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**Transient and rapid QRS widening associated with J-wave pattern predicts impending ventricular fibrillation in experimental myocardial infarction**

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Short title: ***J-wave pattern and ventricular fibrillation in ischemia***

Conflict of interest:

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**Abstract.**

**Background:** Certain types of the early repolarization (ER) phenomenon, previously considered to be benign, have been reported to be associated with ventricular fibrillation (VF), both in population-based studies and in the myocardial infarction (MI) settings.

**Objective:** Our aim was to analyse whether QRS widening and appearance of J-wave-pattern in experimental MI settings is predictive of VF.

**Methods:** MI was induced in 32 pigs by 40-min inflation of an angioplasty balloon in the left descending artery (LAD) and ECG was continuously recorded. Multilead QRS boundaries were computed, and QRS duration was calculated on a beat-to-beat basis during the occlusion period for each pig. Association between QRS-widening and subsequent VF was studied using ROC-curve analysis. ECGs at maximum QRS-duration were reviewed for the presence of J-wave pattern.

**Results:** Sixteen animals had VF episodes during occlusion period. Two peaks of QRS widening were found in all animals: the first peak immediately on LAD occlusion, and the second peak  $19.1 \pm 4.0$  min later. The magnitude of changes in the QRS width over time had significant interindividual differences. QRS-widening  $\geq 28$  ms during a 3-min time window was observed in 14 animals and predicted impending VF (Se=80%, Sp=73%, PPV=57%, NPV=89%,  $p=0.008$ ). In 10 of the 14 pigs, J-wave pattern appeared at maximal QRS duration. Appearance of J-wave-pattern predicted VF with Se=80%, Sp=68%, PPV=53%, NPV=88%  $p=0.02$ .

**Conclusions:** Transient QRS widening, commonly associated with J-wave pattern, appears to predict impending VF in acute ischemia settings and motivates further clinical studies for monitoring immediate risk of VF in MI.

**Key words:** myocardial infarction, ventricular fibrillation, early repolarization, QRS duration, J-wave

**List of abbreviations:** VF - ventricular fibrillation; ER - early repolarization; MI - myocardial infarction; LAD - left descending artery; STEMI - ST elevation myocardial infarction; ECG - electrocardiogram; ROC- curve analysis- receiver operator characteristics curve analysis; IQR - interquartile range;

**Introduction.**

Malignant ventricular arrhythmias, particularly ventricular fibrillation (VF), remain an important contributor to mortality in ST-elevation myocardial infarction (STEMI) (1, 2). The success of VF treatment is determined by time elapsed from VF occurrence to administration of medical care. Therefore, the main strategy in relation to the life-threatening ventricular arrhythmias during ST-elevation myocardial infarction is their prediction and prevention (3). Although several studies proposed predictors of ventricular arrhythmias in STEMI-settings, most of those predictors can be attributed to clinical characteristics (1, 2, 4) while data on dynamic electrocardiographic changes that can predict VF are scarce.

Early repolarization (ER) pattern, including J-point elevation, distinct J-wave with or without ST elevation or slurring of the terminal part of the QRS (5) is generally found in healthy young males and is considered to be a benign electrocardiographic (ECG) phenomenon. (6-8). However, certain types of this J-wave pattern at resting ECG, such as those observed in the inferior leads and associated with the horizontal/descending ST segment, have been linked to increased risk of ventricular arrhythmias and sudden death (5, 9, 10). This association was first reported in animal experiments (11-13) and then in clinic for idiopathic VF (14).

More recent studies demonstrated that association of J-wave pattern with ventricular arrhythmias and sudden death is valid in a broader context of population-based sudden death prediction (9) and in the settings of myocardial ischemia (10, 15-17). Our aim was to analyze the course of QRS morphology and possible appearance of a J-wave pattern during coronary artery occlusion in experiment as predictor of VF.

**Methods:**

## **Experimental protocol**

A porcine model of myocardial infarction was used in this work. The experimental preparation and study protocol have been previously described in detail (18). In brief, in 38 pigs weighing 40-50 kg, anaesthetised with fentanyl and thiopental, an angioplasty balloon was positioned in the mid portion of the left anterior descending coronary artery (LAD), immediately distal to the first diagonal branch. Ischemia was induced by inflation of an angioplasty balloon for 40 min, and 12-lead ECG monitoring (“Kardiotechnica-04-8m”, “INCART”, St. Petersburg, Russia) was started prior to the occlusion and continued throughout the occlusion period. The ECG sampling rate was 1024 Hz, and the amplitude resolution 1.4  $\mu$ V. Completeness of coronary occlusion was verified by coronary angiography.

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

## **ECG analysis**

QRS-complexes were automatically detected and then visually and manually checked. After applying an automatic wavelet-based ECG delineator (19) to precordial leads, beat-to-beat multilead QRS boundaries were computed. For each pig, QRS duration was computed on a beat-to-beat basis as the difference between the QRS onset and QRS end marks along a 40-minute occlusion period for each experimental animal. These series were then resampled by averaging QRS duration every 10 seconds. For each animal, the dynamic changes in QRS duration during the occlusion period

were plotted as a function of time (Fig 1). To quantify QRS-widening, two indices were continuously assessed using a sliding window of 3-min duration: (1) a local QRS duration increase (delta QRS duration) and (2) a maximal absolute QRS duration. Delta QRS duration was calculated as the difference between the QRS duration of the last beat in the window and the narrowest QRS in the 3-min window (20).

ECGs for each pig at baseline and at the time of maximal QRS duration were independently reviewed for presence of QRS complex notching or slurring (J-wave pattern) (21, 22) in  $\geq 2$  contiguous leads by two investigators (PP and MD), blinded to VF occurrence. Notching was defined as a positive deflection at the terminal portion of a positive QRS-complex. Slurring was defined as a smooth transition from the QRS-complex to the ST-segment with upright concavity (Figure 2) (22). The conventional J-wave amplitude criterion could not be applied as the ST-segment was elevated as a result of complete LAD occlusion. We classified the localisation of J-wave pattern as present either in the inferior (II, III, aVF), lateral (I, avL, V<sub>4</sub>-V<sub>6</sub>) or anterior leads (V<sub>1</sub>-V<sub>3</sub>). Anterior precordial leads reflecting the ischemic zone due to LAD-occlusion were not excluded from the analysis.

### **Statistical analysis.**

Data are presented as mean values  $\pm$  standard deviations or median and interquartile range (IQR) in cases of asymmetrical distribution. Fisher's exact test was used for comparisons between study groups.

Receiver operator characteristics curve analysis (ROC curve analysis) was used to identify the optimal cut-off of QRS duration increase for predicting VF during the occlusion period. Statistical significance was accepted at 2-sided  $p < 0.05$ . Factors

associated with VF were identified in univariate logistic regression models with estimation of odds ratios. Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA).

## **Results.**

One pig died during the occlusion period from left main thrombosis. Thus 37 of 38 pigs survived the occlusion period. Five animals were excluded from the analysis due to poor signal quality. Of the remaining 32 pigs, 6 pigs suffered from VF during the first minutes of occlusion – on average  $2.6 \pm 2.1$  (range 0.6-7.0) minutes after occlusion start, and 10 pigs –  $20.9 \pm 4.0$  (range 16.8-30.2) minutes after occlusion start (Figure 3). Since ECG-based prediction of VF was not technically feasible during the first minutes of ischemia, this study focused on the occurrence of late VF episodes (occurring after the 15<sup>th</sup> minute of occlusion).

All the studied animals demonstrated similar dynamics of QRS duration changes characterised by the two peaks of QRS-widening: the first peak immediately after LAD occlusion  $3.7 \pm 1.6$  min, and the second peak  $19.1 \pm 4.0$  min after occlusion start (Figure 4). Significant interindividual differences were observed with regard to the magnitude of changes in QRS width. These differences varied from negligible variation of QRS duration to pronounced QRS widening over short time measured as delta in QRS duration over a 3-min window. The value of QRS duration at baseline, at the first (0-10 min of occlusion period) and the second (10-40 min of occlusion period) peaks of QRS widening and at the end of occlusion period is shown in Figure 5. The QRS duration at baseline was  $78 \pm 11$  ms, at the first peak of QRS widening -  $140 \pm 21$  ms, at the second peak -  $124 \pm 17$  ms,  $p < 0,001$ . The median difference



between maximal QRS duration and QRS duration at baseline was 27 (IQR: 16) ms.

At baseline, no animals demonstrated a J-wave pattern in any lead. At maximal QRS duration, J-wave pattern was found in 15 of 32 animals. Figures 6 and 7 show the typical QRS morphology dynamics during the experiment. Notching or slurring usually appeared on QRS broadening and manifested at maximal QRS duration, with subsequent resolution during continued occlusion.

J-wave pattern in anterior leads, which reflected the ischemic zone caused by LAD occlusion, was found in all 15 animals that showed slurring or notching of QRS complexes at its maximal width. In 8 animals, the J-wave pattern in anterior leads was combined with the J-wave pattern in inferior leads; in 2 animals –in lateral leads; while in 5 animals it was confined to anterior leads only. The most commonly observed J-wave pattern was notching of the terminal QRS complex – in 13 animals; while slurring was noted in 2 animals.

Association between QRS widening and subsequent VF onset was studied using the ROC curve analysis. Two thresholds in delta QRS duration showing a reasonable combination of sensitivity and specificity for VF prediction were 28 ms and 36 ms (Figure 8).

QRS widening of  $\geq 28$  ms in 3 minutes predicted impending VF with Se=80%, Sp=73%, PPV=57%, NPV=89%,  $p=0.008$ . QRS widening of  $\geq 36$  ms in 3 minutes predicted impending VF with Se=70%, Sp=95%, PPV=88%, NPV=88%,  $p<0.001$ . Thus, marked and fast QRS widening predicted VF (OR 10.7, 95%CI 1.7-65.3,  $p=0.010$  for QRS widening of  $\geq 28$  ms in 3 minutes; OR 49.0, 95%CI 4.4-550.7,  $p=0.002$  for QRS widening of  $\geq 36$  ms in 3 minutes), while the absolute value of

maximal QRS duration had no predictive value (OR 3.3, 95%CI 0.5-19.4,  $p=0.180$  for QRS widening  $>120\text{ms}$ ). In the animals that developed VF, the arrhythmia occurred within  $2.9\pm 3.8$  minutes after reaching the maximal QRS duration.

J-wave pattern was observed in 8 out of the 10 pigs that experienced VF and in 7 out of the 22 pigs without VF,  $p=0.02$ . J-wave pattern was found in all 7 animals with QRS duration increase  $\geq 36$  ms, and in 10 of 14 animals with QRS duration increase  $\geq 28$  ms during a 3-min window. Appearance of a J-wave-pattern predicted VF with  $\text{Se}=80\%$ ,  $\text{Sp}=68\%$ ,  $\text{PPV}=53\%$ ,  $\text{NPV}=88\%$  ( $p=0.02$ ) and remained a significant VF predictor in logistic regression analysis (OR=8.6, 95%CI 1.4-51.4,  $p=0.020$ ).

VF occurred in 6 out of 8 animals with J-wave pattern in combination of inferior and anterior leads, and only in 2 out of 7 animals with J-wave pattern in isolated anterior leads and combination of anterior and lateral leads ( $p=0.13$ ) ( $\text{Se}=75\%$ ,  $\text{Sp}=71\%$ ,  $\text{PPV}=75\%$ ,  $\text{NPV}=29\%$ ).

## **Discussion**

### ***J-wave pattern in STEMI***

The association between J-wave pattern and VF in the settings of acute ischemia has been first reported in experimental studies (13, 23) and later observed in a few case reports (24, 25). More recently, the association between the presence of J-wave pattern and myocardial ischemia or infarction was reported in several controlled studies (10, 15-17, 26).

In most studies investigating the predictive value of ER in ischemic patients, the presence of a J-wave-pattern has been assessed on the basis of a historical ECG recorded prior to the ischemic event (10, 15, 16). The association of an initially existing J-wave pattern with future arrhythmic complications during acute STEMI

was explained by the presence of heterogeneity of ventricular repolarization – i.e. a substrate predisposing to the development of ventricular arrhythmias in the setting of an acute ischemic trigger (11, 27). Other studies attempted to evaluate the J-wave pattern during the subacute phase of STEMI (5<sup>th</sup>-7<sup>th</sup> day), i.e. after restoration of blood flow by primary PCI and in the absence of acute ischemia (17, 26). To the best of our knowledge, there have been no reports on the time course of QRS morphology with regard to the occurrence of the J-wave pattern during progression of acute ischemia and infarction.

### ***Ischemia-induced QRS widening and J-wave pattern***

At baseline, QRS was narrow without any signs of J-wave pattern in any of the experimental animals. During the course of ischemia, QRS duration demonstrated dynamic behaviour with two peaks of QRS-widening. Shortening of QRS despite the uninterrupted LAD occlusion is in accordance with previously published experimental data (28).

In order to avoid subjectivity in assessment of QRS borders, we have chosen to use an automatic assessment of QRS duration, which includes terminal slurring and J-wave, if present, as part of QRS complex (22). It is well-known that detection of QRS end in settings of marked ST-elevation is a challenging task, and new technical approaches for assessing QRS width have been proposed (29).

Automatically detected QRS width varied in different leads, and maximal width was reached in anterior leads - the region supplied by LAD, which was the infarct-related artery in our experimental study.

The exact mechanisms underlying J-wave development associated with ischemia and preceding VF episodes cannot be elucidated from our study based on the closed-chest

porcine model of myocardial infarction. In our experiment all animals were on spontaneous sinus rhythm and we did not observe any dramatic changes in heart rate during occlusion period, which could help to differentiate the contribution of repolarization and depolarization abnormalities to the changes in the terminal part of QRS.

Earlier observations made in an open-chest model suggest that J-wave development is caused by the action potential differences between epicardial and endocardial myocardium (12). The decrease in inward currents  $I_{Na}$  and  $I_{Ca}$  and a significant increase in outward currents such as  $I_{K-ATP}$  and  $I_{KAA}$  resulted in prevalence of outward currents in epicardium in give rise to a typical notched configuration of the action potential in epicardium and the development of prominent J-waves (5). Yan et al. were first to report the causative association between the ischemia-induced of  $I_{to}$ -mediated changes in action potential leading to the transmural voltage gradient that predimpose to the phase 2 reentry (13). These experimental studies suggest that the fundamental mechanisms responsible for ST-segment elevation and initiation of VF are similar in the early phases of acute myocardial ischemia and the inherited J-wave syndromes (13, 30).

### ***Ventricular fibrillation during experimental STEMI***

50% of the animals used in this study developed VF during occlusion. The time distribution of ventricular arrhythmias in our study was in agreement with previously published data that describe their occurrence at two distinct periods of ischemia defined as phases 1a (0-10 min from induction of ischemia) and 1b (15-30 min of ischemia) (31, 32).

Since phase 1a arrhythmias occurred almost immediately after LAD occlusion, the

assessment of the steepness of the QRS widening using 3-min window was not technically feasible. Nonetheless, measuring QRS duration, we found dynamic QRS-widening to precede all early VF episodes: QRS duration immediately before VF was  $122\pm 11$  ms vs  $79\pm 13$  ms at baseline. QRS widening is unlikely to be due to conduction delay immediately after occlusion of LAD (23). Terminal notching/slurring induced by ischemia appears to contribute significantly to the automatically assessed prolonged QRS duration. This is also supported by the fact that J-wave pattern was observed in all 6 pigs suffered from early VF.

In clinical settings, phase 1a arrhythmias usually occur long before the first contact with healthcare providers. Since progression of myocardial infarction in pigs is approximately 7 times faster than in humans (33), 20 minutes of coronary artery occlusion in the porcine model corresponds to approximately 2-2.5 hours of myocardial infarction in clinical settings, and prediction of VF in this time period may be clinically relevant. We found that marked and rapid QRS widening and appearance of J-wave pattern predicted imminent ventricular fibrillation.

Several previous studies have reported an increased risk of arrhythmic complications in patients with inferior localization of J-wave pattern (10, 16, 27). In our study, a J-wave pattern, when observed, was present in the anterior leads corresponding to the occluded coronary artery in all affected animals. However, in some of the animals, J-wave pattern in anterior leads was combined with slurring or notching in inferior leads. The presence of J-wave pattern in both anterior and inferior leads was associated with higher incidence of VF than J-wave pattern present in only anterior or anterior and lateral leads, even though this association did not reach statistical significance. However, any extrapolation of topical ECG changes observed in experimental animals to clinical settings should be made with extreme caution.

Because of the presence of marked ST-elevation due to acute myocardial infarction, we have not measured J-point elevation and have not assessed the slope of ST-segment, which previously has also been reported to have predictive value for arrhythmic events (9, 14, 27)

## **Conclusions**

Rapid and marked transient increase in QRS duration commonly associated with J-wave pattern appears to predict impending VF in acute ischemic settings, and warrants further clinical studies for monitoring the immediate risk of VF during the acute phase of myocardial infarction.

## **Funding sources:**

This study was supported by the Swedish Institute (research scholarship for MMD), Donations funds at Skåne University Hospital (PP, MMD) and The Swedish Heart Lung Foundation (PP, MMD), project TEC2010-21703-C03-02 funded by MINECO and FEDER, Spain, and by Gobierno de Aragon and European Social Fund (EU) through Grupo Consolidado GTC (T30) (AMY, PL, JPM).

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### **Figure legends:**

**Figure 1.** Schematic picture showing determining the delta QRS duration in the sliding window during the occlusion period. In our study, the duration sliding window duration was 3 minutes.

**Figure 2** ECG examples in lead V<sub>2</sub>, illustrating different morphology of the ER pattern. A- notch is present in V<sub>2</sub>; B- slur is visible in lead V<sub>2</sub>, ST elevation due to ST elevation myocardial infarction is present in both A and B.

**Figure 3.** Time distribution of VF episodes during coronary occlusion. Two distinct peaks of ventricular arrhythmia occurrence were observed and corresponded to phase 1a (<10 min) and 1b (>15 min).

**Figure 4.** Dynamics of QRS width thorough 40-minute coronary occlusion. A- marked QRS-widening at minutes 2-7 and 17-22 in one pig with VF at 24<sup>th</sup> minute of occlusion. Vertical line shows the time of VF occurrence. B - slight changes in QRS width in an animal without VF.

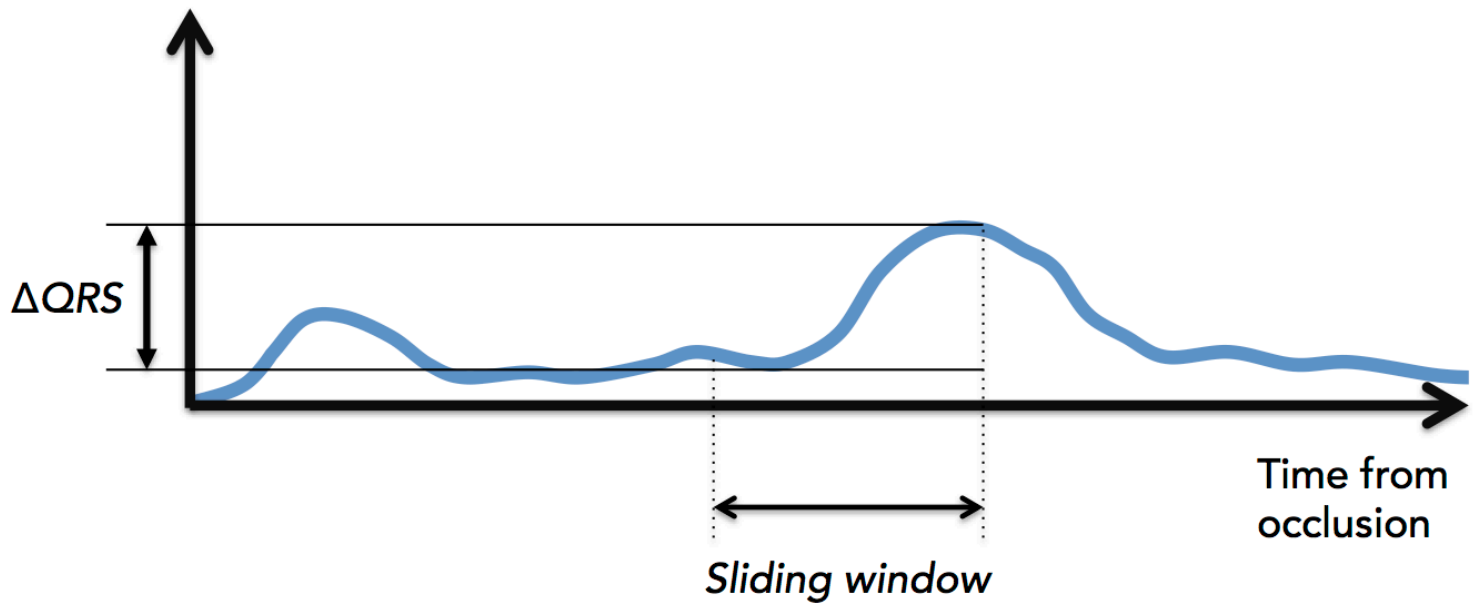
**Figure 5.** QRS duration at baseline, at the first and the second peak of QRS widening \*p<0,001 for comparison with the QRS duration at baseline; †- p<0,001 for comparison with the QRS duration at the first and the second peak of QRS-widening.

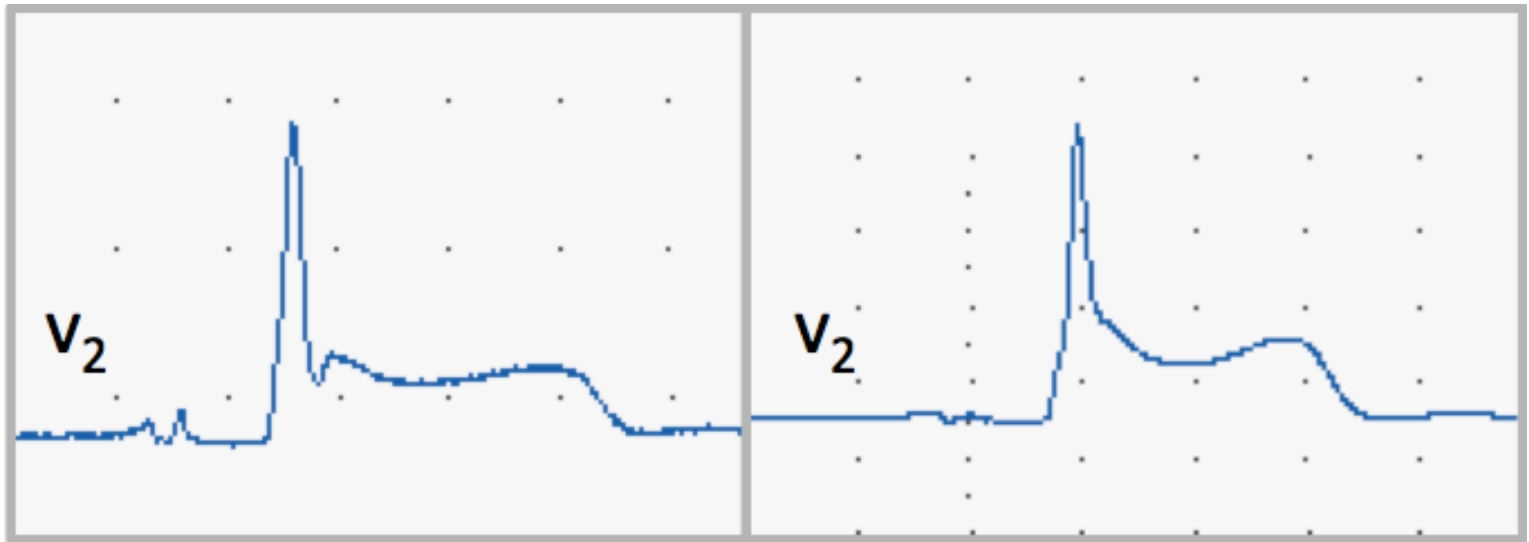
**Figure 6.** Apperance of J-wave pattern in inferior leads (notch in II, III, aVF) at 22<sup>nd</sup> minute of occlusion followed by backward dynamics.

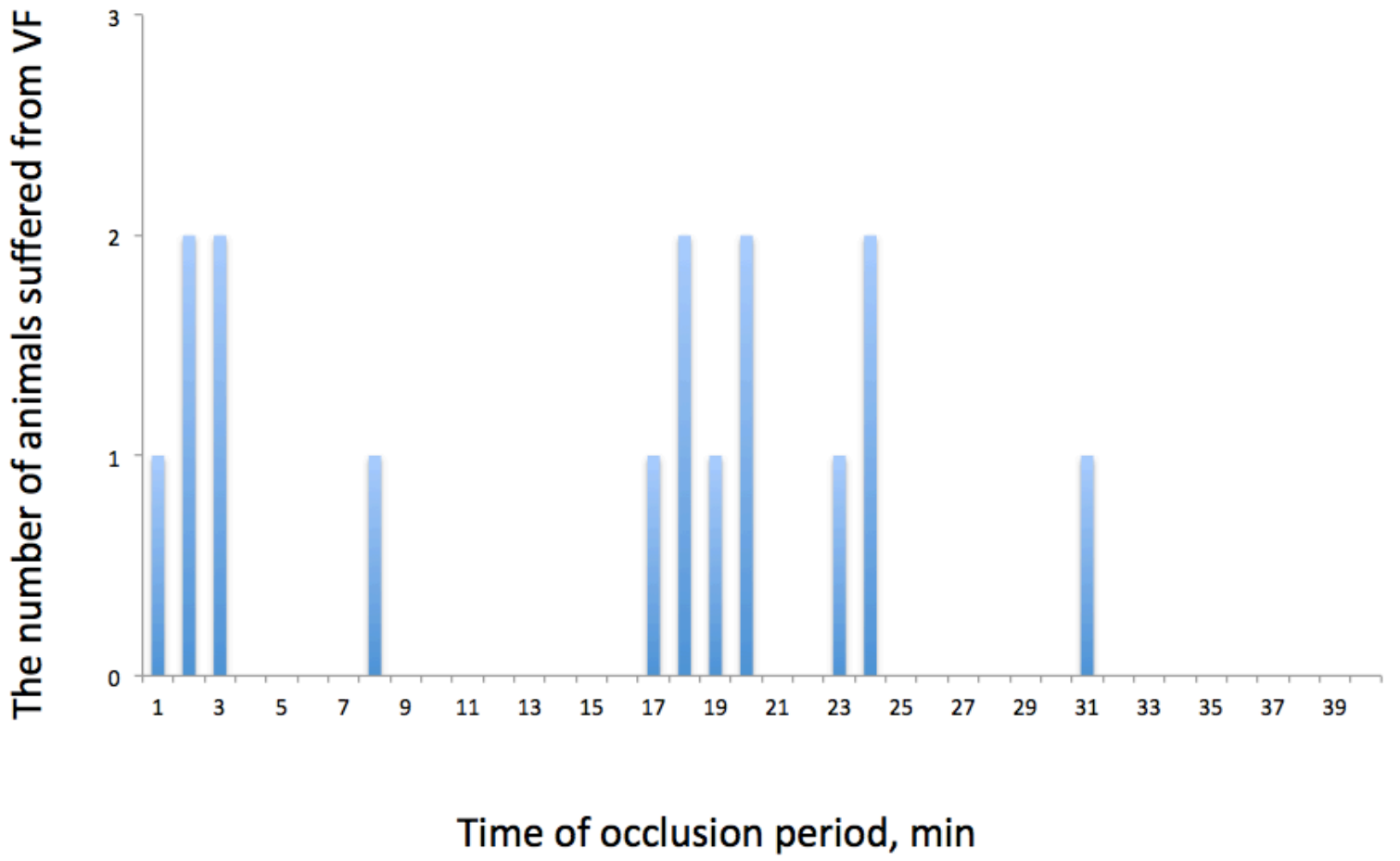
**Figure 7.** Apperance of an J-wave pattern in anterior leads at 20<sup>th</sup> minute of occlusion, immediately preceding VF episode.

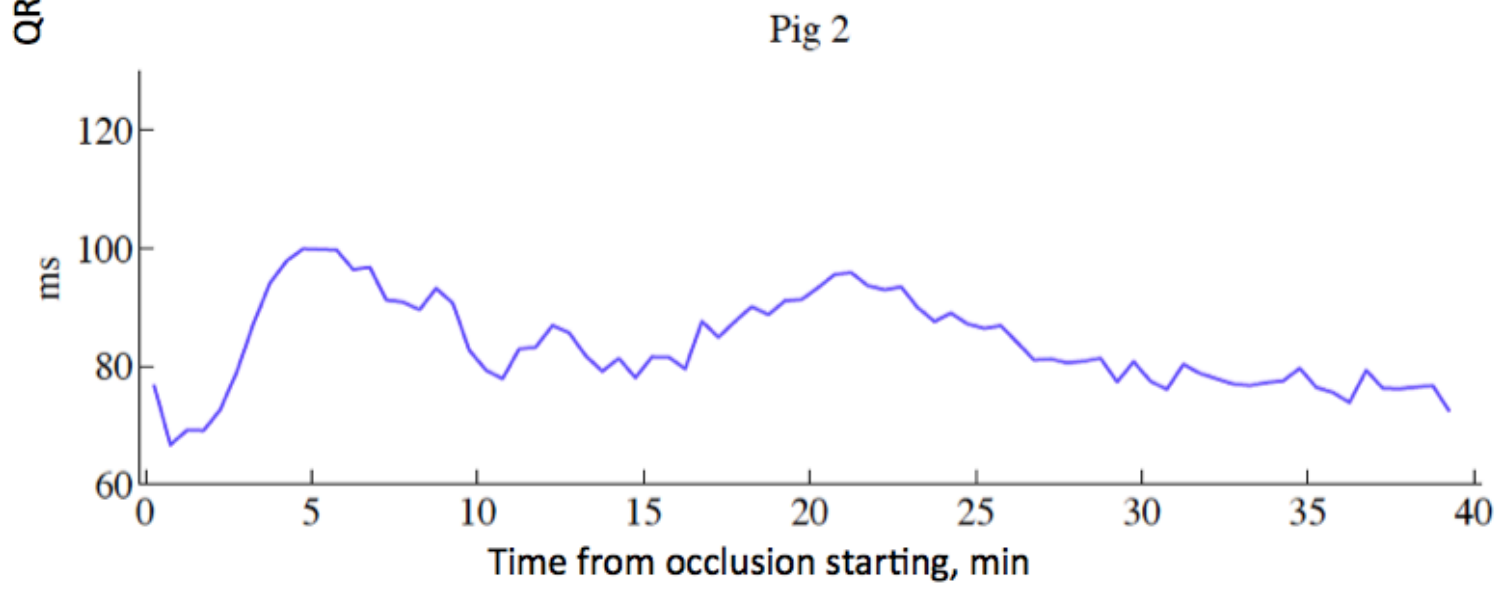
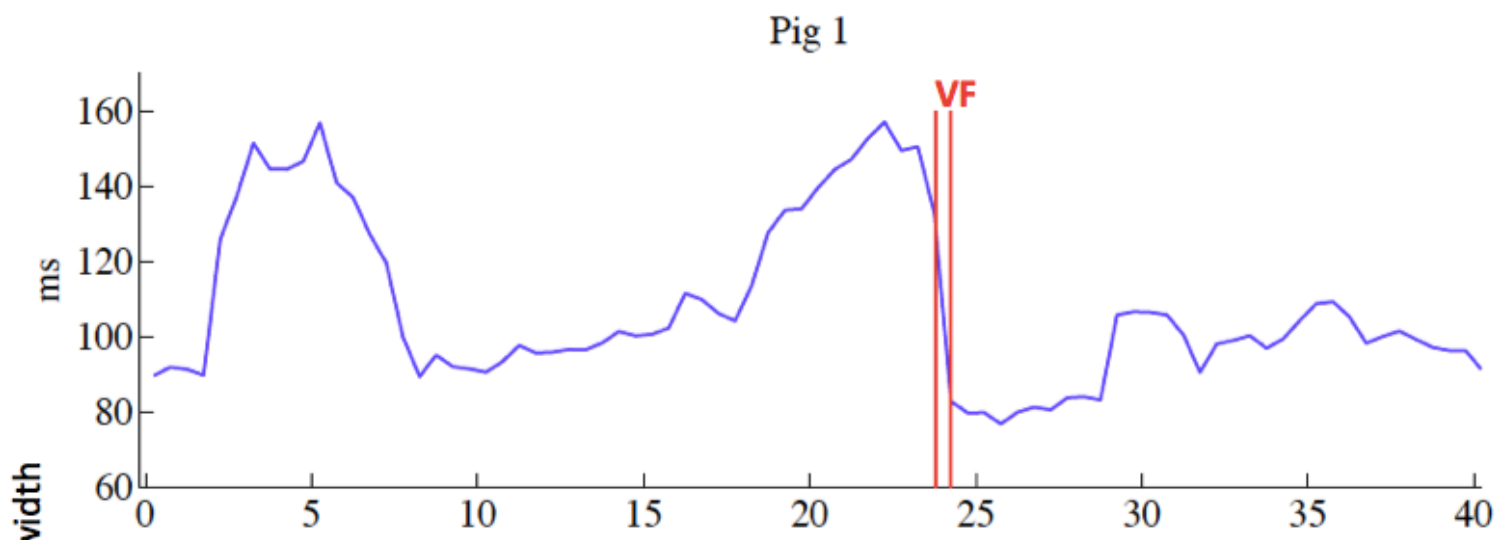
**Figure 8.** ROC curve analysis for identification of optimal QRS duration increase cut-off for predicting VF during occlusion period. Significant points are marked.

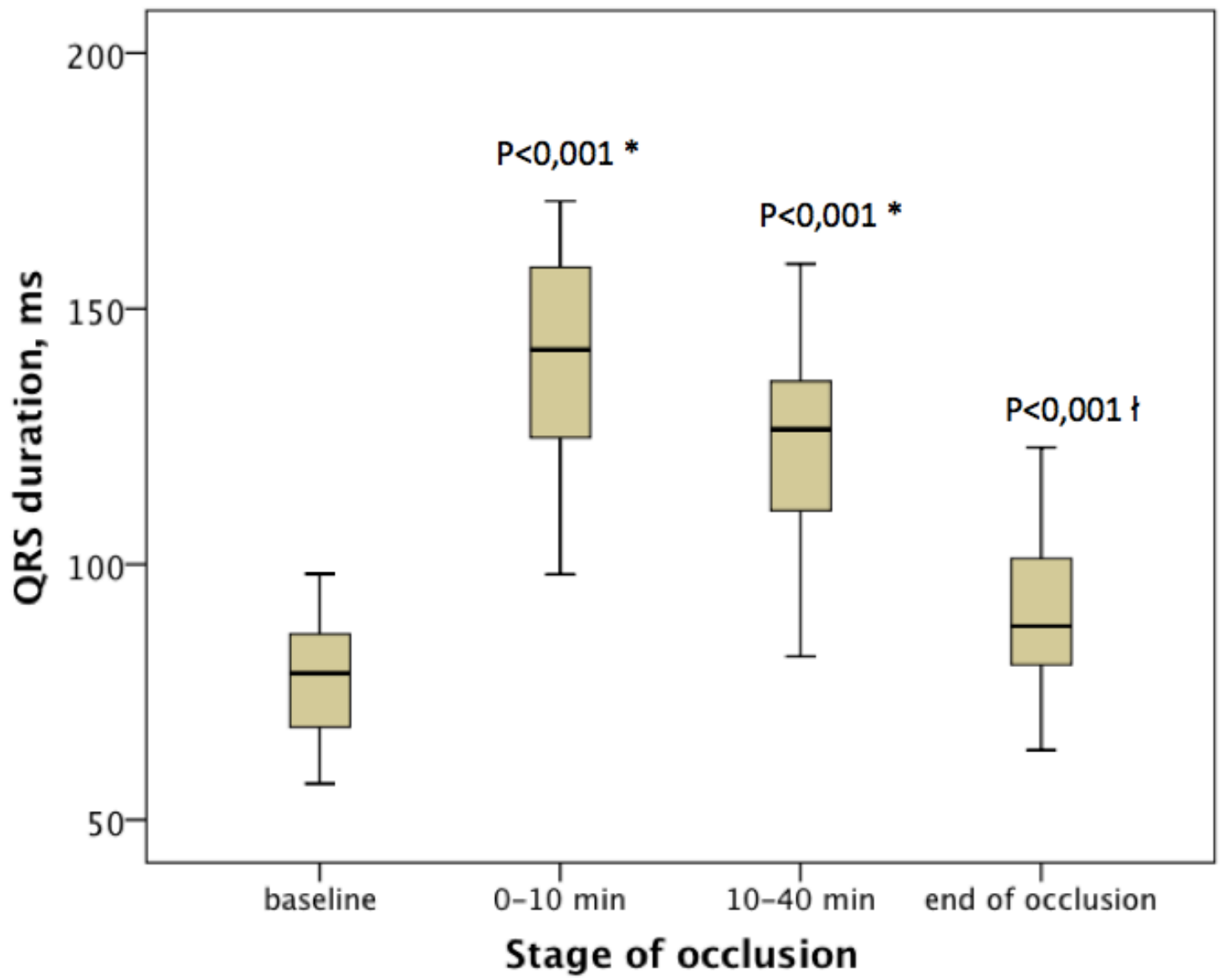
QRS duration

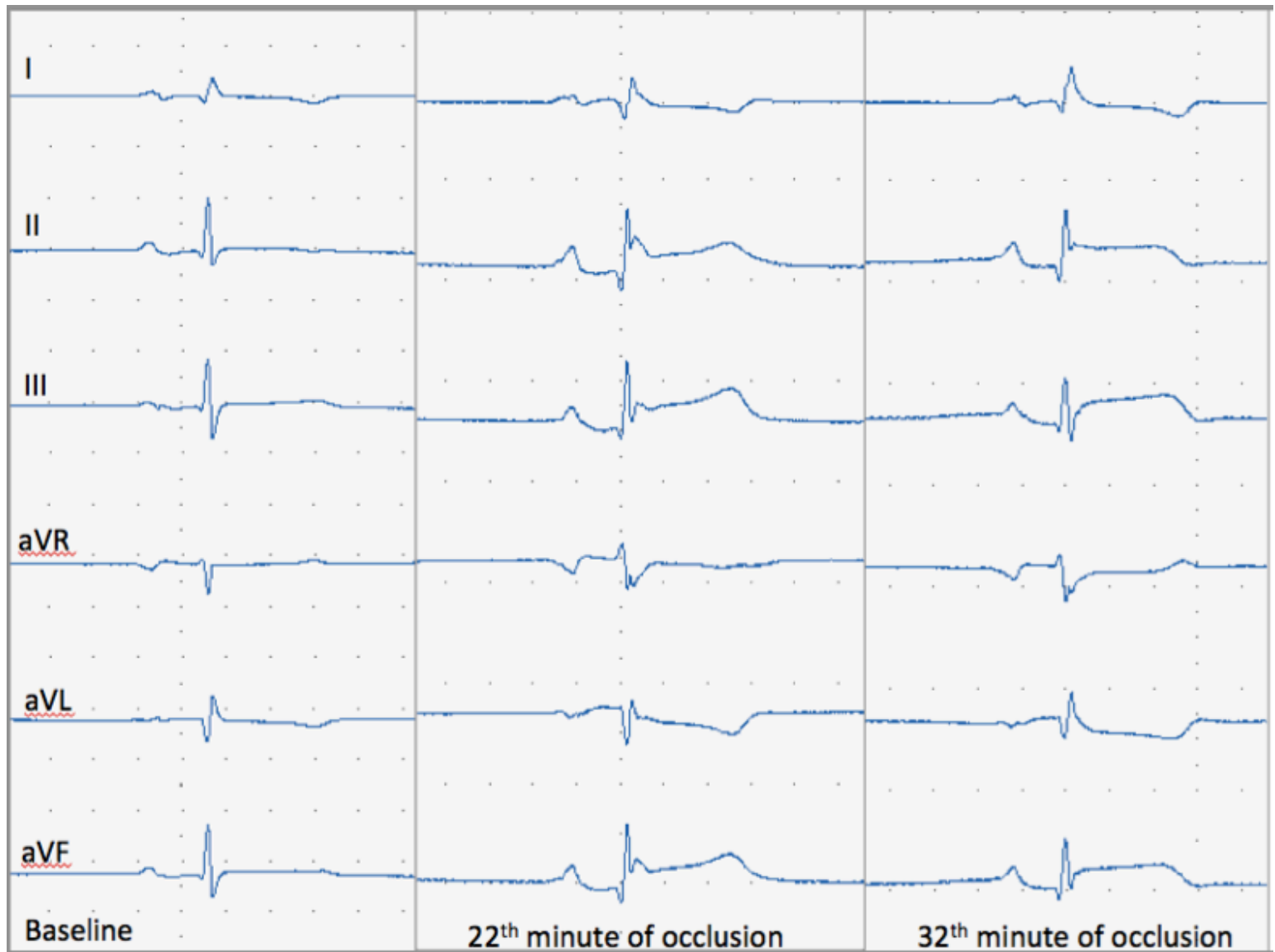




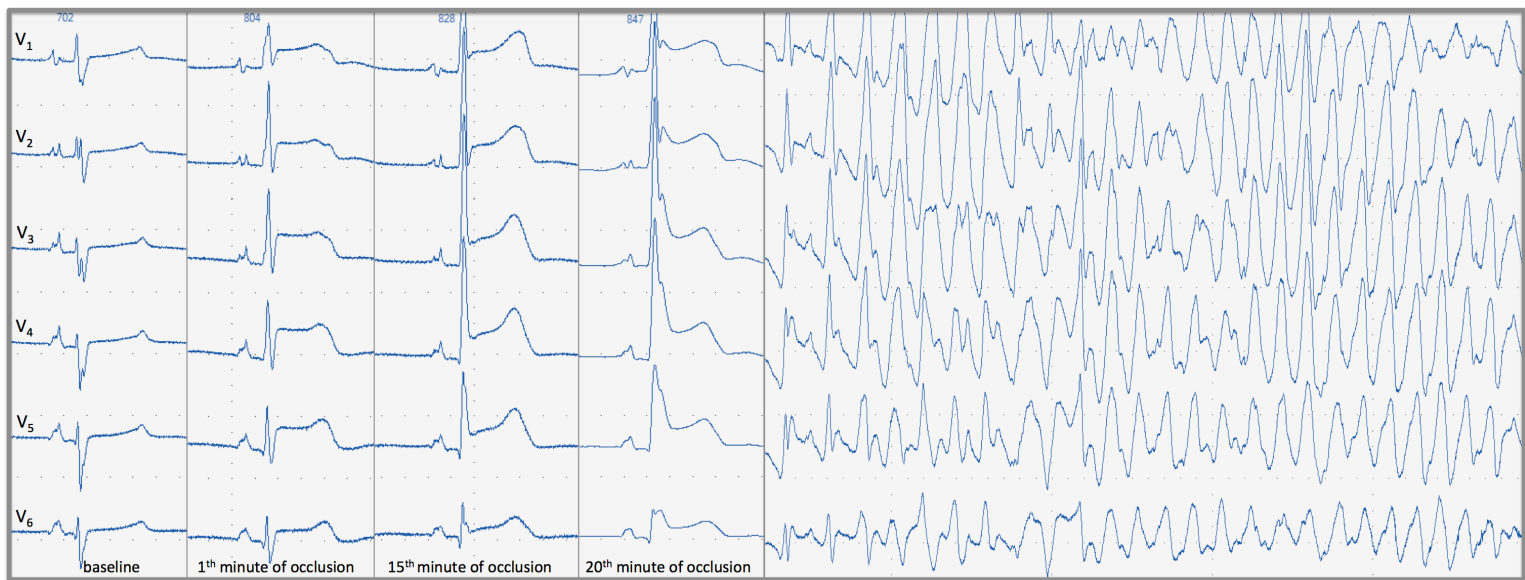












### ROC Curve $\Delta$ QRSd

