Prognostic Role of Electrocardiographic Alternans in Heart Failure Patients with Implanted Cardioverter Defibrillator: Comparison of Machine Learning Methods

Ilaria Marcantoni[1], Erica Iammarino[1], Agnese Sbrollini[1], Cees A Swenne[2], Laura Burattini[1]

[1]Università Politecnica delle Marche, Ancona, Italy
[2] Leiden University Medical Center, Leiden, The Netherlands

Abstract

Implantable cardioverter defibrillator (ICD) is often indicated for the primary prevention of sudden cardiac death in heart-failure (HF) patients, but sometimes, the device remains always inactive, highlighting that the implantation criterium is not specific. The aim of this study is to assess if electrocardiographic alternans (ECGA; an index of cardiac instability) can have a useful prognostic role in improving the identification of HF patients who will experience serious ventricular arrhythmias and truly benefit from the ICD. We analyzed the Leiden University Medical Center database of primary prevention ICD patients by computing ECGA using the enhanced adaptive matched filter (EAMF) method. Patients were categorized into those who needed ICD therapy (40 cases) and those who did not (82 controls) based on their follow-up. ECGA features were used to train and test five machine learning methods (i.e., Decision Tree-DT, Logistic Regression-LR, Naïve Bayes-NB, Linear Discriminant Analysis-LDA, Support Vector Machine-SVM), whose performance was assessed by computing sensitivity (SE), specificity (SP), F1 score (F1) and accuracy (ACC). Results indicated that SVM was the most suitable algorithm (SE=98%; SP=83%; F1=96%; ACC=94%), followed by DT and LR, and ECGA appeared to be a potentially useful tool to improve identification of patients benefiting from ICD.

1. Introduction

The management of heart failure (HF) is one of the most investigated in the field of cardiovascular medicine [1], [2], due to its serious complication, the sudden cardiac death (SCD). Indeed, cardiac arrest affects 30-50% of patients with HF and reduced ejection fraction, causing their death [1]. Current guidelines recommend an implantable cardioverter defibrillator (ICD) for prevention of SCD in patients with HF if their left ventricular ejection fraction (LVEF) is reduced, specifically less than 35% [1], [2]. The 2005 American College of Cardiology/American Heart Association (ACC/AHA) guideline recommended ICD therapy in patients with ischemic cardiomyopathy, a reduced LVEF and New York Heart Association (NYHA) class II or III symptoms while receiving optimal medical treatment. The most recent guidelines retained these recommendations [2].

In general, the advantages of prophylactic ICD implantation do not seem always consistently observed. For example, evidence supporting its benefit is more extensively documented in cases where reduced ejection fraction is due to ischemic causes than in those with non-ischemic origins [1]. In addition, it was observed that in several patients the device is always inactive, highlighting the implantation criterium is not specific.

Identifying patients who will actually benefit prognostically from ICD implantation is a complex decision that should require a well-adjusted assessment of both individual arrhythmic risk and comorbidities-related risk of death [1]. Thus, an effective arrhythmic risk stratification criterion is required in order to avoid unnecessary implant procedures that are costly, can lead to complications, and may have negative outcomes [1], [3].

Among the cardiovascular risk indexes that could be noninvasively identified on the electrocardiogram (ECG) there is the ECG alternans (ECGA). ECGA is defined as the fluctuation of one of the main ECG sections (*i.e.*, P wave, QRS complex, T wave) on every-other-beat basis and has been recognized as an effective biomarker of cardiac instability [4]. Some studies reported an increased risk of severe or malignant arrhythmias and SCD in patients with ischemic and nonischemic chronic HF showing a positive T-wave alternans (TWA) [4]. Moreover, the Alternans Before Cardioverter Defibrillator (ABCD) study by Costantini et al. [5] observed that 93% of patients who receive an ICD based solely on the reduction of LVEF will never use the device therapy, while the addition of TWA reduced this percentage to 65% with only a 1.8% possibility that patients requiring therapy may remain untreated [4]. Despite promising, this evidence needs to be validated and definitely confirmed by further investigations. Therefore, the aim of the present work is to

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confirm the prognostic role of ECGA (considered in all its possible forms, differently from [5]) in improving the identification of HF patients who will truly benefit from the ICD, and to identify the most reliable and accurate ECGA-based classification approach, through a comparative analysis of the most known supervised machine learning methods.

2. Database description

The data used in this study belongs to the Leiden University Medical Center database [6]. The database involves routine clinical data from 266 HF patients who underwent ICD implantation for the primary prevention of SCD [6]. ECG data (lead I, II, V_1–V_6) were collected during a bicycle ergometer test using a CASE 8000 stress-test recorder (GE Healthcare, Freiburg, Germany) and 3 M Red Dot ECG Electrode Soft Cloth 2271 electrodes positioned according to the Mason-Likar configuration. The bicycle ergometer protocol test consisted of an exercise phase, where the workload progressively raised from resting, and a recovery phase. Amplitude resolution and sampling rate of the acquisition system were 4.88 µV/LSB and 500 Hz, respectively [6].

Based on a four-year follow-up, patients were divided into two groups: those who experienced severe arrhythmias and received ICD therapy (cases, N=76) and those whose ICD remained always inactive (controls, N=190). Patients with an ICD that also functioned as a CRT-D dual-chamber pacemaker for cardiac resynchronization therapy (*i.e.*, 36 cases and 100 controls) were excluded. The database also provided the annotations of reference points having same periodicity of the heart rate and other clinical characteristics, which were sex, age (years), body mass index (kg/m^2), LVEF (percentage), and heart rate at rest (bpm). Enrollment criteria based on these clinical characteristics were applied. Specifically, controls with age, body mass index, LVEF, and heart rate at rest comparable with cases were enrolled. The final cohort resulted in 40 cases and 82 controls [7]. The identity of the patients was kept anonymous, and informed consent was not deemed necessary to be enrolled in the study, in accordance with "Guideline for Good Clinical Practice" (European Medicines Agency, CPMP/ICH/135/95) and the data privacy law in the Netherlands [6].

3. Enhanced adaptive matched filter

ECGA detection and quantification was performed by the enhanced adaptive matched filter (EAMF) method [8]. ECGA was detected and characterized in the resting period of the bicycle ergometer test (lasting approximately 1 minute) considering only precordial ECG leads, particularly informative in this population [7], [9].

The EAMF [8] was applied on sliding ECG windows of 64 consecutive heartbeats extracted every second. In the preprocessing phase, ECG data were resampled to 200 Hz, low-pass filtered at 35 Hz using a 6th-order bidirectional Butterworth filter, and the heartbeats of each window were divided into three adjoining sections: the P-wave section (P section), defined from P-wave onset (Pon) to Q-wave onset (Qon), the QRS-complex section (QRS section), defined from Qon to the end of the QRS complex (also called J point), and the T-wave section (T section), defined from J point to the end of the T wave. All fiducial points necessary for defining these sections were annotated in the database but Pon, which was estimated using formulas based on the mean RR interval (mRR, ms) [8]. In particular, if mRR was less than 750 ms, Pon was defined as 160 ms before Qon; if mRR was equal to or longer than 750 ms but less than 1100 ms, Pon was defined as 170 ms before Qon; if mRR was equal to or longer than 1100 ms, Pon was defined as 180 ms before Qon. After that, ectopic heartbeats were detected by computing the correlation between the QRS and T sections of each heartbeat and those of a heartbeat template, defined as the median of all heartbeats within the window. Heartbeats with correlations lower than 0.85 for QRS and/or T sections were considered ectopic and replaced with the template. If less than 5 heartbeats were replaced and the standard deviation of RR intervals was below 10% of mRR, the ECG window was considered suitable for ECGA analysis.

From each suitable window, three enhanced signals were derived by setting to baseline all ECG sections but the one being analyzed for alternans: the P signal (only P sections retained), the QRS signal (only QRS sections retained), and the T signal (only T sections retained). Then, P-wave alternans (PWA), QRS-complex alternans (QRSA) and TWA were quantified on the P signal, QRS signal, and T signal, respectively. Specifically, each signal was band-pass filtered using a 6th-order bidirectional Butterworth filter in a very narrow frequency range around the alternans frequency (by definition, half of the heart rate). The resulting pseudo-sinusoidal signals, termed PWA, QRSA, and TWA signals, respectively, have their maxima and minima aligned to the corresponding ECG sections.

From PWA, QRSA, and TWA signals, two features per heartbeat were extracted: the alternans amplitude (difference between the alternans signal maximum and minimum), and the alternans area (product of alternans amplitude and indicative time duration of the wave under examination, expressed in ms, - fixed to 100 ms for P wave, 80 ms for QRS complex, 200 ms for T wave). Median amplitude and area over the intra-window heartbeats were computed. The alternans duration (number of alternating beats) and the alternans magnitude (product of alternans amplitude and alternans duration) were then computed for each window. Eventually, median features over the windows were computed.

4. Classification and statistical analysis

The ECGA features were used to train and test five different machine learning methods: decision tree (DT), logistic regression (LR), naïve Bayes (NB), linear discriminant analysis (LDA), and support vector machine (SVM). Assessment of the methods was performed by leave-one-out cross-validation approach. Their classification performance was evaluated by computing the confusion matrix, where true positives (TP) were the number of correctly classified cases, true negatives (TN) were the number of correctly classified controls, false negatives (FN) were the number of incorrectly classified cases, and false positives (FP) were the number of incorrectly classified controls. Then, sensitivity (SE), specificity (SP), F1 score (F1) and accuracy (ACC) were computed as in (1)-(4).

$$\mathrm{SE} = \mathrm{TP}/(\mathrm{TP} + \mathrm{FN}) \tag{1}$$

$$\mathrm{SP} = \mathrm{TN}/(\mathrm{TN} + \mathrm{FP}) \tag{2}$$

$$\mathrm{F1} = (2 \cdot \mathrm{TP})/(2 \cdot \mathrm{TP} + \mathrm{FN} + \mathrm{FP}) \tag{3}$$

$$\mathrm{ACC} = (\mathrm{TP} + \mathrm{TN})/(\mathrm{TP} + \mathrm{TN} + \mathrm{FN} + \mathrm{FP}) \tag{4}$$

5. Results

In figure 1, the classification performance of the five algorithms was presented through bar plots, where each bar length is proportional to the SE, SP, F1, and ACC computed for each algorithm. Specifically, SE, SP, F1 and ACC were 94%, 84%, 93% and 91% for DT, 90%, 42%, 83% and 75% for LR, 84%, 33%, 79% and 69% for NB, 89%, 42%, 83% and 74% for LDA, 98%, 83%, 96% and 94% for SVM, respectively. It is possible to infer that SVM was the most suitable algorithm, followed by DT and LR.

6. Discussion and conclusion

In this work, we aimed to confirm the prognostic role of ECGA in improving the identification of HF patients benefiting from ICD implantation, and to identify the best ECGA-based supervised classification approach. Thus, we compared five machine learning methods (DT, LR, NB, LDA, SVM) fed by ECGA features and performing a binary classification between HF patients who require ICD therapy and those who do not, to detect the most reliable and accurate classification approach. The assumptions of this study were: (1) HF patients' need of an effective arrhythmic risk stratification criterion for deciding ICD implantation, due to the lack of specificity sometimes shown by the criteria of the current guidelines; (2) HF patients tend to exhibit higher ECGA levels, likely associated with an increased risk of adverse cardiac events.

The classification algorithms addressed are all supervised and feature-based, guarantee quite good interpretability of the outcomes (important in clinical applications), and require preprocessing of the data. From our analysis, SVM-based approach turned out to be the most reliable and accurate. SVM is an effective classifier in many real-world applications but can be sensitive to

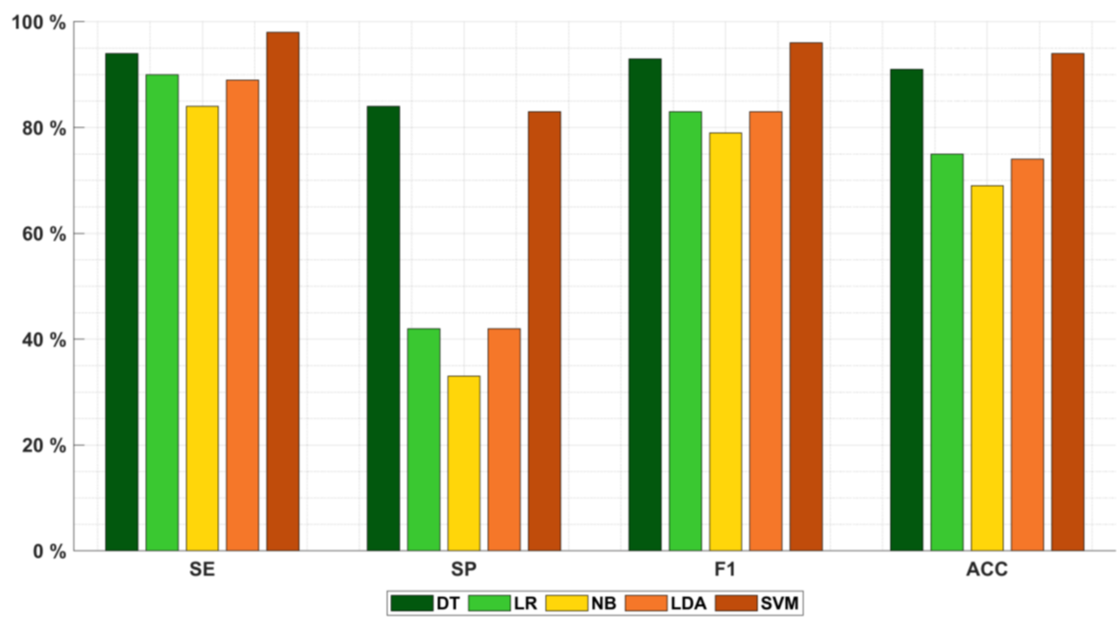

Figure 1. Validation performance of the machine-learning methods in terms of sensitivity (SE), specificity (SP), F1 score (F1) and accuracy (ACC), expressed in percentage: Decision Tree (DT, dark green), Logistic Regression (LR, green), Naïve Bayes (NB, yellow), Linear Discriminant Analysis (LDA, orange), Support Vector Machine (SVM, dark orange).

irrelevant or noisy features [10]. Therefore, identifying an optimal subset of features can help improve classification performance, further reducing false positives and, above all, false negatives (which were, however, less numerous than the former). In medical applications, such as the one addressed in this study in the cardiovascular field, false negatives are much more important than false positives, due to the potentially dangerous conditions in which a patient identified as healthy could be.

In the perspective of focusing on the most relevant features, also reducing both computational load and execution time, we decided to limit the number of ECG leads considered in this study, and only precordial ECG leads (V_1–V_6) were analyzed. ECGA is a lead-dependent phenomenon, meaning that certain ECG leads provide more insight into electrical cardiac instability than others; moreover, the most informative leads can vary between individuals [11]. We have already proved that, in this population, the precordial leads result to be the most informative [7], [9].

In addition, applying the enrollment criteria to the initial population allowed us to match the characteristics of cases and controls, resulting in a more uniform clinical profile between the two groups. This was a crucial step, as it reduced the risk of classification bias due to confounding factors (*e.g.*, spurious correlations), thereby improving the validity and generalizability of the model. A counterpart to this matching operation was the small population we had to manage.

We focused on the ECG data acquired during the resting phase of the acquisition protocol since we observed ECGA features extracted in this condition could highlight difference in the electrical cardiac activity better than the exercise one [9]. This was possible because we performed the study using our EAMF method that is able to work reliably at any heart rate [8]. In this study, all the ECGA forms were considered, but future studies may verify whether classification performance would improve if focusing on PWA, QRSA, or TWA, where QRSA, basing on the current evidence [7], [9], seems to be the most promising. Also, performance of unsupervised classification methods could be investigated.

In conclusion, our SVM-based approach built upon ECGA features provided good classification. Thus, this study confirms that ECGA has a promising role as additional parameter to LVEF for the correct identification of HF patients who will experience serious ventricular arrhythmias and truly benefit from the ICD implantation. Nevertheless, further studies are required due to the limited size of the present study population.

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Address for correspondence:

Laura Burattini.
Università Politecnica delle Marche, Department of Information Engineering, Via Brecce Bianche, 60131 Ancona, Italy.
E-mail address. l.burattini@univpm.it.