

Journal Pre-proof



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PII: S1547-5271(20)30032-1

DOI: <https://doi.org/10.1016/j.hrthm.2020.01.019>

Reference: HRTM 8255

To appear in: *Heart Rhythm*

Received Date: 30 June 2019

Accepted Date: 15 January 2020

Please cite this article as: Stoller M, Boehler A, Bloch N, Seiler C, Heg D, Branca M, Roten L, Effect of Acute Myocardial Ischemia on Inferolateral Early Repolarization, *Heart Rhythm* (2020), doi: <https://doi.org/10.1016/j.hrthm.2020.01.019>.

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Effect of Acute Myocardial Ischemia on Inferolateral Early Repolarization

Running title: Myocardial Ischemia and Early Repolarization

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Word count: 4993

Funding: This work was supported by the Swiss National Science Foundation for research (grant #3200B_141030/1 to CS).

Disclosures: The authors have no conflicts of interest to declare.

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Abstract

Background: Inferolateral early repolarization (ER) is associated with an increase in arrhythmic risk, particularly in the presence of myocardial ischemia.

Objective: To determine the effect of myocardial ischemia on ER.

Methods: We retrospectively analyzed procedural ECGs of patients with ER undergoing a controlled, 1-minute coronary occlusion for collateral function testing. ECG leads with ER were analyzed before (PRE), at 60 seconds of coronary balloon occlusion (OCCL) and >30 seconds after balloon deflation (POST).

Results: Seventy-seven patients with ER in the pre-procedural ECG (86% inferior, 20% lateral) underwent 135 coronary balloon occlusions during which a J wave was recorded in 224 leads (ER leads). From PRE to OCCL, ST-segment amplitude (ST) in the ER lead increased in 94 (44%) cases from 0.00 ± 0.03 mV to 0.05 ± 0.06 mV ($p<0.0001$). In this group, J-wave amplitude (JWA) increased from 0.10 ± 0.07 mV to 0.13 ± 0.09 mV ($p<0.0001$). ST in the ER lead decreased or was unchanged in 121 cases (56%) from PRE to OCCL (0.01 ± 0.05 mV to -0.02 ± 0.04 mV; $p<0.0001$). In this group, JWA decreased from 0.10 ± 0.05 to 0.08 ± 0.07 mV ($p<0.0001$). The change in JWA was related to the change in ST (linear regression analysis; R squared=0.34; $p<0.0001$), while there was no relation between change in R-wave amplitude and change in ST (R squared=0.0003, $p=0.83$).

Conclusions: During acute ischemia, J-wave amplitude mirrors ST-segment changes. This may explain increased arrhythmic vulnerability of patients with ER during myocardial ischemia. It also adds weight to the hypothesis of ER being a phenomenon of repolarization.

Keywords: early repolarization; J wave; myocardial ischemia; ST-segment elevation; electrocardiography

Introduction

Inferolateral early repolarization (ER) is an electrocardiographic (ECG) pattern associated with an increased risk for ventricular fibrillation (VF).¹ However, given that the absolute increase in arrhythmic risk is generally low in patients without evident structural heart disease,² the role of additional proarrhythmic triggers has been discussed.³ In this context, the setting of acute myocardial ischemia has received particular attention.⁴⁻⁷ Case-control studies have demonstrated that ER is more common in victims of sudden cardiac death secondary to an acute coronary event⁴ and that a myocardial infarction is complicated more often by VF in patients with ER, especially in the very early phase.^{5,7}

Pathophysiologically, idiopathic VF episodes in patients with ER are typically preceded by augmentation of the J wave.^{8,9} Similarly, a greater magnitude of the J wave was associated with VF occurrence in patients with an acute MI.⁶ However, the influence of myocardial ischemia on the J wave in patients with ER has so far not been directly investigated.^{10,11}

Methods

Study population

From March 1996 to February 2015, all consecutive patients undergoing quantitative collateral function testing in the Department of Cardiology of the University Hospital in Bern, Switzerland, were screened (n=1458).^{12,13} All study patients were referred for elective coronary angiography for suspected or established stable coronary artery disease. Inclusion criterion was at least one 12-lead resting ECG showing inferolateral ER, as described in the consensus paper by Macfarlane and colleagues.¹⁴ Exclusion criteria were incomplete or complete bundle branch block and QRS duration ≥ 120 ms.

Coronary balloon occlusion and ECG recording

All patients underwent a one-minute coronary balloon occlusion of one or more of the three major coronary arteries: left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA). Simultaneously, a reduced set of ECG leads was recorded: 3-6 frontal ECG leads (I, II, III, aVR, aVL, aVF) and a (pseudo-)unipolar intracoronary ECG derived from the guide wire distal to the occluding coronary balloon catheter, as described previously.¹² All studies were approved by the ethics committee of the Kanton of Bern, Switzerland and all patients gave written, informed consent.

A 12-lead resting ECG was available before collateral function testing in 1238 patients (84.9%). The pattern of inferolateral ER, as described in the consensus paper by Macfarlane et al.,¹⁴ was present in 109 cases (8.8 %). Among these, an ECG of sufficient quality for further analysis was recorded during 102 coronary angiographies in 77 patients (70.6%) with inferolateral ER (Figure 1). A total of 135 balloon occlusions were performed during these procedures with analysis of 224 leads showing a J wave during balloon occlusion.

ECG analysis

Both 12-lead resting ECGs, as well as procedural ECGs were digitized at 300 dpi and analysed using a customized graphical user interface developed in MATLAB Release 2015a. If the procedural ECG had been recorded digitally, a representative QRS complex for analysis was created from an R-peak synchronized average of approximately 10 seconds.

For the ECG analysis of the ER pattern, we used the definitions and measurement recommendations as suggested in the consensus paper by MacFarlane.¹⁴ We assessed the presence of inferolateral ER in the inferior (II, III, aVF), high lateral (I, aVL) and lateral leads (V4-V6).

For each ECG lead with a J wave, we analysed the resting 12-lead ECG and the procedural ECG: we assessed the J-wave amplitude at the onset in case of slurring and at the peak in

case of notching. In the same leads, we additionally measured associated amplitudes of R wave, ST segment (at the QRS offset) and T wave. ST-segment slope was assessed at 100ms after the end of the J wave (interval M according to the consensus document).¹⁴ All amplitude measures were made with reference to the QRS onset. Additionally, we measured the following time intervals: RR, QT¹⁵ and Tpeak-Tend,¹⁶ with calculation of the QTc interval (by Bazett's formula and Karjalainen-Nomogram¹⁷).

Procedural ECGs were analysed at three timepoints: immediately before coronary balloon occlusion (PRE), at the end of the one minute coronary occlusion before release of the occluding balloon (OCCL), and >30 seconds after release of the coronary balloon occlusion (POST). Additionally, the intracoronary ECG was analysed at OCCL.

Statistical analysis

Continuous variables are presented as mean±standard deviation (SD) when normally distributed and as median [interquartile range], when non-normally distributed. Categorical variables are given as number (percentage). For group comparisons we used Fisher's exact test (categorical variables) and parametric or non-parametric tests, as appropriate (continuous variables).

To account for the unbalanced data, the procedural ECG variables were analysed with restricted maximum likelihood linear mixed models using the lme4 package in R (Version 3.4.2). Patient, ECG lead and measure were specified as nested random factors (random intercepts) to control for their associated intra-class correlation (repeated and dependent measures). Random slopes were chosen for each ECG variable, as justified by the data.

We used Kenward-Roger approximate F Tests for inference about the fixed effects, using the car package. For each ECG variable, we tested the fixed effects time (timepoint of measurement), ST-change group (ST-segment change from PRE to OCCL: no change/decrease or increase) and their interaction. In case of a significant effect, we

performed post-hoc pairwise comparisons of the estimated marginal means with false discovery rate (FDR) adjustment for multiple comparison.

To identify significant predictor variables, J-wave amplitude was analysed further with linear-mixed effects models. We started with a null model including only the intercept of the dependent variable J-wave amplitude. For the random-effects structure, we added patient, ECG lead and measure and chose a random slope for the measure after comparing goodness of fit using chi-square test on the log-likelihood values. We then further added predictor variables as fixed effects and interactions between predictor variables incrementally and compared goodness of fit of the models using chi-square tests on the log-likelihood values and Kenward-Roger approximate F Tests for inference about the fixed effects. The models included the maximal random effect structure justified by the data. Variables evaluated as predictors were time (timepoint of measurement), ECG lead, coronary vessel, ST-change group (no change/decrease or increase), ST-segment group at balloon occlusion (ST elevation or no ST elevation), RR interval, R-wave amplitude, J/R ratio before occlusion (J/R-ratio group: >0.5 or ≤ 0.5), predominant ST-segment slope (ascending or horizontal/descending) in the resting 12-lead ECG, predominant ER pattern (notched or slurred) in the resting 12-lead ECG, coronary artery disease and gender. Each variable was further evaluated for interactions with time, ST-change group and time \times ST-change group. Multicollinearity between predictors was checked using the variance inflation factor. We dropped predictor variables when the variance inflation factor exceeded 2.5.

Associations between the change of ECG parameters from PRE to OCCL were analysed using linear regression analysis with the lmer function, which allowed to account for the dependence of repeated measures within the same subject. We used the r.squaredGLMM function (MuMIn package v1.40.4) to calculate the marginal coefficients of determination (R-squared). Statistical significance was defined at a p-level ≤ 0.05 .

Results

Patients

Table 1 shows the clinical characteristics of all patients with a resting 12-lead ECG available before collateral function testing. Mean age was 62 years and the majority of patients had established CAD and were male. Patients in the two groups were similar, except for a higher body mass index and less use of platelet inhibitors (other than aspirin) in the group with inferolateral ER. Inferolateral ER was most prevalent in inferior leads (86%), followed by high lateral (15%) and lateral leads (5%). Except for nitrates use, there was no difference among patients with inferolateral ER and with a suitable procedural ECG for analysis compared to the patients without a suitable ECG (Supplemental Table 1).

Procedures

The 77 patients in the ER group with at least one analysable procedural ECG had a total of 102 exams (median 1 [1-2]) and underwent a total of 135 balloon occlusions (median 1 [1-2]), see Supplemental Table 2 for details). Most often, the LAD underwent balloon occlusion (70 cases), followed by the LCX (39 cases) and the RCA (26 cases). A total of 224 leads showing a J wave were analyzed during balloon occlusion: inferior leads were analysed most often (lead II, n=93; lead aVF, n=74; lead III, n=39), followed by high lateral leads (lead I, n=18; lead aVL, n=0). The intracoronary ECG lead was analysed in 85 of the 135 cases (63%).

Procedural ECG

At coronary occlusion, the intracoronary ECG showed ST elevation ≥ 0.1 mV in 89% of cases, consistent with the presence of myocardial ischemia induced by coronary balloon occlusion.¹⁸ The limb leads showed ischemic ST-segment changes during coronary occlusion in a vessel-specific manner (interaction between vessel, time and lead: $p=0.005$,

Supplemental Figure 1).

Over the three timepoints, the procedural ECG measures did not show significant differences (Supplemental Table 3), except for T-wave amplitude ($p=0.001$). However, when further grouped by ST-segment change from PRE to OCCL (no change/decrease or increase), several ECG parameters showed significant differences over time (significant interaction of ST-change group \times time). Figures 2 and 3 show the procedural ECG measurements grouped by time and ST-segment change. Stratified by ST-segment change, there were significant differences over time for J-wave amplitude, T-wave amplitude, the QT intervals (all $p<0.0001$) and Tpeak-Tend ($p=0.01$). Conversely, R-wave amplitude ($p=0.16$) and RR interval ($p=0.17$) were not different over time, when stratified by ST-change group.

From PRE to OCCL, ST amplitude in the ER lead increased in 94 (44%) cases from 0.00 ± 0.03 mV to 0.05 ± 0.06 mV ($p<0.0001$). In this group, J-wave amplitude increased from 0.10 ± 0.07 mV to 0.13 ± 0.09 mV ($p<0.0001$). ST amplitude in the ER lead decreased or was unchanged in 121 cases (56%) from PRE to OCCL (0.01 ± 0.05 mV to -0.02 ± 0.04 mV; $p<0.0001$). In this group, J-wave amplitude decreased from 0.10 ± 0.05 to 0.08 ± 0.07 mV ($p<0.0001$). Figures 4 and 5 show representative examples for the J-wave behaviour seen in reaction to ST change.

In leads where ST amplitude increased from PRE to OCCL, T-wave amplitude ($p<0.0001$) and Tpeak-Tend interval increased ($p=0.003$) and QT intervals decreased from PRE to OCCL (QT $p=0.0076$, QTc Bazett $p=0.035$, QTc Nomogram $p=0.025$). On the other hand, these parameters remained unchanged when ST amplitude decreased during coronary occlusion (all $p>0.1$).

Predictors of J-wave amplitude

We analysed J-wave amplitude further in linear mixed models to determine predictive variables. Table 2 shows the results for the final model. For all models, the behaviour of J-

wave amplitude over the timepoints was modulated by ST-change group (significant interaction time \times ST-change group, Supplemental Figure 2, panel B). From PRE to OCCL, J-wave amplitude decreased with negative or no ST change and increased with positive ST change. Importantly, this behaviour was not modulated by additional variables, such as coronary vessel, gender, J/R-ratio group, ST-segment slope, ER pattern or CAD (Supplemental Figure 2, right-hand panels).

J-wave amplitude was not influenced by ST-change group, ST-segment slope, gender, ER pattern, CAD, or coronary vessel (Supplemental Figure 2, left panels). The group with J/R ratio >0.5 showed higher J-wave amplitude than the group with J/R ratio ≤ 0.5 ($p < 0.0001$, Supplemental Figure 2, Panel C). Similarly, higher R-wave amplitude predicted higher J-wave amplitude ($p < 0.0001$, Table 2 and Supplemental Figure 3).

Over time, only J/R-ratio group and coronary vessel modulated behaviour of the J-wave amplitude, apart from the aforementioned ST-change group (Supplemental Figure 2, middle panels).

Change in ECG parameters during coronary balloon occlusion

Figure 6 shows the associations of the change from PRE to OCCL in J-wave amplitude, R-wave amplitude and T-wave amplitude with the change in ST segment. The change in J-wave amplitude was linearly related to the change in ST-segment amplitude ($p < 0.0001$, R-squared=0.34). Similarly, the change in T-wave amplitude was linearly related to the change in ST-segment amplitude ($p < 0.0001$, R-squared=0.52). Conversely, no association was found between the change in R-wave amplitude and the ST-segment change ($p = 0.83$, R-squared=0.0003).

Discussion

Major findings

On the whole, this retrospective study provides insight into the effect of controlled, early myocardial ischemia on the early repolarization pattern compared to conventional ECG parameters in an elderly, predominantly male patient population with coronary artery disease. In essence, we found that during myocardial ischemia the J wave behaved similarly to ECG parameters of repolarization: J-wave amplitude increased in leads showing an ST-segment elevation and decreased in leads with ST-segment depression. Therefore, J-wave amplitude is augmented in leads facing the ischemic territory.

Generally speaking, we observed that ECG parameters of depolarization remained unchanged during early myocardial ischemia: R-wave amplitude did not change during brief coronary occlusion and was unrelated to the change of the conventional ECG parameter of ischemia, the ST segment. In contrast, ECG parameters of repolarization were significantly altered during coronary occlusion: ST segment and T wave changed in a lead-vessel specific manner, predominantly showing ST depression (with flattening/inversion of T waves) in leads remote to the ischemic territory and ST elevation (and hyperacute T waves) in leads directly interrogating the ischemic region.

Mechanisms of J-wave formation

Some controversy exists regarding the mechanism of J-wave formation in ER. Indeed, some authors advocate the use of the descriptive term “J-wave syndrome” to avoid a mechanistic attribution as a phenomenon of repolarization,^{19,20} while others support the term.^{21,22} By and large, two main mechanisms have been proposed to explain the formation of J waves: increased dispersion of repolarization or delayed fragmented depolarization.²³ The temporal association of the J wave with the early repolarization phase (phase 1) of the typical ventricular action potential makes it tempting to attribute the J wave to the same mechanism.

Then again, the precise mechanism underlying this waveform has not yet been elucidated, as several changes in the action potential can manifest as a J wave on the surface ECG.²⁴ On balance, the behaviour of the J wave in parallel to ECG phenomena of repolarization (ST segment, T wave), as shown in this study, is consistent with, but not proof for the repolarization theory.²⁴

Role of additional proarrhythmic triggers

Traditionally, ER had been considered a benign ECG variant until the seminal study by Haissaguerre in 2008, which associated it with idiopathic ventricular fibrillation.²⁵ Even earlier, in 2000, Gussak and Antzelevitch advanced experimental data in support of a malignant arrhythmic association with ER.²⁶ By the same token, a significant signal for arrhythmia risk has also been demonstrated in later studies.^{1,2,27} Nevertheless, the generally modest absolute risk increase for a fatal arrhythmia by isolated ER has highlighted the role for additional proarrhythmic triggers.³ As a proarrhythmic factor, myocardial ischemia has received particular attention in this context. Consequently, several studies have demonstrated that ER independently multiplies the already sizeable risk for malignant arrhythmias during acute myocardial ischemia.⁴⁻⁷

Notably, greater magnitude of the J wave in ER has repeatedly been shown to be associated with greater arrhythmia risk,^{1,28} also during myocardial ischemia.⁶ In like manner, an augmentation of the J wave has been observed to precede the onset of ventricular fibrillation in patients with ER.⁸ Finally, electrophysiologic mechanisms implicated in ER have also been shown to facilitate arrhythmogenesis in experimental early myocardial ischemia.²⁹ In this regard, a prominent role has been discussed for potassium currents in both ER and ischemia-related arrhythmias.²⁹⁻³¹

Correspondingly, this study shows an augmentation of J-wave amplitude in leads facing the ischemic region. Altogether, this may provide a mechanistic explanation for the increased arrhythmic risk during myocardial ischemia in ER.

Early repolarization versus fragmented QRS

ER pattern and fragmented QRS share the common ECG characteristic of QRS notching, which can make it difficult to distinguish between them. Specifically, fragmented QRS is often a sign for myocardial scar in patients with structural heart disease and predicts arrhythmic events and mortality in patients with both ischemic and non-ischemic cardiomyopathy.³² In a patient population with CAD, the overlap between ER and fragmented QRS can therefore prove problematic, as any arrhythmic risk could erroneously be attributed to ER or fragmented QRS, respectively. In this context, the recent consensus paper by Macfarlane attempts to separate the two entities by stipulating an arbitrary threshold of a notch or a slur having to occur on the final 50% of the downslope of an R wave in ER. In this study, J-wave amplitude was higher when J/R ratio >0.5 than when J/R ratio was ≤ 0.5 . However, the important observation of J-wave behaviour mirroring ST-segment change was not modulated by J/R-ratio group (>0.5 vs ≤ 0.5).

Study strengths and limitations

This study was retrospective, with the inherent risk of selection bias. The retrospective nature also precluded an assessment of the arrhythmic or mortality risk. The protocol regarding ECG recordings during coronary balloon occlusion was not homogeneous during the study program, limiting ECG assessment in some patients and responsible for dropouts in a significant number of study candidates.

The brevity of coronary occlusion precluded an assessment of arrhythmia induction, which would, however, be ethically questionable. As a further limitation, lateral ECG leads (V4, V5 and V6) were not recorded periprocedurally, such that ER could not be analysed in these leads.

Conclusions

During early, acute myocardial ischemia J-wave amplitude augments in leads with ST elevation, whereas J-wave amplitude decreases in leads with ST depression, thus mirroring ST behavior. This finding presents a possible mechanistic link between ER and an increased arrhythmic risk in acute ischemia. It also adds weight to the hypothesis of ER being a phenomenon of repolarization.

Acknowledgements

We thank Mirko Bristle, MSc for assistance with statistical analysis.

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Tables

Table 1

Patient characteristics, grouped by availability of resting 12-lead ECG and by presence of early repolarization.

Factor	ECG available		
	ER no	ER yes	p
n	1129	109	
Age (years)	62.09 (10.82)	62.36 (10.34)	0.805
Male	852 (75.5)	91 (83.5)	0.061
BMI	27.40 (4.57)	28.33 (4.39)	0.044
CAD	923 (82.5)	97 (89.0)	0.107
Current Smoker	375 (33.9)	32 (29.4)	0.395
Hypertension	666 (60.1)	72 (66.7)	0.215
Dyslipidemia	688 (62.4)	78 (71.6)	0.061
Diabetes	192 (17.3)	28 (25.7)	0.036
Family history of CAD	381 (35.0)	34 (31.5)	0.525
Prior MI	247 (23.1)	30 (27.5)	0.288
Diseased vessels			0.375
none	196 (17.5)	12 (11.0)	
one	329 (29.4)	35 (32.1)	
two	362 (32.4)	38 (34.9)	
three	232 (20.7)	24 (22.0)	
Aspirin	858 (77.6)	93 (85.3)	0.068
Platelet inhibitor	184 (27.6)	20 (18.5)	0.046
Beta blocker	637 (57.3)	64 (58.7)	0.839
Calcium antagonist	168 (15.4)	17 (15.6)	1
ACE inhibitor/ARB	488 (44.1)	46 (42.2)	0.762
Diuretic	230 (20.8)	20 (18.3)	0.620
Nitrate	258 (23.3)	26 (23.9)	0.906
Statin	596 (53.7)	64 (58.7)	0.365
Heart rate (bpm)	71.2 (13.0)	70.1 (11.9)	0.422
LVEF (%)	62.3 (10.7)	62.7 (9.4)	0.714
Location of ER	-		-
Inferior ER		94 (86.2)	
Lateral ER		5 (4.6)	
High lateral ER		16 (14.7)	

Data given as mean (SD) or n (%). ARB = Angiotensin Receptor Blocker, bpm = beats per minute, CAD = coronary artery disease, ER = early repolarization, LVEF = left ventricular ejection fraction, MI = myocardial infarction.

Table 2

Final mixed model analysis on predictors of J-wave amplitude

Factor	Estimate (SE)	df	F	p
Constant	0.0531 (0.0076)			
Coronary vessel occluded		2	1.6319	0.20
LAD	Reference			
LCX	-0.0075 (0.0054)			
RCA	-0.0113 (0.0053)			
Time	0.0039 (0.0031)	2	1.7185	0.18
R-wave amplitude	0.1989 (0.0137)	1	201.8119	<0.0001
J/R-ratio group		1	70.2207	<0.0001
J/R-ratio \leq 0.5	Reference			
J/R-ratio $>$ 0.5	-0.0272 (0.0033)			
ST-change group	-0.0007 (0.0030)	1	2.5459	0.11
Coronary vessel \times time		4	3.0772	0.018
LAD \times time	Reference			
LCX \times time	-0.0042 (0.0037)			
RCA \times time	-0.0038 (0.0041)			
ST-change group \times time		2	8.8672	0.0002
without ST increase* \times time	Reference			
with ST increase* \times time	-0.0006 (0.0022)			
J/R-ratio group \times time		2	3.4158	0.035
J/R-ratio group \leq 0.5 \times time	Reference			
J/R-ratio group $>$ 0.5 \times time	0.0012 (0.0019)			

* from PRE to OCCL

LAD = left anterior descending artery, LCX = left circumflex artery, OCCL = at end of coronary occlusion, PRE = before coronary occlusion, RCA = right coronary artery, SE = standard error.

Figures

Figure 1 Flowchart of the study population.

ER = early repolarization.

Figure 2 Procedural ECG amplitudes grouped by ST-segment change at coronary occlusion.

Boxplots and individual data points for ECG amplitudes. Post-hoc pair-wise comparisons are given for ECG variables with significant differences over time by ST-change group.

Pre = before coronary occlusion, Occl = at end of coronary occlusion, Post = after release of coronary occlusion, LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery.

Figure 3 Procedural ECG intervals grouped by ST-segment change at coronary occlusion.

Boxplots and individual data points for ECG intervals. Post-hoc pair-wise comparisons are given for ECG variables with significant differences over time by ST-change group.

PRE = before coronary occlusion, OCCL = at end of coronary occlusion, POST = after release of coronary occlusion.

Figure 4 Evolution of J wave in ECG leads facing myocardial ischemia.

Peripheral ECG leads with inferior ER pattern, before (PRE), at the end of 1 minute of RCA occlusion (OCCL) and after release of RCA occlusion (POST). During RCA occlusion, leads II and aVF show an increase in J-wave amplitude with ST-segment elevation, with reciprocal ST-segment changes in leads I and aVL. Paper speed 25mm/sec (panel A), 10mm/sec (panel B).

RCA = right coronary artery.

Figure 5 Evolution of J wave in remote ECG leads during myocardial ischemia

Peripheral ECG leads with inferior ER pattern, before (left figures), at the end of 1 minute of coronary occlusion (middle figures) and after release of coronary occlusion (right figures). During coronary occlusion, leads II, III and aVF show a decrease in J-wave amplitude with ST-segment depression. ST-segment elevation is observed in leads I and aVL. LAD occlusion in panel A, LCX occlusion in panel B (different patients).

LAD = left anterior descending artery, LCX = left circumflex artery.

Figure 6 Associations between procedural ECG variables.

Changes (OCCL minus PRE) in ST amplitude vs J-wave amplitude (left panel), R-wave amplitude (middle panel) and T-wave amplitude (right panel). Regression lines (dashed lines) derived from linear regression.

PRE = before coronary occlusion, OCCL = at end of coronary occlusion.

Figure 1

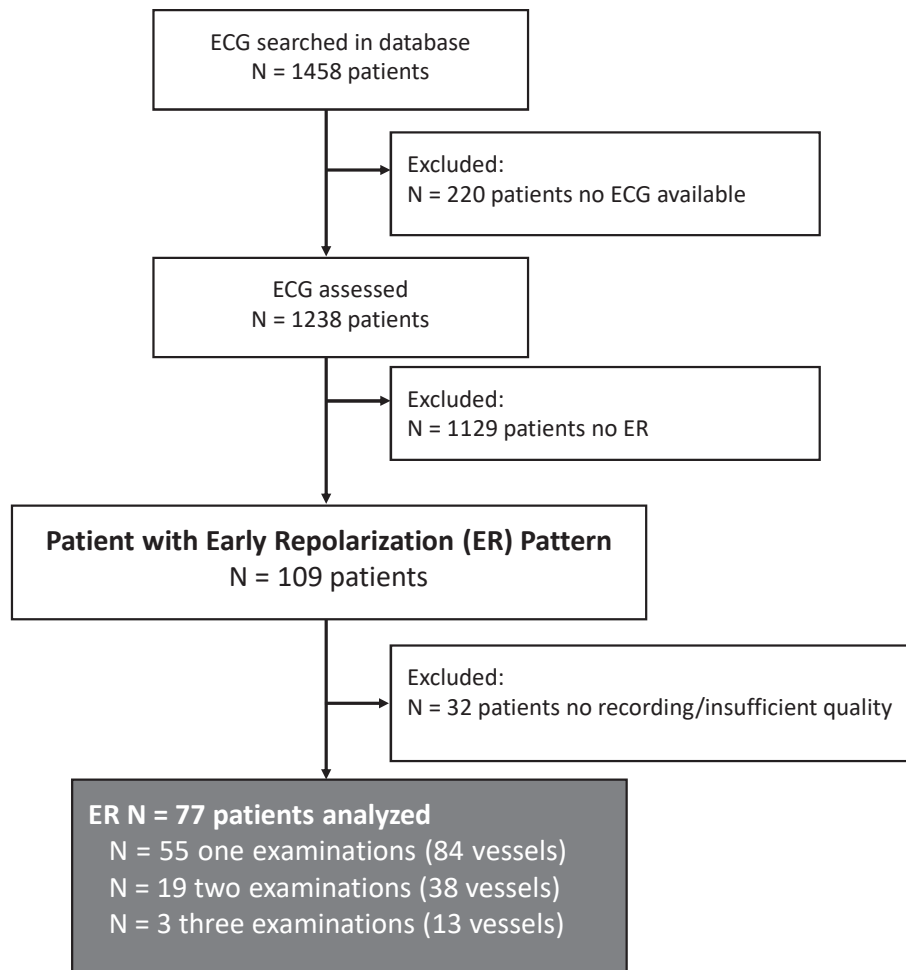


Figure 2

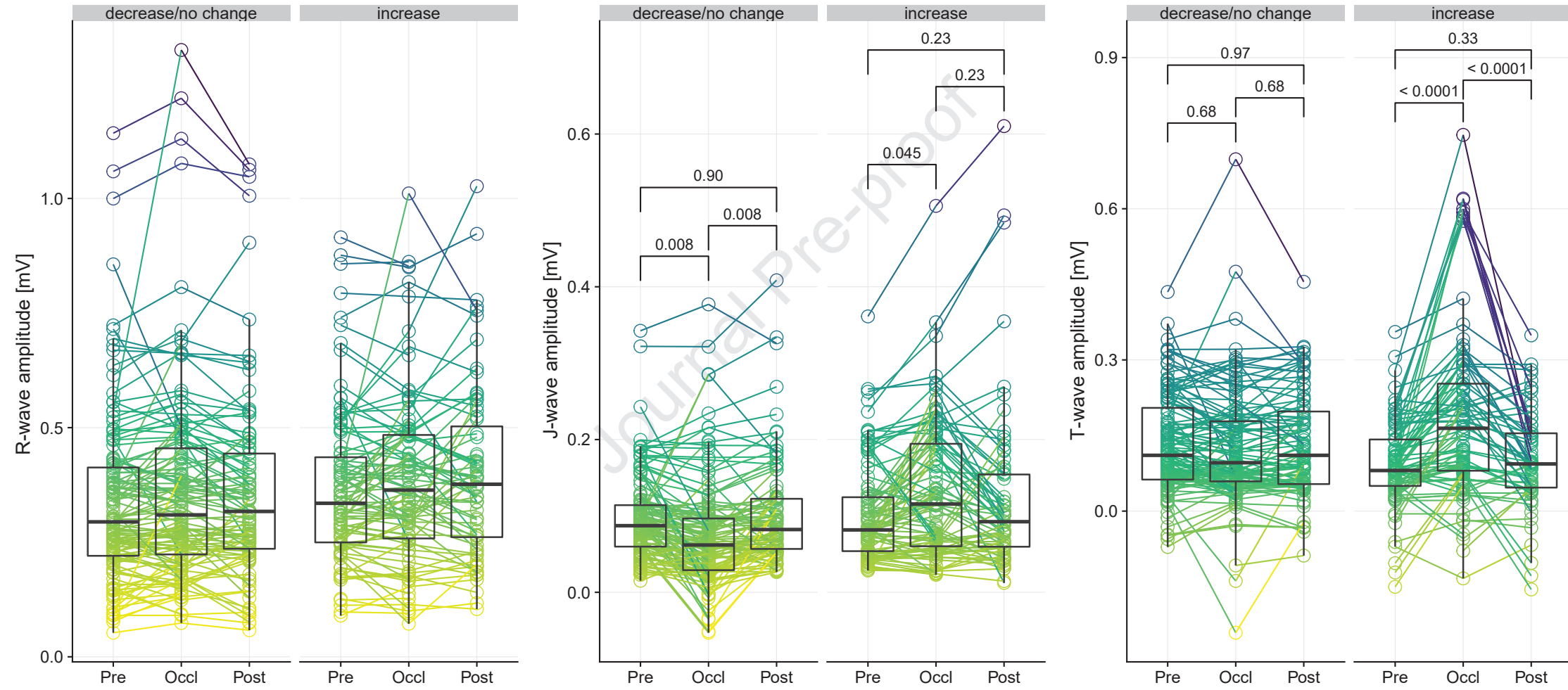
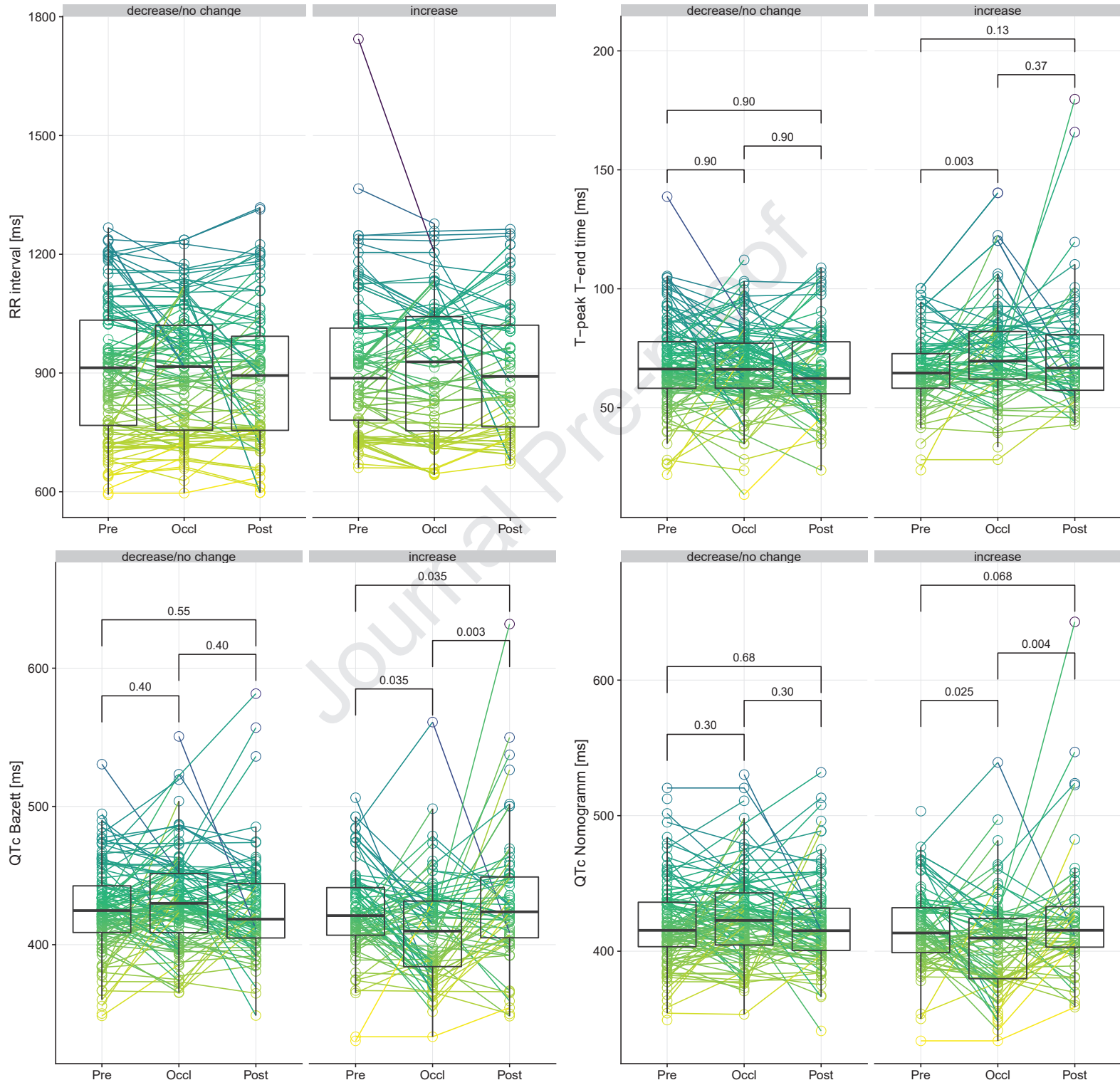
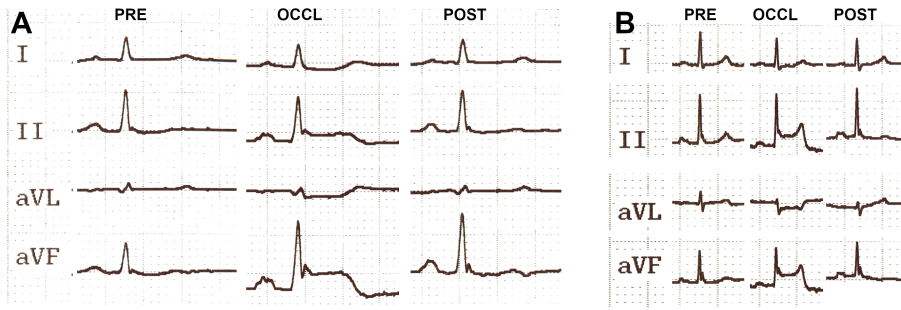


Figure 3

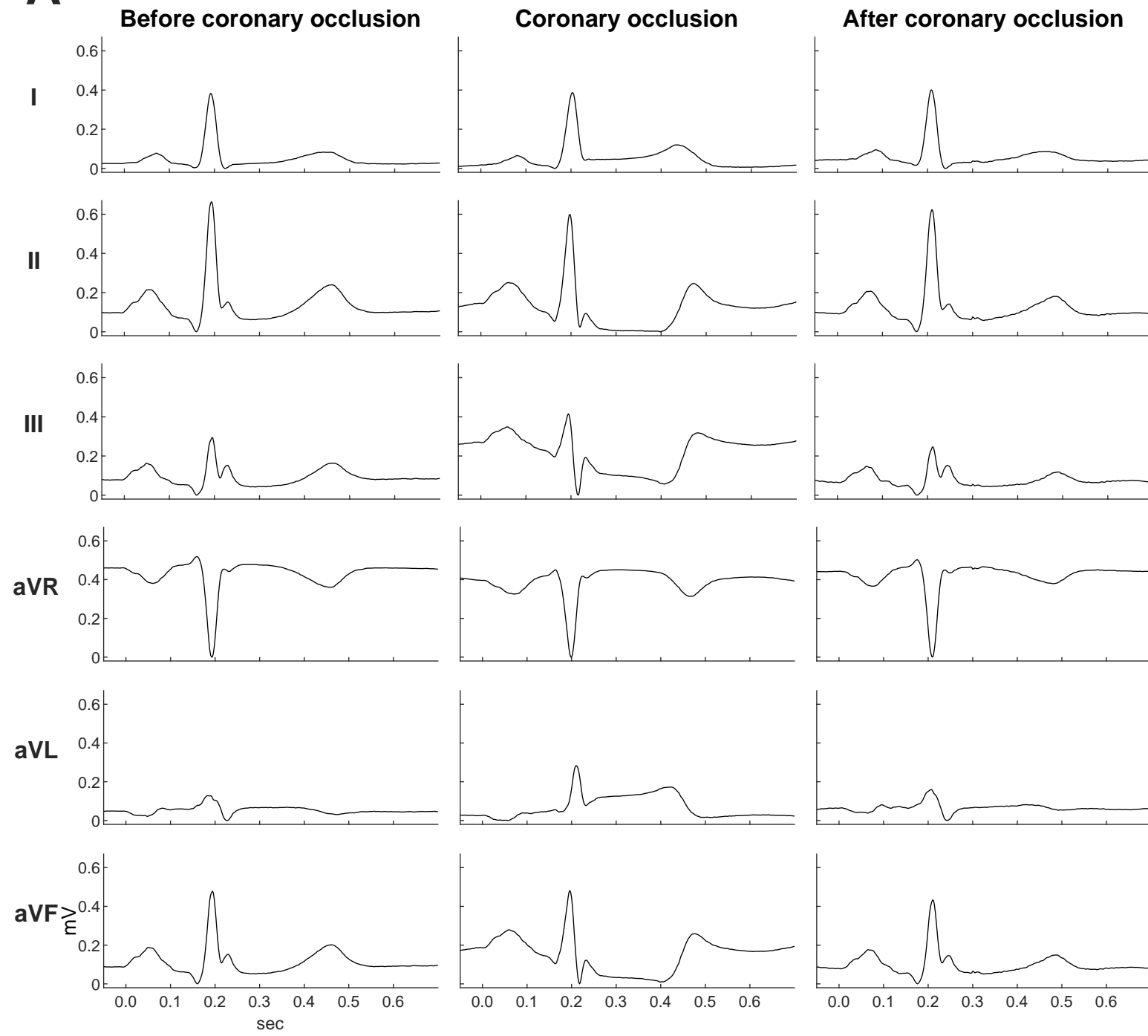




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Figure 5

A



B

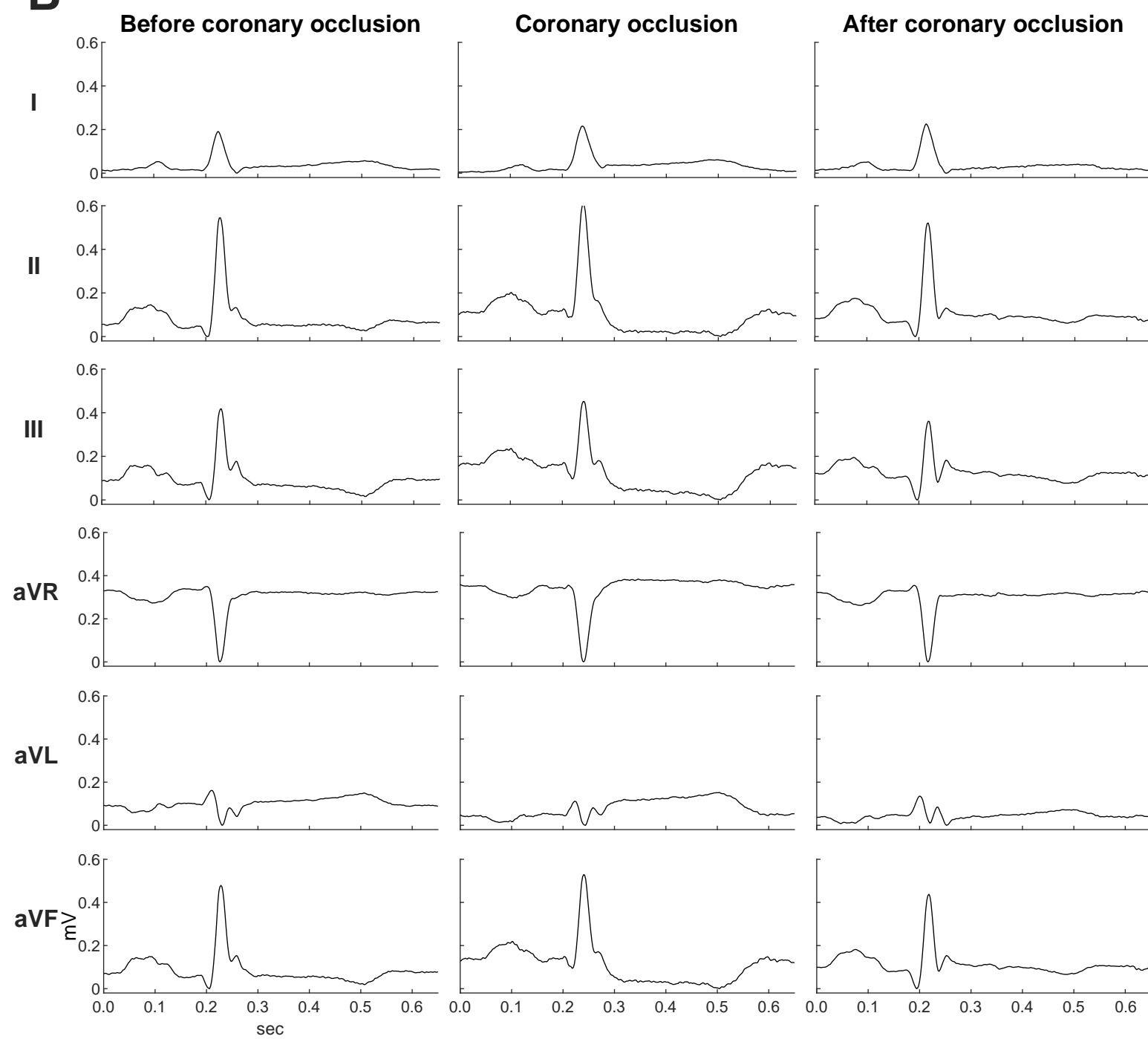


Figure 6

