

ORIGINAL ARTICLE

Sudden Cardiac Arrest Associated with Early Repolarization

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ABSTRACT

BACKGROUND

Early repolarization is a common electrocardiographic finding that is generally considered to be benign. Its potential to cause cardiac arrhythmias has been hypothesized from experimental studies, but it is not known whether there is a clinical association with sudden cardiac arrest.

METHODS

We reviewed data from 206 case subjects at 22 centers who were resuscitated after cardiac arrest due to idiopathic ventricular fibrillation and assessed the prevalence of electrocardiographic early repolarization. The latter was defined as an elevation of the QRS–ST junction of at least 0.1 mV from baseline in the inferior or lateral lead, manifested as QRS slurring or notching. The control group comprised 412 subjects without heart disease who were matched for age, sex, race, and level of physical activity. Follow-up data that included the results of monitoring with an implantable defibrillator were obtained for all case subjects.

RESULTS

Early repolarization was more frequent in case subjects with idiopathic ventricular fibrillation than in control subjects (31% vs. 5%, $P < 0.001$). Among case subjects, those with early repolarization were more likely to be male and to have a history of syncope or sudden cardiac arrest during sleep than those without early repolarization. In eight subjects, the origin of ectopy that initiated ventricular arrhythmias was mapped to sites concordant with the localization of repolarization abnormalities. During a mean (\pm SD) follow-up of 61 ± 50 months, defibrillator monitoring showed a higher incidence of recurrent ventricular fibrillation in case subjects with a repolarization abnormality than in those without such an abnormality (hazard ratio, 2.1; 95% confidence interval, 1.2 to 3.5; $P = 0.008$).

CONCLUSIONS

Among patients with a history of idiopathic ventricular fibrillation, there is an increased prevalence of early repolarization.

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SUDDEN CARDIAC ARREST REMAINS A MAJOR public health problem that accounts for approximately 350,000 deaths annually in the United States. Despite advances in emergency medical systems, only 3 to 10% of patients who have an out-of-hospital cardiac arrest are successfully resuscitated. The majority of such sudden cardiac arrests are caused by ventricular tachyarrhythmias, which occur in persons without structural heart disease in 6 to 14% of cases.^{1,2} Some of the latter cases are related to well-recognized electrocardiographic abnormalities that affect ventricular repolarization (e.g., long or short QT intervals or the Brugada syndrome), whereas other cases, in which there are no signs during sinus rhythm, are described as idiopathic ventricular fibrillation.³⁻¹⁰

Early repolarization is a common electrocardiographic finding that affects 1 to 5% of persons.^{11,12} Although the condition is usually considered benign, its potential arrhythmogenicity has been suggested by experimental studies.¹³ However, supporting clinical evidence is lacking. We performed a case-control study involving 206 case subjects with idiopathic ventricular fibrillation to assess the prevalence of early repolarization and evaluated its potential relationship with any observed arrhythmias and the subsequent outcome, as monitored by implantable defibrillators.

METHODS

STUDY POPULATION

Case subjects under the age of 60 years were enrolled at 22 international tertiary care arrhythmia centers. All subjects with the diagnosis of idiopathic ventricular fibrillation in this age group were selected from the databases of patients who had received an implantable defibrillator; all patients 60 years of age or older were excluded to minimize the risk of subclinical structural heart disease. Oral informed consent was obtained from all enrolled subjects.

We evaluated baseline electrocardiograms for the presence of early repolarization, which was defined as an elevation of the QRS-ST junction (J point) in at least two leads, at the time of implantation of the defibrillator. The amplitude of J-point elevation had to be at least 1 mm (0.1 mV) above the baseline level,^{11,12} either as QRS slurring (a smooth transition from the QRS segment to the ST segment) or notching (a positive J deflection inscribed on the S wave) in the inferior lead (II, III, and aVF), lateral lead (I, aVL, and V₄ to V₆),

or both. The anterior precordial leads (V₁ to V₃) were excluded from the analysis to avoid the inclusion of patients with right ventricular dysplasia or the Brugada syndrome.^{6,8}

On the basis of published guidelines,^{1,2} patients were classified as having idiopathic ventricular fibrillation if they had no identifiable structural heart disease demonstrated by normal echocardiographic biventricular dimensions and function, no detectable coronary artery disease on coronary angiography or exercise testing, and no known repolarization abnormalities. Case subjects were excluded if they had a QT interval corrected for heart rate (QTc) of less than 340 msec (short QT interval) or more than 440 msec (long QT interval) at baseline and before arrhythmia.^{5,9} Patients with the Brugada syndrome, defined as right bundle-branch block and ST-segment elevation (>0.2 mV) in precordial leads V₁ to V₃, without intervention or following infusion of a sodium-channel blocker,^{8,10} were also excluded. In addition, patients with catecholaminergic arrhythmias, defined as arrhythmias during catecholamine infusion or exercise testing, were excluded.

We assessed the prevalence and amplitude of early repolarization in a control group of 412 consecutive subjects. This population was composed of health care professionals with normal echocardiographic biventricular dimensions and function and no history of syncope. Global frequency matching was used for the distribution of known confounding factors (age, sex, race, and level of physical activity).

DATA COLLECTION

We collected the following clinical data: a history of unexplained syncope, circumstances of sudden cardiac arrest, a family history of unexplained sudden death (at <60 years of age), the level of physical activity (>10 hours or ≤10 hours of activity a week), results on signal-averaged electrocardiography (both standard amplification and high amplification), and results of pharmacological testing and invasive electrophysiological testing. Electrocardiographic readings were measured with the use of automated online software and were verified manually. The QTc interval was calculated after correction for heart rate with Bazett's formula.

ELECTROPHYSIOLOGICAL STUDY

We performed electrophysiological testing with the use of multielectrode catheters introduced percutaneously through the femoral vessels. Programmed

Table 1. Characteristics of the Case Subjects.*

Characteristic	Early Repolarization (N = 64)	No Early Repolarization (N = 142)	P Value
Demographic and clinical			
Male sex — no. (%)	46 (72)	76 (54)	0.007
Age — yr	35±13	37±13	0.49
Race or ethnic group — no. †			0.69
White	58	132	
Asian	5	9	
Black	1	1	
History of unexplained syncope — no. (%)	24 (38)	35 (25)	0.06
Family history of unexplained sudden death — no. (%)	10 (16)	13 (9)	0.17
Physical activity — no. (%) ‡	4 (6)	18 (13)	0.11
Activity at the time of initial sudden cardiac arrest — no. (%)			
Sleeping	12 (19)	6 (4)	0.03
Physical effort	6 (9)	19 (13)	
Other activity	46 (72)	117 (82)	
Occurrence of initial ventricular fibrillation — no. (%)			
Out of hospital	52 (81)	126 (89)	0.15
In hospital for syncope or other reason	12 (19)	16 (11)	
Electrocardiographic			
Prolonged PR interval (>200 msec) — no. (%)	3 (5)	7 (5)	0.93
Duration of QRS complex — msec	91±10	92±15	0.39
Duration of QTc interval — msec	392±22	401±23	0.01
Presence of late potentials — no./total no. (%) §	5/44 (11)	8/63 (13)	0.84
Electrophysiological			
His bundle–ventricular interval — msec	45±7	46±10	0.77
Inducibility of ventricular fibrillation — no./total no. (%)	16/47 (34)	17/85 (20)	0.07
Inducible with 3 extrastimuli — %	81	85	0.96
Shortest coupling interval — msec	209±30	209±23	0.84
Confirmation of idiopathic ventricular fibrillation			
Coronary angiogram — no. (%) ¶	62 (97)	128 (90)	0.09
Right ventricular angiogram or MRI — no. (%)	50 (78)	107 (75)	0.66
Sodium-blocker infusion — no. (%)	54 (84)	81 (57)	<0.001
Exercise test or catecholamine infusion — no. (%)	54 (84)	69 (49)	<0.001

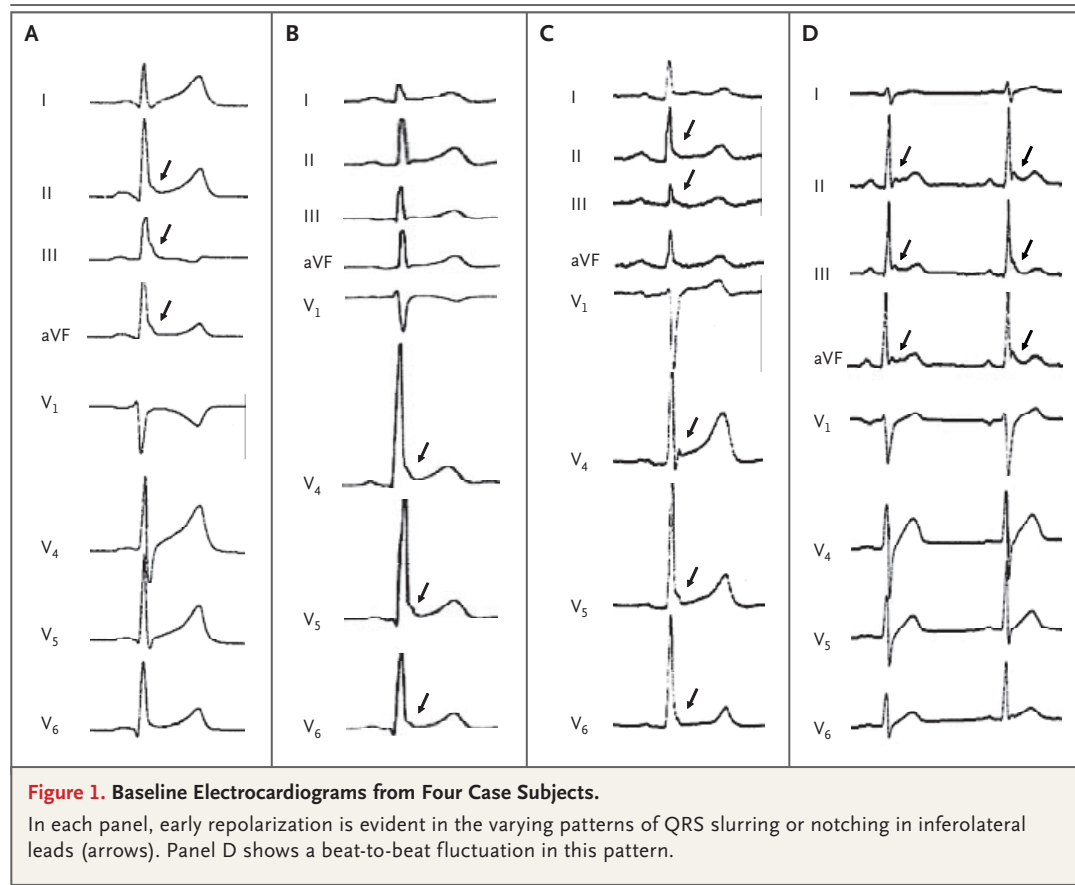
* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. MRI denotes magnetic resonance imaging.

† Race or ethnic group was self-reported.

‡ Physical activity was defined as more than 10 hours of activity a week.

§ High-amplification, signal-averaged electrocardiograms were considered to indicate the presence of late ventricular potentials when two of the following measurements were recorded: a QRS duration of more than 120 msec, a root mean square of terminal QRS of less than 25 mV, and a low-amplitude signal lasting more than 40 msec.

¶ Subjects who did not undergo coronary angiography had normal exercise testing.



ventricular stimulation was performed with the use of a maximum of two or three ventricular extrastimuli from two separate ventricular sites. Ventricular fibrillation was considered to be inducible if it lasted for more than 30 seconds or required electrical cardioversion. No subject had inducible monomorphic ventricular tachycardia.

In case subjects with recurrent ventricular fibrillation despite the administration of antiarrhythmic drugs, catheter ablation that targeted the initiating ventricular ectopy was performed as described previously.¹⁴ Such ectopy was localized by mapping the earliest electrical activity, either Purkinje or myocardial, relative to the onset of the QRS complex. Ablation was performed with the use of radiofrequency energy.

THERAPY AND FOLLOW-UP

All case subjects received an implantable defibrillator that provided accurate information on recurrence of ventricular fibrillation. The subjects were seen routinely every 6 to 12 months for clinical review and device interrogation or as necessary in

the event of the onset of symptoms or device discharges. In subjects with recurrent arrhythmias, the choice of antiarrhythmic drugs was made by individual physicians.

STATISTICAL ANALYSIS

Continuous variables were reported as means \pm SD or medians (with 25th and 75th percentiles), as appropriate. A comparison between the two groups was performed with Student's t-test or the non-parametric Wilcoxon rank-sum test, as appropriate, and with Student's t-test for paired data. Categorical variables were compared with Fisher's exact test. The prevalence of early repolarization was compared between case subjects and control subjects with the use of logistic-regression analysis (reported as odds ratios with 95% confidence intervals) and was adjusted for matching variables. The number of recurrences of ventricular fibrillation was compared with the use of the Wilcoxon test, and the recurrence rate was assessed with the use of actuarial curves. Hazard ratios from Cox proportional-hazards models were used to estimate

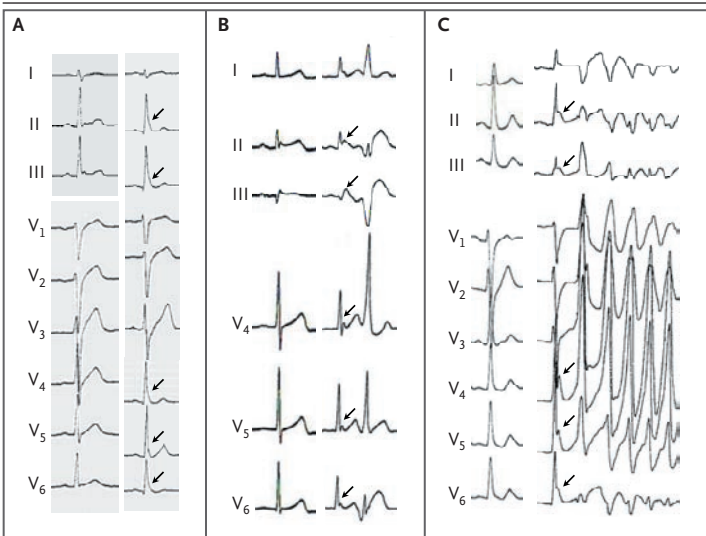


Figure 2. Electrocardiograms from Three Case Subjects with Early Repolarization Associated with Ventricular Fibrillation.

Each panel shows the first QRS complex recorded at baseline (left) and the subsequent complexes recorded before an arrhythmic event (right), with clear accentuation of early repolarization (arrows), as compared with baseline. In the patient whose electrocardiogram is shown in Panel A, ventricular fibrillation occurred the following night. Panel B shows a ventricular premature beat (with a left axis); a similar beat triggered ventricular fibrillation a few hours later, as documented on monitoring. Panel C shows the onset of ventricular fibrillation.

the relative risk associated with early repolarization. All tests were two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

EARLY REPOLARIZATION

The group of case subjects with idiopathic ventricular fibrillation included 123 men and 83 women with a mean age of 36 ± 11 years. The control group included 412 persons who were well matched for age (36 ± 12 years), sex (270 men and 142 women), race (380 white, 27 Asian, and 5 black), and physical activity (44 subjects engaged in more than 10 hours of activity weekly).

Early repolarization occurred in 64 case subjects (31%), as compared with 21 control subjects (5%, $P < 0.001$) and was greater in magnitude in case subjects than in control subjects (J-point elevation, 2.0 ± 0.9 mm vs. 1.2 ± 0.4 mm; $P < 0.001$). After adjustment for age, sex, race, and level of physical activity, the odds ratio for the presence of

early repolarization in case subjects, as compared with control subjects, was 10.9 (95% confidence interval [CI], 6.3 to 18.9).

Case subjects with early repolarization were more likely to be male, to have a history of unexplained syncope or sudden cardiac arrest during sleep, and to have a shorter QTc interval than those without early repolarization. The characteristics of the case subjects are summarized in Table 1.

At baseline, early repolarization was present in the inferior lead in 28 subjects, in the lateral lead in 6 subjects, and in both inferior and lateral leads in 30 subjects (Fig. 1). This pattern was considered repolarization rather than late depolarization because of its slower inscription, spontaneous fluctuation in morphologic pattern or amplitude in the face of stable QRS complexes, and amplitude varying concurrently with ST segment. The absence of late potentials on high-amplification electrocardiography further supported a repolarization pattern (Table 1). This pattern occurred in isolation or was followed by negative T-wave elevation or discrete ST-segment elevation (horizontal or displaying upward concavity). Electrocardiograms that had been obtained weeks to years before sudden cardiac arrest were available for 22 subjects and showed the pattern of early repolarization (as defined above).

Electrocardiography was performed during an arrhythmic period (including frequent ventricular ectopy and episodes of ventricular fibrillation) in 18 subjects, and all studies showed a consistent increase in the amplitude of early repolarization, as compared with baseline (Fig. 2). The J-point amplitude increased from 2.6 ± 1 mm to 4.1 ± 2 mm ($P < 0.001$). In most of the case subjects, ectopy had a positive QRS morphologic pattern in leads V_1 to V_2 , which indicated an origin from the left ventricle and a short coupling interval initiating ventricular fibrillation (mean, 326 ± 41 msec; range, 260 to 400).

Exercise testing or the infusion of isoproterenol consistently reduced or eliminated early repolarization. Isoproterenol infused in two subjects during repetitive episodes of ventricular fibrillation eliminated all arrhythmias when the sinus heart rate was increased above 120 beats per minute. In contrast, beta-blockers accentuated repolarization abnormalities. The effects of antiarrhythmic drugs are summarized in Table 2. Their

Table 2. Outcome after Initial Aborted Sudden Cardiac Arrest.*

Variable	Early Repolarization (N = 64)	No Early Repolarization (N = 142)	P Value
Duration of follow-up (mo)			0.81
Mean	60±45	62±52	
Median	49	54	
Interquartile range	24–90	17–92	
No. of recurrent episodes of ventricular fibrillation per patient			0.001
Median	8	2	
Interquartile range	2–35	1–6	
Successful treatment (no./total no.)†			
Beta-blockers	2/13	9/17	
Amiodarone	0/7	3/7	
Flecainide, cifenline, or pilsicainide	0/10	2/4	
Quinidine or disopyramide	4/4	1/3	
Verapamil	0/5	3/8	
Mexiletine	0/5	0/2	
Catheter ablation	5/8	6/7	
Current outcome			
No. of subjects alive	63	142	
No. of subjects with recurrence in the past 12 mo	5‡	5	

* Plus–minus values are means ±SD.

† Successful treatment was defined as no ventricular fibrillation for at least 12 months, as documented by an implantable defibrillator.

‡ Quinidine was recently prescribed for three subjects.

inefficacy led to attempts at catheter ablation of ventricular premature beats, which triggered ventricular fibrillation in some subjects.

ORIGIN OF ECTOPY IN EARLY REPOLARIZATION

Mapping was performed in eight case subjects. In two case subjects, mapping of both ventricles did not show results during ventricular depolarization that were coincident with a wide terminal QRS abnormality, confirming that the latter was related to repolarization. A total of 26 ectopic patterns were mapped either to the ventricular myocardium (16 patterns) or to Purkinje tissue (10 patterns). In six subjects with early repolarization recorded only in inferior leads, all ectopy originated from the inferior ventricular wall. In two subjects with widespread early repolarization, as recorded by both inferior and lateral leads, ectopy originated from multiple regions. Catheter ablation eliminated all ectopy in five subjects and did not eliminate the condition in three subjects.

OUTCOME IN CASE SUBJECTS

Table 2 summarizes the outcome during a mean period of 61±50 months (median, 51 months; interquartile range, 19 to 90) after the initial event, with no case subject lost to follow-up. Arrhythmic recurrences were more frequent in subjects with early repolarization than in those without such repolarization (41% vs. 23%). The hazard ratio for recurrence was 2.1 (95% CI, 1.2 to 3.5; P=0.008), even after adjustment for sex (Fig. 3). The three subjects with the highest J-point elevation (>5 mm) had more than 50 episodes of ventricular fibrillation, leading to death in one. Four subjects with multiple episodes were treated with quinidine, which diminished the repolarization abnormality and eliminated arrhythmia recurrences.

DISCUSSION

Sudden cardiac arrest from arrhythmia may occur in persons who do not have structural heart dis-

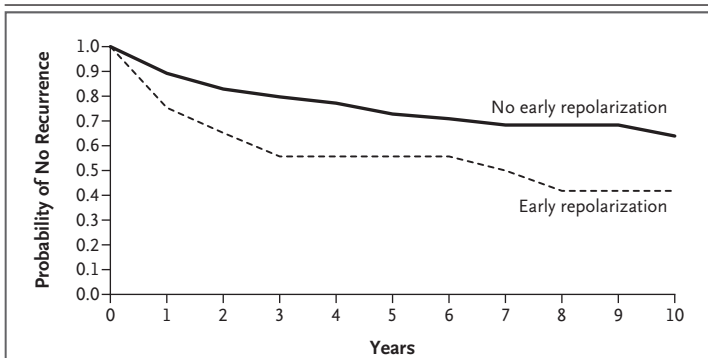


Figure 3. Actuarial Curves for Case Subjects, According to the Presence or Absence of Early Repolarization.

Case subjects with a repolarization abnormality were at increased risk for recurrent ventricular fibrillation, as compared with those without such an abnormality (hazard ratio, 2.1; 95% CI, 1.2 to 3.5; $P=0.008$).

ease or evident electrocardiographic abnormalities during sinus rhythm. In our study, such case subjects had a significantly higher prevalence of early repolarization than control subjects, in whom the prevalence was similar to that among healthy subjects in studies reported previously.¹¹⁻¹³ In nearly one third of case subjects, electrocardiograms obtained before cardiac arrest were available, and they showed early repolarization, which indicated that this abnormality could not be the result of the trauma of sudden cardiac arrest, resuscitation efforts, or drugs used for resuscitation.

It is unlikely that this abnormality is simply more common among the survivors of cardiac arrest than among nonsurvivors, because the single most important factor determining successful resuscitation is access to prompt defibrillation.¹⁵ This electrocardiographic pattern was also associated with an increased incidence of recurrent ventricular arrhythmias during follow-up with defibrillator monitoring.

Our results suggest a relationship between early repolarization and sudden cardiac arrest, a conclusion that is at odds with the seemingly benign nature of this common phenomenon. First, this finding may be due to the definition of early repolarization, since we specifically included abnormalities in the inferolateral leads, whereas the broad traditional definition of early repolarization involves varying amplitude, configuration, and extent of the electrocardiographic patterns, most commonly in the right precordial leads. Second, few of the case subjects in our study belonged to

subgroups that have a high prevalence of early repolarization (e.g., athletes and blacks), which suggested that cofactors influence the association with sudden cardiac arrest. Third, the benign nature of early repolarization is challenged by experimental findings indicating the presence of a form of transmural electrical heterogeneity, which can be dramatically amplified under certain conditions (the use of specific drugs and various levels of autonomic tone and electrolytes) resulting in malignant arrhythmias.¹³ The potential arrhythmogenicity is thus dependent on defective modulation of repolarization, which is in accordance with the dynamic changes temporally related to arrhythmias that we observed in our case subjects.

The link between this electrocardiographic pattern and malignant arrhythmias is supported by both the accentuated repolarization before the onset of arrhythmia in the case subjects and the origin of triggering beats from the region of early repolarization. Quinidine, which has been shown to restore transmural electrical homogeneity and abort arrhythmic activity in this condition,¹³ diminished the electrocardiographic pattern and eliminated recurrent arrhythmias in four subjects.

Finally, although to our knowledge no multicenter study has specifically examined the association between early repolarization and sudden cardiac arrest, anecdotal reports (mostly from Southeast Asia) have described patients who had sudden cardiac arrest associated with abnormal J waves.¹⁶⁻²³ The repolarization abnormality that is recorded by inferolateral leads, as described in our report, may be a marker of underlying electrical vulnerability that increases the risk of fatal arrhythmias under conditions that need to be investigated. These conditions include the presence of genetic defects related to cardiac ion channels, as suggested by the fact that 10 of our case subjects had a family history of sudden cardiac arrest.

These findings are potentially relevant to the assessment of patients with syncope or a family history of sudden death. Arrhythmias that are related to a repolarization abnormality may be responsible for a proportion of unexplained deaths, predominantly in young men, as reported previously.²⁴⁻²⁶ Such arrhythmias may also be responsible for some undiagnosed causes of syncope that have been reported to increase the risk of premature death.²⁷

The results of our study, which require confirmation by other investigators, have several limitations. Although the cohort included subjects with strictly defined common features, data collection was not uniform among centers. In our study population, we had no subjects with structural heart disease and few athletes or blacks, so the results may not apply to these subgroups. Most important, although our results suggest that early repolarization is a marker of a disorder associated with malignant arrhythmias, natural-history studies predict a benign course for most of these patients. Further research is required to identify factors that modulate underlying arrhythmogenicity and to predict which patients are at risk.

In conclusion, this multicenter study showed a higher-than-expected prevalence of early repolar-

ization (as seen on inferolateral leads) in patients younger than 60 years of age who had idiopathic ventricular fibrillation that caused syncope and sudden cardiac arrest.

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