Ventricular Arrhythmias Assessment: a New Repolarization Index of Risk

Corrado Giuliani[1], Cees A Swenne[2], Sumche Man[2], Angela Agostinelli[1], Laura Burattini[1]

[1]Department of Information Engineering, Polytechnic University of Marche, Ancona, Italy
[2]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Abstract

Defects in the cardiac repolarization are associated to cardiac electrical instability but no repolarization index has proven sufficient sensitivity and specificity to justify preventive interventions yet. Aim of the present study was to propose a new repolarization frequency-based index, termed f99, and to test its predictive power on exercise 15-lead (X, Y, Z, V1 to V6, I to III, aVr, aVl, aVf) ECG recordings from 266 ICD patients, of which 76 developed ventricular tachycardia or fibrillation during the 4-year follow-up (ICD_Cases), and 190 did not (ICD_Controls). After performing the frequency-content evaluation of the repolarization signal (RPS) at the maximum heart-rate reached during exercise, f99 was computed as the frequency at which the RPS energy first reaches or overcomes 99%. Eventually, f99 single-lead values were maximized over lead-systems (MaxXYZ, MaxV1-V6 and Max12L), and predictive power of these parameters was evaluated as the area-under the receiver operating curve (AUC). Compared to the ICD_Controls, the ICD_Cases showed significantly higher values of MaxXYZ (38 vs. 27 Hz; AUC=0.61), MaxV1-V6 (42 vs. 33 Hz; AUC=0.60) and Max12L (46 vs. 37 Hz; AUC=0.65). Thus, the new f99 represents a promising tool to identify the risk of ventricular tachycardia or fibrillation, with Max12L showing the best predictive power.

1. Introduction

Defects in the cardiac repolarization are known to be associated to several life-threatening diseases [1-4]. In the electrocardiogram (ECG) such defects appear as abnormalities of the ST segment and T wave, which can be non-invasively characterized by means of indexes. The most popular ECG repolarization indexes is the QT interval [2,3]. Despite QT-interval prolongation being the standard indicator of cardiac safety in clinical trials, several limitations affect it, such as inter-lead QT-interval variability, also known as QT dispersion [5-7], and inter-method QT variability (few tens of ms), which is instead associable to the different automatic algorithms used for its detection [8]. Other proposed repolarization indexes for risk stratification are the T-wave alternans (TWA) [4,9], the T-wave duration parameters [10,11], the T-wave amplitude parameters [12,13] and others [14-18]. Despite all of them appearing as a promising tools for cardiovascular risk evaluation [4,19], none of them has shown sufficient sensitivity and specificity to justify preventive interventions, such as such as ICD implantation [20]. Thus, the search of new, more reliable repolarization indexes for risk assessment 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 [21,22]. Thus, the aim of the present study was to propose an automatic method for the digital ECG analysis finalized to characterize repolarization by means of a new frequency-based index, termed f99. Usefulness of this index in discriminating patients at increased risk of arrhythmic events was tested in two populations of ICD patients, ICD_Cases and ICD_Controls, respectively developing and not developing ventricular tachycardia or fibrillation during the 4-year follow-up.

2. Methods

2.1. Study population and clinical data

Our study population consisted of exercise ECG recordings 266 patients (Leiden University Medical Center, The Netherlands) with an ICD for primary prevention because of a depressed left ventricular ejection fraction (LVEF<35%). All patients underwent an exercise test which consisted of an approximately 10-min bicycle ergometer 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 leads (I, II, V1 to V6) ECG recordings were obtained using a CASE 8000 stress test recorder

(GE Healthcare, sampling rate: 500 Hz; resolution: 4.88 μV/LSB). After the exercise test, all patients underwent a 4-year follow-up at the end of which they were classified as either ICD_Cases (76 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 (190 patients) otherwise.

2.2. Preprocessing

First, 15 ECG leads (X, Y, Z, V1 to V6, I to III, aVr, aVl, aVf) were derived through the Dower's transform [23] from the 8 recorded ones. Then, before T-wave frequency-content evaluation, ECG tracings underwent a preprocessing stage consisting of Fs=200 Hz resampling, low-frequency (≤ 0.5 Hz) noise removal and 50 Hz power-line noise removal. Eventually, after R-peak detection, a 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 2 ectopic beats and artifacts) was extracted from each recording in correspondence of the maximum HR (i.e. maximum workload). Patients for which this window was not available at least in 1 out of 15 leads were rejected.

2.3. Repolarization characterization

Repolarization frequency-content evaluation was independently performed in each lead of the ECG window. From the median beat, computed using the ECG beats included in the 30-s window, repolarization onset (RepOn) and offset (RepOff) were identified as follows:

$$\text{RepOn} = 70\ \text{ms} \quad \text{from the R peak} \tag{1}$$

$$\text{RepOff} = \text{RepOn} + 0.3\sqrt{\text{medianRR}} \cdot 1000\ \ \text{ms} \tag{2}$$

Eq. (2) represents an adjustment of an empirical formula previously proposed in [24] finalized to avoid cases of P-wave inclusion in the T-wave window; and medianRR (in s) is the median RR interval. The median repolarization waveform was then forced to be 260 ms long by opportune wave stretching or compression. Eventually, the repolarization signal (RPS) was constructed by zero padding everything outside the resampled median repolarization waveform till 1 second.

RPS frequency-content evaluation was performed by computing the Fourier power spectrum (PSRPS(k); Eq. 3) and the energy signal (ERPS(k); Eq. 4)):

$$PS_{RPS}(k) = \sum_{n=0}^{N_s - 1} RPS(n) \cdot exp^{-j2\pi \frac{k}{N_s} n} \tag{3}$$

$$E_{RPS}(k) = \sum_{m=0}^{k} PS_{RPS}(m) \tag{4}$$

where Ns is the number of samples (Ns=200), and n and k are adimensional indexes to get time and frequency as tn=n·(1/Fs)=n·0.005 s, with n=1, 2, …Ns, and fk=k Hz, with k=1, 2, …Ns/2, respectively. After having computed the total energy (ERPS_Total; Eq. 5), the PSRPS(k) and the ERPS(k) were normalized and expressed as percentages (PSRPS%(k) and ERPS%(k), respectively; Eq. 6 and Eq. 7):

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

$$PS_{RPS}\%(k) = \frac{PS_{RPS}(k)}{E_{RPS}\_Total} \cdot 100 \tag{6}$$

$$E_{RPS}\%(k) = \frac{E_{RPS}(k)}{E_{RPS}\_Total} \cdot 100 \tag{7}$$

By definition, ERPS%(k) is a monotonically increasing function which saturates at 100%. The frequency at which ERPS% first reaches or overcomes 99%, called f99, was chosen as an index to characterize repolarization (Fig.1).

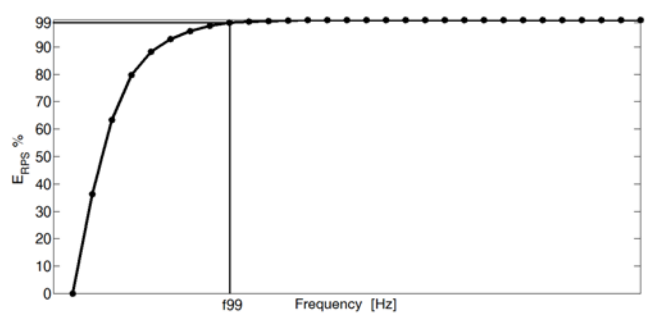

Fig. 1. Definition of f99 index as the frequency at which ERPS% first reaches or overcomes 99%.

2.4. Lead-system analysis

A value of f99 was first obtained for each one of the 15 available ECG leads. Then, the single-lead *f99* values were maximized over the Frank's orthogonal XYZ leads

(MaxXYZ), over the 6 precordial leads (MaxV1-V6) and over the 12 standard leads (Max12L) in order to obtain lead-system repolarization indexes after checking satisfaction of the following inclusion criteria:

- f99 available in at least 2 out of 3 leads when computing MaxXYZ;
- f99 available in at least 3 out of 6 leads when computing MaxV1-V6;
- f99 available in at least 6 out of 12 leads when computing for Max12L;

2.5. Statistics

Normality of parameters distributions was tested using the Lilliefors test. Not-normal distributions were described by providing the 50^{th} [25^{th}, 75^{th}] percentile and compared using Wilcoxon rank-sum test. Eventually, f99 ability to identify an increased risk of arrhythmic events was evaluated using the area under the receiver operator curve (AUC) when discriminating ICD_Controls from ICD_Cases. Statistical significance level was set at 0.05.

3. Results

The preprocessing step led to subjects' or leads' removal due to the presence of ectopic beats and artifacts or to unstable heart rate. Moreover, the inclusion criteria described in 2.4 led to a supplementary reduction of the number of subjects available for statistical analysis, as showed in Table 1.

Table 1. Number of subjects available for the two ICD populations for each lead-system parameter.

	ICD_Controls (N=190)	ICD_Cases (N=76)
MaxXYZ	131 (69%)	46 (61%)
MaxV1-V6	130 (68%)	44 (58%)
Max12L	107 (56%)	39 (51%)

Consequently, in all distributions, f99 values were significantly higher for ICD_Cases than for the ICD_Controls (Table 2). Moreover, AUC values resulted 0.61, 0.60 and 0.65 for MaxXYZ, MaxV1-6 and Max12L, respectively (Table 2, Fig.2).

4. Discussion

This study aimed to characterize cardiac repolarization through frequency-content evaluation. To this aim, the Leiden University Medical Center database of exercise ECGs in 266 heart failure patients

Table 2. Values of f99 for the three distributions expressed as 50^{th} [25^{th}, 75^{th}] percentiles.

	ICD_Controls f99 [Hz]	ICD_Cases f99 [Hz]	AUC
MaxXYZ	27 [16, 43]	38* [23, 54]	0.61
MaxV1-V6	33 [21, 52]	42* [28, 65]	0.60
Max12L	37 [24, 58]	46° [38, 66]	0.65

*: P<0.05 for ICD_Controls vs ICD_Cases;
°: P<0.01 for ICD_Controls vs ICD_Cases;
AUC: Area under the ROC curve

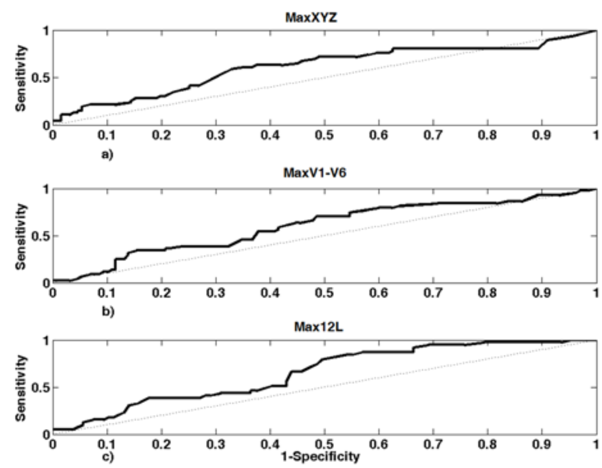

Fig. 2. ROC curves for MaxXYZ (panel a), MaxV1-V6 (panel b) and Max12L (panel c).

with ICDs, grouped in 76 ICD_Cases (i.e. patients who developed ventricular tachycardia or ventricular fibrillation during follow-up) and 190 ICD_Controls (i.e. patients who did not develop ventricular arrhythmias during follow-up), was employed. Several (31-49%) ICD patients were found to be not suitable for repolarization characterization because of two inclusion criteria: one on the HR stability and one on the signal quality. Repolarization characterization was performed at maximum HR, at which index identification may be more reliable because at high frequency HR is more stable and repolarization defects are often magnified [25].

On the subjects found to be suitable for repolarization analysis, we performed the frequency-content evaluation by means of spectral techniques. More specifically, we defined an index to characterize repolarization, called f99, as the frequency at which the energy of the repolarization signal (ERPS%) first reaches or overcomes 99%, and computed it for each lead.

As a result, we found that f99 values were significantly higher for ICD_Cases than for the ICD_Controls in all the leads groups in analysis. More specifically, Max12L was found to be as the preferable leads' group for discriminating the two populations, since P<0.01 and AUC=0.65.

4. Conclusion

Our new f99 index proved to be able to discriminate between ICD_Cases and ICD_Controls. Thus, it represents a promising non-invasive tool to identify the risk of ventricular tachycardia or fibrillation.

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Laura Burattini
Department of Information Engineering,
Polytechnic University of Marche
60131 Ancona, Italy
l.burattini@univpm.it