Risk assessment of all-cause mortality in ICD patients using a novel QRS fragmentation score

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Abstract

Fragmented QRS complexes are QRS complexes with one or more deflections. They are known risk factors for cardiac events in several patient groups. Detection is done visually, which is a time-consuming process that may lead to subjective results, limiting the clinical use of this parameter.
We propose an automated method to calculate an fQRS score which gives an indication of the severity of fQRS in a channel. To compute the score, 10 features are calculated using Phase Rectified Signal Averaging and Variational Mode Decomposition and used in a SVM classifier. The fQRS score is then used to assess the risk of all-cause mortality in a dataset of ICD patients. An optimal cut point is defined for each channel to dichotomize the fQRS scores. Bootstrapping is used to reduce variability in cutpoint selection. Results on an independent test set indicate that the fQRS score of 3 channels leads to survival curves with statistically significant differences.
This novel way of detecting and quantifying QRS fragmentation is therefore a promising way to promote the clinical usefulness of the parameter.

1. Introduction

QRS fragmentation (fQRS) is defined as QRS complexes which contain one or more deflections, notches or slurs [1]. Fragmentation can be caused by myocardial scarring, and its presence in certain cardiac regions has been shown to be predictive for all-cause mortality and ICD shocks in different patient groups [1, 2].
In clinical practice, detection is mostly done visually by inspecting the ECG signal and binary scoring each lead. Analysis of interrater agreement indicates that this can lead to subjective results that are dependent on the experience of the raters [3]. Because scoring is done lead-by-lead, it is furthermore a time-consuming process. The availability of an automated method to score signals on the presence of QRS fragmentation would therefore benefit the practical usefulness of this parameter. Automated methods would also lead to repeatable results over multiple datasets, which facilitates analysing the relation between fQRS and patient outcome in larger multicenter populations.
QRS fragmentation can have many forms, since the location and number of deflections can vary largely. Binary scoring might therefore not be optimal, since it cannot capture the differences between different types of QRS fragmentation. We therefore propose a method to automatically calculate an objective fQRS score that represents the level of QRS fragmentation in each lead, with a higher value indicating signals with more extensive fragmentation. A previous study already used Phase Rectified Signal Averaging to detect fQRS [4], here Variational Mode Decomposition is also used for feature extraction. The objective of this study is to examine whether this novel score can be used as a prognostic risk factor for all cause mortality in ICD patients and which channels are more useful to identify patients in a high-risk group.

2. Material and methods

2.1. Dataset

The dataset used in this study contains 12-lead ECG signals from 616 patients who received an ICD in the University Hospitals Leuven. Each signal is 10 seconds long and sampled at 250Hz. All leads of all signals were annotated on the presence of QRS fragmentation by 5 experienced raters. For all patients, the date and cause of death were collected. The mean follow-up time in the complete database was 4.2 ± 3.3 years. An extensive summary of database characteristics (including inter- and intrarater variability) is provided in [3].

2.2. Feature extraction

After preprocessing to remove baseline wander and high frequency noise, QRS segmentation is done. All non-QRS segments of the ECG signal are set to zero. 10 features are then extracted from the QRS complexes from each lead individually. The features can be divided in 2 groups: features derived from Phase-Rectified Signal Averaging (PRSA) and Variational Mode Decomposition (VMD).
Feature extraction using PRSA was described in a previous study [4]. In short, in a first step all increasing points on the QRS complexes of a channel are used as anchor points. Fixed size windows of 50 samples around each anchor point are segmented and aligned. The first two steps are repeated, this time selecting the decreasing points as anchor points. Finally the PRSA curve is constructed by taking the mean of the aligned windows. The PRSA curve is then approximated by a linear fit. In channels with fragmentation, this curve will be less steep since anchor points are dispersed over the complete QRS complex. Derived features are the mean slope of the PRSA curve, and both the slope and intercept of the linear approximation. More details on the differences in feature values between normal and fragmented complexes can be found in [4].
Variational mode decomposition splits the ECG signal in *k* discrete bands which are compact around a central frequency. It is similar to empirical mode decomposition, but uses non-recursive techniques and has been shown to be more robust to noise [5]. When *k* is fixed to 5, the QRS complex is contained in the high-frequency bands 3, 4 and 5. Fragmentation introduces extra high-frequency components to the QRS complex, which are also present in the output of VMD. More specifically, fragmentation can introduce extra peaks in the QRS bands and will also increase their central frequency. The average number of peaks per QRS complex in bands 3, 4 and 5 and their central frequency are therefore selected as additional features. A last feature is extracted directly from the ECG signal, namely the average number of local optima per QRS complex.

2.3. QRS fragmentation score

The features calculated in the previous step are used as input to an SVM classifier with RBF kernel. Only signals with perfect agreement among all 5 raters are used for training. 75% of this subset is randomly chosen for training, the remainder as test set. A second test set combines the first test set with the signals where no perfect agreement is reached. The hyperparameters of the SVM are optimized using 10-fold crossvalidation. The output of the SVM (e.g. the score belonging to the positive class) is finally transformed to a value between 0 and 1 with Platt scaling, which fits a logistic regression model to the scores [6]. The QRS fragmentation score is determined for each channel individually.

2.4. Optimal cut point determination

The endpoint considered in this study is all-cause mortality at 7.5 years. We will dichotomize the fQRS score of each lead by determining an optimal cut point θ_{ch} for each channel to distinguish a high-risk and low-risk group. The patients are first divided in a training and test set: $\frac{2}{3}$ of the patients are used to determine the cut points, the remainder is used to validate the results. Training and test groups contain equal ratios of censored and non-censored patients.
Since the focus of this study is to determine the usability of the fQRS score for risk assessment, only univariate analyses are considered here. Kaplan-Meier analysis is used to construct survival curves, and differences between curves of 2 groups are analysed with logrank tests.
In order to get a robust estimate of the optimal cut point that is less dependent on the choice of training set, we use bootstrapping to generate 2500 bootstrap samples. Each bootstrap sample is drawn randomly with replacing from the training set. Optimal cut points for each channel *ch* and each bootstrap sample *i* are determined with the minimum p-value approach, e.g. for each possible threshold a logrank test is performed, and the threshold which generates the lowest p-value is selected as cut point $\hat{\theta}_{i,ch}$. The optimal cutpoint θ_{ch} for each channel is then defined as the median of the cutpoints $\hat{\theta}_{i,ch}$ of all bootstrap samples. These values are used for analysis of the test set. 95% confidence intervals for the median are calculated as described in [7]:

$$\text{C.I.} = \theta_{opt} \pm 1.7\frac{1.25R}{1.35\sqrt{N}} \tag{1}$$

with R the interquartile range and N the number of bootstrap samples.
The optimal cutpoints θ_{ch} are finally used to dichotomize the test set and construct the corresponding survival curves. Differences are again evaluated with the logrank test, with $p<0.05$ considered statistically significant.

3. Results

3.1. Classification results

Application of the SVM classifier on the first test set of signals with perfect agreement resulted in an ROC curve with an AUC of 0.926.
Figure 1 shows the results on the second test set (including the signals without perfect agreement). The signals are grouped by their total score from all raters, e.g. the numbers of raters that agreed on the presence of fragmentation. Boxplots show the median value for each group together

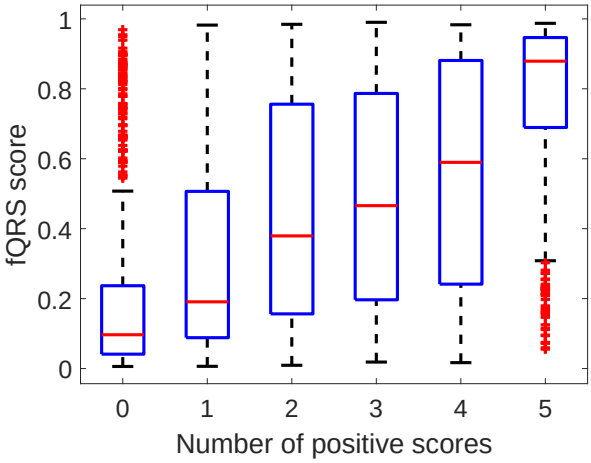


Figure 1: fQRS scores for the second test set, grouped by total score from all raters.

	Training set		Test set	
Channel	θ_{opt}	**95%C.I.**	**p-value**	**HR**
I	0.47	0.4574-0.4856	0.484	1.25
II	0.24	0.2239-0.2560	0.112	1.76
III	0.44	0.4368-0.4431	0.887	0.96
aVL	0.43	0.4189-0.4410	0.589	1.18
aVF	0.65	0.6355-0.6644	0.464	0.8
V1	0.52	0.5137-0.5263	0.757	1.15
V2	0.66	0.6531-0.6669	0.218	1.58
V3	**0.58**	**0.5633-0.5967**	**0.014**	**2.23**
V4	**0.25**	**0.2446-0.2553**	**0.028**	**1.98**
V5	0.77	0.7671-0.7728	0.102	1.73
V6	**0.68**	**0.6690-0.6910**	**0.047**	**1.94**

Table 1: Optimal cut points, 95% confidence intervals and results on the test set for each channel.

with the interquartile range of the fQRS score. From Figure 1 we can conclude that the automatically defined fQRS score increases monotonically with increasing total score.

3.2. Survival analysis results

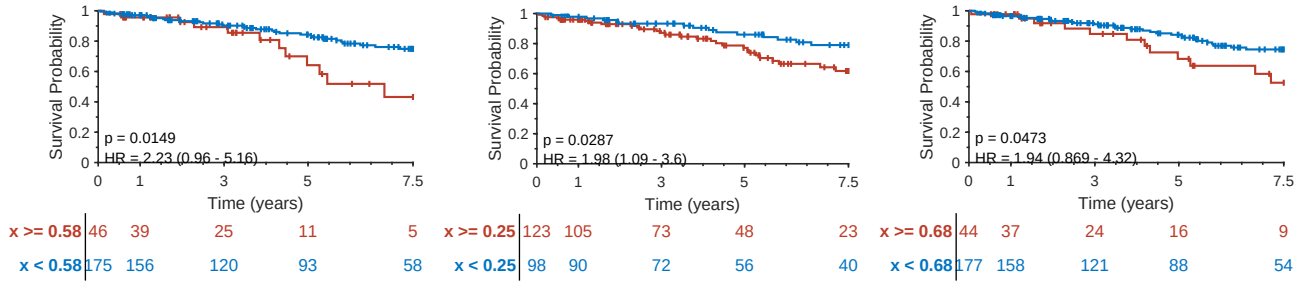
Table 1 shows the value of the optimal cut point and confidence interval (determined on the training set) for each channel and the results on the test set. For 3 channels, applying the optimal cutpoint on the independent test set leads to statistically significant differences in survival times between both groups: V3, V4 and V6. The corresponding Kaplan-Meier curves for these channels can be seen on Figure 2. Two additional channels, II and V5 show notable trends ($p \approx 0.1$).

4. Discussion

The output of the SVM classifier is a score between 0 and 1 which represents the severity of QRS fragmentation in one lead. The method is trained on a set of signals where five raters agree on the presence of fQRS, and results on the first test set show that the method is able to distinguish signals with clear fQRS from normal signals (AUC = 0.926). To evaluate whether the fQRS score is related to the degree of fragmentation, it is compared to the total score given by all raters. The total score can be seen as an indication of the severity of fragmentation in a lead: When fragmentation is clearly present in a signal (e.g. when there are more or larger deflections), more raters will agree on the presence of fragmentation compared to cases where fragmentation is less clearly defined, or consists of only small variations. Figure 1 shows that the fQRS scores are in line with the total scores from all raters. The difference between the most extreme groups, 0 and 5, is most obvious, which is expected since signals in these groups vary most. Boxplots of groups 2 and 3 are rather similar: while the median value of group 3 is slightly higher than in group 2, the interquartile ranges are comparable. This is not unexpected: signals in groups 2 and 3 are all signals where the presence of fragmentation is not clear and approximately half of the raters disagree with each other.

In the second part of this study, we have used the fQRS scores in different channels to divide a dataset of ICD patients in two groups in order to assess their risk on all-cause mortality. Dichotimization of continuous variables in surivival analysis is a debatable subject since the choice of optimal cut point should be done in a way so results can be generalized. The use of bootstrapping on the training set and validation of the results on an independent test set ensures that the optimal cut points determined here are minimally dependent on the choice of training set.

Results on the test set indicate that the fQRS score in 3 different channels (V3, V4 and V6) can be used as an indication of the risk on all-cause mortality in ICD patients. Hazard ratios derived from the Kaplan Meier plots shown in Figure 2 are approximately 2 (1.94-2.23). This means that the probability of all-cause mortality for patients with fQRS in these channels is roughly double the probability for other patients. V3 and V4, the channels with lowest p-values are located in the anterior regions of the heart. This corresponds with findings in [2], where the presence of fQRS in anterior channels was an independent risk factor for mortality in a subset of the same patient population. Clinically, presence of fQRS in a cardiac region is determined based on a combination of channels rather than single channels. Combining scores per cardiac region is therefore a logical extension of this study. This can be done by simply summing scores of individual channels or by more advanced machine learning techniques. An example are



(a) Channel V3 (b) Channel V5 (c) Channel V6

Figure 2: Kaplan-Meier plots of channels with statistically significant differences ($p < 0.05$) between survival curves.

Interval Coded Survival methods [8] which are based on SVMs and capable of modeling both linear and non-linear trends in data in an interpretable way. Furthermore (adjusted) Cox proportional-hazards regression models can be used to perform a full multivariate analysis by including the effects of additional clinical variables.

5. Conclusion

In this paper, we present an automated method to quantify the amount of fragmentation in a single lead ECG signal. The results of both the classification and the survival analysis indicate that representing fQRS as a score instead of a binary value is a promising risk factor for all-cause mortality in ICD patients. Currently, the practical use of fQRS is limited because the parameter relies on visual annotations. The advantages of using the fQRS score proposed here are that the method produces objective results directly derived from the ECG signal and that such results can be reproduced more reliably. This novel way of detecting and quantifying QRS fragmentation is therefore a promising way to promote the clinical usefulness of the parameter.

Acknowledgements

Griet Goovaerts is supported by a predoctoral mandate from IWT Vlaanderen. Carolina Varon is a postdoctoral fellow of the Research Foundation-Flanders (FWO). The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC Advanced Grant: BIOTENSORS (n 339804). This paper reflects only the authors' views and the Union is not liable for any use that may be made of the contained information.

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