Clinical Characteristics and Outcomes Associated With the Natural History of Early Repolarization in a Young, Biracial Cohort Followed to Middle Age

The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Background—Early repolarization (ER), a common electrocardiographic phenotype, has been associated with increased mortality risk in middle-aged adults. Data are sparse on long-term follow-up and outcomes associated with ER in younger adults.

Methods and Results—We prospectively examined 5039 participants (mean age, 25 years at baseline, 40% black) from the Coronary Artery Disease Risk in Adults (CARDIA) cohort for 23 years. Twelve-lead ECGs were recorded and analyzed at years 0, 7, and 20 and coded as definite or probable ER using a standardized algorithm. Cox regression was used, and models were adjusted for important baseline and clinical covariates. Kaplan–Meier curves were created for presence of ER and total mortality and cardiovascular mortality. Participants with ER were more likely to be black, male, smoke, have higher systolic blood pressure, lower heart rate and body mass index, higher exercise duration, and longer PR, QRS, and QT intervals. ER was associated with total mortality (hazard ratio, 1.77; confidence interval, 1.38–2.28; \( P<0.01 \)) and cardiovascular mortality (hazard ratio, 1.59; confidence interval, 1.01–2.50; \( P=0.04 \)) in unadjusted analyses, but adjustment for age, sex, and race attenuated associations almost completely. Sex-race stratified analyses showed no significant associations between ER and outcome for any of the subgroups except blacks.

Conclusions—The presence of ER at any time point during 23 years of follow-up was not associated with adverse outcomes. Black race and male sex confound the unadjusted association of ER and outcomes, with no race–sex interactions noted. Additional studies are necessary to understand the factors associated with heightened risk of death in those who maintain ER into and beyond middle age. (Circ Arrhythm Electrophysiol. 2014;7:392-399.)

Key Words: electrocardiography ■ mortality

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Original Article

Received February 5, 2013; accepted March 14, 2014.

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Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org DOI: 10.1161/CIRCEP.113.000874

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of this important ECG phenotype and may help elucidate and refine which phenotypes may be associated with an increased risk of mortality and sudden cardiac death.

Methods

Study Sample

The CARDIA cohort was initiated to investigate the development of heart disease risk factors beginning in young adulthood. Details of the study design and procedures have been previously published. Briefly, 5115 men and women aged 18 to 30 years with appropriate balance in distribution of sex, race (black and white), and education were enrolled in 1985 and 1986 from 4 field centers: Birmingham, AL (University of Alabama at Birmingham); Chicago, IL (Northwestern University); Minneapolis, MN (University of Minnesota); and Oakland, CA (Kaiser Permanente Northern California). Participants were examined at baseline (Y0) and at follow-up examinations in year 2 (Y2), Y5, Y7, Y10, Y15, Y20, and Y25. The CARDIA study has had a high retention rate, with 72% completing the in-person examination at Y20. With the addition of telephone contact with participants who did not attend exams, follow-up has been maintained on 91% of all baseline participants. For the present analysis, we used data from participants attending the Y0, Y7, and Y20 examination dates from whom resting 12-lead ECGs were obtained. Outcomes were adjudicated through Y23. Of the initial 5115 participants, there were 34 participants with missing baseline ECG’s and 12 with ECG abnormalities that preclude the diagnosis of ER. Therefore, the total number of participants included in the present analysis is 5039 for Y0. Using hierarchical exclusion procedures for participants with missing ECGs (n=1193 for Y7, n=2546 for Y20), ECGs with abnormalities precluding the diagnosis of ER, such as paced rhythms, Wolff–Parkinson–White, QRS duration >120 ms (n=2 for Y7; n=10 for Y20), or medications affecting ST segment, such as antiarrhythmic drugs (n=5 for Y7; n=8 for Y20), there were 3676 participants available for the Y7 analysis and 2523 for Y20. All participants signed informed consent at each examination, and the institutional review boards at each site approved study protocols.

Clinical Characteristics

Demographic, anthropometric, physiological, and laboratory measurements for each participant were obtained according to previously published standardized protocols. Briefly, clinical covariates from years 0 and 20, selected a priori because of their known association with cardiovascular diseases, included age, sex, race, measures of blood pressure, height and weight, body mass index (BMI), smoking history, and total and high-density lipoprotein (HDL) cholesterol. Race and sex were reported by the study participants. Weight was measured with the use of a standard balance beam scale, with the participant wearing light clothing without shoes. The BMI was calculated as the weight in kilograms divided by the square of the height in meters. Diabetes mellitus was considered to be present if the person was taking medication for diabetes mellitus. Total cholesterol and HDL cholesterol were measured from fasting samples.

Echocardiographic Imaging

As part of the examination at Y5, CARDIA participants underwent 2-dimensional and M-mode echocardiography performed on an Acuson cardiac ultrasound (Siemens) machine. Measurements were performed using standard echocardiogram definitions.

ECG Analysis

Resting ECGs were obtained in conjunction with the CARDIA Fitness Study, an ancillary study of the main CARDIA cohort during examinations at Y0, Y7, and Y20. ECGs were recorded immediately before the exercise portion of examination visits Y0, Y7, and Y20. For resting electrocardiography, all participants had standard limb and precordial ECG leads placed, with use of the Heartsquare device to determine appropriate placement of the precordial leads (V1 through V6). Identical electrocardiographs (at Y20, GE MAC1200 Marquette Electronics, Milwaukee, WI) were used in all clinical centers. For the year 0 and 7 ECGs, hard copies of the tracings were sent to the Central ECG Laboratory (Epidemiological Cardiology Research Center, Wake Forest University, Winston-Salem, NC) and visually read for the ECG definitions of ER used specifically for this study. At Y20, ECG recordings were transmitted via modem to the Epidemiological Cardiology Research Center for reading using Marquette 12SL (GE Marquette, Milwaukee, WI). All ECGs received were inspected visually to detect technical errors, missing leads, and inadequate quality, and such records were rejected from electrocardiographic data files.

Definition and Coding of ER

ER was diagnosed using a definition developed by the Epidemiological Cardiology Research Center (Winston-Salem, NC), which is based on application of strict criteria selected from previous publications as follows: (1) definite ER: STJ elevation >1 mm in ≥50% of beats, T-wave amplitude ≥± mm, prominent J point, upward concavity of the ST, and a distinct notch or slur on the downstroke of the R wave in any of V1 through V6; or STJ elevation >2 mm in ≥50% of beats, T-wave amplitude ≥± mm, prominent J point and upward concavity of the ST segment in any of V1 through V6. For the STJ elevation, there had to be >1 mm in ≥50% of beats, where there is at least >1 mm elevation at the J point that maintains ≥1 mm elevation until the end of the ST segment. (2) Probable ER: STJ elevation >1 mm in ≥50% of beats, prominent J point, and upward concavity of the ST segment in any of V1 through V6 and T-wave amplitude ≥± mm in any of the chest leads. For the STJ elevation, there had to be >1 mm in ≥50% of beats, where there is at least >1 mm elevation at the J point that maintains ≥1 mm elevation until the end of the ST segment; and (3) possible ER: presence of Minnesota code 9–2 (ST-segment elevation >1.0 mm in any of leads I, II, III, aVL, aVF, V4, V5, or V6) or ST-segment elevation >2.0 mm in any of leads V1 through V6 or Minnesota code 9–5 (T-wave amplitude ≥± mm in any of leads I, II, III, aVL, aVF, V4, V5, V6, V1, V2, V3, Figure 1). Possible ER and no ER are combined as 1 group in the analysis. All ECGs were read for ER characteristics by a single reader. Details of the reproducibility and repeatability of this coding algorithm have been previously reported.

Similar to all Minnesota codes, definite and probable are in hierarchical order, where the most serious/most confirmed overrides the less serious/less confirmed. Therefore, definite is defined first (ie, the denominator is all participants), then among the remaining participants who are not classified as definite, probable is then explored (ie, the denominator is everyone that is not classified as definite). Using this hierarchical methodology, categories of ER were created as defined above.

Outcomes Adjudication

Participants were followed for the development of incident cardiovascular events ≥23 years from their baseline examinations. Trained personnel abstracted any medical records suggesting possible cardiovascular events. Physicians from the CARDIA study events committee, blinded to CARDIA study data and ECG results, independently reviewed all medical records for end point classification using prespecified criteria. Event classification was determined by reviewers, and adjudication was performed as necessary. Reviewers classified myocardial infarction (MI) as definite, probable, or absent based on prespecified criteria, including symptoms (eg, chest pain), ECG abnormalities, and cardiac biomarker levels. These criteria have been previously described. Total mortality was death from any cause. Cardiovascular death was death from any cardiovascular cause. We also included a separate analysis incorporating the addition of MI. In categories where MI was included as an outcome measure, such as total death+MI or cardiovascular death+MI, we counted the first event of an MI (fatal or nonfatal) or a death from any cause or the first event of an MI (fatal or nonfatal) or a death because of some other cardiovascular cause.

Statistical Analysis

All analyses were performed using SAS version 9.1 (SAS institute, Cary, NC). Participant were classified into ER presence (ER+: definite/
probable ER) versus no ER presence (ER−). Baseline characteristics were compared by ER status using generalized linear models for continuous variables and χ² tests for categorical variables, as appropriate. We classified outcomes as total mortality alone, total mortality or MI, cardiovascular mortality, and cardiovascular mortality or MI. Kaplan–Meier curves were constructed to illustrate the cumulative incidence of event outcomes by ER status. We tested the association of ER and outcomes using Cox proportional hazards regression analysis. All the models were fitted initially unadjusted; adjusted for age alone; sex alone; race alone; age, sex, and race; and a model adjusted for age, sex, race, and clinical covariates. The covariates included factors known to be associated with cardiovascular risk, including systolic blood pressure, BMI, total cholesterol/HDL ratio, current smoker, blood pressure treatment, baseline heart rate, and fitness level. Fitness was defined by exercise duration on a graded exercise treadmill test. For purposes of this analysis, we performed secondary analyses a priori, stratifying participants into low and high fitness based on the median value. No statistically significant interactions were present. Proportional hazards assumptions were checked and found to be appropriate.

We also performed secondary analyses for the following: (1) total mortality alone with definite ER alone; (2) definite ER and total mortality or cardiovascular mortality separately, (3) maintainers of ER (from Y0 to Y7) and total mortality or cardiovascular mortality. A P value <0.05 (2-tailed) was considered statistically significant.

Results

Study Sample
Baseline characteristics of the study sample, categorized by status of ER (Y0, Y7, and Y20), are shown in Table 1. The study sample consisted of 5039 participants at Y0, of whom 941 (18.7%) had definite ER, 314 (6.2%) had probable ER, and 265 (5.2%) had possible ER. Compared with participants without ER at baseline (Y0), participants with definite/probable ER were more likely to be black, male, smoke, have higher systolic blood pressure, lower heart rate and BMI, total cholesterol, HDL, higher physical activity and fitness levels, and longer PR, QRS, and QT intervals (all statistically significant). Year 5 echocardiographic left ventricular (LV) mass, LV end-diastolic diameter, and left ventricular posterior wall thickness were also higher in those with baseline ER. The prevalence of definite/probable ER diminishes over time: Y0 (24.8%), Y7 (14.7%), and Y20 (6.6%). Characteristics of participants with and without ER at Y7 and Y20 generally followed similar patterns of association, although risk factor levels and prevalence were higher, as expected. Two exceptions of note include increasing prevalence of black participants in those with ER at Y7 and Y20 and increasing LV mass metrics over time in those without ER versus stable levels of LV mass in those with ER.

At Y20, characteristics more likely to be associated with definite/probable ER include male sex, black race, higher systolic blood pressure less likely to be taking antihypertensive treatment, lower BMI, higher HDL, longer exercise duration, and higher physical activity score. Higher LV mass was more prevalent in those without than with definite/probable ER at Y20.

Event Rates
The Kaplan–Meier curves for ER+ (definite and probable) and ER− with total mortality and cardiovascular mortality are shown in Figure 2A and 2B. Among 5039 participants eligible for analysis with baseline ECGs, of whom 1249 had Y0 ECG ER+, crude event rates are shown in Table 2. Event rates in 1000 person-years are as follows for the outcomes of interest: 2.59 per 1000 person-years for total mortality, 2.91 per 1000 person-years for total mortality+MI, 0.83 per 1000 person-years for cardiovascular mortality, and 1.18 per 1000 person-years for cardiovascular mortality+MI.

Total Mortality Association with ER

Our models exploring outcomes associated with ER are shown in Table 2. The total death rate (per 1000 follow-up year) is 3.83 for definite ER, 3.91 for probable ER, 5.3 for possible ER, and 1.9 for no ER. ER was associated with total death in unadjusted analysis (hazard ratio [HR], 1.77; confidence interval [CI], 1.38–2.28; P<0.01). When adjusting for age or race alone, the findings remained significant (age: HR, 1.80; CI, 1.40–2.32; race: HR, 1.72; CI, 1.37–2.16).
ER also was associated with cardiovascular death in unadjusted analysis (HR, 1.63; CI, 1.03–2.56; P=0.04), whereas adjustment for race (HR, 1.51; CI, 0.96–2.38; P=0.07) and sex alone (HR, 0.97; CI, 0.59–1.61; P=0.91) yielded no statistically significant association. When additional adjustment for age, sex, and race was performed, in addition to multivariable adjustment for clinical covariates, findings were sharply attenuated to nonsignificance (Table 2). When we analyzed the outcome of cardiovascular mortality or MI with ER, we found a similar pattern of results, but findings remained statistically significant when performing age and race adjustments separately. Unadjusted HRs for all outcomes were higher for those with lower fitness than those with higher fitness, but adjustment for sex and race attenuated associations of ER with outcomes to nonsignificance in both fitness strata.

Cardiovascular Mortality Association With ER
ER also was associated with cardiovascular death in unadjusted analysis (HR, 1.59; CI, 1.01–2.50; P=0.04), as well as after adjustment for age alone (HR, 1.63; CI, 1.03–2.56; P=0.04), whereas adjustment for race (HR, 1.51; CI, 0.96–2.38; P=0.07) and sex alone (HR, 0.97; CI, 0.59–1.61; P=0.91) yielded no statistically significant association. When additional adjustment for age, sex, and race was performed, in addition to multivariable adjustment for clinical covariates, findings were sharply attenuated to nonsignificance (Table 2). When we analyzed the outcome of cardiovascular mortality or MI with ER, we found a similar pattern of results, but findings remained statistically significant when performing age and race adjustments separately. Unadjusted HRs for all outcomes were higher for those with lower fitness than those with higher fitness, but adjustment for sex and race attenuated associations of ER with outcomes to nonsignificance in both fitness strata.

Outcomes Stratified by Fitness Levels
Low fitness levels uniformly were associated with higher hazard ratios across all our models. ER also was associated with total

Table 1. Baseline Characteristics of the Study Population by Status of Early Repolarization*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ER Y0</th>
<th>ER Y7</th>
<th>ER Y20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>24.9±3.7</td>
<td>24.5±3.6</td>
<td>32.1±3.6</td>
</tr>
<tr>
<td>Female, %</td>
<td>69.5</td>
<td>8.8</td>
<td>62.3</td>
</tr>
<tr>
<td>Black, %</td>
<td>50.0</td>
<td>56.5</td>
<td>46.0</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>109.2±10.9</td>
<td>113.8±10.3</td>
<td>108.1±12.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>68.3±9.5</td>
<td>69.6±9.8</td>
<td>69±10</td>
</tr>
<tr>
<td>Anti-HTN Rx</td>
<td>2.4</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.7±5.4</td>
<td>23.7±3.3</td>
<td>27.1±6.3</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>28.6</td>
<td>35.5</td>
<td>25.2</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>177.8±33.5</td>
<td>173.5±33.1</td>
<td>177.0±33.8</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>53.5±13.3</td>
<td>52.1±12.9</td>
<td>50.1±14.1</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>109.7±31.3</td>
<td>106.8±30.9</td>
<td>107.9±31.2</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>82.1±16</td>
<td>84.1±16.1</td>
<td>91.8±18.6</td>
</tr>
<tr>
<td>Insulin</td>
<td>11.4±8.4</td>
<td>9.4±6.3</td>
<td>14.6±18.1</td>
</tr>
<tr>
<td>Exercise duration, min</td>
<td>9.0±3.0</td>
<td>11.5±2.7</td>
<td>8.7±2.9</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>388.1±285.9</td>
<td>516.9±321.9</td>
<td>321.8±267.5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.5±10.6</td>
<td>57.7±9.0</td>
<td>65.1±10.7</td>
</tr>
<tr>
<td>PR, ms</td>
<td>146.8±22.1</td>
<td>152.2±23.6</td>
<td>150.1±21.8</td>
</tr>
<tr>
<td>QRs, ms</td>
<td>81.7±7.3</td>
<td>86.1±8.8</td>
<td>82.7±7.4</td>
</tr>
<tr>
<td>QT, ms</td>
<td>385±26.3</td>
<td>393.6±26.8</td>
<td>385.0±25.4</td>
</tr>
<tr>
<td>QT index</td>
<td>96.2±4.6</td>
<td>94.4±4.4</td>
<td>96.6±4.3</td>
</tr>
<tr>
<td>Cornell product LVH</td>
<td>1184±397</td>
<td>1165±551</td>
<td>1232.4±410</td>
</tr>
<tr>
<td>ECG LV mass index</td>
<td>32.2±5.5</td>
<td>33.4±5</td>
<td>34.2±6.0</td>
</tr>
<tr>
<td>Y 5 echocardiographic LVEDD, cm</td>
<td>4.9±0.48</td>
<td>5.1±0.45</td>
<td>4.93±0.49</td>
</tr>
<tr>
<td>Y 5 echocardiographic LVPWT, cm</td>
<td>0.83±0.14</td>
<td>0.89±0.13</td>
<td>0.84±0.14</td>
</tr>
</tbody>
</table>

Means±SD unless otherwise indicated. BMI indicates body mass index; DBP, diastolic blood pressure; ER, early repolarization; HTN Rx, hypertension treatment; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVH, LV hypertrophy (see below for definition); LVPWT, left ventricular posterior wall thickness; and SBP, systolic blood pressure.

*ER defined as definite or probable by uniform criteria.
†Defined as self-reported yes or fasting glucose ≥126 mg/dL.
‡qtdur1×(h+100)/656.
§Cornell voltage >2200 μV for women; >2800 μV for men.
mortality in unadjusted analysis, stratified by low and high fitness levels (unadjusted low: HR, 2.77; CI, 1.83–4.20; \( P < 0.01 \)), compared with high fitness levels (unadjusted high: HR, 1.58; CI, 1.12–2.24; \( P = 0.009 \)). After age, sex, and race adjustment, findings were attenuated to nonsignificance. Our findings were similar when analyzing ER with cardiovascular mortality.

**Patterns of Association by Sex–Race Groups**

We performed sex-race stratified analyses, specifically examining the outcome of total mortality. The association of ER and total mortality was not significant for any of the subgroups explored except in blacks, although tests for interactions were not significant. Twenty-three year event rates were as follows.
for ER− versus ER+: white men, 6.8% versus 5.8%; white women, 2.8% versus 0%; black men, 9.8% versus 11.7%; black women, 4.3% versus 4.8%. As expected, event rates were higher for men compared with women and for black compared with white participants in our younger adult cohort.

Exploratory Analyses

None of our sensitivity analyses demonstrated a statistically significant association between ER and outcome. We examined associations by ER pattern over time (ER maintainers, losers, gainers, never, from Y0 to Y20) with outcomes. Event rates by ER pattern, respectively, were 3.1%, 1.4%, 0%, and 1.4% for total mortality and 1.0%, 0.8%, 0%, and 0.8% for cardiovascular mortality. Event rates were too small by category of ER pattern over time to identify robust associations. We currently do not have the power to answer the question whether ER that is detected at age 25 years and persists into middle age is associated with elevated risk.

Discussion

In this large, biracial cohort followed prospectively from young age through middle age, we observed that ER is associated with total and cardiovascular mortality in unadjusted analyses. However, after multivariable adjustment, the association of ER and total mortality and cardiovascular mortality was not statistically significant. The associations between ER and our primary outcome measures were largely confounded by sex and race, but no sex–race interactions were noted. Young adult men and blacks had higher prevalence of ER at baseline and over follow-up, and these groups also had higher event rates of our primary outcome measures. However, the presence of ER was not independently associated with adverse outcomes once we adjusted for sex and race. In addition, when we explored outcomes with the pattern of ER over time (eg, maintenance, loss, gain, or never presence of ER), there were no statistically robust associations.

The vast majority of ER in our study sample regressed by Y20. In the 4.7% of whom definite ER remained prevalent at Y20, characteristics associated with predicting maintenance of ER from Y0 to Y20 were black race (odds ratio, 2.62; 95% CI, 1.61–4.25), BMI (0.62 per 1 SD; CI, 0.40–0.94), serum triglycerides (0.66 per 1 SD; CI, 0.45–0.98), and QRS duration (1.68 per 1 SD; CI, 1.37–2.06) at baseline.4 Importantly, even among this sample of participants who maintained ER for 20 years, the majority of whom were black, there was no increased risk of total mortality or cardiovascular mortality.

Our findings support the hypothesis that the pattern of definite/probable ER from young adulthood to middle age is largely a benign phenotype. The observation that black race predominantly attenuates the association between ER and outcomes suggests that this ER phenotype in younger adults and blacks may represent a different phenotype, a more benign electrophysiological entity than that reported by other investigators in those of European descent in middle age.5,6 Furthermore, we found no statistically significant associations between ER and adverse outcomes in those who maintain ER.

### Table 2. Association of Definite/Probable* Early Repolarization at Baseline Y0 and Outcome at Year 23 in Unadjusted and Adjusted Models

<table>
<thead>
<tr>
<th>Models</th>
<th>Total Death n=262 (Event Rate, 5.2%)</th>
<th>Cardiovascular Death n=84 (Event Rate, 1.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>HR (95% CI) P</td>
<td>HR (95% CI) P</td>
</tr>
<tr>
<td>Low fit†</td>
<td>1.77 (1.38–2.28) &lt;0.01</td>
<td>1.59 (1.01–2.50) 0.04</td>
</tr>
<tr>
<td>High fit</td>
<td>2.77 (1.83–4.20) &lt;0.01</td>
<td>2.25 (1.04–4.88) 0.04</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.58 (1.12–2.24) 0.009</td>
<td>1.59 (0.85–2.97) 0.15</td>
</tr>
<tr>
<td>Low fit</td>
<td>1.80 (1.40–2.32) &lt;0.01</td>
<td>1.63 (1.03–2.56) 0.04</td>
</tr>
<tr>
<td>High fit</td>
<td>2.80 (1.85–4.24) &lt;0.01</td>
<td>2.27 (1.05–4.92) 0.04</td>
</tr>
<tr>
<td>Sex adjusted</td>
<td>1.61 (1.13–2.28) 0.008</td>
<td>1.64 (0.88–3.09) 0.12</td>
</tr>
<tr>
<td>Low fit</td>
<td>1.13 (0.85–1.50) 0.42</td>
<td>0.97 (0.59–1.61) 0.91</td>
</tr>
<tr>
<td>High fit</td>
<td>1.27 (0.79–2.05) 0.33</td>
<td>0.94 (0.39–2.23) 0.88</td>
</tr>
<tr>
<td>Race adjusted</td>
<td>1.13 (0.79–1.63) 0.50</td>
<td>1.09 (0.57–2.09) 0.79</td>
</tr>
<tr>
<td>Low fit</td>
<td>1.72 (1.33–2.21) &lt;0.01</td>
<td>1.51 (0.96–2.38) 0.07</td>
</tr>
<tr>
<td>High fit</td>
<td>2.65 (1.75–4.04) &lt;0.01</td>
<td>1.87 (0.86–4.06) 0.11</td>
</tr>
<tr>
<td>Age/sex/race adjusted</td>
<td>1.32 (0.93–1.88) 0.12</td>
<td>1.29 (0.68–2.45) 0.43</td>
</tr>
<tr>
<td>Low fit</td>
<td>1.07 (0.81–1.42) 0.63</td>
<td>0.90 (0.55–1.45) 0.69</td>
</tr>
<tr>
<td>High fit</td>
<td>1.22 (0.76–1.98) 0.41</td>
<td>0.79 (0.33–1.87) 0.58</td>
</tr>
<tr>
<td>Full model</td>
<td>1.07 (0.74–1.53) 0.73</td>
<td>1.04 (0.54–1.99) 0.91</td>
</tr>
<tr>
<td>Full model adjusted</td>
<td>1.16 (0.85–1.57) 0.35</td>
<td>0.96 (0.56–1.65) 0.88</td>
</tr>
<tr>
<td>Low fit</td>
<td>1.30 (0.78–2.17) 0.32</td>
<td>0.70 (0.27–1.85) 0.47</td>
</tr>
<tr>
<td>High fit</td>
<td>1.05 (0.72–1.53) 0.79</td>
<td>1.10 (0.56–2.17) 0.78</td>
</tr>
</tbody>
</table>

*Early repolarization represents definite or probable early repolarization using uniform criteria.
†Fitness: low (<50% vs high ≥50%).

Full model adjusted for systolic blood pressure, body mass index, total cholesterol/high-density lipoprotein ratio, smoker, blood pressure treatment, heart rate at baseline, and exercise fitness (low vs high, see text). CI indicates confidence interval; and HR, hazard ratio.

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or in those whose ER phenotype regresses or emerges over time in this cohort.

Perhaps the risk of mortality and sudden death becomes more heightened in those in whom ER persists into middle age but not for the vast majority of those in whom it is present in young adulthood. Prospective studies exploring the more ominous phenotype in young adults seem warranted. Whether it is ER alone or the presence of ER and subsequent accrual of risk factors or triggers (such as MI or structural heart disease) that elevates this risk in middle age requires additional study. Recent studies have implicated ER and a trigger (eg, ST-segment–elevation myocardial infarction) or a fixed substrate (eg, myocardial scar) as factors that increase the risk of ventricular arrhythmias\(^{16–18}\) in middle-aged and older patients.

Our study is consistent with previous reports on several levels. First, a prior report\(^6\) has suggested that ER may, in fact, be more common in blacks. Second, ER seems to be more common in those with greater exercise duration/fitness.\(^{19}\) Third, certain characteristics seem to be more commonly associated with ER, including lower heart rate, less BMI, and longer PR, QRS, and QT intervals. Whether these are characteristics that are more likely noted with cardiovascular fitness and greater vagal tone is not well understood but suggests that certain environmental factors may increase the prevalence of ER. The observation that there is an inverse relationship between advancing age and ER regression suggests, perhaps, that regression of ER may be related to poor or loss of cardiovascular fitness (as our findings suggest), and, therefore, maintenance of ER over time may imply a heritable component, as described by Noseworthy et al.\(^{20}\)

Our findings extend prior observations that young adults, both blacks and whites, followed prospectively from young adulthood into middle age, have a low risk of total and cardiovascular mortality associated with ER. There are several plausible hypotheses for this observation at this time. First, differences in ethnicities or genetic background may explain differences in total and cardiovascular risk in our study compared with those demonstrating a higher risk. Studies in those of European and Asian ancestry have reported heightened risk, whereas reports in blacks have not. Moreover, several studies\(^7,8\) implicating elevated risk of the ER phenotype investigated participants with clinical manifestations, which may be consistent with a risk marker of arrhythmia (eg, syncope, aborted sudden death). Second, ER may be an underlying electrophysiological substrate, which may require a trigger (eg, MI)\(^{16–18}\) to heighten sudden death risk. Because participants live longer and become exposed to greater cardiovascular risk factors, the presence of ER into middle age, for example, may increase risk of death, as has been reported in several middle-aged population studies. One study\(^21\) using J point elevation alone, not ER as defined in our study, suggested that whites were more likely to experience sudden cardiac death. Whether blacks, who typically have a greater burden of cardiovascular risk factors with advancing age, are more likely to experience adverse outcomes in middle age and beyond bears additional investigation in older, multiracial/ethnic cohorts.

**Clinical Implications**

Although previous studies have suggested that the ER phenotype is benign, recent data suggest that there may be substantial risk with certain ER phenotypes. Therefore, the clinician is faced with uncertainty about the consequences of this phenotype in young age. Using a visually confirmed definition of ER commonly used in clinical practice, our study found that the vast majority of participants in the CARDIA study do not have a heightened risk of adverse outcomes, whether the participant maintains or loses the phenotype, to middle age. We acknowledge that it is possible that we have not yet followed our study population long enough to manifest a heightened risk. At this time, although it is unreasonable to expect clinical practice to change, those who maintain the ER phenotype into middle and older age years may benefit from ECG monitoring until additional studies explore the associations of ER and adverse outcomes in these middle age and older patient groups.

**Strengths and Limitations**

Strengths of our study include its prospective nature, uniform definition of ER, phenotypic characterization, biracial study population, and a high retention rate for outcomes ascertainment. This is the largest prospective study to date of a young biracial cohort with ER and outcomes that uses serial ECG assessment. Given that ER may disappear, emerge, or be maintained over time allows us an opportunity to analyze outcomes associated with the natural history of ER in this unique cohort.

Limitations of our study include the different definition used by Epidemiological Cardiology Research Center compared with prior published reports. One such difference is the absence of inferior lead characterization of ER for definite or probable ER, which has been reported to be an important regional risk marker of ER, particularly in those who experience sudden cardiac death. However, the prevalence of inferior lead ER pattern has been reported to be low in middle age (3.8%) and younger (2.5%) study populations; therefore, its prognostic significance for this study population overall is likely limited but unknown. In addition, the purpose of our study was not to apply the more uncommon phenotype of ER to the CARDIA cohort but to use the more common ER phenotype seen in clinical practice to understand prospective risk. Because we cannot specify risk based specifically on regionalality of ECG lead placement in our study, it is unknown whether even a small prevalence of ER in the inferior leads may have altered our findings. Our differing definition from that reported by Haissaguerre, Tikkanen, and Rosso may explain differences in outcomes noted between studies and may limit the external validity of our sample to the sudden cardiac death population of interest. A limitation of our article may be that we have preselected an ER phenotype that may represent a benign phenotype. What is not known, however, is whether this phenotype increases the risk of death in middle age subjects who are exposed to a potential trigger (eg, MI). Additional studies are needed to better define these prospective associations. Nonetheless, our analysis remains clinically important and generalizable to the everyday clinician, as the proposed definition in this article is the commonly accepted electrocardiographic syndrome of ER.

**Sources of Funding**

Work on this article was supported (or partially supported) by contracts University of Alabama at Birmingham, Coordinating Center, N01-HC-95095; University of Alabama at Birmingham, Field Center,
N01-HC-48047; University of Minnesota, Field Center and Diet Reading Center (Year 20 Exam), N01-HC-48048; Northwestern University, Field Center, N01-HC-48049; and Kaiser Foundation Research Institute, N01-HC-48050 from the National Heart, Lung, and Blood Institute. Dr Lloyd-Jones was supported by RO1 HL086792-01.

Disclosures

None.

References


Clinical Perspective

Several investigators recently have observed that certain patterns of early repolarization (ER) confer increased mortality and sudden death risk. Although the more ominous ER pattern is rarely discovered in clinical practice, the classic ER pattern is commonly encountered. Data regarding the prognostic significance of the classic ER phenotype in young adults are sparse, and evaluation has been limited to middle-aged participants, limited race/ethnicity groups, and abbreviated follow-up. In this article, we provide prospective evaluation of ER for 23 years in a young biracial cohort balanced on sex and race starting at age 25 years and followed to middle age. Using the Coronary Artery Disease Risk in Adults (CARDIA) study, we found that ER was more common in young men and blacks. ER was associated with total and cardiovascular mortality in unadjusted analysis. However, after adjustment for age, sex, and race, findings were attenuated almost completely, indicating that ER was merely a marker for the higher death rates observed in young men and blacks. Our data provide additional support for the potential benign nature of the classic ER phenotype, at least through young adulthood to middle age. Whether the phenotype increases risk of death beyond middle age, however, is not currently known. Such knowledge supports current understanding regarding the classic ER phenotype and extends our understanding of the natural history and outcomes associated with this important and commonly encountered ECG phenotype in clinical practice.
Clinical Characteristics and Outcomes Associated With the Natural History of Early Repolarization in a Young, Biracial Cohort Followed to Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study
Leonard Ilkhanoff, Elsayed Z. Soliman, Ronald J. Prineas, Joseph A. Walsh III, Hongyan Ning, Kiang Liu, J. Jeffrey Carr, David R. Jacobs, Jr and Donald M. Lloyd-Jones

_Circ Arrhythm Electrophysiol._ 2014;7:392-399; originally published online April 23, 2014; doi: 10.1161/CIRCEP.113.000874

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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