor (HR 4,3 after adjustment; AUC 0,75), surpassing SDNN [28].

More recent studies include Rohila and Sharma (2020; 240 random 5-minute Holter segments from 20 SCD patients in the SDDB database), which showed significantly lower values of five entropy measures (SampEn, PEn, etc.) and α_1 DFA in the SCD group. Using these in a random forest classifier yielded an accuracy of 91,67% [29].

Yan et al. (2023; 22 Holter recordings from SCD patients in SDDB and AHADB databases) found reduced HRV SampEn to be a significant, though less powerful, SCD risk marker (AUC 0,66) compared to conventional HRV parameters (SDNN, RMSSD, LF) [30].

A large prospective study by Hernesniemi et al. (2024; 2794 1-minute ECGs from the FINCAVAS cohort, median follow-up 8,3 years, 83 SCD events) demonstrated that DFA with nonlinear detrending identified a significant correlation between reduced fractal HRV properties (lower α_1) and increased SCD risk (HR 2,4 per 1 SD), whereas differences in conventional HRV parameters were not significant. This study stands out for its large sample size and for proposing a spectral HRV analysis method applicable to ultrashort (1-minute) recordings, potentially enabling use in wearable devices [31].

Across long-term studies, reduced entropy and fractal measures in high-risk SCD patients is a notably consistent finding. Limitations include small and clinically heterogeneous samples in most reports. Future research should explore combined models incorporating both fractal and entropy measures in well-characterized cohorts, to facilitate validation, synthesis, and translation into clinical practice.

The first systematic studies on short-term SCD prediction using nonlinear HRV analysis date to the 2010s. A notable series by Ebrahimzadeh et al. (2014-2019), using the MIT-BIH database (35-40 Holter recordings with VF, 18 control sinus rhythm recordings), developed and refined prediction methods combining established linear HRV measures (time- and frequency-domain) with novel nonlinear indices (Poincaré plot cloud width and length, α DFA) and machine learning models (multilayer perceptron, support vector machines, k-nearest neighbors, mixture of experts). These approaches achieved VF prediction up to 13 minutes before onset [32-34]. Interestingly, α_1 DFA was significantly higher before VF onset (1,12 vs. 0,83 in controls), in contrast to findings in long-term SCD risk studies. In an early work [32], reported sensitivity was 83,75% but specificity only 0,159%, likely due to calculation error or classifier overfitting for sensitivity at the expense of specificity; later works did not replicate this issue.

Shi et al. (2020), also using MIT-BIH data (20 VF recordings, 18 controls), applied ensemble empirical mode decomposition (EEMD) to HRV data. Classification based on entropy measures and k-nearest neighbors achieved higher predictive accuracy in the first 2-minute interval before VF (94,7%) than a model using only linear parameters (86,8%), and the combined model reached 96,1%. The best-performing entropy measures were FuEn and improved MPE. Significant parameter changes were detectable up to 14 minutes before VF onset. The EEMD method's adaptability and noise robustness make it promising for wearable device applications [35].

Yang et al. (2023) reported a major advance in early SCD detection. They introduced a novel nonlinear multiscale index, Sv, derived from Poincaré plots. Using MIT-BIH data (20 VF Holter recordings, 18 without VA), a combined model incorporating Sv, ShanEn, and SDNN with an SVM classifier achieved 91,22% predictive accu-

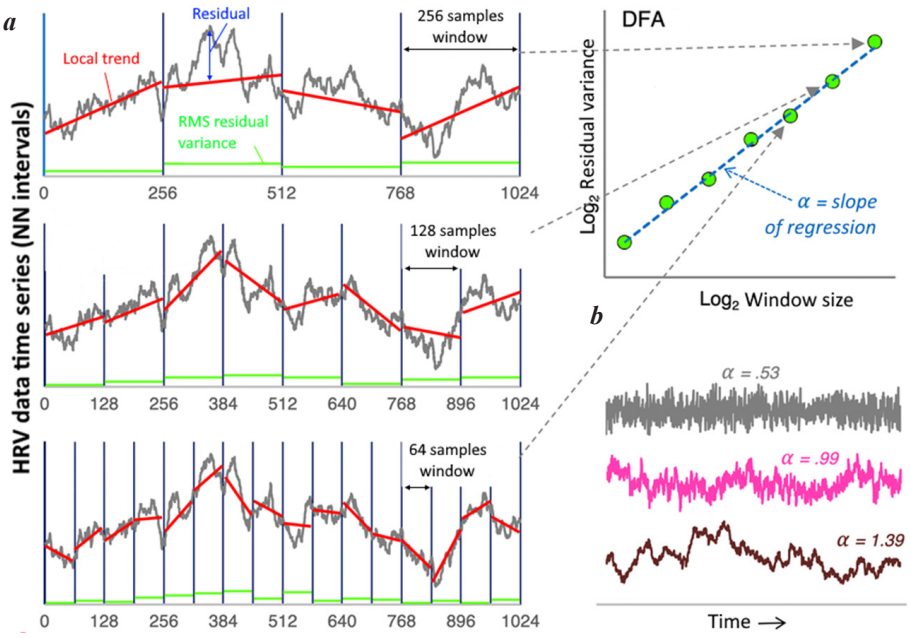

Fig. 7. Detrended fluctuation analysis (DFA) method. a - algorithm for DFA calculation: calculation of root-mean-square (RMS) residual variance (deviation from local trend) at various time scales, plot of residual variance against time scale and the regression approximating the variance-scale relation. Slope of regression line reflects the strength of self-similarity at various time scales (fractality). b - examples of signals with various level of self-similarity: low α signifies prevalence of small-scale oscillations and lack of longer-range patterns (chaotic behavior), α close to 1 reflects a balanced relation between amplitude and scale of oscillations (fractal-like behavior), high α demonstrates prevalence of long-range patterns over small-scale variation (rigid behavior, long-term «memory»: of the signal). Adapted from [45].

racy 60-70 minutes before SCD - a fivefold improvement in lead time compared to prior studies [36].

These short-term prediction studies benefit from the standardization inherent to public ECG databases but are limited by small sample sizes (35-40 recordings). Such methods may be particularly useful in ECG monitoring devices for high cardiovascular risk patients. Future directions include evaluating EEMD and combined DFA/Sv models on ECG recordings of varying quality and duration, and in diverse clinical populations, to define practical applicability.

Entropy and fractal properties of repolarization

An original approach to nonlinear ECG analysis was proposed by DeMazumder et al. (2016) [37]. The authors hypothesized that the degree of repeatability in ventricular repolarization patterns, assessed via QT interval variability, reflects the functional state of the body's regulatory systems. They introduced the repolarization entropy index (proprietary term EntropyXQT), an enhanced version of SampEn designed to assess the complexity and repeatability of ventricular repolarization patterns. This index is derived from QT interval variability analysis, thereby capturing embedded periodic oscillations in interval duration. Due to its calculation method, EntropyXQT can be considered a «hybrid» index, reflecting both complexity and fractality (scale invariance) of cardiac dynamics.

The prognostic value of EntropyXQT for life-threatening VA was assessed in the PROSe-ICD study [38]. The primary endpoint was the first appropriate ICD therapy delivery for VT or VF, the secondary endpoint was a composite of the primary and all-cause mortality. Over a mean follow-up of 45 ± 24 months, 134 patients reached the primary endpoint and 300 reached the secondary endpoint (166 deaths without prior ICD therapy). EntropyXQT's predictive value was evaluated in two models: the Seattle Heart Failure Model (SHFM) [39] and a baseline model incorporating clinical and laboratory variables plus established ECG measures, including HRV, QRS duration, late potentials, and repolarization indices (QTc, QT/RR, QTVi). High EntropyXQT values (fifth quintile) were independently associated with more than a threefold increased risk of ICD intervention, even after adjustment for 30 additional parameters. The prognostic value of EntropyXQT was independent of other repolarization indices, including QTVi. Adding EntropyXQT to the baseline model improved net reclassification by 31-36%, and adding it to the SHFM improved reclassification by 40%. The authors noted EntropyXQT's potential utility for primary prevention of SCD, its robustness to noise, its ease of calculation from short ECG recordings, and its consistency with prior research on entropy measures of cardiac activity for predicting pathological states [40, 41].

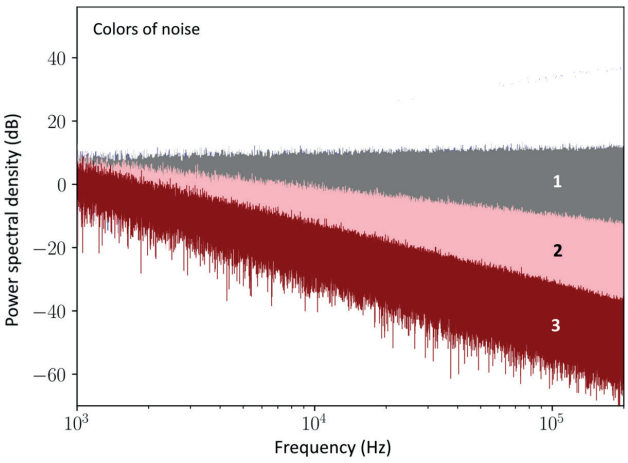

Fig. 8. Colors of noise. 1 - white noise characteristic of random processes with no autocorrelation. 2 - pink "fractal" 1/f noise characteristic of normally functioning systems containing multiple hierarchical levels of control and balanced autocorrelation. 3 - Brownian ("brown" or "red") noise characteristic of systems with strong dependence on past states and strong autocorrelation. Adapted from [46].

A noteworthy contribution comes from M. Murugappan et al. (2020), who focused on nonlinear analysis of the R-Tend segment for short-term SCD prediction, using the MIT-BIH database (18 Holter recordings with VF, 18 controls without VA). For each of the five consecutive 1-minute segments preceding VF onset, they calculated ApEn, SampEn, the largest Lyapunov exponent and the Hurst exponent - thus incorporating both entropy and fractal measures. Classification was performed using subtractive fuzzy clustering, neuro-fuzzy clustering and SVM. The best results were obtained with SVM: on the fifth minute before VF onset, predictive accuracy reached 100% for SampEn, 98,68% for ApEn, 97,37% for the largest Lyapunov exponent, and 94,74% for the Hurst exponent. The remarkably high accuracy for ApEn and SampEn contrasts with their more modest performance in HRV-based short-term SCD prediction. A major strength of the study is the novelty of analyzing the R-Tend segment, while its main limitation is the small sample size dictated by the MIT-BIH SCD database [42].

Of particular interest is the dynamic behavior of nonlinear HRV indices in long-term risk versus immediate pre-SCD states. While some entropy measures decrease over the long term, others exhibit a sharp rise immediately before fatal VA onset. Notably, for repolarization entropy, such a paradox was not observed. Clinically, these patterns may reflect two complementary pathological processes:

Chronic phase (entropy decrease): loss of the «healthy chaos» in heart rhythm characteristic of effective autonomic regulation [43], consistent with the depletion of adaptive reserves seen in CHF patients or those with prior MI.

Acute phase (entropy increase in HRV and repolarization): manifestation of critical MEI and increasing electrical heterogeneity, creating a substrate for fatal arrhythmias - consistent with the theory of «critical slowing down» in complex systems approaching a transition state.

Importantly, this acute-phase rise was most prominent for multiscale and adaptive measures (e.g., IMPE, FuEn) of HRV, whereas traditional single-scale measures (ApEn, SampEn) of HRV were less informative. For repolarization entropy, ApEn and SampEn also rose significantly, likely reflecting disorganization of ventricular electrical processes rather than changes in autonomic modulation.

A similar biphasic pattern was observed for fractal characteristics:

- Optimal regulation (α DFA ≈ 1,0): represents balanced vagal-sympathetic interaction and nested regulatory loops of the CV system, producing a "pink noise" spectrum.

• Long-term risk (α → 0,5; high EntropyXQT due to loss of self-similar oscillations): indicates disintegration of regulatory mechanisms, loss of correlations, and a random response pattern ("white noise" spectrum).
• Immediate SCD threat (α >1,5): may reflect sympathetic hyperactivation with dominance of low-frequency oscillations, increased «memory» and rigidity of the system, locking it onto a trajectory toward pathological state («brown noise» spectrum) (Fig. 8).

CONCLUSION

Modern approaches to the risk stratification of sudden cardiac death and life-threatening ventricular arrhythmias extend beyond traditional ECG markers, offering novel methods for assessing myocardial electrical instability. The groups of novel markers reviewed here reflect different aspects of arrhythmogenesis.

The key advantage of GEH vector parameters lies in their ability to quantify the spatiotemporal heterogeneity of depolarization and repolarization, which is particularly important in patients with both ischemic and non-ischemic cardiomyopathies. Interpretation of these markers requires careful consideration of the underlying myocardial pathology, given the differences in prognostic significance across conditions.

The distinctive value of frequency-domain MEI markers stems from their capacity to reflect disturbances in autonomic regulation and electrical heterogeneity of repolarization - both of which are critical components of arrhythmogenesis in post-MI and heart failure patients. Clinical implementation of frequency-based markers requires standardization of ECG acquisition and analysis protocols.

Nonlinear MEI markers - encompassing entropy and fractal properties of HRV and specific ECG components - represent a novel conceptual framework for understanding arrhythmogenesis, framing it as a multi-level collapse of the cardiovascular system's adaptive potential, a breakdown in the balance between chaos and order, and a simplification of regulatory mechanisms, where excessive rigidity of control (sympathetic hyperactivation) coexists with micro-level electrical fragmentation. This perspective is new and potentially highly promising, but it demands multidisciplinary collaboration between cardiologists, electrophysiologists, physicists, mathematicians and computer science specialists.

The challenges pertaining to research of novel MEI markers are typical for any rapidly evolving field in the process of evidence accumulation and synthesis: considerable heterogeneity of study populations, lack of standardized acquisition protocols for the studied indices, and, in many cases, contradictory results. These issues are likely to be temporary and should be resolved as the field progresses toward integrating findings and developing practical clinical applications.

Promising directions include exploring combined marker models from different groups using machine learning for long-term arrhythmic risk stratification, as well as identifying short-term SCD predictors in high cardiovascular risk populations - particularly through long-term monitoring, wearable medical electronics, and on-demand ECG analysis.

In summary, novel ECG MEI markers do not replace but rather complement traditional approaches, providing a deeper understanding of arrhythmogenesis pathophysiology and forming a basis for more flexible SCD prevention strategies. Future research will likely focus on validating these indices in large prospective cohorts and developing standardized algorithms for their practical clinical use.

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