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Automatic SVM classification of sudden cardiac death and pump failure death from autonomic and repolarization ECG markers☆

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Abstract

Background: Considering the rates of sudden cardiac death (SCD) and pump failure death (PFD) in chronic heart failure (CHF) patients and the cost-effectiveness of their preventing treatments, identification of CHF patients at risk is an important challenge. In this work, we studied the prognostic performance of the combination of an index potentially related to dispersion of repolarization restitution ($\Delta\alpha$), an index quantifying T-wave alternans (IAA) and the slope of heart rate turbulence (TS) for classification of SCD and PFD.

Methods: Holter ECG recordings of 597 CHF patients with sinus rhythm enrolled in the MUSIC study were analyzed and $\Delta\alpha$, IAA and TS were obtained. A strategy was implemented using support vector machines (SVM) to classify patients in three groups: SCD victims, PFD victims and other patients (the latter including survivors and victims of non-cardiac causes). Cross-validation was used to evaluate the performance of the implemented classifier.

Results: $\Delta\alpha$ and IAA, dichotomized at 0.035 (dimensionless) and 3.73 μV, respectively, were the ECG markers most strongly associated with SCD, while TS, dichotomized at 2.5 ms/RR, was the index most strongly related to PFD. When separating SCD victims from the rest of patients, the individual marker with best performance was $\Delta\alpha \geq 0.035$, which, for a fixed specificity (Sp) of 90%, showed a sensitivity (Se) value of 10%, while the combination of $\Delta\alpha$ and IAA increased Se to 18%. For separation of PFD victims from the rest of patients, the best individual marker was TS $\leq$ 2.5 ms/RR, which, for Sp = 90%, showed a Se of 26%, this value being lower than Se = 34%, produced by the combination of $\Delta\alpha$ and TS. Furthermore, when performing SVM classification into the three reported groups, the optimal combination of risk markers led to a maximum Sp of 79% (Se = 18%) for SCD and Sp of 81% (Se = 14%) for PFD.

Conclusions: The results shown in this work suggest that it is possible to efficiently discriminate SCD and PFD in a population of CHF patients using ECG-derived risk markers like $\Delta\alpha$, TS and IAA.

Keywords: SCD; Pump failure death; Support vector machine; ECG; CHF; Tpe/RR dynamicity; T-wave alternans; Heart rate turbulence

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Introduction

Mortality rate in patients with chronic heart failure (CHF) remains high despite advancement in modern treatment [1]. In clinical practice, a distinction is frequently made between sudden or unexpected cardiac death (SCD) and pump failure death (PFD) [2]. Several studies have shown that the development of effective targeted therapeutic interventions such as implantable cardioverter defibrillators (ICDs) reduce SCD mortality in CHF populations [3]. On the other hand, successful methods in preventing PFD include therapeutic drugs, medical management, long-term or destination mechanical circulatory support and cardiac resynchronization therapy [4]. Considering the rates of SCD and PFD in CHF patients and the cost-effectiveness of the above mentioned treatments, identification of CHF patients most likely to develop each of these fatal complications is an important clinical challenge.

Invasive and non-invasive markers have been proposed as SCD and/or PFD predictors, including electrophysiological testing [5], invasive hemodynamic evaluation [6], left ventricular ejection fraction (LVEF) [7], T-wave alternans (TWA) [8], an index measuring the slope of the T-peak-to-end (Tpe)/RR regression [9] or autonomic indices such as heart rate variability or turbulence (HRV, HRT) [10]. From a clinical point of view, an algorithm with a high specificity (Sp) for separating modes of cardiac death (CD) is preferred particularly because the prevalence of SCD and PFD is relatively low. A common limitation of individually using the above mentioned risk markers is that they do not provide a high enough sensitivity (Se)/Sp ratio. Our hypothesis is that, if such indices reflect different underlying physiological phenomena, they might add complementary information to each other and, consequently, a combined index might improve the capability for risk-stratification of patients.

In this work, we studied the performance of the combination of three electrocardiogram (ECG)-derived indices to classify CHF patients in the following possible groups: SCD, PFD and others, where the last one includes survivors and victims of non-cardiac causes. The three ECG indices, which have already shown potential to predict SCD or PFD in CHF patients in previous studies [8–10], are: $\Delta\alpha$ (an index possibly related to dispersion of repolarization restitution), IAA (an index quantifying TWA) and TS (an index measuring HRT slope).

Methods

Study population

Consecutive patients with symptomatic CHF of New York Heart Association (NYHA) classes II and III were enrolled in the MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, which was a prospective, multicenter study designed to investigate risk predictors of cardiovascular mortality in ambulatory CHF patients [11]. Holter recordings of 650 patients with sinus rhythm were available for the present study, although only 597 patients had computable $\Delta\alpha$, IAA and TS. Patients were consecutively enrolled from the specialized HF clinics of eight University Hospitals between April 2003 and December 2004. This study included patients with either depressed or preserved LVEF, ranging from 10% to 70%. Patients with preserved LVEF were included if they had HF symptoms and a prior hospitalization for HF or some objective signs of HF confirmed by chest X-ray and/or echocardiography. Patients with a recent acute coronary syndrome or severe valvular disease amenable for surgical repair were excluded. Patients with other concomitant diseases expected to reduce life-expectancy were also excluded. A two- or three-lead 24-h Holter ECG (ELA Medical, Sorin Group, Paris, France) sampled at 200 Hz was recorded in each patient at enrolment. No medications were withdrawn during the Holter monitoring. The study protocol was approved by institutional investigation committees and all patients gave written informed consent.

Follow-up visits were conducted on an outpatient basis every 6 months, for a median of 44 months. SCD was defined as (a) a witnessed death occurring within 60 min from the onset of new symptoms unless a cause other than cardiac failure was obvious, (b) an unwitnessed death (<24 h) in the absence of preexisting progressive circulatory failure or other causes of death, or (c) death during attempted resuscitation. PFD was defined as death occurring in hospitals as a result of refractory progressive end-stage CHF death. SCD and PFD endpoints were reviewed and classified by the MUSIC Study Endpoint Committee [11].

ECG risk markers

$\Delta\alpha$, an index potentially related to dispersion in repolarization restitution, was computed by analyzing the relationship between the Tpe and RR intervals of the ECG [9]. $\Delta\alpha$ was calculated as the derivative of the Tpe interval with respect to a surrogate of the RR interval that accounts for the Tpe memory dependence on RR (see [12] for details). The computation of $\Delta\alpha$ was performed at the High Performance computing platform of the NANBIOSIS ICTS, CIBER-BBN and I3A, Zaragoza, Spain.

IAA, an index reflecting the average TWA activity during a 24-h period, was computed by automatic ECG analysis [8]. The analysis was performed on every ECG recording in 3 steps: (a) selection of signal segments (of 128 beats with a 50% overlap between adjacent segments) that were suitable for automatic analysis, (b) estimation of TWA amplitude in those segments with a multi-lead scheme that combines periodic component analysis with the Laplacian likelihood ratio method, and (c) computation of the average of all segments' TWA amplitudes [8].

TS, a parameter measuring the turbulence slope of HRT, was calculated as in [10], considering patients having at least 1 ventricular premature beat (VPB) during the 24-h ECG recording. Details on TS calculation can be found in [10].

Classification

A classifier was implemented based on a two- and three-class support vector machine (SVM) in the form of *C*-support vector classification [13]. The SVM classifier was optimized by quadratic programming [14] and the selected kernel for the proximity mapping was the inhomogeneous first order polynomial mapping [15]. Other more complex kernels were tested, but they increased complexity without improving the discriminative power of the SVM. We used the *prtools* toolbox [16] from MatLab® to train and test the SVM models.

To train the SVM models, 5-fold cross validation was performed [17]. *C*-SVM classification adds a penalty parameter, *C*, in the optimization. Increasing *C* makes the optimization to attempt a stricter separation between modes of CD. Equivalently, reducing *C* towards 0 produces a smoother decision boundary at the expense of increasing the probability of misclassifying a patient (that would be treated as an outlier). The decision boundary of the SVM classifier was configured in two ways. The first configuration set a high value of *C*, defined as $C_1 = (1 - \text{abs}(Lp - Lm)/(Lp + Lm))$, where C_1 represents the theoretical maximum of *C* that guarantees convergence of the optimization and Lp (Lm) is the number of positive (negative) samples [16]. The value of *C* used for the second configuration (C_2) (theoretical minimum value of *C* that guarantees convergence) was estimated by the "leave-one-error" of the "1 − Nearest Neighbor" rule [18]. In order to perform three-class classification, three two-class classifiers between each of the three classes (SCD, PFD, others) and the remaining two classes were computed. Each two-class classifier returned a score for each observation that could be interpreted as the probability of belonging to each class. Then, the final output class was chosen as the one associated with maximum score over the two-class classifiers [13].

Statistical analysis

Data are presented as median (interquartile range) for continuous variables and as number and percentage for categorical variables. Two-tailed Mann–Whitney and Fisher exact tests were used for univariate comparison of quantitative and categorical data, respectively. Receiver operating characteristic (ROC) curves were used for $\Delta\alpha$, IAA and TS for the entire population to compare the parameters' ability to predict SCD and PFD. Simultaneous maximization of Se and Sp (minimum Euclidean distance from the ROC curve to the upper-left corner) was applied to select the threshold, with an area under the curve > 0.55 required for setting the classification cut-off point. Patients who died from causes other than SCD or PFD were censored at the time of death when studying SCD and PFD mortality, respectively. The performance of the classifier was evaluated in terms of Se, Sp and the Cohen's Kappa coefficient (κ) from a confusion matrix. κ measures pairwise agreement between the expected and the true modes of CD, correcting for expected chance agreement. When there is no greater agreement than that which would be expected by chance, κ is zero. When there is total agreement, κ is one [19]. To calculate Se and Sp for each mode of death, that particular mode of death was defined as a positive event and all other modes of death as well as survival outcome were defined as a negative event. The final values of Se, Sp and κ were calculated as the mean of each individual measurement of the cross-validation. A p-value < 0.05 was considered as statistically significant. Data were analyzed by using version 22.0 of SPSS software.

Results

Clinical characteristics of the study population

The study population consisted of 597 patients with sinus rhythm. During the 4-year follow up, 134 (22%) patients died. Of these, 111 (19% of the total sample) were CD victims and 23 (4%) non-CD victims. Among CD victims, 49 (8% of the total sample) were categorized as SCD and 62 (10%) as PFD.

425 patients were men and 172 were women aged 18 to 89 years, with median (interquartile range), 65 (17) years. 17% of the patients were in heart failure NYHA class III (while the remaining 83% were in NYHA class II) and 56% of the patients had LVEF ≤ 35%. 38% of the patients suffered from diabetes mellitus. 71% were in beta-blockers treatment, 9% were in amiodarone treatment and 80% had ARB or ACE inhibitors. The average, maximum and range of heart rate were, respectively, 70 (15), 113 (23) and 64 (21) beats/min. 41% of patients had a QRS wider than 120 ms. 26% of patients had both non-sustained ventricular tachycardia and more than 240 ventricular premature beats in 24 h. No significant differences in these clinical variables were found between the groups of SCD victims and PFD victims.

Relation of cardiac death mode with heart failure NYHA class and left ventricular ejection fraction

7% of patients in heart failure NYHA class II vs. 14% of patients in NYHA class III were SCD victims, $p = 0.047$. Regarding PFD, 8% of patients in NYHA class II vs. 20% of patients in NYHA class III suffered from this outcome, $p = 0.001$.

The number of SCD victims was significantly higher in patients with LVEF ≤ 35% than in patients with LVEF > 35% (11% vs. 5%, $p = 0.010$). The group of patients with LVEF ≤ 35%, although non-significantly, presented a higher number of PFD victims than the group formed by patients with LVEF > 35% (13% vs. 8%, $p = 0.058$).

The median value of TS was significantly lower in patients with LVEF ≤ 35% with respect to patients with LVEF > 35% (2.127 (3.71) ms/RR vs. 3.529 (5.11) ms/RR, $p < 10^{-6}$) and in patients in NYHA class III as compared to patients in NYHA class II (1.582 (2.11) ms/RR vs 3.173 (4.44) ms/RR, $p < 10^{-6}$). No significant differences in $\Delta\alpha$ and IAA median values were found between low and preserved LVEF and between NYHA classes II and III.

Separation of populations according to cardiac death mode

$\Delta\alpha$ values were significantly higher in SCD victims than in the rest of patients ($p = 0.004$), and showed a trend towards being lower in PFD than in the rest of patients with only borderline significance ($p = 0.068$) (see Table 1). When only considering CD victims, i.e. SCD and PFD victims, both modes of death presented statistically significant differences in terms of $\Delta\alpha$ values (Table 1). No significant differences were found in IAA values for any of the comparisons (Table 1). TS values were significantly lower in SCD and PFD victims as compared, in each case, with the rest of patients. However, when considering only the group of CD victims, no significant differences were found in TS between SCD and PFD victims (Table 1).

Table 1
Univariate comparison of median value of risk markers among modes of cardiac death. Significant data are indicated in bold.

Risk Markers	Pairwise mode of death comparisons								
	SCD vs. PFD and survivors			PFD vs. SCD and survivors			SCD vs. PFD		
	Median (IQ)	Median (IQ)	p-value	Median (IQ)	Median (IQ)	p-value	Median (IQ)	Median (IQ)	p-value
Δα	0.039 (0.04)	0.024 (0.03)	**0.004**	0.019 (0.03)	0.026 (0.03)	0.068	0.039 (0.04)	0.019 (0.03)	**0.003**
IAA	3.207 (2.21)	2.907 (1.23)	0.510	2.758 (1.31)	2.923 (1.28)	0.866	3.207 (2.21)	2.758 (1.31)	0.966
TS	1.597 (4.28)	2.912 (4.17)	**0.001**	1.245 (1.61)	3.105 (4.29)	$\mathbf{<10^{-8}}$	1.597 (4.28)	1.245 (1.61)	0.353

Two-class classification of cardiac death mode using one ECG index

ROC curve analysis showed that the optimal dichotomization thresholds for Δα were 0.035 for SCD (Δα ≥ 0.035 had 13% of SCD victims vs 6% in the Δα < 0.035 group, p = 0.001) and 0.022 for PFD (Δα ≤ 0.022 had 15% of PFD victims vs. 7% in the Δα > 0.022 group, p = 0.003). IAA was only associated with SCD (3.73 μV being the optimal threshold, IAA ≥ 3.73 μV had 14% of SCD victims vs 6% in the IAA < 3.73 μV group, p = 0.008). The optimal cut-off point for TS was 2.5 ms/RR for both SCD and PFD (TS ≤ 2.5 ms/RR had 12% of SCD and 17% of PFD victims, vs. 5% of SCD and 4% of PFD in the TS > 2.5 ms/RR group, p = 0.004 and $p < 10^{-8}$, respectively).

For classification of SCD vs. the rest of patients, Δα ≥ 0.035 and IAA ≥ 3.73 μV were the risk markers with maximum value of κ (0.10 in both cases), with a Se of 55% and a Sp of 68% for the former and a Se of 41% and a Sp of 78% for the latter (Table 2). For classification of PFD vs. the rest of patients, TS ≤ 2.5 ms/RR was the ECG index with maximum κ (0.14), showing a Se of 79% and a Sp of 57%, improving the performance of Δα ≤ 0.022 (κ =0.10, 63% Se and 57% Sp) (Table 2).

Two-class classification of cardiac death mode using a combination of ECG indices

The combination of Δα and IAA showed the maximum value of κ for both configurations (C_1 and C_2, respectively) of the SVM two-class classifier for separating SCD from the rest of patients. With the first configuration (C_1), the combination of Δα and IAA showed a Se of 12%, a Sp of 97% and a κ value of 0.10. With the second configuration Se was of 53%, Sp of 69% and κ of 0.08. To compare the performance of the combination of Δα and IAA with that of Δα on its own, we fixed Sp at 90%. For such Sp value, Δα showed a Se of 10%, while Δα and IAA produced a Se of 18%.

For the first configuration (C_1) of the SVM two-class classifier, the combination of risk markers with the maximum κ for separating PFD from the rest of patients was Δα and TS, with a Se of 47%, a Sp of 84% and a κ value of 0.22. For the second configuration (C_2), the combination of TS and IAA showed the maximum κ, with a Se of 86%, a Sp of 51% and a κ value of 0.13. By setting the value of Sp to 90%, single ECG markers Δα and TS showed a Se of 11% and 26%, respectively, while Se increased to 34% for the combination of Δα and TS.

Table 2
Two-class classification performance for SCD vs the rest of patients and PFD vs. the rest of patients using individual markers Δα, IAA and TS. The optimum risk marker for each mode of cardiac death is indicated in bold.

Risk Markers	SCD			PFD		
	Se (%)	Sp (%)	κ	Se (%)	Sp (%)	κ
Δα+	**55**	**68**	**0.10**	63	57	0.10
IAA+	41	78	0.10	Non significant		
TS+	67	55	0.07	**79**	**57**	**0.14**

Δα + represents Δα ≥ 0.035 for SCD and Δα ≤ 0.022 for PFD. IAA+ represents IAA ≥ 3.73 for SCD. TS+ represents TS ≤ 2.5ms/RR for both SCD and PFD.

Three-class classification of cardiac death mode using a combination of ECG indices

Table 3 summarizes the performance of the two configurations of the SVM three-class classifier for separating SCD from PFD and from the rest of patients in the overall population, in patients with LVEF ≤ 35% and in patients with LVEF > 35%. The combination of risk markers with the highest κ when evaluating the overall population and patients with LVEF > 35% was TS and IAA (κ = 0.11 and κ = 0.17, respectively), using the first configuration of the classifier. However, when evaluating the performance of the classifier in patients with LVEF ≤ 35%, Δα and TS was the second combination with the highest value of κ (κ = 0.17), with the first one being that formed by Δα, IAA and TS (κ = 0.18).

TS and IAA, in the first configuration (C_1), also showed the highest values of κ in patients in NYHA class II (Se of 20%, Sp of 14% for SCD, Se of 79%, Sp of 80% for PFD, κ = 0.11) and in NYHA class III (Se of 37%, Sp of 32% for SCD, Se of 75%, Sp of 79% for PFD, κ = 0.30). For the second configuration (C_2), Δα and TS was the combination with the highest κ values in NYHA class II (Se of 35%, Sp of 66% for SCD, Se of 44%, Sp of 41% for PFD, κ = 0.09) and in NYHA class III (Se of 27%, Sp of 24% for SCD, Se of 56%, Sp of 59%, κ = 0.13 for PFD) patients (Table 4).

Discussion

In this study, we investigated the combination of several ECG indices computed from 24-h ambulatory recordings, namely Δα, IAA and TS, to classify a population of CHF patients into three groups: SCD victims, PFD victims and others (i.e. survivors and victims of non-cardiac causes). We proposed two- and three-class first order polynomic SVM classifiers and compared the performance of the combined vs individual ECG indices. The possibility of providing a

Table 3
Three-class classification performance for separating SCD victims, PFD victims and others (non-CD and survivors) in the overall population, in patients with LVEF ≤ 35% and in patients with LVEF > 35%. The optimum combination for each configuration (*C1* and *C2*, see text) and mode of cardiac death is indicated in bold.

Combination	Configuration	Sample population	SCD		PFD		κ
			Se (%)	Sp (%)	Se (%)	Sp (%)	
	C_1	Overall population	8.2	84.8	5.0	87.1	0.06
		LVEF > 35%	6.7	87.6	5.0	90.2	0.05
Δα and TS		LVEF ≤ 35%	8.6	77.5	39.2	74.6	0.17
	$\mathbf{C_2}$	**Overall population**	**32.9**	**56.0**	**48.2**	**54.7**	**0.11**
		LVEF > 35%	**0.0**	**61.7**	**45.0**	**59.9**	**0.05**
		LVEF ≤ 35%	**56.4**	**43.5**	**56.1**	**43.3**	**0.15**
	C_1	Overall population	4.2	85.0	0.0	87.5	0
		LVEF > 35%	13.3	89.6	5.0	92.6	0.11
Δα and IAA		LVEF ≤ 35%	2.9	82.2	2.5	83.9	0
	C_2	Overall population	50.9	51.0	11.7	55.6	0.03
		LVEF > 35%	13.3	55.3	25.0	55.8	0.01
		LVEF ≤ 35%	47.5	44.8	28.6	47.4	0.06
	$\mathbf{C_1}$	**Overall population**	**18.0**	**78.7**	**13.8**	**80.5**	**0.11**
		LVEF > 35%	**30.0**	**72.9**	**35.0**	**73.8**	**0.17**
TS and IAA		**LVEF ≤ 35%**	**18.6**	**70.7**	**16.9**	**72.2**	**0.13**
	C_2	Overall population	20.4	56.6	50.5	54.1	0.10
		LVEF > 35%	16.7	41.8	50.0	39.7	0.02
		LVEF ≤ 35%	69.3	40.8	15.0	48.1	0.12
	C_1	Overall population	12.2	84.3	5.0	86.9	0.09
		LVEF > 35%	0.0	88.4	10.0	90.2	0.05
Δα, IAA and TS		LVEF ≤ 35%	8.6	79.8	26.7	78.7	0.13
	C_2	Overall population	36.9	55.4	36.3	55.8	0.10
		LVEF > 35%	10.0	59.7	40.0	58.6	0.05
		LVEF ≤ 35%	58.9	45.5	60.3	45.0	0.18

classifier to identify SCD and PFD victims among CHF patients is of high clinical relevance given the mortality rates related to SCD and PFD and the cost-effectiveness of associated treatments.

We started by evaluating the performance of the three investigated individual ECG markers for classifying the two modes of CD: SCD and PFD. Our results confirmed that Δα (an index possibly related to dispersion of repolarization restitution) was able to distinguish between modes of CD, with higher values of Δα being associated with SCD, as published in [9], and lower values of Δα with PFD. If Δα was effectively associated with repolarization restitution dispersion, our results on the relation between high Δα and SCD would be in agreement with [20], where an increased spatial heterogeneity in ventricular restitution was shown to be linked to inducibility of ventricular arrhythmia. Regarding IAA (an index measuring the amplitude of T-wave alternans), we did not find significant differences between the two CD modes using the continuous IAA variable. When IAA was dichotomized, we found that higher T-wave alternans amplitudes were associated with SCD risk, in accordance with the results presented in [8]. The third investigated index was TS, quantifying the slope of HRT, which we found to be the risk marker most strongly associated with PFD, while presenting a less relevant relation to SCD. According to our results, both SCD and PFD showed lower HRT slope values as compared to the rest of CHF patients, confirming results reported in previous studies [10]. We could not find, however, significant differences in TS between SCD and PFD victims.

We next considered combinations of the three analyzed ECG indices. The combination of Δα and IAA showed to be the one with the best performance in two-class SVM classification of SCD vs. the rest of patients. Despite the fact that the dichotomized ECG marker, Δα ≥ 0.035, and the combination of Δα and IAA (in the first configuration of the classifier) provided the same value of κ, the combined

Table 4
Three-class classification performance for separating SCD victims, PFD victims and others (non-CD and center survivors) in the overall population, in patients in NYHA class II and in patients in NYHA class III for the optimum combination for each configuration (*C1* and *C2*, see text).

Combination	Sample population	SCD		PFD		κ
		Se (%)	Sp (%)	Se (%)	Sp (%)	
	Overall population	18.0	78.7	13.8	80.5	0.11
TS and IAA (C_1)	NYHA II	20.0	14.2	79.1	80.3	0.11
	NYHA III	36.7	32.0	74.5	78.5	0.30
	Overall population	32.9	56.0	48.2	54.7	0.11
Δα and TS (C_2)	NYHA II	34.3	65.8	44.0	41.3	0.09
	NYHA III	26.7	24.0	55.9	59.2	0.13

index showed a significantly higher Sp value. Considering the clinical need for a highly specific classifier to improve stratification of CHF patients who would benefit from ICD implantation, the combination of $\Delta\alpha$ and IAA would be preferred over the individual $\Delta\alpha$ index for separating SCD from the rest of patients. This result confirmed the hypothesis that $\Delta\alpha$ and IAA add complementary information and, consequently, their combination would improve the stratification of CHF patients at risk of SCD, with higher values of the combined $\Delta\alpha$ and IAA index indicating higher propensity to suffer from a SCD event.

Regarding two-class classification of PFD vs the rest of patients, $TS \leq 2.5$ was the dichotomized individual risk marker with the highest association with this mode of CD, presenting a value of κ higher than that of $\Delta\alpha \leq 0.022$. When combining ECG indices, the combination of TS and IAA was the one with the highest κ coefficient for the second configuration of the classifier, but not improving the performance of TS individually, indicating that the classifying performance of the combined index was merely due to the power of TS. For the first configuration of the classifier, $\Delta\alpha$ and TS showed a notably higher κ value than the individual TS marker. This is concordant with the fact that $\Delta\alpha$ was also associated with PFD, although to a lesser extent than with SCD. Since for a given Sp value, the combination of $\Delta\alpha$ and TS presents higher Se than any individual index, this combination would be recommended for PFD classification, with lower values of the combined TS and $\Delta\alpha$ indicating higher propensity to suffer from PFD outcome.

In the three-class classification of SCD, PFD and others (i.e. survivors and non-CD victims), the combination of TS and IAA showed to be the one with the best performance for the first configuration of the classifier, while $\Delta\alpha$ and TS was the best one for the second configuration. Considering the higher Sp values in the identification of SCD and PFD for the first configuration of the classifier, the combination of TS and IAA would more robustly distinguish CHF patients at no risk of SCD or PFD. $\Delta\alpha$ and TS achieved higher Se (at the expense of lower Sp) in the second configuration of the classifier, indicating that $\Delta\alpha$ and TS would be capable of more powerfully identifying CHF patients at SCD or PFD risk.

To assess to which extent our results would vary when applied to populations of CHF patients with depressed or preserved LVEF or with different NYHA classes, we evaluated our SVM classifiers in these subpopulations. The classification performance in patients with depressed LVEF was improved with respect to that in the overall study population. Similarly, the performance of the classifier was improved in NYHA class III patients with respect to the results obtained when analyzing the overall population.

Our results indicate that improved risk stratification of CHF patients can be achieved based on the combination of ECG risk markers. The three markers investigated in the present study provide complementary information for identification of SCD and PFD. The index $\Delta\alpha$ and the index IAA are both indicative of processes related to ventricular repolarization and the two of them have shown strong association with SCD. Regarding IAA, autonomic neurotransmitters decompensation and changes in myocardial substrate can lead to elevated levels of TWA, serving as arrhythmogenic factors. Clinical studies have shown the value of high TWA magnitudes as a marker of increased risk for ventricular tachyarrhythmias in CHF patients [8,21]. Regarding $\Delta\alpha$, it has been hypothesized that larger heterogeneities in repolarization restitution within the ventricles could lead to increased values of $\Delta\alpha$ and could possibly contribute to increased arrhythmic risk [12]. Further studies are needed to confirm this hypothesis and to assess additional autonomic modulation of this marker. On the other hand, HRT is a recently recognized electrocardiographic phenomenon reflecting minute hemodynamic disturbance caused by a ventricular premature beat. Lower TS (HRT slope) values would reflect a reduced baroreflex mediated response of the sinus node to this disturbance and thus poor regulation properties of the autonomic nervous system. Several clinical studies have established that HRT is a strong and independent risk predictor of PFD and, to a lesser extent, SCD [22]. The results in the present work are in line with the fact that abnormal repolarization patterns are more strongly related with arrhythmic risk while indices reflecting cardiac autonomic modulation are more likely to predict PFD and, thus, the combination of all of them would allow for improved separation of the two modes of cardiac death.

Limitations

This study used fully automated ECG measurements ($\Delta\alpha$, IAA and TS) that are likely to suffer imprecision, especially when applied to abnormal ECGs in CHF patients. Until detailed visual inspection is used to verify the measurements, the results can only be considered preliminary. A retrospective study of this kind may only be hypothesis generating. Prospective studies are needed to verify that the observations presented here have a role in SCD and PFD classification in CHF patients. Both tachycardia and bradycardia cases were likely included. The number of SCD and PFD victims was relatively low in comparison with survivors. This might have imposed some limitations on the decision boundary for the classifiers. Future studies should include the validation of the method in an independent dataset, instead of using cross-validation.

Conclusions

Two- and three-class SVM classifiers can be used to automatically separate CHF patients according to their clinical outcome using combinations of ECG indices obtained from 24-h Holter ECG recordings. A classifier including ECG risk markers quantifying the slope of the Tpe/RR regression, T-wave alternans and heart rate turbulence slope efficiently discriminates between SCD, PFD and other outcomes.

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