Heritability of Early Repolarization
A Population-Based Study

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Background—Early repolarization (ER), defined by J-point elevation in 12-lead ECG, was recently associated with increased risk for idiopathic ventricular fibrillation and cardiovascular mortality. The determinants of ER are unknown. We investigated its heritability in a large, family-based cohort.

Methods and Results—The study sample comprised 1877 individuals from 505 white nuclear families representative of the British general population. Standard 12-lead ECGs were evaluated for the presence of ER, defined as J-point elevation of $\geq 0.1$ mV in at least 2 adjacent inferior (II, III, and aVF) or anterior lateral (I, aVL, and V4 through V6) leads. Narrow sense heritability estimates were computed adjusting for age, age$^2$, and sex. The prevalence of ER was 7.7% (n=145) in the whole cohort, 5.9% (n=56) in parents, and 9.6% (n=89) in offspring. Heritability estimate for the presence of ER was calculated at $h^2=0.49$ (standard error=0.14; $P=2.7*10^{-4}$) and was higher when restricted to its presence in inferior leads ($h^2=0.61$, standard error=0.18, $P=4.3*10^{-4}$) or for the notching ER morphology ($h^2=0.81$, standard error=0.19, $P=2.4*10^{-5}$). Individuals with at least 1 affected parent had a 2.5-fold increased risk for presenting with ER on ECG (odds ratio, 2.54; 95% confidence interval, 1.33 to 4.84; $P=0.005$). Familial transmission was more frequent when the mother was affected (odds ratio, 3.84; 95% confidence interval, 1.41 to 10.43; $P=0.008$) than when the father was affected (odds ratio, 1.82; 95% confidence interval, 0.82 to 4.03; $P=0.141$), although this difference was not statistically significant ($P=0.18$).

Conclusions—ER is a heritable phenotype. Offspring of ER-positive parents have a 2.5-fold increased risk of presenting with ER on their ECG. (Circ Cardiovasc Genet. 2011;4:134-138.)

Key Words: electrocardiography ■ genetics ■ early repolarization ■ J-point elevation ■ heritability

Early repolarization (ER) is a common ECG finding defined by elevation of the junction between the end of the QRS complex and the beginning of the ST segment (J-point). Although ER was regarded as harmless for decades, a compelling body of evidence has recently associated J-point elevation in leads other than V1 through V3 with electric instability and sudden cardiac death.1–4 Moreover, long-term follow-up data found a strong association between presence of the ER pattern, particularly in the inferior leads, and cardiovascular mortality.5,6 Despite its prognostic importance, the pathophysiological mechanisms underlying ER are not yet understood. Experimental data suggest alterations in cardiac transmembrane ion currents leading to transmural electric heterogeneity and susceptibility to malignant ventricular arrhythmias.7 The biological determinants of this ECG phenotype are not clear. However, given that a single mutation has been identified as a primary molecular defect of a rare syndrome of ventricular fibrillation clustering with ER,8 and that interindividual variation in several other quantitative ECG parameters, such as QT interval, is to a large extent genetically controlled,9–11 we hypothesized that ER may be a heritable phenotype. We tested this in a large sample of nuclear families derived from the British general population.

Clinical Perspective on p 138

Methods

Subjects
Analyses were performed in the GRAPHIC (Genetic Regulation of Arterial Pressure of Humans in the Community) cohort, which has...
been previously described in detail.12-13 Briefly, the GRAPHIC study recruited nuclear families from the general population in Leicestershire, United Kingdom, by writing to women ages 40 to 69 years registered with participating family practitioners and inviting them and their family to participate. Families were included if both parents aged 40 to 60 years and 2 offspring >18 years of age wished to participate. A detailed medical history was obtained from study subjects by standardized questionnaires, and clinical examination was performed by research nurses following standard operating procedures. Measurements included height, weight, waist-hip ratio, clinic and ambulatory blood pressure, and 12-lead ECGs. Blood samples were obtained for laboratory analysis. Of 2037 individuals from 520 nuclear families, 160 subjects were excluded because of missing or poor-quality ECG recordings, abnormal rhythms, or significant ventricular conduction delay (QRS complex duration >120 ms). The present analysis is based on 1877 GRAPHIC participants from 505 families.

The study was approved by the Leicestershire Research Ethics Committee, and all subjects provided written informed consent. The study conforms to the principles outlined in the Declaration of Helsinki, and all procedures followed were in accordance with institutional guidelines.

### ECG Analyses

Paper-printed 12-lead ECGs (all automatically produced in the same format and written at 25 mm/s) were independently read by 2 experienced clinicians who were blinded with respect to age, sex, and family structure. ER was defined by the criteria proposed by Haux and authors,1 that is, the presence of J-point elevation ≥0.1 mV in at least 2 adjacent leads in inferior (II, III, and aVF) or anterolateral leads (I, aVL, and V6 through V2). J-point elevation was measured by ruler-based visual inspection using Spacelab magnifying glasses for ECG diagnostics. Leads V1 through V6 were excluded from the analysis to avoid confusion with Brugada syndrome and right ventricular dysplasia. The presence or absence of ST-segment elevation in addition to J-point elevation was not taken into account. Nonspecific intraventricular conduction delay was excluded. ER was specified by localization (inferior, anterolateral, or both), being coded as present in both inferior and anterolateral leads if at least 2 adjacent leads in 1 region and at least 1 additional lead in the complementary region showed J-point elevation ≥0.1 mV. ER was furthermore characterized by ECG morphology (notching, slurring, or both) and maximum J-point elevation amplitude (mV).

There was strong agreement between the 2 interpreters (κ = 0.61; proportion agreement, 95%). In the case of disagreement, ECGs were jointly reassessed by the 2 readers, and a final decision was achieved by consensus. Additional ECG characteristics (heart rate, PQ interval, QRS duration, QT interval) were derived from computerized measurements derived from the widely used University of Glasgow ECG analysis program.14 QT interval was corrected for heart rate using 2 approaches: the Framingham formula and the Bazett formula.15,16

### Statistical Analyses

Statistical analyses were performed using STATA 11 software. Normality of the distribution of traits was assessed by visual inspection of histograms. Continuous and binary traits were compared by univariate linear and logistic regression models, respectively, via generalized estimating equations with an exchangeable correlation structure to account for familial correlation. Heritability estimates for ER according to different phenotypic criteria were calculated using variance component analyses as implemented in SOLAR version 4.2.7 and adjusted for age, age2, and sex. In brief, phenotypic variance of ER was partitioned into components attributable to genetic and environmental effect. The genetic component was further divided into polygenic additive effect (narrow sense heritability explained by the regression slope) and the nonadditive effect of alleles (dominant effect, the source of deviation from the slope). The likelihood of presence of ER in at least 1 offspring of affected parents was calculated using logistic regression, conditioned on the presence of ER in any or either of the parents.

### Table 1. Prevalence and Characteristics of ER in the Study Population (n=1877)

<table>
<thead>
<tr>
<th>Group</th>
<th>ER Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both sexes, n (%)</td>
<td>145 (7.7)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>110 (11.7)*</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>35 (3.7)*</td>
</tr>
<tr>
<td>Parents, n (%)</td>
<td>56 (5.9)*</td>
</tr>
<tr>
<td>Offspring, n (%)</td>
<td>89 (9.6)†</td>
</tr>
</tbody>
</table>

*P value, men vs women ER prevalence: P=4.4*10^-5.
†P value, parental versus offspring ER prevalence: P=3.3*10^-3.

### Results

#### Prevalence of ER and Baseline Characteristics of the Study Population

ER was present in 145 individuals (7.7%), with significant predominance in men (Table 1). In the whole cohort, prevalence of ER in men was 11.7% as compared with 3.7% in women (P=4.4*10^-5). Parents had a lower ER prevalence as compared with the offspring generation (5.9% versus 9.6%; P=3.3*10^-5). In those with ER, it was present in inferior leads only in 37.9% of subjects, anterolateral leads in 27.6%, and in both in 34.5%. A combination of both notching and slurring pattern (46.2% of those with ER) was the most common ER morphology. Notching and slurring morphology alone were identified in 42.1% and 11.7% of subjects with ER, respectively.

Clinical and ECG characteristics of ER-positive versus ER-negative subjects, partitioned by parental and offspring generation, are listed in Table 2. In both parents and offspring, ER-positive individuals were predominantly men and had a shorter QTc interval. In addition, in the offspring generation, subjects with ER were younger and had a lower body mass index. Moreover, in this generation, ER-positive individuals had a lower average resting heart rate, a longer QRS duration, and a higher prevalence of left ventricular hypertrophy as measured by Sokolow-Lyon index.

#### Heritability of ER

Heritability estimation for the presence of ER was h2 = 0.49 (standard error [SE] = 0.137, P = 2.7*10^-4) after adjusting for age, age2, and sex in a variance components analysis (Table 3). Heritability estimates were even higher if the ER pattern was restricted to the inferior leads (h^2 = 0.61, SE = 0.183, P = 4.3*10^-4). Moreover, heritability appeared particularly high for the notching ER morphology (h^2 = 0.81, SE = 0.194, P = 2.4*10^-5) (Table 3). Heritability of slurring morphology could not be assessed because of the lack of corresponding families. To assess potential confounding by the use of...
Table 3. Heritability Estimates of ER According to Different Phenotypic Criteria

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Heritability (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER, n=145</td>
<td>0.487 (0.137)</td>
<td>2.7*10^-4</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER in inferior leads, n=55</td>
<td>0.611 (0.183)</td>
<td>4.3*10^-4</td>
</tr>
<tr>
<td>ER in anterolateral leads, n=40</td>
<td>0.351 (0.305)</td>
<td>0.151</td>
</tr>
<tr>
<td>ER in both regions, n=50</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER of notchting morphology, n=61</td>
<td>0.810 (0.194)</td>
<td>2.4*10^-5</td>
</tr>
<tr>
<td>ER of slurring morphology, n=17</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>ER of both morphologies, n=67</td>
<td>0.516 (0.221)</td>
<td>9.6*10^-3</td>
</tr>
</tbody>
</table>

Calculations were adjusted for age, sex, and region.

*Heredity estimates for ER in both inferior+anterolateral leads, and ER of slurrying morphology could not be assessed because of lack of adequate number of families with the respective phenotype in parental and offspring generation.

Discussion

The ECG pattern of ER has been known for decades, and was generally considered a benign normal variant of the surface ECG. Recently, however, evidence of the potentially hazardous nature of ER has emerged, when ER was associated with an increased risk for idiopathic ventricular fibrillation and cardiovascular and all-cause mortality. The pathophysiological mechanisms of ER are unclear. Therefore, we ana-

Figure. Representative examples of ER in a GRAPHIC nuclear family with the presence of ER in the inferior leads of different morphology in the mother and both children.

Table 2. Characteristics of Parental and Offspring Generation

<table>
<thead>
<tr>
<th></th>
<th>Parents (n=945)</th>
<th>Offspring (n=932)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ER Positive</td>
<td>ER Negative</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>38 (67.9)</td>
<td>431 (48.5)</td>
</tr>
<tr>
<td>Age, y</td>
<td>52.3±3.9</td>
<td>52.8±4.3</td>
</tr>
<tr>
<td>Body mass index, kg/m</td>
<td>27.4±4.0</td>
<td>27.4±4.3</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio, n=1818</td>
<td>4.4±1.0</td>
<td>4.2±1.2</td>
</tr>
<tr>
<td>Past or present smoking, %, n=1867</td>
<td>33 (58.9)</td>
<td>440 (49.8)</td>
</tr>
<tr>
<td>History of hypertension, %, n=1867</td>
<td>27 (48.2)</td>
<td>377 (42.7)</td>
</tr>
<tr>
<td>History of angina pectoris, %, n=1875</td>
<td>0</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>History of diabetes mellitus, %, n=1876</td>
<td>1 (1.79)</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td>Chronotropic medication, %</td>
<td>6 (10.7)</td>
<td>32 (3.6)</td>
</tr>
<tr>
<td>ECG characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>63±8</td>
<td>65±10</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>92±8</td>
<td>91±10</td>
</tr>
<tr>
<td>QTc interval (Framingham),† ms</td>
<td>401±17</td>
<td>410±22</td>
</tr>
<tr>
<td>QTc interval (Bazett),† ms</td>
<td>403±18</td>
<td>415±23</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (Sokolow-Lyon Index), %</td>
<td>3 (5.4)</td>
<td>16 (1.8)</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD, dichotomous data as n (%).

*Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or intake of antihypertensive medication.

†QT interval was corrected according to the Framingham formula: QTc (Framingham) = QT (ms) – 0.154*[RR (ms) – 1000], or to the Bazett formula: QTc (Bazett) = QT (ms)/RR (s).
alyzed the heritability of ER in families representative of the British normal population to investigate a potential genetic basis underlying the ER pattern.

We found that ER is a highly heritable trait in the GRAPHIC Study, a population-based cohort representative of the UK white population in terms of its characteristics, blood pressure, and prevalence of hypertension.12 Almost 50% of variation in the presence of the trait was attributed to heritable factors. An even higher heritability was observed for the notching ER morphology.

Another interesting finding of this study was a strong heritability in families with ER in the inferior leads, whereas anterolateral occurrence of the trait appears to have a lesser genetic contribution. This observation is of importance because a prior study by Tikkanen et al6 showed significant risk increase for cardiac mortality only for ER if present in the inferior leads; also, previous analyses of our group demonstrated that ER in the inferior leads confers higher risks for both cardiovascular and all-cause mortality than ER in any other region.6 The results of a relevant genetic contribution support the notion that the suspected pathophysiological link between ER in the inferior leads and increased mortality risk might indeed lie within variation of certain regions of the genome. Further analyses are warranted to identify the genes that affect the phenotype.

The prevalence of 7.7% of ER that we observed is similar to that reported in previous studies.1,2,4–6 Similarly, the significant predominance of men with a 3-fold higher prevalence than in women is in line with published work.1,6,17 The pathophysiological mechanism underlying these relations are currently unclear. Because a lower resting heart rate and normal QTc interval generally go along with reduced cardiovascular risk,19–22 it could be speculated that the effects of ER on cardiovascular mortality may be independent of these ECG phenotypes.

Another interesting finding is that heritability of ER may be influenced by the sex of the parent. Presence of the trait in the mother increases the risk in children 3.8-fold, whereas presence of ER in the father was associated with a nonsignificant 1.8-fold risk increase in risk. The basis for this potential difference is unclear. Recognized reasons for unequal transmission from parents include effects mediated via the sex chromosomes, parental imprinting of autosomal genes, or transmission through mitochondrial DNA.23–25 However, the observed difference in paternal versus maternal ER transmission was not statistically significant. Further confirmation of this finding is required before definitive conclusions can be drawn.

Current experimental data support the concept that J-point elevation of ER is a marker of increased transmural electric heterogeneity, leading to higher susceptibility for malignant ventricular arrhythmias.7,26,27 As seen for a number of other ECG-derived traits, for example, resting heart rate or QT interval,9–11,28 we found a significant heritable component, explaining a large part of the interindividual variability of ER. This heritable constituent together with certain external triggers might play an important role in the modulation of the degree of arrhythmogenicity. Further research is now needed to determine the underlying genetic contributors. Possible mechanisms include genetically determined channelopathies or structural heart diseases, since ER has been linked to both electrophysiological vulnerability and cardiomyopathies.29

In summary, we present the first study examining the heritability of the ER pattern in a large family-based British cohort. ER is a highly heritable trait, and about 50% of the variation in the presence of ER can be attributed to genetic factors. Genetic analyses are now warranted to elucidate the underlying pathophysiological principles.

Acknowledgments

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Early repolarization (ER) is a common ECG phenomenon that recently received great attention when it was associated with sudden cardiac arrest in otherwise healthy individuals. Subsequently, the long-term outcome associated with ER was studied in 2 large, population-based cohorts, where it conferred an elevated risk of cardiovascular and all-cause mortality. Despite its prognostic importance, the pathophysiological mechanisms and biological determinants underlying ER are not yet understood. In the present investigation, the researchers investigated whether the presence of ER is influenced by genetic factors by estimating its heritability in a large, family-based cohort. The investigators report that that ER is a highly heritable trait, with almost 50% of variation of the trait being attributable to genetic factors. Heritability estimates are even higher if the ER pattern is restricted to an inferior localization. If at least 1 parent has ER, the risk for the offspring of also presenting with this ECG trait is 2.5-fold elevated. These findings substantiate a significant heritable component of ER and should propel intensive clinical and experimental research to determine the underlying genetic contributors of ER.
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