Early Repolarization Associated With Ventricular Arrhythmias in Patients With Chronic Coronary Artery Disease

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Background—Early repolarization, indicated on the standard 12-lead ECG, has recently been associated with idiopathic ventricular fibrillation in patients without structural heart disease. It is unknown whether there is an association between early repolarization and ventricular arrhythmias in the coronary artery disease (CAD) population.

Methods and Results—Patients with CAD with implantable cardioverter-defibrillators in the healed phase of myocardial infarction were analyzed. In a case-control design, 60 patients who had ventricular arrhythmic events were matched for age and sex with 60 control subjects. ECGs were analyzed for early repolarization, defined as notching or slurring morphology of the terminal QRS complex or J-point elevation >0.1 mV above baseline in at least 2 lateral or inferior leads. Results were adjusted for left ventricular ejection fraction. Overall, early repolarization in 2 or more leads was more common in cases than control subjects (32% versus 8%, \( P \leq 0.005 \)). Early repolarization was noted more commonly in inferior leads (23% versus 8%, \( P = 0.03 \)), and a trend was noted in leads V4 through V6 (12% versus 3%, \( P = 0.11 \)). Early repolarization was uncommon in leads I and aVL in cases and control subjects (3% versus 0%). Notching was more common in cases than control subjects (28% versus 7%, \( P = 0.008 \)). Slurring and J-point elevation were not associated with ventricular arrhythmias.

Conclusions—Early repolarization and, in particular, notching in the inferior leads is associated with increased risk of life-threatening ventricular arrhythmias in patients with CAD, even after adjustment for left ventricular ejection fraction. Our findings suggest early repolarization, and a notching morphology should be considered in a risk prediction model for arrhythmias in patients with CAD. (Circ Arrhythm Electrophysiol. 2010;3:489-495.)

Key Words: coronary disease ■ electrocardiography ■ arrhythmia ■ tachycardia ■ fibrillation

Patients with coronary artery disease (CAD) are at an increased risk for ventricular tachyarrhythmia (VTA) and sudden cardiac death (SCD).\(^1\) Left ventricular ejection fraction (LVEF) \( \leq 35\% \) in CAD patients is commonly used to assess arrhythmia risk.\(^5,7\) However, studies have shown that low LVEF alone is not a specific predictor of SCD in the CAD population.\(^8,11\) As a result, several other noninvasive measures have been implicated as risk factors for ventricular tachycardia (VT) and ventricular fibrillation (VF) in this high-risk population, including T-wave alternans, heart rate variability, and heart rate turbulence.\(^11,17\)

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Early repolarization, often manifested as notching and slurring morphology of the QRS complex or J-point elevation on the standard 12-lead ECG, has commonly been regarded as a benign finding because it is associated with young, healthy individuals without structural heart disease.\(^18\) Although considered innocuous, the potential role of early repolarization in arrhythmogenicity has been suggested in experimental studies.\(^19\) In addition, several recent studies have shown that early repolarization, in the inferior and lateral leads of the standard 12-lead ECG, is associated with idiopathic VF in otherwise healthy patients.\(^20-24\)

In the report by Haissaguerre et al,\(^21\) early repolarization was characterized by J-point elevation (at the QRS-ST junction), or a morphological finding of slurring or notching of the terminal portion of the QRS complex. However, no distinction was made among these morphological patterns in terms of their predictive value for ventricular arrhythmia events. There are no studies that assess the association between VTAs and early repolarization in patients with structural...
heart disease. Because CAD patients are at higher risk for VTAs, we performed a case-control study to determine whether early repolarization—characterized by notching, slurring, or J-point elevation—is associated with life-threatening VTAs in CAD patients with implantable cardioverter-defibrillators (ICDs) who were in the healed phase of myocardial infarction (MI).

**Methods**

**Patient Population**

This was a case-control study that matched patients with CAD and ICDs who had sustained arrhythmic events (cases) to a control group who had CAD and ICDs but did not have sustained arrhythmic events. The study population was chosen from 2 databases of patients with CAD and ICDs from Northwestern Memorial Hospital (NMH) and Tufts Medical Center (TMC). The patient database at NMH consisted of 749 subjects, and the database from TMC was composed of 2734 subjects. Patients were included in the study on the basis of presence of CAD and prior MI. Criteria for the diagnosis of CAD were a positive exercise stress test or angiography (82%, n = 49) captured before the time of the ICD shock. Thus, the median time at which control ECGs were recorded was 12 months (IQR, 0 to 36 months) after ICD implant dates. Twelve-lead ECGs from NMH were digitally downloaded from the GE Marquette MUSE system (GE Medical Systems, Milwaukee, Wis). Twelve-lead ECGs from TMC were downloaded from the Philips TraceMaster ECG system (Philips Medical System, Andover, Mass). The digital ECGs from each system were analyzed off-line using custom-designed software developed using MATLAB (Mathworks, Natick, Mass) for semiautomated measurement of early repolarization. Three trained investigators independently performed manual overreading of the automated analysis to verify correct early repolarization markings (notching, slurring, or J-point elevation) on the ECGs. In the event of a misplaced marking by automated analysis, all 3 investigators were required to be in agreement of the true early repolarization marking to alter the marking. ECGs were coded to determine the location of prior MI and previous MI. In control subjects, ECGs were obtained at the time of ICD implantation. Thus, the median time at which control ECGs were recorded was 0 months (IQR, 0 to 1 month) after ICD implant dates. In cases, ECGs were obtained within 2 months of appropriate ICD shock to capture the electrophysiological substrate at the time of ICD shock, with the majority of ECGs (82%, n = 49) captured before the time of the ICD shock. Thus, the median time at which case ECGs were recorded was 12 months (IQR, 0 to 36 months) after ICD implant dates. Twelve-lead ECGs of control subjects were randomly selected and qualified for inclusion if they had not had appropriate ICD shocks or antitachycardia pacing due to VTAs during follow-up after ICD implantation.

**ECG Analysis**

ECGs were obtained from NMH and TMC. In control subjects and cases, ECGs were recorded after patients were diagnosed with CAD and previous MI. In control subjects, ECGs were obtained at the time of ICD implantation. Thus, the median time at which control ECGs were recorded was 6 months (IQR, 0 to 1 month) after ICD implant dates. In cases, ECGs were obtained within 2 months of appropriate ICD shock to capture the electrophysiological substrate at the time of ICD shock, with the majority of ECGs (82%, n = 49) captured before the time of the ICD shock. Thus, the median time at which case ECGs were recorded was 12 months (IQR, 0 to 36 months) after ICD implant dates. Twelve-lead ECGs from NMH were digitally downloaded from the GE Marquette MUSE system (GE Medical Systems, Milwaukee, Wis). Twelve-lead ECGs from TMC were downloaded from the Philips TraceMaster ECG system (Philips Medical System, Andover, Mass). The digital ECGs from each system were analyzed off-line using custom-designed software developed using MATLAB (Mathworks, Natick, Mass) for semiautomated measurement of early repolarization. Three trained investigators independently performed manual overreading of the automated analysis to verify correct early repolarization markings (notching, slurring, or J-point elevation) on the ECGs. In the event of a misplaced marking by automated analysis, all 3 investigators were required to be in agreement of the true early repolarization marking to alter the marking. ECGs were coded to blind investigators from clinical characteristics and patient grouping.

Early repolarization was defined as notching, slurring, or J-point elevation ≥0.1 mV above baseline in at least 2 inferior or lateral leads. The terminal QRS was characterized as exhibiting notching or slurring if it met amplitude criteria. As defined by prior studies, notching was noted as a positive deflection at the terminal portion of a positive QRS complex (Figure 1). Slurring was defined as a smooth transition from QRS complex to ST segment with upright concavity (Figure 1). The J-point amplitude was measured at the QRS-ST junction and relative to the QRS onset to minimize baseline wandering effect. Anterior precordial leads (V1 to V3) were excluded from analysis for early repolarization to remove potential confounding from patients with a Brugada pattern.

ECGs also were assessed to determine the location of prior MI using the Novacode coding system. Coded 12-lead ECGs were read...
by an investigator blinded to patient and clinical information. Infarct locations were categorized as anterior, posterior, lateral, or inferior. ECGs with no evidence of pathological Q-waves were categorized separately as “indeterminate.” No evidence of aneurysm was noted by ECG criteria.

Computer Simulation of Notching
To gain insight into the cellular action potential origins of notching, a computer model of the electric activation of the left ventricular free wall was designed using the action potential model developed by Bueno-Orovio.28 The 4 variables of this model control the fast inward, slow inward, and slow outward currents with parameters that can be adjusted to fit the desired profile of action potential duration and conduction velocity restitution as well as action potential shapes.28 The specific parameters provided by Bueno-Orovio et al were used to simulate the human ventricular action potentials from the endocardium, midmyocardium, and epicardium. A cross section of left ventricular free wall was simulated in 2-dimensional configuration (1.5 cm x 1.5 cm), where endocardium, midmyocardium, and epicardium have a distribution of 50%, 30%, and 20%, respectively. Two separate simulations were run: 1 with the epicardium having a classic “spike-and-dome” morphology and 1 with the epicardium having the same morphology as the endocardium (ie, no “spike-and-dome”).

Pseudo-ECGs for both simulations were created assuming an infinite volume conductor and using the equation

\[ \text{ECG} = \int \frac{|\text{dV} \cdot \text{r}|}{|\mathbf{r}|} \, \text{dx} \]

where D is a constant, \( \text{dV} \) is the voltage gradient, and \( \text{r} \) is the vector from the recording electrode to a point in the tissue. The recording electrode was assumed to be 10 cell lengths away from the epicardium.

Statistical Analysis
Continuous variables are reported as mean±SD and categorical variables are presented as number and percentage in each group. Comparison of continuous variables between cases and control subjects was performed with Student t test for paired data, as all continuous variables were normally distributed. Comparison of categorical variables was performed with the McNemar test. Comparison of follow-up times between cases and control subjects was performed with Student t test for paired data due to the normal distribution of the differences in follow-up times. Follow-up times are reported as median and IQR. The incidence of early repolarization between cases and control subjects was assessed by conditional logistic regression analysis; odds ratios were adjusted for LVEF. All analyses were considered significant at \( P<0.05 \) (2-tailed). All statistics were performed with SAS statistical software.

Results
Baseline Characteristics
Table 1 shows baseline characteristics of the study population. Case subjects with VTAs included 51 men and 9 women with a mean age of 67.6±10.2 years. The control group consisted of 60 patients matched for age (67.3±10.7 years) and sex (51 men and 9 women). The median follow-up time for control subjects (5.60 years; IQR, 4.12 to 7.22) was significantly longer than that of cases (1.75 years; IQR, 0.68 to 4.69; \( P<0.001 \)), because cases were censored at the time of arrhythmic event. Of the 60 cases, 32 patients had VF, and 28 patients had sustained VT after ICD implantation. Additionally, there were no differences in location of infarcts or QRS duration between cases and control subjects. Moreover, there was a similar prevalence of non-Q-wave MI in cases (15%, n=9) and control subjects (13%, n=8) (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of Cases and Control Subjects</th>
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<tr>
<td></td>
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<tr>
<td>Age, y, mean±SD</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>LVEF, %, mean±SD</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>ACE inhibitor</td>
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<tr>
<td>( \beta )-blocker</td>
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<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
</tr>
<tr>
<td>Spironolactone</td>
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<tr>
<td>Infarct location</td>
</tr>
<tr>
<td>Anterior</td>
</tr>
<tr>
<td>Inferior</td>
</tr>
<tr>
<td>Lateral</td>
</tr>
<tr>
<td>Posterior</td>
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<tr>
<td>Indeterminate (non-Q-wave MI)</td>
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<tr>
<td>QRS duration, ms, mean±SD</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

Early Repolarization
Early repolarization, characterized by notching, slurring, or J-point elevation of the terminal QRS complex, was more common in cases than among matched control subjects (32% versus 8%, \( P=0.006 \)), even after adjusting for LVEF (\( P=0.005 \)). When regional leads were analyzed, early repolarization was noted more frequently in inferior leads of cases than control subjects before statistical adjustment for LVEF (23% versus 8% \( P=0.03 \)) and after adjusting for LVEF (\( P=0.03 \)). Early repolarization tended to be more common in cases than control subjects in leads \( V_4 \) through \( V_6 \) (12% versus 3%, \( P=0.11 \)). In contrast, early repolarization in leads I and aVL was uncommon in both cases and control subjects (3% versus 0%, \( P=NS \)). Because of low incidence of notching, slurring, and J-point elevation in lateral limb leads (I and aVL) and lateral precordial leads (\( V_4 \) through \( V_6 \)), multivariable analysis was not possible (Table 2). There was a higher incidence of early repolarization in cases with VT (39%, \( n=11 \)) than in cases with VF (25%, \( n=8 \)).

Comparison of Notching, Slurring, and J-Point Elevation
With respect to morphological characteristics, notching of the terminal portion of the QRS complex was more common in cases than control subjects after unadjusted analysis (28% versus 7%, \( P=0.01 \)) and after adjustment for LVEF (\( P=0.008 \)). In contrast, the incidence of slurring was similar in both cases and control subjects (7% versus 3%, unadjusted \( P=0.42 \)). The small number of patients with slurred QRS complexes prevented multivariable analysis to be performed.

J-point elevation alone was noted in 4 cases (7%) and in 2 control subjects (3%) (unadjusted \( P=0.42 \)). Among the cases
and control subjects with J-point elevation, the amplitude for cases was 0.12±0.05 mV and the amplitude for control subjects was 0.12±0.007 mV (P=0.052, by unpaired t test; Table 3).

**Computer Simulation of Notching**

One possible mechanism of J-point elevation, demonstrated through computer simulation, is shown in Figure 2. Without the classic “spike-and-dome” of the epicardial action potential, notching of the terminal QRS in the pseudo-ECG is absent. The presence of a prominent spike-and-dome morphology in the simulated epicardial action potential is a requirement for notching in this model. In addition, the notch of the pseudo-ECG is shown to correspond in timing with the notch of the epicardial action potential. Thus, the results of the simulation suggest that notching of the QRS complex could be caused by early repolarization of parts of the ventricular epicardium. The computer model is consistent with experimental studies, which have demonstrated the temporal similarity between the notching on the ECG and the spike of the epicardial action potential.29

**Discussion**

Early repolarization has historically been considered a benign finding among healthy, young individuals.18 However, recent evidence has linked early repolarization to idiopathic VF in patients without structural heart disease.19–24 In light of this evidence, the association between early repolarization and VTAs in this study cannot entirely be explained by several clinical factors shown to predict arrhythmias in patients with CAD. Factors associated with arrhythmia risk or cardiac mortality, including sex30 and site of MI,31 did not differ between cases and control subjects. Furthermore, no significant differences in medications, such as β-blocker use, accounted for differences in arrhythmia risk.

It is possible that ST-elevation and early repolarization in patients with healed MI may manifest due to the severity of their prior infarction. This could more fully be evaluated by detection of the presence of aneurysm, for example, by imaging studies, such as cardiac MRI, which has been associated with ventricular arrhythmias in both ischemic and nonischemic cardiomyopathy patients.32 However, we did not have this information consistently available, and we attempted to adjust for this variable in our analysis by adjusting for LVEF and carefully analyzing ECG characteristics for the presence or absence of aneurysm. In addition, patients who had acute MI during follow-up were excluded from our study.

<table>
<thead>
<tr>
<th>Table 2. Incidence of Early Repolarization Among 60 CAD Cases With VTA and 60 CAD Control Subjects Matched for Age and Sex</th>
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<tbody>
<tr>
<td><strong>Cases</strong></td>
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<tr>
<td><strong>Value</strong></td>
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<tr>
<td>Overall (all leads)</td>
</tr>
<tr>
<td>Inferior (II, III, aVF)</td>
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<tr>
<td>Lateral limb (I, aVL)</td>
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<td>Lateral precordial (V1-V5)</td>
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CI indicates confidence interval; and OR, odds ratio.
*Calculated by conditional logistic regression.
†Insufficient data for multivariable analysis.
‡Adjusted for LVEF.

<table>
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<tr>
<th>Table 3. Incidence of Notching, Slurring, and J-Point Elevation Among 60 CAD Cases With VTA and 60 CAD Control Subjects Matched for Age and Sex</th>
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<tr>
<td><strong>Cases</strong></td>
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<tr>
<td><strong>Value</strong></td>
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<tr>
<td>Notching</td>
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<tr>
<td>Slurring</td>
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<td>J-point elevation</td>
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CI indicates confidence interval; and OR, odds ratio.
*Calculated by conditional logistic regression.
†Insufficient data for multivariable analysis.
‡Adjusted for LVEF.
The heterogeneity of ventricular repolarization is seen as a “notch” in the epicardial action potential during Phase I, which is absent in the action potential of the endocardium. Early epicardial repolarization is largely mediated by a 4-aminopyridine sensitive transient outward current (I\textsubscript{o})\textsuperscript{29}. Disparity of outward I\textsubscript{o} current density between segments of the ventricular epicardium has the potential to cause ventricular tachyarrhythmias under certain conditions.\textsuperscript{19} This is due to a dispersion of repolarization, allowing for Phase II cardiac reentry between repolarized epicardium and epicardium that has maintained its action potential.\textsuperscript{19} Thus, early repolarization could represent an arrhythmogenic substrate in patients with CAD.

It is possible that early repolarization of the ventricles has a genetic origin, attributed to variable expression of the I\textsubscript{o} current. The transmural gradient in I\textsubscript{o} current in dog myocardium has been attributed to the transmural distribution of 3 genes: (1) KCND3 gene, which encodes the \alpha subunit of the I\textsubscript{o} channel,\textsuperscript{28} (2) IRX5, a transcriptional factor regulating KCND3,\textsuperscript{36} and (3) KChIP2, a \beta-subunit of the I\textsubscript{o} channel.\textsuperscript{37} One could speculate that an interaction between polymorphisms of these 3 genes and myocardial scar from previous MI may provide the conditions necessary for the generation of life-threatening VTAs. The molecular basis of the transmural distribution of I\textsubscript{o} is still debated, however, and further research is required to assess its genetic basis in humans. Larger studies of patients with CAD and findings of early repolarization on the standard 12-lead ECG will be needed to prospectively validate the preliminary results of this study.

Study Limitations
There are several limitations to our study. This is a small, case-control study. The small sample size limits our power and is reflected in the broad confidence intervals, most notably in the adjusted statistical analyses regarding the incidence of early repolarization. Because early repolarization in this study was defined by the existing criteria of J-point elevation, notching, or slurring, it is also possible that we overestimated the true incidence of early repolarization, as other physiological processes such as intraventricular conduction delay may mimic these findings. Provocative testing, such as signal averaged ECG, might be helpful or necessary to reliably distinguish intraventricular conduction delay from early repolarization.\textsuperscript{21} In the Haissaguerre et al\textsuperscript{21} study, only a minority of patients with early repolarization had “late potentials,” suggesting that the findings represent “early repolarization” rather than “delayed depolarization.” We did not systematically perform signal averaged electrocardiography on this patient group.

Early repolarization may be more common just before onset of VTAs. Unfortunately, in this study, ECGs before the MI were not generally available. As a result, it was not possible to know whether the observed early repolarization existed before the MI. Similarly, the degree of change in early repolarization over time is not available due to lack of consistently available serial ECGs. Because of the sample size, there were few women included in the analysis, which prevented a comparison of early repolarization by sex. Also, programming information regarding ICDs was not accessible.

Implications of Early Repolarization
As described by Haissaguerre et al.\textsuperscript{21} and others, early repolarization can manifest as notching or slurring of the terminal portion of the QRS complex. In our study, notching of the terminal portion of the QRS complex occurred more frequently in cases than control subjects. Thus, notching may be more useful in identifying patients at greater risk for ventricular arrhythmia events. In contrast, slurring of the terminal portion of the QRS complex and true J-point elevation were relatively uncommon in both cases and control subjects; although they occurred with higher frequency in the cases than control subjects, this was not a statistically significant finding, possibly due to the low incidence. To date, there have been no attempts to delineate whether there are different prognostic implications of these various manifestations of early repolarization. Further evaluation of these important ECG phenotypic distinctions and underlying mechanisms for their expression will be important in refining arrhythmic risk criteria in these patients. Our results support that notching of the terminal portion of the QRS complex is associated with life-threatening ventricular arrhythmias in patients with a history of CAD and prior healed MI.

Potential Role of Early Repolarization in Arrhythmogenicity
Our findings provide further support that early repolarization may not be a benign finding in patients with prior MI and history of CAD. Because early repolarization occurs after ventricular activation (QRS complex), its presence indicates a transient transmural voltage gradient during early ventricular repolarization.\textsuperscript{19,28,29,33} Such a gradient is caused by the early repolarization of the epicardium but not endocardium.\textsuperscript{19,29}
Thus, there could have been variability in shocks based on the specific programming criteria. Furthermore, we had no CAD subjects who had acute MI during follow-up; therefore, our results may not apply to this subgroup. Although we controlled for a number of key variables associated with ventricular arrhythmias, other potential contributors to ventricular arrhythmias, including heart failure status, presence and extent of myocardial scar/fibrosis as identified by imaging techniques, and antiarrhythmic drug use, were not available and could have impacted the results of this study. With the exception of β-blocker use, the use of antiarrhythmic medication was not collected in either database and thus was not available for comparison. Moreover, although no statistical difference was noted between cases and control subjects, we acknowledge the lack of robust penetrance of optimal medical therapy in these patients with chronic CAD, which may have affected the degree to which VTA therapies were noted.

Conclusion

Our study suggests that early repolarization, indicated by notching of the terminal portion of the QRS complex, most notably in the inferior leads on the standard 12-lead ECG, is associated with life-threatening ventricular tachyarrhythmias in patients with chronic CAD, independent of LVEF. Our findings provide support for the consideration of early repolarization in risk prediction models for ventricular arrhythmias in patients with CAD in the healed phase of MI.

Sources of Funding

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Disclosures

None.

References

Early repolarization on the standard 12-lead ECG has generally been considered a benign finding, but a recent report by Haissaguerre et al suggested that early repolarization may be a useful marker in predicting sudden cardiac death. Its utility as a predictor of lethal ventricular tachyarrhythmias (VTAs) in patients with prior healed myocardial infarction has not been studied. In a population of patients with coronary artery disease and implantable cardioverter-defibrillators placed for primary prevention, we performed a retrospective, nested, case-control study in which we found an increased association of VTA events by adjudicated implantable cardioverter-defibrillator interrogation in cases with early repolarization. Although definitions and criteria for “early repolarization” continue to evolve, we found that a notching morphological inscription on the terminal portion of the QRS complex in the inferior leads was associated with VTAs. Our study provides further support for early repolarization—specifically notching in the inferior leads—as a potentially useful marker in predicting VTAs events in patients with healed myocardial infarction. Further prospective validation is necessary to confirm these findings.
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