

# Increase of QRS Duration as a Predictor of Impending Ventricular Fibrillation During Coronary Artery Occlusion

Alba Martín-Yebra<sup>1,2</sup>, Marina Demidova<sup>3,4</sup>, Pyotr Platonov<sup>3</sup>, Pablo Laguna<sup>2,1</sup>, Juan Pablo Martínez<sup>2,1</sup>

<sup>1</sup> CIBER en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Zaragoza, Spain

<sup>2</sup> Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain

<sup>3</sup> Department of Cardiology, Lund University, Lund, Sweden

<sup>4</sup> Federal Center of Heart, Blood and Endocrinology, St.Petersburg, Russia

## Abstract

*Increased QRS duration (QRSd) has been observed during acute myocardial ischemia and infarction, indicating conduction deterioration in the myocardial tissue. It has been reported that intramyocardial conduction velocity slowing induced by ischemia is associated with the occurrence of malignant ventricular arrhythmias. However, clinically useful QRSd cut-offs that would predict immediate ventricular fibrillation (VF) onset have not been identified. In this work, we studied the association between QRSd prolongation and VF occurrence in a porcine model of myocardial infarction. Infarction was induced in 32 pigs by 40-minute-long balloon inflation in LAD coronary artery under continuous ECG monitoring. After applying a wavelet-based delineator to the ECG precordial leads, QRSd was measured and its local increase in a sliding window of 3 minutes ( $\Delta$ QRSd) was continuously computed during the occlusion. Choosing a threshold for  $\Delta$ QRSd = 28ms from a ROC curve analysis, 8 out of 10 VF episodes could be predicted (Se=80%, Sp=90.9%, NPV=90.9%, PPV=80%). Results suggest that a transient increase in QRSd may be a sensitive and specific index for monitoring immediate risk of malignant ventricular arrhythmias during acute myocardial ischemia.*

## 1. Introduction

Malignant ventricular arrhythmias, particularly ventricular fibrillation (VF), remain an important contributor to infarct related mortality [1]. The success of VF treatment is determined by time from VF occurrence to medical care, therefore the main strategy in relation to live-threatening ventricular arrhythmias during ST-elevation myocardial infarction (STEMI) is their prediction and prevention [2]. Severe myocardial ischemia is known to slow local activation conduction velocity in the myocardial tissue [3], thus inducing changes in the depolarization phase (QRS com-

plex). It results in a prolongation of QRS duration as well as in amplitude changes of R and S waves in leads with ST-segment elevation [4–7]. In earlier studies, this delay in the intramyocardial conduction has been also closely associated with the occurrence of malignant arrhythmias [8,9]. Nevertheless, all these results have not been yet implemented in the clinical practice and QRSd cut-offs that would predict the immediate appearance of ventricular arrhythmias, as VF, remains to be identified.

Thus, on the basis of the association of both, ventricular arrhythmias and QRS prolongation, with alterations in intramyocardial conduction it was of considerable interest to study the potential clinical importance of QRSd alterations as a marker for subsequent malignant ventricular arrhythmias in an experimental model of myocardial infarction.

## 2. Experimental data

Data from a porcine model of myocardial infarction were used in this work. A detailed description of the experimental protocol is given in [10]. After being anesthetized, thirty-two pigs with a weight range between 40-50 kg, underwent the inflation of a percutaneous transluminal balloon for 40 minutes, positioned at the mid-portion of the left anterior descending coronary artery (LAD).

Continuous standard 12-lead ECG monitoring (“Kardiotechnica - 04-8m”, Incart, St. Petersburg, Russia) with a sampling frequency of 1024 Hz and an amplitude resolution of 1.4  $\mu$ V was initiated before starting the occlusion and lasted throughout all the period of occlusion.

The study conforms to the Guide for Care and Use of Laboratory Animals, US National Institute of Health (NIH Publication No. 85-23, revised 1996) and was approved by the local animal research ethics committee.

### 3. Methods

#### 3.1. Preprocessing of the ECG signal

All ECG recordings were preprocessed before computing QRS boundaries. In a first stage, QRS complexes were automatically detected [11] and then visually and manually checked using the BiosigBrowser tool [12]. Subsequent steps were: baseline wander cancellation by cubic-spline interpolation and delineation of ECG boundaries using a wavelet-based technique [11]. Only precordial leads V1 to V6 were considered for the analysis.

#### 3.2. Multilead delineation

After applying the wavelet-based delineator to the ECG precordial leads, beat-to-beat multilead QRS boundaries (QRSon and QRSoﬀ marks) were computed. This multilead approach allows to obtain global marks based on a post-processing selection rule over all single-lead locations, considering the possibly different latencies among leads, and with the aim to achieve a more robust delineation. It has to be taken into account that significant ST-elevation during acute myocardial ischemia makes delineation of QRSoﬀ mark a challenging task, since it appears a gradual transition between both complexes. Because of that, wavelet-based delineator had to be adapted to this model of acute ischemia.

Post-processing rules for boundaries consisted of ordering all 6 single-lead marks and setting the onset of the wave (QRSon) as the earliest mark, whose  $k=3$  following neighbors were within a  $\delta_1$  ms interval. In the same way, the end of the wave (QRSoﬀ) was set as the latest annotation mark with  $k=3$  nearest marks in a  $\delta_2$  ms interval.

Once multilead delineation was obtained for all pigs, QRS duration was computed in a beat-to-beat basis as the difference between the position of the two multilead QRS boundaries, generating a  $QRSd[l]$  beat-to-beat series along the 40-minute occlusion period for each pig. These series were then resampled by averaging  $QRSd[l]$  every 10 seconds, generating a new series,  $QRSd[n]$ .

#### 3.3. QRS duration analysis

Using a short-term sliding window, local increments of QRSd,  $\Delta QRSd[n]$ , were defined as the difference between the current  $QRSd[n]$  value, which corresponds to the last value in the analysis window, and the minimum QRSd value in that window.

$$\Delta QRSd[n] = QRSd[n] - QRSd[n_{min}] \quad (1)$$

where  $n_{min}$  is the instant within the analysis window at which the QRSd is minimum being  $n_{min} \leq n$ . This stage is illustrated in Fig. 1.

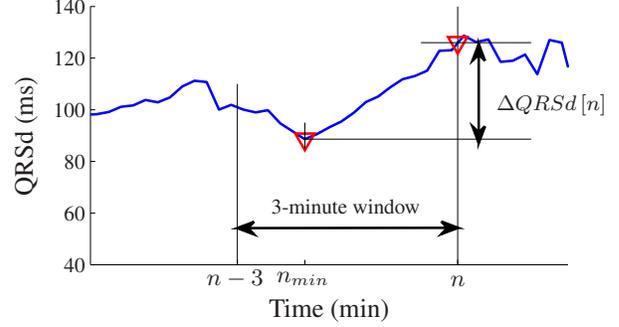


Figure 1. Example of  $\Delta QRSd[n]$  at a particular instant  $n$  in one recording analyzed in this study.

In order to determine whether an increment in  $QRSd$  can be considered as a VF predictor, two different sizes for the sliding window of  $L_1 = 30$  and  $L_2 = 18$  samples, corresponding to 5 and 3 minutes respectively, were tested.

Association between  $\Delta QRSd[n]$  and subsequent VF onset was studied using a ROC curve analysis. The optimum value for the local widening  $\Delta QRSd$  in terms of sensitivity and specificity was established.

Besides this local increment an additional condition was imposed, requiring that QRS duration has to be larger than a threshold to consider the animal susceptible to suffer from VF within a few minutes, that is,  $QRSd[n] \geq \gamma$ . Three different situations were studied: (a) no restriction in  $QRSd$  was imposed ( $\gamma_1=0$ ); (b) an increase of at least 50% of the mean  $QRSd$  during the first 5 seconds of occlusion was required ( $\gamma_2=1.5QRSd[n_0]$ ); and, finally, (c) using an absolute value of  $\gamma_3=120$  ms, based on previous studies that associated this cut-point with mortality [13].

Finally, pigs were classified as QRSd(+) if at any instant  $QRSd[n] \geq \gamma_i$  and the local increment for that instant,  $\Delta QRSd[n]$ , exceeded a minimum value. On the contrary, pigs were labeled as QRSd(-) if any of these two conditions were not satisfied.

Therefore, ROC curve analysis was repeated three times, using  $\gamma_1$ ,  $\gamma_2$  and  $\gamma_3$ , for each window size ( $L_1, L_2$ ) and varying the minimum local increment  $\Delta QRSd[n]$  from 0 to 60 ms in 2-ms steps.

### 4. Results

An immediate significant increase in QRS duration was found in all pigs during the first 5 minutes of occlusion, corresponding to the first phase of ventricular arrhythmias. However, in this study, we considered only late VF episodes (after 10 min of occlusion). Those late episodes of ventricular fibrillation were found in 10 out of 32 pigs (VF-group) whereas a total of 22 pigs did not present late VF episodes at any moment (control group). In VF-group, episodes appeared from 17 to 31 minutes after the onset

of occlusion (mean±std: 21.34±4.11 min). In order to exclude early VF episodes, time analysis was limited between minute 10 and minute 25 after the onset of occlusion. In VF-group,  $QRSd$  monitoring was only performed until the onset of the VF episode.

Fig. 2 shows  $QRSd$  series of two pigs: upper panel corresponds to one pig who had a VF episode 23.8 minutes after balloon inflation and the bottom panel to an arrhythmia-free pig. Immediate increase during the first 5 minutes of occlusion is observed in both panels, whereas second increase in QRS duration immediately before the VF episode is clearly more pronounced on the upper one.

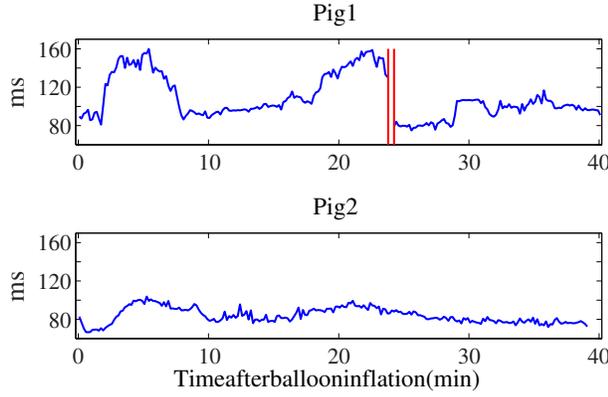


Figure 2.  $QRSd$  series of two individual pigs. Fig 1 presented a VF episode delimited by red vertical lines, 23.8 min after occlusion. Fig 2 did not have VF at any moment.

ROC curves for both 3- and 5-minute windows, using the three  $\gamma_i$  values are shown in Fig. 3. We found that using a 3-minute sliding window, QRS(+) classified recordings showed higher presence of VF episodes. Moreover, defining a minimum value for the instantaneous  $QRSd$  always improves prediction accuracy.

From the ROC curve analysis, a minimum local increase of  $\Delta QRSd[n] = 28$  ms and  $QRSd[n] \geq 120$  ms ( $\nabla$  point in Fig. 3) was chosen. Using that threshold, 8 out of 10 pigs with VF episodes would be classified as QRS(+), whereas only 2 out of 22 animals who did not presented VF would be labeled as QRS(+). Thus, VF episodes would be successfully predicted with a sensitivity and specificity rates  $Se = 80\%$  and  $Sp = 90.9\%$  ( $Acc = 87.5\%$ ,  $NPV = 90.9\%$ ,  $PPV = 80\%$ ).

In QRS(+) pigs, the combined criterion was fulfilled, on average,  $4.3 \pm 3.8$  minutes before the VF episode (median = 3.17 minutes).

Maximum local QRS widening in VF-group was  $\Delta QRSd = 44.2 \pm 16.3$  ms, whereas in control pigs, this widening was significantly lower  $\Delta QRSd = 25 \pm 7.7$  ms (Mann-Whitney test,  $p = 0.003$ ). In the same way, maximum absolute QRS duration for VF-pigs was, on average,  $QRSd = 132.4 \pm 19.1$  ms, being  $QRSd =$

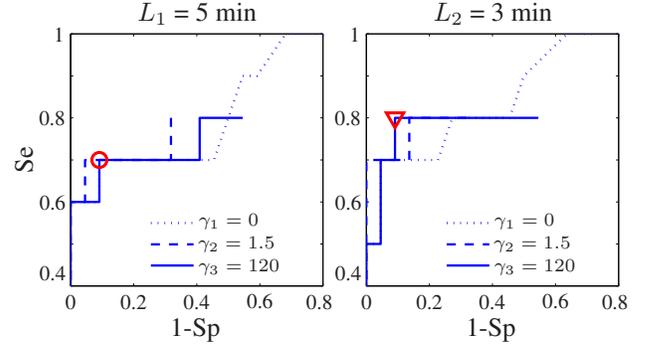


Figure 3. ROC curves for each defined threshold:  $\gamma_1 = 0$  (dotted line),  $\gamma_2 = 1.5 QRSd[n_0]$  (dashed line) and  $\gamma_3 = 120$  ms (solid line) using 5 and 3-minute sliding window. Significant points are marked.

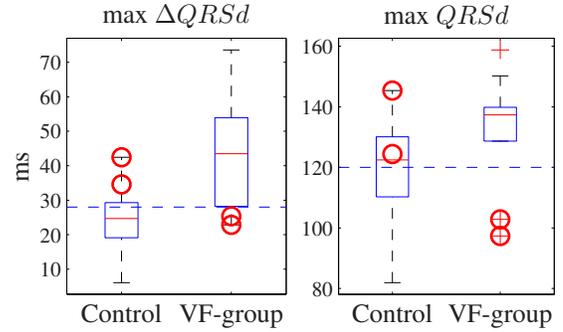


Figure 4. Maximum  $\Delta QRSd$  (left) and maximum  $QRSd$  (right) detected in all pigs. Red circles correspond to false positive (control) and false negative (VF-group) detections. Horizontal dashed lines represent minimum values to consider a QRS(+) pig, 28 and 120 ms respectively.

$119.4 \pm 14.8$  ms in control group of pigs (Mann-Whitney test,  $p = 0.031$ ). Distribution of both, maximum  $\Delta QRSd$  and  $QRSd$ , in VF and Control groups is shown in Fig. 4.

## 5. Discussion and conclusion

Previous studies have observed a QRS prolongation in animal models of coronary artery ligation and PTCA interventions in humans [4–6]. In this study, changes in QRS duration during acute myocardial ischemia have been associated with the subsequent presence of malignant ventricular arrhythmias. The occurrence of malignant ventricular arrhythmias during experimental myocardial ischemia has also been well established [8, 9, 14] and both, QRS prolongation and the incidence of arrhythmias, are associated to alterations and delays in local conduction velocity.

After applying a wavelet-based delineator to the 6 precordial leads V1-V6 and multilead post-processing rules,  $QRSd$  was continuously computed along 40 minutes of LAD occlusion by PTCA intervention in 32 pigs. On average,  $QRSd$  series present a biphasic distribution with

an immediate increment within the first 5 minutes of ischemia which is diminished by minute 10, and a second, less-pronounced increase around minute 20 after the onset of occlusion. This two-peaked pattern is in agreement with the two phases of arrhythmia-incidence in a canine myocardial infarction model, previously reported in [14]. The first phase, named Ia phase, occurs from 2 to 10 minutes after the onset of ischemia, whereas the second phase, or Ib phase, appears after an arrhythmia-free interval, between 12 and 30 minutes. Since Ia and Ib phases suggest different mechanisms [14, 15], only late arrhythmias were considered in this study.

There is considerable interest in using noninvasive methods to identify patients with high propensity to suffer from malignant ventricular arrhythmias, such as VF, since they can lead to a fatal outcome such as sudden cardiac death. Using this experimental model of acute ischemia, we have shown that a rapid increase in  $QRSd$  of 28 ms in less than 3 minutes, together with a  $QRSd$  exceeding 120 ms, was a sensitive and specific predictor of an imminent VF episode. It has to be taken into account that we evaluated the performance in the same data used to compute the threshold. We did so due to the reduced VF group in the database and it supposes a limitation of this work.

One constraint in measuring QRS duration is the difficulty to determine the end of the QRS complex, as there is a gradual transition between the QRS and the ST-segment. In order to overcome that problem, wavelet-based-delineation parameters have been adapted to this acute-ischemic scenario. Another important consideration is the variability among leads, especially when limb leads and precordial leads were compared. Incidence in  $QRSd$  and ST-segment elevation depends on the mass of myocardial tissue involved in the artery occlusion. Since LAD artery mainly supplies anterior area of the heart, changes induced by its occlusion will be more evident in V2-V4 precordial leads. The multilead approach at the delineation stage using only precordial leads may have helped to avoid this phenomenon, yielding more robust delineation marks while ischemic effects were also well-projected using that set of leads.

In summary, results of this study suggest that a transient increase in QRS duration may be a sensitive and specific index for monitoring the immediate risk of VF in experimental myocardial infarction. The prognostic value of this phenomenon and  $QRSd$  cut-off for VF prediction in clinical settings of STEMI remains to be determined.

## Acknowledgements

This work was supported by CIBER-BBN through Instituto de Salud Carlos III and FEDER (Spain), project TEC2010-21703-C03-02 funded by MINECO and FEDER, and by DGA and European Social Fund (EU) through Grupo Consolidado GTC (T30). MMD received research schol-

arship from Swedish Institute.

## References

- [1] Volpi A, Cavalli A, Santoro L, Negri E. Incidence and prognosis of early primary ventricular fibrillation in acute myocardial infarction—results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) database. *Am J Cardiol.* 1998;82(3):265-71.
- [2] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace.* 2006;8(9):746-837.
- [3] Kleber AG, Janse MJ, Wilms-Schopman FJ, Wilde AA, Coronel R. Changes in conduction velocity during acute ischemia in ventricular myocardium of the isolated porcine heart. *Circulation* 1986;73:189-198.
- [4] Cinca J, Janse MJ, Morena H, Candell J, Valle V, Durrer D. Mechanism and time course of the early electrical changes during acute coronary artery occlusion. An attempt to correlate the early ECG changes in man to cellular electrophysiology in the pig. *Chest* 1980;77:499-505.
- [5] Cantor AA, Goldfarb B, Ilia R. QRS prolongation: A sensitive marker of Ischemia During Percutaneous Transluminal Coronary Angioplasty. *Characterization and Cardiovascular Interventions* 2000;50:177-183.
- [6] Janse MW, Kleber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischemia. *Circulation Research* 1981;49:1069-1081.
- [7] Charlap S, Shani J, Schulho N, Herman B, Lichstein E. R- and S-wave amplitude changes with acute anterior transmural myocardial ischemia. *Chest* 1990;97:566-571.
- [8] Bigger JT Jr, Dresdale RJ, Heissenbuttel RH, Weld FM, Wit AL. Ventricular arrhythmias in ischemic heart disease: mechanism, prevalence, significance and management. *Prog Cardiovascular Dis* 1977;19:255-300.
- [9] David D, Naito M, Michelson EL et al. Intramyocardial conduction: a major determinant of R wave amplitude alterations during acute myocardial ischemia. *Circulation* 1981;65:161-167.
- [10] Demidova M, van der Pals J, Ubachs J, Kanski M, Engblom H, Erlinge D, Tichonenko VM, Platonov P. ST-segment dynamics during reperfusion period and the size of myocardial injury in experimental myocardial infarction. *Journal of Electrocardiology* 2011;44(1):74-81.
- [11] Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. Wavelet-based ECG delineator: evaluation on standard databases. *IEEE Transactions on Biomedical Engineering* 2004;51:570-581.
- [12] Bolea J, Almeida R, Laguna P, Sormmo L, Martínez JP. BioSig-Browser, biosignal processing interface. *ITAB 2009: 9th IEEE Int. Conf. on Information Technology and Applications in Biomedicine* 2009:1-4.
- [13] Brenyo A, Zareba W. Prognostic significance of QRS duration and morphology. *Cardiology Journal* 2011;18(1):8-17
- [14] Kaplinsky E, Ogawa S, Balke CW, Dreifus LS. Two periods of early ventricular arrhythmia in the canine acute myocardial infarction model. *Circulation* 1979;60:397-403.
- [15] Smith WT, Fleet WF, Johnson TA, Engle, CL, Cascio WE. The Ib Phase of Ventricular Arrhythmias in Ischemic In Situ Porcine Heart Is Related to Changes in Cell-to-Cell Electrical Coupling. *Circulation* 1995;92:3051-3060.

Address for correspondence:

Alba Martín, albamartinyebra@gmail.com

María de Luna I, Ed. Ada Byron L3.07, 50018, Zaragoza (Spain)