

Pairwise Feature Interactions to Predict Arrhythmic Risk of Brugada Syndrome

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Abstract

Electrocardiographic (ECG) indices were used for risk stratification in Brugada syndrome (BrS). However, nonlinear interactions between risk factors were ignored.

Therefore, we adapted a generalized additive model with pair-wise interactions (GA2M) to predict BrS with spontaneous ventricular tachycardia/fibrillation (VT/VF) as outcomes based on specific ECG markers. A total of 191 adult patients with BrS from three centres (Germany, Greece and Hong Kong) were included for analysis. Depolarization and repolarization ECG markers were measured from the right precordial leads (V1 to V3).

The proposed GA2M-based risk prediction model successfully identified a set of risk factors and their pair-wise interactions in addition to the dispersion of repolarization/total repolarization ($T_{peak}-T_{end}$ x mean QT). The model outperformed the baseline logistic model based on the same set of ECG measurements.

In conclusion, the inclusion of pairwise interactions improved predictive performance and enabled more effective risk stratification in BrS.

1. Introduction

Brugada syndrome (BrS) is an inherited cardiac ion channelopathy that predisposes the affected patients to syncope, ventricular tachycardia/ fibrillation (VT/VF) and sudden cardiac death. Despite our improved understanding of its electrophysiological mechanisms, risk stratification remains suboptimal. Therefore, improved risk stratification strategies for better clinical decision-making are needed.

Previous investigators have recognized the importance of both repolarization and depolarization abnormalities [1], few studies have investigated indices incorporating both processes, which may not be entirely independent of each other. Whilst risk scores incorporating depolarization, repolarization and clinical features are available, these are based on simple logistic regressions without consideration of interactions amongst different features. Detailed investigations into the possible

interactions between different depolarization and repolarization parameters are lacking.

To investigate such interactive relationships, advanced risk prediction models that go beyond standard linear models and are interpretable to healthcare professionals are needed. In this study, we adapted the generalized additive model with pair-wise interactions (GA2M), the latest variant of the Generalized Additive Model (GAM) that can characterize the pairwise interactions, to predict spontaneous VT/VF as outcome based on ECG markers.

2. Methods

In this section, we first describe our multi-centre dataset, and then introduce four different classes of predictive models that were used for risk stratification in BrS. The model fitting and model validation were done using the R statistical programming language.

2.1. Patient Data

This retrospective study received ethics approval from the NTEC-CUHK Research Ethics Committee, the Medical Ethical Review Committee of the Evangelismos General Hospital of Athens and The University Hospital Münster Ethics Review Board.

Data on BrS patients from three centres were retrospectively analysed. The ECG diagnosis of BrS was using the 2017 diagnostic criteria proposed by the Expert Consensus Statement [2]. The joint guidelines from Heart Rhythm, European and Asian Society guidelines were adopted for drug challenge tests due to the use of older guidelines in past practice. The presence of structural heart disease was excluded in all subjects by cardiac catheterization or echocardiography.

The data contains the following demographic and clinical details: age, sex, electrophysiological studies, sodium channel challenge test, genetic testing, family history of BrS, syncope and spontaneous ventricular tachycardia/ventricular fibrillation (VT/VF). Spontaneous VT/VF of the monomorphic and polymorphic types was included. The primary outcome was spontaneous VT/VF.

2.2. Electrocardiographic Parameters

The standard 12-lead ECGs were recorded at a paper-speed of 25 mm/s with an amplification of 10 mm/mV. The ECG parameters were obtained through manual measurements. The end of the T-wave was determined using the baseline method, where it was defined as the intersection between the recorded waveform with the isoelectric line. This method was selected over the tangent method to capture all of the repolarization time. The following ECG markers derived from the right precordial leads (V1 to V3) were evaluated in BrS subjects. All ECG measurements were performed by two independent investigators who were blinded to other patient information. When measurements were not identical, the mean of the values was calculated.

Depolarization parameters included the QRS duration (beginning of Q to the end of S), QRS dispersion (maximum difference of QRS values between two precordial leads) and JT interval (calculated by subtracting QRS duration from QT interval).

Repolarization parameters included the QT interval (onset of the QRS complex to the end of the T wave at T-P baseline), QTc (correction using Bazett's formula), QT dispersion (maximum difference of QT intervals between two precordial leads), $T_{\text{peak}} - T_{\text{end}}$ (peak of T-wave to end of T-wave), $(T_{\text{peak}} - T_{\text{end}})/\text{QT}$ ratio, $T_{\text{peak}} - T_{\text{end}}$ dispersion (maximum difference of $T_{\text{peak}} - T_{\text{end}}$ between 2 precordial leads), maximum $T_{\text{peak}} - T_{\text{end}}$ (maximum of $T_{\text{peak}} - T_{\text{end}}$ in V1 to V3), JT_{peak} (J point to peak of T-wave), and JT_{end} (J point to end of T-wave). Cumulative depolarization-repolarization indices included the index of Cardiac Electrophysiological Balance (iCEB, QT/QRS), iCEBc (QTc/QRS), $(T_{\text{peak}} - T_{\text{end}})/\text{QRS}$, $T_{\text{peak}} - T_{\text{end}} / (\text{QT} \times \text{QRS})$, $\text{QRS}_d \times (T_{\text{peak}} - T_{\text{end}}) / \text{QRS}$, $\text{QRS}_d \times (T_{\text{peak}} - T_{\text{end}})/(\text{QT} \times \text{QRS})$.

2.3. Risk Stratification Problem in Brugada Syndrome

Let $\mathcal{D} = \{(\mathbf{x}_i, y_i)\}_{i=1}^N$ denote a training data set for risk stratification in BrS with N subjects (here $N = 191$). $\mathbf{x}_i = (x_{i1}, x_{i2}, \dots, x_{ij})$ represents a feature vector with J features and a binary indicator $y_i \in \{-1, +1\}$ represents the risk outcome (+1 for positive case and -1 for negative case). The developed risk stratification models aim to estimate the relationship between features $\mathbf{X} = (\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N)$ and the corresponding outcome label $\mathbf{Y} = (y_1, y_2, \dots, y_N)$. The risk stratification problem in BrS is a binary classification problem. For continuous independent features in descriptive statistics, we can determine their distributions by analysing them concerning spontaneous VT/VF as the dependent feature, from which we can infer that the median ‘‘QRSd’’ content

is higher for subjects who show spontaneous VT/VF in BrS, i.e, spontaneous VT/VF =+1. Similar inferences can be drawn for the rest of the features.

GAM represents the gold standard for learning interpretability in the case that low-dimensional terms are considered [3]. Standard GAM consists of additive regression models and takes the form as follows:

$$g(E[y]) = \alpha + \sum_{j=1}^J f_j(\mathbf{x}_j) \quad (1)$$

where g is the link function; f_j denotes the function of the feature j and $E[f_j] = 0$. The function f_j can be either non-parametric scatter plot smoothers or regression splines.

However, equation (1) does not capture any interactions among features, leading to lower accuracy as compared to full complexity models. To improve accuracy, pair-wise feature interactions are added to standard GAM, yielding the GA2M as follows

$$g(E[y]) = \alpha + \sum_{j=1}^J f_j(\mathbf{x}_j) + \sum_{j=j'}^J f_{jj'}(\mathbf{x}_j, \mathbf{x}_{j'}) \quad (2)$$

Note that GA2M remains intelligible since pair-wise feature interactions can be easily visualized and interpreted for practical use. GA2M builds the best GAM, and then detects all possible pairs of interactions in the residuals. Due to the large number of possible pair-wise feature interactions to consider, GA2M only includes ‘‘true’’ interactions that pass statistical testing. Furthermore, according to predictive significance, we can efficiently rank all the pair-wise interactions close to a ground truth ranking.

In this study, standard GAM was constructed using all the features in which 16 ECG measurements were modelled using regression smoothing splines each with 6 degrees of freedom. GA2M was fit that consisted of the above GAM along with all the pairwise feature interactions.

2.4. Prediction Performance

To compare the prediction performance of each statistical method, the data were randomly divided into training and test sets. Two-thirds of data were used for model training and the remaining one-third was used for model validation [4]. Each training set consisted of 128 subjects, while each test set consisted of 64 subjects. We fit each model on the training set and use the trained model to predict the outcome of each patient in the test set. We then adopted the ten-fold cross-validation to ensure the robustness of the results.

The predictive performance of a particular model can be represented by the receiver operating characteristic curve (ROC). The area under the curve (AUC) was adopted to measure the predictive accuracy of each model. We summarize the model area under ROC curve for both the training and validation samples. Specifically, we trained and tested the model ten times using ten different samples, and then use the averaged AUC as the

measure of the model accuracy.

3. Results

A total of 191 adult patients with BrS from Germany, Greece and Hong Kong were included (157 males (82%), median age 50 [39-60] years). The disease presentation prior to diagnosis could be divided into asymptomatic (n=102, 53%), syncope (n=66, 35%) or VT/VF (26, 14%). Three patients had both syncope and VT/VF. The baseline clinical characteristics are shown in *Table 1*. An initial type I Brugada pattern was observed in 84 (44%) patients. Overall, syncope and spontaneous VT/VF occurred in 73 (38%) and 33 (17%) patients, respectively.

3.1. Model Performances

For GA2M, a total of $\binom{17}{2} + 17 = 153$ features (17 individual features and 136 pair-wise feature interactions) were included. In addition to the significantly predictive individual features, the ten most predictive pair-wise feature interactions for predicting spontaneous VT/VF were also identified. These nonlinear interaction features were included for fitting nonlinearities in GA2M.

Figure 1 shows the pair-wise feature interactions captured by the GA2M for predicting spontaneous VT/VF, and reveals the importance of one feature for risk prediction (i.e, the influence sensitivity) heavily depends on the value of the other features, and vice versa. *Figure 1* can be interpreted as a topographic map of hilly terrain: the contour lines connect different points on the surface with the same height. The closer the contour lines are to each other, the steeper the surface. Regions where there are closer lines (i.e, steeper surface) indicate a stronger influence of the interaction of two features together on the outcome.

3.2. Comparison of Predictive Performance

The average AUC values for each model on both the in-sample training set and the out-of-sample test set are shown in *Table 2*. GA2M shows a much better capability ability to capture the interaction effects among features to obtain highly accurate risk predictions than BLR with interaction model.

4.1 Discussion

The novelty of this paper is the consideration of pairwise interaction patterns between ECG variables for BrS risk prediction from three centres. The main findings are that a GAM and GA2M provided superior discriminative values for predicting spontaneous VT as outcome compared to a traditional BLR-based model.

Risk stratification in BrS remains an unresolved

problem in clinical practice [5, 6]. Different risk factors have been identified as being important determinants of adverse outcomes. The ECG is a useful and non-invasive tool used for the diagnosis of BrS and ECG indices based on depolarization or repolarization can yield important prognostic information. In our study, QT dispersion, maximum $T_{peak}-T_{end}$ intervals and $T_{peak}-T_{end}$ dispersion were significant predictors of arrhythmic outcomes.

Previous studies have devised different scoring systems based on the different risk factors for improving risk stratification strategies. Typically, these are based on significant features identified in the logistic regression analysis and converted into a point-based system. [7, 8]. Our score similarly shows an excellent performance with an AUC of 0.86 for spontaneous VT/VF.

Of particular importance in arrhythmia is the interaction between depolarization and repolarization wavefronts, which can generate re-entry. A numerical representation is the excitation wavelength, given by the product of conduction velocity and repolarization time. In this study, we used a GA2M method that takes into account both individual features and their pair-wise interactions for risk prediction in BrS.

The constructed risk prediction model for BrS is both accurate and interpretable. Interpretability refers to the requirement that clinicians can easily understand the contribution of each feature and also how two features together can interactively predict the response outcome. Once the impact of each feature and each pair-wise feature interaction on response outcome can be quantified and visualized, clinical practitioners can have interpretable supporting evidence for relevant medical decision-making.

4.2 Limitations

The major limitation of this study is that it was retrospective in nature and may be subjected to certain types of bias. Nevertheless, the common clinical practice is at least annual consultations for most patients with some receiving them at six-monthly intervals. Moreover, for the patients from Hong Kong, if they are admitted to hospitals other than their usual hospital, their case records can be tracked by linked records centrally. For those from Athens, patients generally attend the same hospital for subspecialty services such as arrhythmia management. Additionally, the ECG measurements were obtained manually, which is susceptible to human error.

5 Conclusions

The pairwise interaction between depolarization and repolarization abnormalities can be extracted by advanced machine-learning models and their inclusion improved predictive performance. Translational application of such

insights can enhance risk stratification in BrS.

6. Tables and figures

Table 1. Baseline Characteristics

Characteristic	Total (Percentage/ Q1-Q3)
Male	157 (82%)
Age at diagnosis	50 (39-60)
Family history of BrS	16 (8%)
Initial type 1 Brugada pattern	84 (44%)
Asymptomatic	102 (53%)
Syncope	66 (35%)
VT/VF	26 (14%)

Table 2. Comparisons of the predictive performance of in both training (T) and validation set (V).

Model	AUC (T)	AUC (V)
BLR	0.69	0.62
BLR with interaction	0.73	0.71
GAM	0.82	0.81
GA2M	0.90	0.88

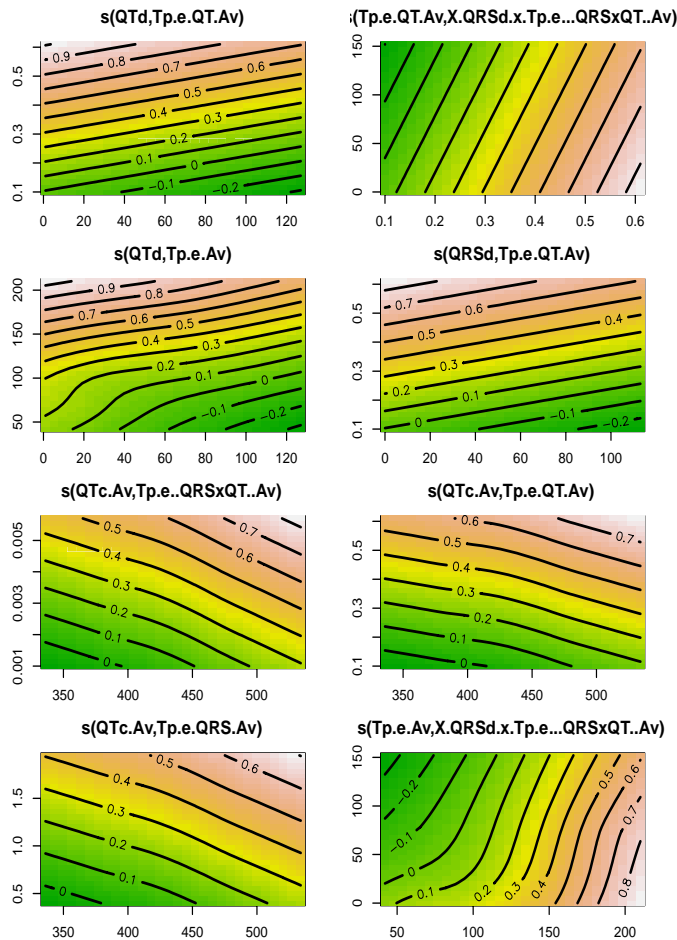


Figure 1. Contour plots of feature interaction effects in the GA2M with spontaneous VT/VF as the outcome.

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