Computers in Biology and Medicine 42 (2012) 485–491

Contents lists available at SciVerse ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Assessing common classification methods for the identification of abnormal repolarization using indicators of T-wave morphology and QT interval

Saeed Shakibfar [a,*], Claus Graff [b], Lars H. Ehlers [c], Egon Toft [a], Jørgen K. Kanters [d,e], Johannes J. Struijk [b]

[a] Center for Sensory Motor Interaction (SMI), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
[b] Medical Informatics (MI), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
[c] Department of Business Studies, Aalborg University, Aalborg, Denmark
[d] Department of Cardiology P, Gentofte University Hospital, Gentofte, Denmark
[e] Danish National Research Foundation, Center for Cardiac Arrhythmia (DARC), University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 26 January 2011
Accepted 6 January 2012

Keywords:
Discriminant analysis
Fuzzy clustering
T-wave morphology
QT interval
Long QT syndrome

ABSTRACT

Various parameters based on QTc and T-wave morphology have been shown to be useful discriminators for drug induced I_{Kr}-blocking. Using different classification methods this study compares the potential of these two features for identifying abnormal repolarization on the ECG. A group of healthy volunteers and LQT2 carriers were used to train classification algorithms using measures of T-wave morphology and QTc. The ability to correctly classify a third group of test subjects before and after receiving D,L-sotalol was evaluated using classification rules derived from training. As a single electrocardiographic feature, T-wave morphology separates normal from abnormal repolarization better than QTc. It is further indicated that nonlinear boundaries can provide stronger classifiers than a linear boundaries. Whether this is true in general with other ECG markers and other data sets is uncertain because the approach has not been tested in this setting.

1. Introduction

Several drugs have been associated with the occurrence of the life-threatening arrhythmia Torsades de Pointes (TdP) and sudden cardiac death [1,2]. For this reason, a number of drugs have been withdrawn from the market or have had their use restricted [2,3]. The common denominator for these drugs is QT prolongation on the surface ECG caused by inhibition of the rapidly activating rectifier potassium current, I_{Kr} [4]. Therefore, registration of new drugs now involves a Phase I clinical study with focus on QT prolongation. This study is known as the Thorough QT/QTc Study (TQTS) and is based on the consensus guideline ICH-E14 [5]. The TQTS requires the analysis of thousands of ECGs in order to evaluate the effects of a new drug on cardiac repolarization. Several new compounds fail those trials [6], which may indeed prohibit the release of potentially proarrhythmic drugs. On the other hand, the potential for QT interval prolongation is not specific to I_{Kr} blocking (many other, less dangerous, cellular mechanisms may cause QT prolongation) and the QT interval is a poor marker for arrhythmic risk [4]. In addition, there is a growing body of research suggesting that other ECG-derived biomarkers, such as T-wave morphology may also contribute in important ways to the evaluation of cardiac safety [7–15].

In type 2 of the congenital Long QT Syndrome (LQT2) the cardiac potassium channel responsible for I_{Kr} current is (partially) blocked as a result of mutations in the *KCNH2* (hERG) gene. This relatively common form of LQTS has specific T-wave morphology characteristics, which have been used in a linear discriminant function to quantify drug-induced I_{Kr} channel blocking [10,13,15]. Whether a linear discriminant function as a classification rule is the optimal solution for this problem is not clear since the variances may be different before and after administration of I_{Kr}-blocking drugs.

Undoubtedly, the accuracy of classification depends considerably on which ECG features are used, but it has been demonstrated that the choice of classification method also influences the achieved accuracy [16].

The literature contains applications of various classification rules, including linear discriminant functions [15], neural networks [17], fuzzy adaptive resonance theory mapping [18], self-organized maps [19], etc. The selection of an appropriate classification rule depends greatly on the specific application, the particularities of the ECG descriptors, available computational resources and possible real-time operation.

According to Cristov et al. [20] a cluster approach resembles the subjective assessment done by a cardiologist more compared to other classification methods. The conventional (crisp)

* Corresponding author. Tel.: +45 9940 9790.
E-mail address: saeedsh@hst.aau.dk (S. Shakibfar).

0010-4825/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.compbiomed.2012.01.001

clustering methods put each point of the data set in exactly one cluster. However, since Zadeh [21] proposed fuzzy sets that use the idea of a partial membership, which are described by a membership function, many new fuzzy clustering methods have been introduced [22–26].

The fuzzy c-means (FCM) clustering algorithm, proposed by Dunn [22] and extended by Bezdek [23], is the most well-known and commonly used method in fuzzy clustering. Gustafson and Kessel (GK) [24] extended the standard fuzzy c-means algorithm by employing an adaptive distance norm, in order to detect clusters of different geometrical shapes in one data set and a numerically robust GK algorithm was described by Babuska et al. [25]. Contrary to the GK algorithm, Gath and Geva (GG) [26] reported that fuzzy maximum likelihood estimates (FMLE), which employ a distance norm involving an exponential term, is able to detect clusters of varying shapes, sizes and densities. However, this algorithm is less robust in the sense that it needs a good initialization because the exponential distance norm converges to a near local optimum.

In this paper, we present a comparative study of two ECG feature sets, the Fridericia corrected QT interval (QTcF) and T-wave morphology as assessed by the morphology combination score (MCS) [8–13]. We used three classification rules to estimate the potential for QTcF and MCS to identify abnormal repolarization, including fuzzy GK clustering, linear and quadratic discriminant analysis with the intention of suggesting the optimal classifier rule for the two ECG features within this framework.

2. Methods

2.1. Study design

Three different study groups were used in this study. One group of healthy volunteers served as an electrocardiographic reference for normal repolarization, and a second group of LQT2 carriers served as a reference for abnormal repolarization due to I_{Kr} malfunctioning. Both groups were used to train fuzzy clustering and discriminant classification algorithms using measures of T-wave morphology and QTcF in combination and as single features. Classifier performances were evaluated using ECG recordings from a third test group of healthy subjects on baseline and after receiving 160 mg and 320 mg doses of the antiarrhythmic I_{Kr}-blocking drug D,L-sotalol. The ability to correctly classify the group of test subjects before receiving D,L-sotalol as belonging to the same category as the healthy training subjects were evaluated. After D,L-sotalol was given, classification performance was evaluated based on the feature similarity between D,L-sotalol and LQT2 patients because the I_{Kr}-blocking drug has been shown to induce LQT2 phenotypic ECG characteristics [10].

2.2. Study population

There were 30 healthy Caucasian volunteers (11 women, 29 men; age 18–45 years; mean $\pm$ SD $=27\pm8$ years) in the training set reflecting normal repolarization and 29 genetically confirmed hERG mutation carriers (LQT2) (19 women, 10 men; age 19–68 years; mean $\pm$ SD $=45\pm14$ years) in the training set reflecting abnormal repolarization. Test data for classification included 21 healthy subjects (all males) on baseline (day 1) and after 160 mg (day 2) and 320 mg (day 3) doses of D,L-sotalol were given. All subjects in the training and test sets were between 18 and 45 years of age. Healthy status was confirmed by history, physical examination, normal blood pressure and no use of concomitant medication. Informed consent was obtained. Detailed demographic information on LQT2 patients and subjects receiving D,L-sotalol can be found in Graff et al., 2009 [10].

2.3. ECG acquisition

For classifier training, standard 12-lead digital ECGs of 10 second durations were recorded in triplicates at 500 Hz from each healthy subject (Mortara Instrument, Inc, Milwaukee, WI) and each LQT2 patient (MAC5000, GE Medical Systems, Milwaukee, WI). Triplicate recordings were less than 2 min apart. For classifier testing, 10 s 12-lead digital Holter recordings (H12 Recorder, Mortara Instrument, Milwaukee, WI) were used for the study time 3.5 h after 320 mg D,L-sotalol dosing on day 3 and at corresponding study times for 160 mg dose on day 2 and on the baseline day 1. Each ECG extracted from Holter was resampled from 180 Hz to 500 Hz as previously described [10].

2.4. ECG Processing

Each 10 s ECG was used to form a median beat in the recorded leads using MUSE/Interval Editor software (GE Healthcare, Milwaukee, WI, USA). Global leads were formed from principal component decomposition of the median beats by principal component analysis. The first principal component lead was filtered using a low-pass Kaiser FIR filter with a cutoff frequency of 20 Hz. The filtered principal component median beat T-waves were subsequently used for analysis of T-wave morphology. Fiducial point detection and QT measurements were made automatically using the 12SL algorithm (12SL, GE Healthcare, Milwaukee, WI, USA). QT intervals were corrected for heart rate with Fridericia's equation: $QTcF=QT/RR^{1/3}$. The composition of T-wave morphology was not corrected for heart rate because the MCS has been shown to be practically independent of heart rate [7].

2.5. Morphology measures

A morphology combination score (MCS) was used to describe the T-wave shapes in terms of: asymmetry, flatness and notching [7–13]

$$\mathrm{MCS}=\mathrm{Asymmetry}+\mathrm{Notch}+1.6\,\mathrm{Flatness}$$

where asymmetry was defined as the average squared difference (d) between the ascending and descending slope segments of the T-wave (Eq. (1)) [10,13].

$$\mathrm{Asymmetry}=\frac{\sum_{n=1}^{N} d(n)^2}{N} \tag{1}$$

Notch was measured on a unit amplitude T-wave and assigned to one of the three categories based on deflections in curvature: no deflection=0, moderate notch (perceptible bulge)=0.5 and pronounced notch (distinct protuberance above the apex)=1.0. A curvature signal was obtained from the first and second derivatives of T-waves (Eq. (2)) [10,13].

$$\mathrm{Curvature}=-\frac{d^2y/dx^2}{[1+(dy/dx)^2]^{3/2}} \tag{2}$$

Flatness was calculated as a modified version of the standard kurtosis measure, which is often used to describe the peakedness of a probability distribution. The T-wave was normalized to unit area, and central moments were calculated using eq. (3).

$$M_k=\left[\sum_{n=1}^{N}(n-M_1)^k ECG(n)\right]^{1/k} \quad M_1=\sum_{n=1}^{N} nECG(n), \tag{3}$$

The fourth central moment (M_4) was normalized with the squared second moment (M_2) and subtracted from 1 to let increasing values of flatness reflect increasing flatness of the