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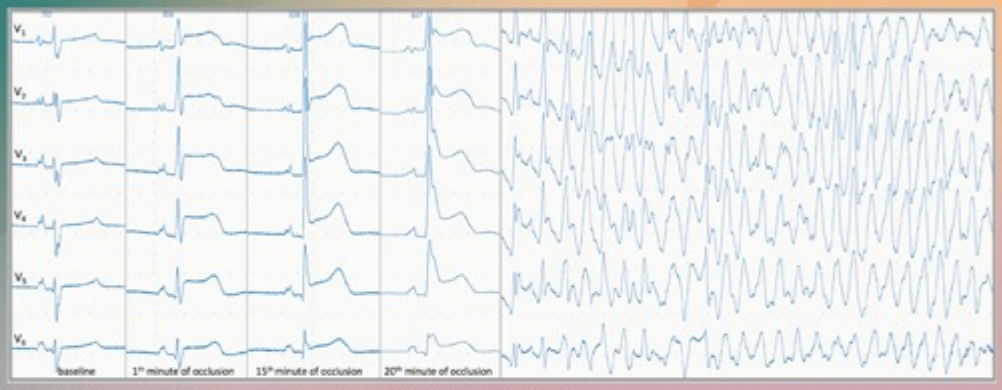
Volume 11, Issue 7, July 2014

HeartRhythm

THE OFFICIAL JOURNAL OF THE HEART RHYTHM SOCIETY

The Official Journal of the Cardiac Electrophysiology Society



Transient QRS widening and J-wave pattern predict impending VF in acute ischemia

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

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BACKGROUND Certain types of the early repolarization 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 To analyze whether QRS widening and appearance of a J-wave pattern in experimental MI settings is predictive of VF.

METHODS MI was induced in 32 pigs by 40-minute inflation of an angioplasty balloon in the left descending artery, and electrocardiogram 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. An association between QRS widening and subsequent VF was studied using receiver operating characteristic curve analysis. Electrocardiograms at maximum QRS duration were reviewed for the presence of a J-wave pattern.

RESULTS Sixteen animals had VF episodes during the occlusion period. Two peaks of QRS widening were found in all animals: the first peak immediately on left descending artery occlusion and the second peak 19.1 ± 4.0 minutes later. The magnitude of changes in the QRS width over time had significant interindividual differences. A QRS widening of ≥28 ms during a 3-minute time window was observed in 14 animals and predicted impending VF (selectivity 80%, specificity 73%, positive predictive value 57%, and negative predictive value 89%; $P = .008$). In 10 of 14 (71%) pigs, a J-wave pattern appeared at maximal QRS duration. The appearance of a J-wave pattern predicted VF with selectivity 80%, specificity 68%, positive predictive value 53%, and negative predictive value 88% ($P = .02$).

CONCLUSION Transient QRS widening, commonly associated with a 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.

KEYWORDS Myocardial infarction; Ventricular fibrillation; Early repolarization; QRS duration; J wave

ABBREVIATIONS **ECG** = electrocardiogram/electrocardiographic; **ER** = early repolarization; **LAD** = left descending artery; **MI** = myocardial infarction; **PPV** = positive predictive value; **NPV** = negative predictive value; **Se** = selectivity; **Sp** = specificity; **STEMI** = ST-segment elevation myocardial infarction; **VF** = ventricular fibrillation

(Heart Rhythm 2014;11:1195–1201)

Introduction

Malignant ventricular arrhythmias, particularly ventricular fibrillation (VF), remain an important contributor to mortality in ST-segment elevation myocardial infarction (STEMI).[1,2] The success of VF treatment is determined by time elapsed between the occurrence of VF and the administration of medical care. Therefore, the main strategy in relation to the life-threatening ventricular arrhythmias during STEMI 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

This study was supported by the Swedish Institute (research scholarship to Dr Demidova), by donation funds at Skåne University Hospital (to Dr Platonov and Dr Demidova) and the Swedish Heart-Lung Foundation (to Dr Platonov and Dr Demidova) by Ministerio de Economía y Competitividad, Spain, and Fondo Europeo de Desarrollo Regional, European Union, under projects TEC2010-21703-C03-02, TEC2013-42140, and by Aragon Government and European Social Fund through Grupo Consolidado BSICoS (Ms Martín-Yebra, Dr. Laguna and Dr. Martínez). **Address reprint requests and correspondence:** Dr Marina M. Demidova, Department of Cardiology, Lund University, 22185 Lund, Sweden. E-mail address: marina.m.demidova@gmail.com.

clinical characteristics[1,2,4] while data on dynamic electrocardiographic (ECG) changes that can predict VF are scarce.

The early repolarization (ER) pattern, including J-point elevation, distinct J wave with or without ST-segment elevation, or slurring of the terminal part of the QRS complex,[5] is generally found in healthy young male individuals and is considered to be a benign 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 an 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 the association of a 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 the experiment as a predictor of VF.

Methods

Experimental protocol

A porcine model of myocardial infarction (MI) was used in this work. The experimental preparation and study protocol have previously been described in detail.[18] In brief, in 38 pigs weighing 40–50 kg, anaesthetized with fentanyl and thiopental, an angioplasty balloon was positioned in the midportion of the left descending artery (LAD), immediately distal to the first diagonal branch. Ischemia was induced by inflation of an angioplasty balloon for 40 minutes, and 12-lead ECG monitoring ("Kardiotechnica-04-8m," INCART, St. Petersburg, Russia) was started before the occlusion and continued throughout the occlusion period. The ECG sampling rate was 1024 Hz, and the amplitude resolution was 1.4 μV. The 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 the 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

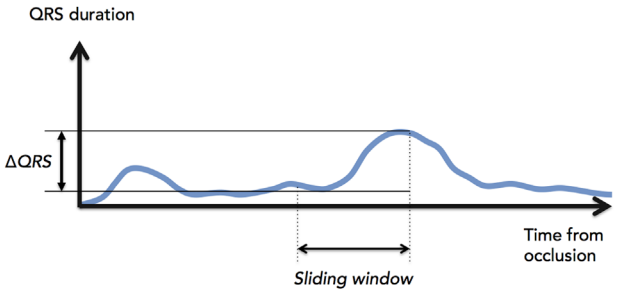

Figure 1 Schematic illustration showing the delta QRS duration in the sliding window during the occlusion period. In our study, the sliding window duration was 3 minutes.

(Figure 1). To quantify QRS widening, 2 indices were continuously assessed using a sliding window of 3-minute 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-minute window.[20]

ECGs for each pig at baseline and at the time of maximal QRS duration were independently reviewed for the presence of QRS complex notching or slurring (J-wave pattern)[21,22] in ≥ 2 contiguous leads by 2 investigators (P.G.P. and M.D.) who were 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 localization of the J-wave pattern as that present in either the inferior (leads II, III, and aVF), lateral (leads I, avL, and V_4–V_6), or anterior (leads V_1–V_3) leads. Anterior precordial leads reflecting the ischemic zone due to LAD occlusion were not excluded from the analysis.

Statistical analysis

Data are presented as mean ± SD or as median and interquartile range in cases of asymmetrical distribution. The Fisher exact test was used for comparisons between study groups.

Receiver operating characteristic curve analysis was used to identify the optimal cutoff of QRS duration increase for predicting VF during the occlusion period. Statistical significance was accepted at $P < .05$ (2-sided). 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, IL).

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 because of the poor-quality signal. Of the remaining

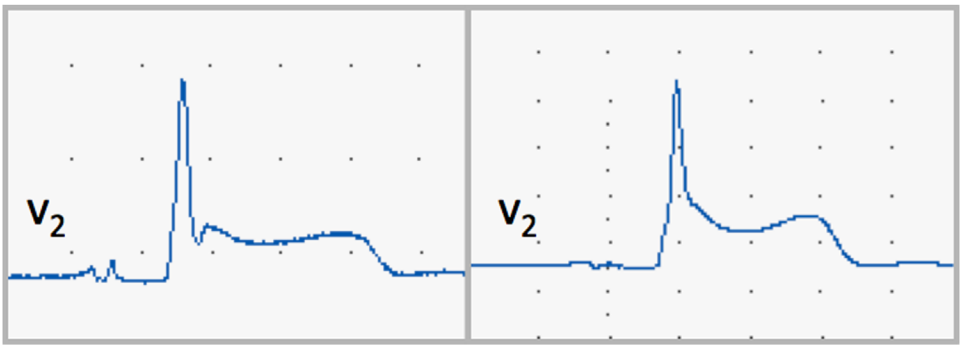

Figure 2 Electrocardiographic examples in lead V_2, illustrating different morphologies of the early repolarizations pattern. **A:** Notch is present in lead V_2. **B:** Slur is visible in lead V_2. ST-segment elevation due to ST-segment elevation myocardial infarction is shown in both panels A and B.

32 pigs, 6 pigs suffered from VF during the first minutes of occlusion, on average 2.6 ± 2.1 (range 0.6–7.0) minutes after occlusion start, and 10 pigs, on average 20.9 ± 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 15th minute of occlusion).

All the studied animals demonstrated similar dynamics of QRS duration changes characterized by the 2 peaks of QRS widening: the first peak immediately after LAD occlusion 3.7 ± 1.6 minutes and the second peak 19.1 ± 4.0 minutes after occlusion start (Figure 4). Significant interindividual differences were observed with regard to the magnitude of changes in QRS width. These differences varied from the negligible variation in QRS duration to pronounced QRS widening over short time measured as delta QRS duration over a 3-minute window. The value of QRS duration at baseline, at the first (0–10 minutes of the occlusion period) and the second (10–40 minutes of the occlusion period) peaks of QRS widening, and at the end of the occlusion period is shown in Figure 5. The QRS duration at baseline was 78 ± 11 ms, and at the first peak of QRS widening 140 ± 21 ms, and at the second peak −124 ± 17 ms ($P < .001$). The median difference between maximal QRS duration and QRS duration at baseline was 27 ms (interquartile range 16 ms).

At baseline, no animals demonstrated a J-wave pattern in any lead. At maximal QRS duration, a 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 widening and manifested at maximal QRS duration, with subsequent resolution during continued occlusion.

The J-wave pattern in anterior leads, which reflected the ischemic zone caused by LAD occlusion, was found in all 15 animals, which 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; 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.

The association between QRS widening and subsequent VF onset was studied using the receiver operating characteristic curve analysis. Two thresholds in delta QRS duration showing a reasonable combination of sensitivity and

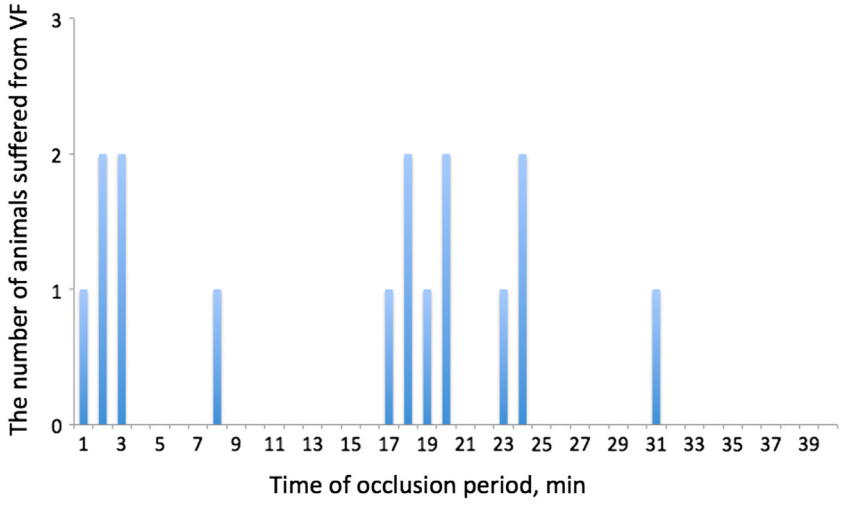

Figure 3 Time distribution of ventricular fibrillation (VF) episodes during coronary occlusion. Two distinct peaks of ventricular arrhythmia occurrence were observed and corresponded to phase 1a (<10 minutes) and 1b (>15 minutes).

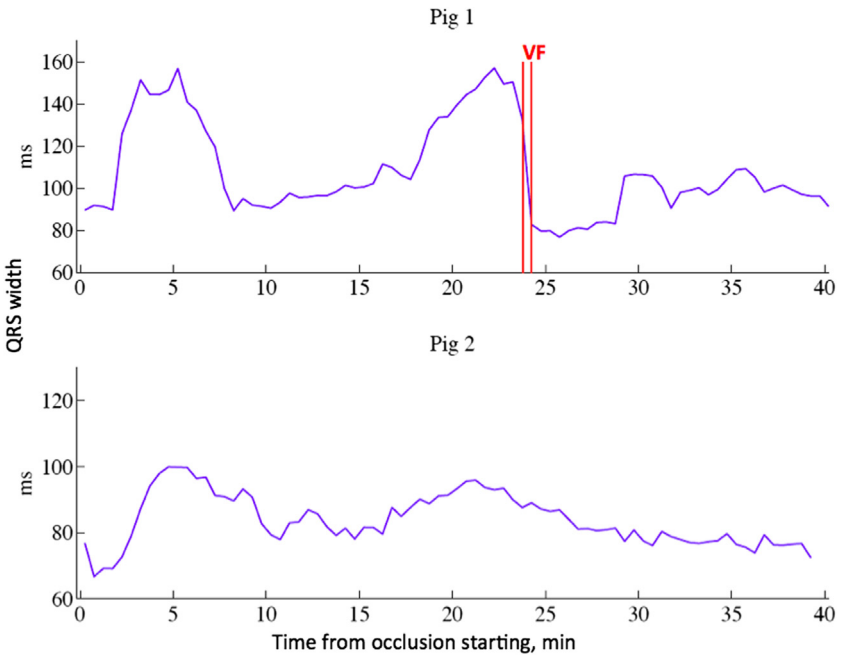

Figure 4 Dynamics of QRS width through 40-minute coronary occlusion. **A:**Marked QRS widening at 2–7 and 17–22 minutes in 1 pig with ventricular fibrillation at the 24th minute of occlusion. Vertical line shows the time of VF occurrence. **B:** Slight changes in QRS width in an animal without ventricular fibrillation.

specificity for VF prediction were 28 and 36 ms, respectively (Figure 8).

A QRS widening of ≥28 ms in 3 minutes predicted impending VF with selectivity (Se) 80%, specificity (Sp) 73%, positive predictive value (PPV) 57%, and negative predictive value (NPV) 89% ($P = .008$). A QRS widening of ≥36 ms in 3 minutes predicted impending VF with Se 70%, Sp 95%, PPV 88%, and NPV 88% ($P < .001$). Thus, marked and fast QRS widening predicted VF (OR 10.7, 95% CI 1.7–65.3, $P = .010$ for a QRS widening of ≥28 ms in 3 minutes; OR 49.0, 95% CI 4.4–550.7, $P = .002$ for a QRS widening of ≥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, $P = .180$ for a QRS widening of >120 ms). In the animals that developed VF, the arrhythmia occurred within 2.9 ± 3.8 minutes after reaching the maximal QRS duration.

A J-wave pattern was observed in 8 of 10 pigs that experienced VF and in 7 of 22 pigs without VF ($P = .02$). A J-wave pattern was found in all 7 animals with a QRS duration increase of ≥36 ms and in 10 of 14 animals with a QRS duration increase of ≥28 ms during a 3-minute window. The appearance of a J-wave pattern predicted VF with Se 80%, Sp 68%, PPV 53%, and NPV 88% ($P = .02$) and remained a significant VF predictor in logistic regression analysis (OR 8.6; 95% CI 1.4–51.4; $P = .020$).

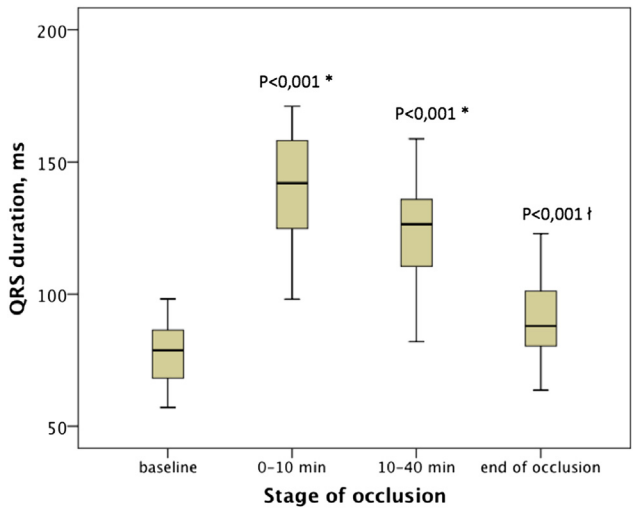

Figure 5 QRS duration at baseline and at the first and the second peak of QRS widening. $^{*}P < .001$ for comparison with the QRS duration at baseline; $^{\dagger}P < .001$ for comparison with the QRS duration at the first and the second peak of QRS widening.

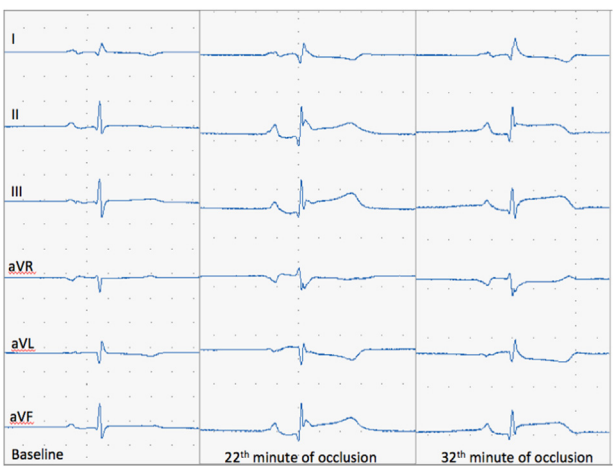

Figure 6 Appearance of a J-wave pattern in inferior leads (notch in leads II, III, and aVF) at the 22nd minute of occlusion followed by backward dynamics.

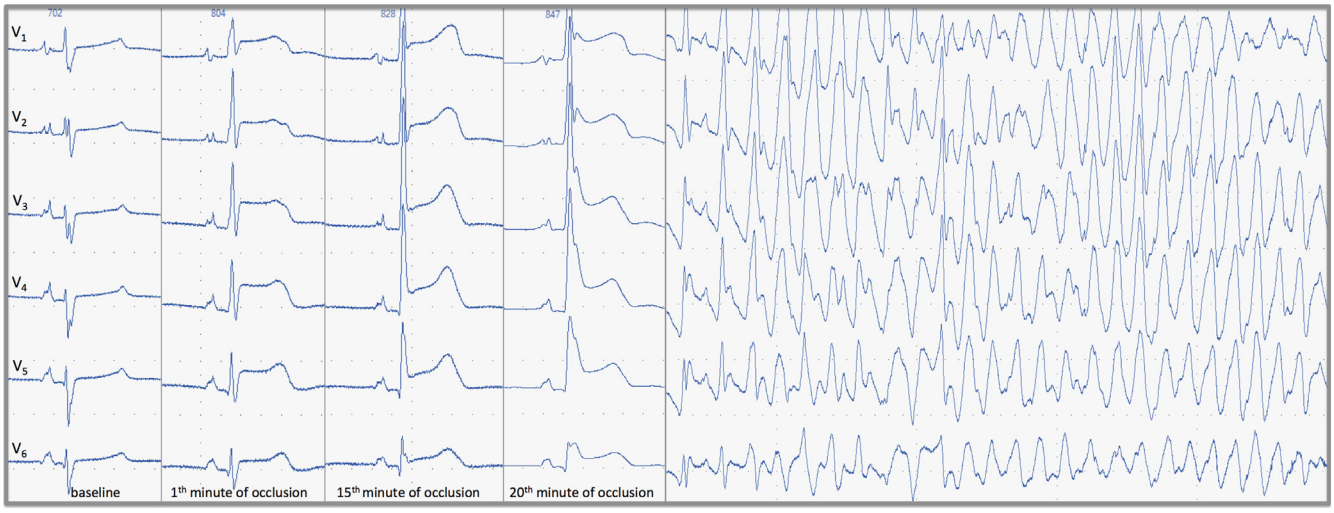

Figure 7 Appearance of a J-wave pattern in anterior leads at the 20th minute of occlusion immediately preceding a ventricular fibrillation episode.

VF occurred in 6 of 8 animals with a J-wave pattern in a combination of inferior and anterior leads and only in 2 of 7 animals with a J-wave pattern in isolated anterior leads and a combination of anterior and lateral leads (Se 75%, Sp 71%, PPV 75%, and NPV 29%; $P = .13$).

Discussion

J-wave pattern in STEMI

The association between a 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 a 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 before 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, that is, 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 (5th–7th day), that is, after the restoration of blood flow by primary percutaneous coronary interventions (PCI) and in the absence of acute ischemia.[17,26] To 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 the progression of acute ischemia and infarction.

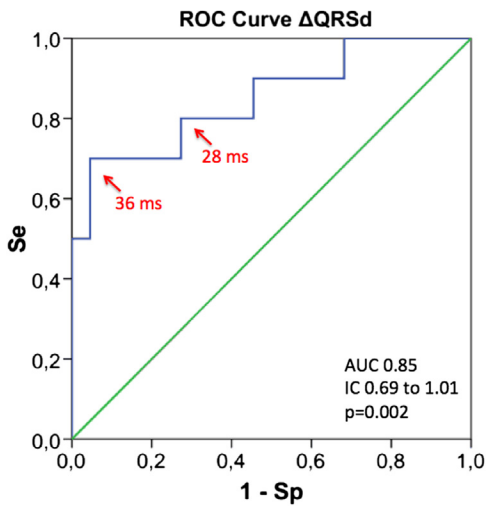

Figure 8 Receiver operating characteristic (ROC) curve analysis for the identification of optimal QRS duration increase cutoff for predicting ventricular fibrillation during the occlusion period. Significant points are marked. AUC = area of the curve; ΔQRSd = delta QRS duration; Se = sensitivity; Sp = specificity.

Ischemia-induced QRS widening and J-wave pattern

At baseline, the QRS complex was narrow without any signs of a J-wave pattern in any of the experimental animals. During the course of ischemia, QRS duration demonstrated dynamic behavior with 2 peaks of QRS widening. Shortening of QRS duration despite the uninterrupted LAD occlusion is in accordance with previously published experimental data.[28]

In order to avoid subjectivity in the 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 the QRS complex.[22] It is well known that the detection of QRS end in the settings of marked ST-segment 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 on the basis of the closed-chest

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

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

VF during experimental STEMI

Fifty percent 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 2 distinct periods of ischemia, which are defined as phase 1a (0–10 minutes from the induction of ischemia) and phase 1b (15–30 minutes of ischemia).[31,32]

Since phase 1a arrhythmias occurred almost immediately after LAD occlusion, the assessment of the steepness of QRS widening using a 3-minute window was not technically feasible. Nonetheless, upon measuring QRS duration, we found dynamic QRS widening to precede all early VF episodes: QRS duration immediately before VF was 122 ± 11 ms vs 79 ± 13 ms at baseline. QRS widening is unlikely to be due to conduction delay immediately after LAD occlusion.[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 a J-wave pattern was observed in all 6 pigs suffering from early VF.

In clinical settings, phase 1a arrhythmias usually occur long before the first contact with health-care professionals. Since the progression of MI in pigs is approximately 7 times faster than that in humans,[33] 20 minutes of coronary artery occlusion in the porcine model corresponds to approximately 2–2.5 hours of MI 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 a J-wave pattern predicted imminent VF.

Several previous studies have reported an increased risk of arrhythmic complications in patients with the inferior localization of a 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, a J-wave pattern in anterior leads was combined with slurring or notching in inferior leads. The presence of a J-wave pattern in both anterior and inferior leads was associated with a higher incidence of VF than did the presence of a 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-segment elevation due to acute MI, we have not measured J-point elevation and have not assessed the slope of ST segment, which has also been previously reported to have a predictive value for arrhythmic events.[9,14,27]

Conclusion

Rapid and marked transient increase in QRS duration commonly associated with a 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 MI.

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