Heritability of Early Repolarization
A Population-Based Study

Wibke Reinhard, MD, MBA*; Bernhard M. Kaess, MD*; Radoslaw Debiec, MD; Christopher P. Nelson, PhD; Klaus Stark, PhD; Martin D. Tobin, MD, MFPHM; Peter W. Macfarlane, DSc, FRCP, FESC; Maciej Tomaszewski, MD, FAHA; Nilesh J. Samani, MD, FMedSci; Christian Hengstenberg, MD

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 ≥0.1 mV in at least 2 adjacent inferior (II, III, and aVF) or anterolateral (I, aVL, and V4 through V6) leads. Narrow sense heritability estimates were computed adjusting for age, age², 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 h²=0.49 (standard error=0.14; P=2.7*10⁻⁴) and was higher when restricted to its presence in inferior leads (h²=0.61, standard error=0.18, P=4.3*10⁻⁴) or for the notching ER morphology (h²=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 V₄ 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 Haissaguerre et al,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 V4 through V6). J-point elevation was measured by ruler-based visual inspection using Spacelab magnifying glasses for ECG diagnostics. Leads V1 through V5 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 good strength of 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 estimation 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, sex, and in the offspring, 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>
<thead>
<tr>
<th>Region</th>
<th>Offspring, n (%)</th>
<th>Parents, n (%)</th>
<th>Women, n (%)</th>
<th>Men, n (%)</th>
<th>Both sexes, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior leads</td>
<td>55 (37.9)</td>
<td>35 (3.7)</td>
<td>110 (11.7)*</td>
<td>145 (7.7)</td>
<td>255 (13.5)</td>
</tr>
<tr>
<td>Anterolateral leads</td>
<td>40 (27.6)</td>
<td>20 (2.1)</td>
<td>60 (6.3)</td>
<td>100 (5.3)</td>
<td>160 (8.5)</td>
</tr>
<tr>
<td>Both regions</td>
<td>50 (34.5)</td>
<td>25 (2.6)</td>
<td>75 (7.8)</td>
<td>125 (6.6)</td>
<td>200 (10.6)</td>
</tr>
<tr>
<td>Notching morphology, n (%)</td>
<td>61 (42.1)</td>
<td>28 (3.0)</td>
<td>89 (9.6)</td>
<td>150 (7.5)</td>
<td>239 (12.6)</td>
</tr>
<tr>
<td>Slurring morphology, n (%)</td>
<td>17 (11.7)</td>
<td>9 (0.9)</td>
<td>36 (3.7)</td>
<td>66 (3.5)</td>
<td>102 (5.4)</td>
</tr>
<tr>
<td>Both morphologies, n (%)</td>
<td>67 (46.2)</td>
<td>37 (3.9)</td>
<td>124 (12.6)</td>
<td>211 (10.9)</td>
<td>335 (17.4)</td>
</tr>
</tbody>
</table>

*P value, men vs women ER prevalence: P=4.4*10^-3.
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^-3). Parents had a lower ER prevalence as compared with the offspring generation (5.9% versus 9.6%; P=3.3*10^-3). 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, sex, and in a variance components analysis (Table 3). Heritability estimates were even higher if the ER pattern was restricted to the inferior leads (h²=0.61, SE=0.183, P=4.3*10^-4). Moreover, heritability appeared particularly high for the notching ER morphology (h²=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 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 (n=56)</td>
<td>ER Negative (n=889)</td>
</tr>
<tr>
<td></td>
<td>ER Positive (n=89)</td>
<td>ER Negative (n=843)</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th></th>
<th>Parents</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±8</td>
<td>65±10</td>
</tr>
<tr>
<td>Body mass index, kg/m</td>
<td>92±8</td>
<td>91±10</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>CHD, %, 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>
</tbody>
</table>

ECG characteristics

<table>
<thead>
<tr>
<th></th>
<th>Parents</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (ms)</td>
<td>63±8</td>
<td>65±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).

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.1,5,6 The pathophysiological mechanisms of ER are unclear. Therefore, we ana-

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 notching 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, age², and sex.

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

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. The mother shows a clear notching morphology of ER, the daughter presents with both notching (lead II) and slurring (lead aVL) type ER, and the son exhibits a slurring ER morphology.
lyzed 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. Almost 50% of variation in the presence of the trait was attributed to heritable factors. A more even 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 al 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. 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. Similarly, the significant predominance of men with a 3-fold higher prevalence than in women is in line with published work. 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.

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

We appreciate the contribution of participants of the GRAPHIC Study.

Sources of Funding

The GRAPHIC Study was funded by the British Heart Foundation. Dr Hengstenberg holds a grant of the German National Genome Research Network (NGFNplus, D0G080832). Dr Samani holds a personal chair funded by the British Heart Foundation. This study is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease. Dr Tobin holds a Medical Research Council (MRC) Clinician Scientist Fellowship (G0501942). Dr Reinhard holds a research grant funded by the UKR-Regensburger Forschungsfoerderung Medizin (ReForM-B).

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 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 genetic contributors of ER.
Heritability of Early Repolarization: A Population-Based Study
Wibke Reinhard, Bernhard M. Kaess, Radoslaw Debiec, Christopher P. Nelson, Klaus Stark, Martin D. Tobin, Peter W. Macfarlane, Maciej Tomaszewski, Nilesh J. Samani and Christian Hengstenberg

Circ Cardiovasc Genet. 2011;4:134-138; originally published online January 31, 2011;
doi: 10.1161/CIRCGENETICS.110.958298

Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circgenetics.ahajournals.org/content/4/2/134

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Genetics can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Genetics is online at:
http://circgenetics.ahajournals.org//subscriptions/