Predictive Power of f99 Repolarization Index for the Occurrence of Ventricular Arrhythmias

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Background: Defects of cardiac repolarization, noninvasively identifiable by analyzing the electrocardiographic (ECG) ST segment and T wave, are among the major causes of sudden cardiac death. Still, no repolarization-based index has so far shown sufficient sensitivity and specificity to justify preventive treatments. Thus, the aim of this work was to evaluate the predictive power of our recently proposed f99 index for the occurrence of ventricular arrhythmias.

Methods: Our study populations included 170 patients with implanted cardiac defibrillator (ICD), 44 of which developed ventricular tachycardia and/or fibrillation during the 4-year follow-up (ICD_Cases) and 126 did not (ICD_Controls). The f99 index, defined as the frequency at which the repolarization normalized cumulative energy reaches 99%, was computed in each of the 15 (I to III, aVI, aVr, aVf, V₁–V₆, X, Y, Z) available ECG leads independently, and then maximized over the 6 precordial leads (f99_MaxV₁–V₆), 12 standard leads (f99_Max12STD) and three orthogonal leads (f99_MaxXYZ) to avoid dispersion-related issues. Each index predictive power was quantified as the area under the receiving operating characteristic curve (AUC).

Results: Median f99_MaxV₁–V₆, f99_Max12STD and f99_MaxXYZ values were significantly higher in the ICD_Cases than in the ICD_Controls (48 Hz vs. 35 Hz, $P < 0.05$; 51 Hz vs. 43 Hz, $P < 0.05$; 45 Hz vs. 31 Hz, $P < 10^{-3}$; respectively), indicating a more fragmented repolarization in the former group. The AUC values were 0.62, 0.63 and 0.68, respectively.

Conclusions: The f99 represents a promising risk index for the occurrence of ventricular arrhythmias, especially when maximized over the three orthogonal leads.

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digital electrocardiography; repolarization variability; sudden cardiac death; T-wave frequency content; risk assessment.

Despite recent advances in the treatment of life-threatening ventricular arrhythmias, sudden cardiac death (SCD) remains one of the leading causes of death in developed countries.¹

Nowadays, patients are selected for clinical evaluation and treatment of ventricular arrhythmias only after they have experienced and survived a major cardiac event. Thus, preventive identification and

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treatment of these high-risk subjects is expected to have a great impact on the problem of SCD.

Defects of cardiac repolarization, noninvasively identifiable in the electrocardiographic (ECG) ST segment and T wave, are among the major causes of SCD.²⁻⁵ The most popular repolarization marker of risk is the QT interval,^{3,4} defined as the time distance between the Q-wave onset and the T-wave offset, thus representing the total duration of the ventricular contraction and subsequent relaxation. Despite QT-interval prolongation being the standard indicator of cardiac safety in clinical trials, several limitations affect it. First, there is a large interlead QT-interval variability, known as QT dispersion.⁶⁻⁸ Moreover, the T-wave offset is usually hardly identifiable due to the T-wave varying morphology, the possible existence of the U wave, and the presence of noise and artifacts affecting the real ECGs. Consequently, QT measurements suffer of a large variability (few tens of milliseconds) associable to the different automatic algorithms used for its detection.⁹ Eventually, the QT interval is correlated with heart rate (HR) for which it is usually corrected using the Bazett's formula.¹⁰ Such correction, however, tends to undercorrect the QT interval at low HRs (<60 bpm) and to overcorrect it at high HRs (>60 bpm).¹¹

The difficulties in accurately measuring the QT interval, together with the clinical observation that not all prolonged QT intervals necessarily lead to ventricular arrhythmias,¹² have stimulated the identification of alternative markers of abnormal repolarization,¹³ among which T-wave alternans,^{5,14} T-wave duration parameters,^{15,16} T-wave amplitude parameters^{17,18} and others.¹⁹⁻²³ Still, none of these indexes has shown sufficient sensitivity and specificity to justify diagnostic and therapeutic procedures in previously asymptomatic patients, so that the search for new repolarization indexes of cardiac risk is still an open issue.

Abnormalities in the repolarization morphology are reflected, in the frequency domain, in a variation of the T-wave frequency content. Though, indexes based on this feature have only occasionally been proposed.²⁴⁻²⁶ Recently we proposed a new frequency-based repolarization index, termed f99, defined as the frequency at which the repolarization normalized cumulative energy reaches 99%.²⁶ The f99 index proved to be able to discriminate pathological T waves

due to acute myocardial infarction from healthy T waves.²⁶ Still, so far, the f99 utility in the cardiac risk assessment has not been tested. Thus, the aim of the present study was to investigate f99 as an index of cardiac risk by evaluating its predictive power for the occurrence of malignant ventricular arrhythmias. To this aim we retrospectively analyzed ECG repolarization in two groups of patients with an implanted cardiac defibrillator (ICD), namely the ICD_Cases and the ICD_Controls, respectively developing and not developing ventricular tachycardia or fibrillation during the 4-year follow-up.

METHODS

Study Populations

The study population consisted of 170 patients with an ICD for primary prevention because of a depressed left ventricular ejection fraction (LVEF < 35%), all belonging to the Leiden (The Netherlands) University Medical Center database of exercise ECGs in heart failure patients with ICDs. All patients underwent a 4-year follow-up starting from the ICD implantation date. During the follow-up patients were receiving standard care, which included periodic visits to the outpatient clinic, amongst others, to assess validity by bicycle ergometry. The bicycle ergometer test consisted of an approximately 10-minute bicycle test during which the workload was incremented from zero to the patient's maximal capacity by applying load-increments of 10% of the expected maximal capacity every minute. During the bicycle ergometer test, 8-lead (I, II, V₁-V₆) ECG recordings were obtained using a CASE 8000 stress test recorder (GE Healthcare, Freiburg, Germany; sampling frequency: 500 Hz; resolution: 4.88 μ V/LSB) and the 3M Red Dot ECG Electrode Soft Cloth 2271 electrodes, specifically meant for conditions in which skin moisture is an issue, like stress testing. The skin was first cleaned with alcohol and abraded, to reduce electrode resistance. Electrode resistance was measured by the electrocardiograph, and considered acceptable if <5 kOhm. Electrodes were applied in the Mason-Likar position.

According to the data collection protocol, during the follow-up patients could undergo more than one exercise tests. Eventually, at the end of

the follow-up, patients were classified as either "ICD_Cases" (44 patients) if, during the follow-up, they had developed ventricular tachycardia or ventricular fibrillation (treated with antitachycardia pacing and/or shock therapy), or "ICD_Controls" (126 patients) if no device therapy had emerged. ICD_Cases exercise tests were excluded when a major cardiac event (infarction, VT ablation, coronary artery bypass graft) occurred between the exercise test and the moment of VT/VF, because ablation modified their arrhythmogenic substrate with respect to the state in which it was when the ICD was implanted. If more than one exercise test remained available for analysis, the one closest in time (either before or after) to the VT/VF episode was selected so that the substrate during the stress test would be as close as possible to the substrate during the actual arrhythmia. In ICD_Controls with more than one suitable exercise test, the earliest available one was selected. Eventually, only one ECG tracing per patient was made available for the database.

According to "Guideline for Good Clinical Practice" (European Medicines Agency, CPMP/ICH/135/95) and the data privacy law the Netherlands, for being enrolled in the present study, which is retrospective, observational and on standard clinical data, no informed consent from patients (whose identity is kept secret) was needed because no interventions had taken place.

Clinical ECG Data

The clinical data consisted of 15-lead (I, II, III, aVl, aVr, aVf, V₁, V₂, V₃, V₄, V₅, V₆, X, Y, and Z) ECG tracings during the first minute of the recording (almost at rest). ECG leads III, aV1, aVr aVf, X, Y, Z were obtained from leads I, II, V₁-V₆ by application of well-known transformations.²⁷ Each lead was resampled at 200 Hz and preprocessed for noise removal (0.5–35 Hz bandpass filtering) and baseline subtraction by means of a third-order spline interpolation.¹⁷ After R-peak detection, the first 30-second 15-lead ECG window characterized by stable HR (RR-interval standard deviation < 10% of mean RR) and clean and sinus rhythm (no more than two ectopic beats and artifacts) was extracted from each 1-minute recording. Only patients for which this window was available in at least three out of the six precordial (V₁-V₆) leads, or in at least 6 out of 12 standard (I-III, aVl, aVr, aVf, V₁-V₆) leads, or in

at least two out of three orthogonal (X, Y, and Z) leads were enrolled in the study.

Repolarization Frequency-Content Characterization

Repolarization frequency-content evaluation was performed in each ECG lead independently. The R peaks were initially identified to localize the cardiac beats present in the 30-second ECG window in order to compute the median beat. Then, the median beat was used to identify repolarization onset (RepOn) and offset (RepOff) according to the following formulae:

$$\text{RepOn} = 70 \text{ milliseconds from the R peak} \quad (1)$$

$$\text{RepOff} = 0.3\sqrt{\text{medianRR}} \cdot 1000 \text{ milliseconds from the RepOn point.} \quad (2)$$

Equation (2) is an adjustment of an empirical formula²⁸ finalized to avoid cases of P-wave inclusion in the T-wave window, and medianRR (seconds) is the median RR interval. The median repolarization waveform (i.e., the portion of the median beat included between RepOn and RepOff) was then forced to be 260 milliseconds long by opportune resampling²⁶ in order to adjust for repolarization-duration variations due to HR. Eventually, the repolarization signal (RPS) was constructed by zero padding the resampled median repolarization waveform till 1 second.

RPS frequency-content was evaluated by computation of the RPS Fourier power spectrum ($\text{PS}_{\text{RPS}}(k)$; Eq. (3) and energy signal ($\text{E}_{\text{RPS}}(k)$; Eq. (4)):

$$\text{PS}_{\text{RPS}}(k) = \sum_{n=0}^{N_s-1} \text{RPS}(n) \cdot \exp^{-j2\pi \frac{k}{N_s} n} \quad (3)$$

$$\text{E}_{\text{RPS}}(k) = \sum_{m=0}^k \text{PS}_{\text{RPS}}(m), \quad (4)$$

where N_s is the number of samples ($N_s = 200$), and n and k (and thus m) are adimensional indexes to get time and frequency as $t_n = n \cdot (1/F_s) = n \cdot 0.005$ second, with $n = 1, 2, \dots, N_s$, and $f_k = k$ Hz, with $k = 1, 2, \dots, N_s/2$, respectively. After having computed the total energy ($\text{E}_{\text{RPS_Total}}$; Eq. (5)),

Figure 1. Graphical identification of f99 index, defined as the frequency at which the repolarization normalized cumulative energy ($E_{RPS}\%$) reaches 99%.

the $PS_{RPS}(k)$ and the $E_{RPS}(k)$ were normalized and expressed as percentages ($PS_{RPS}\%(k)$ and $E_{RPS}\%(k)$, respectively; Eqs (6) and (7)):

$$E_{RPS-Total} = \sum_{k=0}^{\frac{N_s}{2}-1} PS_{RPS}(k) \quad (5)$$

$$PS_{RPS}\%(k) = \frac{PS_{RPS}(k)}{E_{RPS-Total}} \cdot 100 \quad (6)$$

$$E_{RPS}\%(k) = \frac{E_{RPS}(k)}{E_{RPS-Total}} \cdot 100 \quad (7)$$

By definition, $E_{RPS}\%(k)$ is a monotonically increasing function which saturates at 100%. The frequency at which $E_{RPS}\%$ first reaches or overcomes 99%, called f99, represents an index to characterize repolarization²⁶ (Fig. 1).

To avoid repolarization-dispersion issues, repolarization analysis was performed as follows:

- maximizing the single-lead f99 values over the six precordial leads ($f99_MaxV_1-V_6$), if at least three out of six values were available;
- maximizing the single-lead f99 values over the 12 standard leads ($f99_Max12STD$), if at least six out of 12 values were available; and
- maximizing the single-lead f99 values over the three orthogonal X, Y, and Z leads ($f99_MaxXYZ$), if at least two out of three values were available

Statistics

Normality of parameters distributions was tested using the Lilliefors test. Parameters characterized by normal and not-normal distributions were described in terms of mean and standard deviation ($mean \pm SD$) and or terms of 25th, 50th (median), and 75th percentiles (median (25th, 75th percentiles)) and compared using the T test or the Wilcoxon rank-sum test, respectively. Binary parameters distributions were compared using the chi-square test or, when not possible (expected cell frequency < 5), the Fisher's exact one-tailed probability test. To evaluate a parameter predictive power for the occurrence of ventricular arrhythmias the area under the receiving operating characteristic curve (AUC) was used. Associations between two parameters distributions were evaluated using the correlation coefficient (ρ). Statistical significance level was 0.05 in all cases.

RESULTS

Clinical information relative to the ICD.Cases and ICD.Controls are reported in Table 1. The two groups were characterized by comparable general clinical parameters (age, gender, body mass index, and HR; Table 1) with the only exception of LVEF, that was significantly lower in the ICD.Cases than in the ICD.Controls ($31 \pm 12\%$ vs. $39 \pm 13\%$; $P < 10^{-5}$). If used as a parameters to discriminate ICD.Cases from ICD.Controls (i.e., for risk assessment), the LVEF provided an AUC of 0.70. The number of patients with ischemic underlying heart disease type was comparable (in percentage) in the two ICD populations (ICD.Controls: 63%; ICD.Cases: 64%). Twenty seven (61%) out of 44 ICD.Cases had VT/VF episodes characterized by fast HR (≥ 200 bpm), and six (14%) had VF. Eventually, 25 (57%) ICD.Cases

Table 1. Clinical Information (Mean $\pm$ SD or Number of Occurrences) Relative to the Study ICD Groups.

	ICD_Controls (126)	ICD_Cases (44)	P Value
General			
Age (years)	61 $\pm$ 12	59 $\pm$ 11	NS
Gender (male)	107 (85%)	39 (89%)	NS
BMI (kg/m ²)	26 $\pm$ 4	27 $\pm$ 4	NS
LVEF (%)	39 $\pm$ 13	31 $\pm$ 12	<10 ⁻⁵
HR at rest (bpm)	71 $\pm$ 11	72 $\pm$ 10	NS
HR at test (bpm)	82 $\pm$ 10	79 $\pm$ 11	NS
NYHA functional class			
I-II	86 (68%)	22 (50%)	NS
III-IV	40 (32%)	22 (50%)	NS
Underlying heart disease type			
Ischemic	79 (63%)	28 (64%)	NS
Nonischemic	47 (37%)	16 (36%)	NS
Therapies and medications			
CRT-D	39 (31%)	23 (52%)	<0.05
Beta-blocker	105 (83%)	39 (89%)	NS
Amiodarone	11 (9%)	16 (36%)	<0.01
Calcium antagonists	14 (11%)	1 (2%)	NS
Flecainide	0 (0.0%)	1 (1%)	NS
Digoxin	6 (5%)	9 (20%)	<0.05
ACE inhibitor/AT antagonist	114 (90%)	40 (91%)	NS
Diuretics for CHF	86 (68%)	39 (89%)	NS
Statins	94 (75%)	37 (84%)	NS

ACE = angiotensin converting enzyme; AT = angiotensin; BMI = body mass index; CHF = congestive heart failure; CRT_D = cardiac resynchronization therapy with defibrillator; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York heart association; NS = not statistically significant ($P \geq 0.05$).

Table 2. Number of Patients Involved in the Repolarization Analysis Performed Maximizing f99 Over the Six Precordial Leads (f99_MaxV₁-V₆), the 12 Standard Leads (f99_Max12STD) and the Three Orthogonal X, Y, and Z Leads (f99_MaxXYZ).

	ICD_Controls	ICD_Cases
f99_MaxV₁-V₆	122 (97%)	43 (98%)
f99_Max12STD	103 (82%)	38 (86%)
f99_MaxXYZ	115 (91%)	42 (95%)

were treated with shock therapy and 28 (64%) with antitachycardia pacing (nine with both therapies).

In this study, no ICD patient was rejected because of the HR criterion, whereas the number of patients rejected for not reaching the minimum required number of single-lead f99 values (see Methods) varied with the kind of analysis: 1 ICD_Case and 4 ICD_Controls were rejected when computing f99_maxV₁-V₆; 6 ICD_Cases and 23 ICD_Controls were rejected when computing f99_max12STD; and 2 ICD_Cases and 11 ICD_Controls were rejected when computing f99_XYZ (Table 2).

Median f99_MaxV₁-V₆, f99_Max12STD, and f99_MaxXYZ values were all significantly higher

(Table 3, Fig. 2) in the ICD_Cases than the ICD_Controls (48 Hz vs. 35 Hz, $P < 0.05$; 51 Hz vs. 43 Hz, $P < 0.05$; 45 Hz vs. 31 Hz, $P < 10^{-3}$; respectively), indicating that repolarization in the former group is characterized by significantly higher frequency components than in the latter group. When used to discriminate the two ICD groups (i.e., to assess cardiovascular risk), f99_MaxV₁-V₆, f99_Max12STD, and f99_MaxXYZ values provided AUC values between 0.62 and 0.68, with f99_MaxXYZ providing the highest value (0.68; Fig. 3).

The AUC values provided by f99_MaxV₁-V₆, f99_Max12STD, and f99_MaxXYZ were close to that provided by the LVEF (0.70), indicating a comparable predictive power for the occurrence of VT/VF. Still, the correlation analysis performed on the three f99 parameters against LVEF provided $|\rho| < 0.14$ with $P > 0.05$ in all cases, indicating that f99_MaxV₁-V₆, f99_Max12STD, and f99_MaxXYZ are independent from LVEF.

DISCUSSION

This retrospective, observational study on standard clinical data investigated the predictive power

Table 3. Repolarization Analysis Reporting Single-Lead f99 (Median (25th, 75th Percentiles)) Values Maximized Over the Six Precordial Leads (f99_MaxV₁–V₆), the 12 Standard Leads (f99_Max12STD) and the Three Orthogonal X, Y, and Z Leads (f99_MaxXYZ), and Their Corresponding Ventricular-Arrhythmias Predictive Value in Terms of AUC.

	ICD_Controls	ICD_Cases	AUC	P
f99_MaxV ₁ –V ₆ (Hz)	35 (20, 56)	48 (34, 62)	0.62	P < 0.05
f99_Max12STD (Hz)	43 (27, 62)	51 (44, 63)	0.63	P < 0.05
f99_MaxXYZ (Hz)	31 (18, 49)	45 (32, 58)	0.68	P < 10 ^{−3}

AUC: area under the receiving operating characteristic curve.

Figure 2. Graphical representation of the distributions of the single-lead f99 values maximized over the six precordial leads (f99_MaxV₁–V₆), the 12 standard leads (f99_Max12STD), and the three orthogonal leads (f99_MaxXYZ).

Figure 3. Receiving operating characteristic curves relative to the single-lead f99 values maximized over the six precordial leads (f99_MaxV₁–V₆), the 12 standard leads (f99_Max12STD), and the three orthogonal X, Y, and Z leads (f99_MaxXYZ).

of our recently proposed²⁶ f99 repolarization index for the occurrence of ventricular arrhythmias. To this aim, 170 ICD patients were used, of which 44 (ICD_Cases) and 126 (ICD_Controls), respectively did and did not develop ventricular tachycardia or fibrillation during the 4-year follow-up. All patients underwent a HR-increasing bicycle ergometer test during which ECG tracings were recorded. Still, risk assessment was evaluated at the beginning of the recording (within 1 minute) when HR is low and close to resting. Indeed, it is commonly observed that HRs immediately preceding arrhythmias are mostly not particularly elevated. Oftentimes, HR increases before the onset of VT/VF, but not above 90 bpm.^{29,30} Since f99 is proposed here as an innovative risk index for the occurrence of VT/VF, then it made sense to initially measure it at the HR at which arrhythmias is more likely to occur. Thus, evaluating the dependence of f99 on increasing HR was beyond the scope of this study, and will be matter of future investigations.

Enrollment criteria were based on both HR stability and level of noise (see Methods). The noise-removal procedure was applied to each ECG lead independently, and consisted of bandpass filtering (0.5–35 Hz); baseline subtraction; and ectopic beats and/or artefacts replacement. For a patient to be enrolled in the study, his/her ECG had to show a stable rhythm (RR-interval standard deviation < 10% of mean RR) for at least 30 consecutive seconds within the first minute. If this was the case, f99 was computed only in those leads with no more than two replaced beats. Eventually, only patients for which f99 was available in at least three out of the six precordial leads, or in at least six out of 12 standard leads, or in at least two out of three orthogonal leads were definitively enrolled in the study. Clearly, if a lead was rejected because not satisfying the HR stability condition, all leads of the same recording also were. Instead, the number of artefacts affecting each single lead could be different; consequently the number of replaced beats could also be different, and f99 could result available for some leads and not available for others. Results indicate all ICD patients satisfied the HR-stability criterion, whereas the number of patients involved in the repolarization analysis performed using f99_MaxV₁–V₆, f99_Max12STD and f99_MaxXYZ (Table 2) was ≤ 44 (i.e., the initial number of ICD_Cases) for the ICD_Cases and ≤ 126 (i.e., the initial number of ICD_Controls) for the ICD_Controls, due to rejections that could occur because of too high level of noise affecting specific leads. Most of rejections (6 ICD_Cases and 23 ICD_Controls) occurred in correspondence of f99_Max12STD analysis, since such parameter required the highest number of single-lead f99 measurements (six instead of three or two). For each kind of analysis the percentage number of enrolled patients in the ICD_Cases and ICD_Controls was comparable (98% vs. 97% for f99_maxV₁–V₆; 86% vs. 82% for f99_max12STD; and 95% vs. 91% for f99_XYX) in accordance with the fact that the ECG recording procedure was the same for both ICD groups and that they were classified as ICD_Cases and ICD_Control only a posteriori after the follow-up. These percentages are quite high (between 82% and 98%) indicating that repolarization characterization by f99 is quite robust to noise, especially when performed by maximizing on the six precordial leads or on the three orthogonal leads, for which the percentages are above 90%.

The proposed f99 index is one of the few ECG risk repolarization indexes defined in the frequency domain.^{24–26} Its quantification does not depend on the exact identification of the T-wave end points. Indeed, the repolarization segment is first determined by means of empirical formulae (Eqs. 1 and 2) and, subsequently, is modulated to force its length to be exactly 260 milliseconds. Such operation represents a normalization for HR and is based on the assumption that, in first approximation, the repolarization-segment duration is directly linearly dependent on previous RR. A zero padding procedure is then applied so that each heart cycle becomes exactly 1 second long. Consequently, the normalized power spectrum does not provide the frequency content of the real T wave but, rather, the amplitude of the harmonics after forcing the fundamental frequency to be at 1 Hz. Eventually, f99 is defined as the frequency at which the modulated repolarization waveform energy reached 99%.²⁶ Thus, although expressed in Hz for simplicity and clarity, f99 represents the number of harmonics the normalized cumulative energy needs to reach 99%.

By definition, f99 is higher for fragmented (i.e., less smoothed) T waves, characterized by higher frequency components. Figure 4 displays some modelled monophasic and biphasic T waves with the corresponding f99 values. As can be seen, even though some morphological aspects of the T-wave shape determine the f99 value, this cannot be used for T-wave morphological classification (for example, to distinguish monophasic from biphasic T waves). Rather, it provides information about how smooth the T wave is, and thus how smoothly cardiac electrical repolarization occurs.

To overcome dispersion-related (i.e., variability among leads) issues, repolarization frequency evaluation was performed by maximizing the f99 value over the six precordial leads, the 12 standard lead, and the three orthogonal leads. The ICD_Cases showed higher amplitude high-frequency components (i.e., f99_MaxV₁–V₆, f99_Max12STD and f99_MaxXYZ values) than the ICD_Controls, finding that could indicate a more fragmented repolarization in the former than in the latter group. Consequently, an elevated f99 associates to an increased susceptibility to arrhythmic events. The f99 predictive value, quantified by the AUC, was between 0.62 and 0.68, and reached its maximum (0.68) when maximizing

Figure 4. Examples of monophasic (first column) and biphasic (second column) T waves with corresponding f99 values. More specifically: (A) monophasic T wave; (B) symmetric biphasic T wave; (C) notched T wave; (D) asymmetric biphasic T wave; (E) fragmented monophasic T wave; and (F) fragmented asymmetric biphasic T wave.

f99 over the three orthogonal leads. Such value was comparable to the AUC value obtained using the LVEF (0.70) which is, at the present time, the most commonly used parameter for risk assessment. The lack of correlation between f99 index and LVEF suggests that the two parameters are independent predictors and that, if used in a combined way, they could more powerfully indicate a risk condition. Thus, our future research will be focused on the identification of a proper combination of f99 index with LVEF in order to significantly increase f99 predictive power for the occurrence of ventricular arrhythmias.

In conclusion, our f99 index represents a promising frequency index of cardiovascular risk based on repolarization. When maximized over the three orthogonal lead, it provided a predictive power for the occurrence of ventricular arrhythmias comparable to that of the LVEF, from which it results linearly independent.

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