Heritability of Early Repolarization – A Population-Based Study

Running title: Reinhard et al.; Heritability of Early Repolarization

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Abstract:

**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 Caucasian 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 two adjacent inferior (II, III, aVF) or antero-lateral (I, aVL, V4-6) leads. Narrow sense heritability estimates were computed adjusting for age, age$^2$ and gender. The prevalence of ER was 7.7% (n=145) in the whole cohort, 5.9% (n=56) in parents and 9.5% (n=89) in offspring. Heritability estimate for the presence of ER was calculated at $h^2=0.49$ (standard error (SE)=0.14; $p=2.7*10^{-3}$) and was higher when restricted to its presence in inferior leads ($h^2=0.61$, SE=0.18, $p=4.3*10^{-4}$) or for the notching ER morphology ($h^2=0.81$, SE=0.19, $p=2.4*10^{-5}$). Individuals with at least one affected parent had a 2.5-fold increased risk for presenting with ER on ECG (odds ratio (OR) 2.54, 95% confidence interval (CI): 1.33-4.84; $p=0.005$). Familial transmission was more frequent when the mother was affected (OR 3.84, CI: 1.41-10.43; $p=0.008$) than when the father was affected (OR 1.82; CI: 0.82-4.03; $p=0.141$), although this difference was not statistically significant ($p=0.18$).

**Conclusion**— ER is a heritable phenotype. Offspring of ER positive parents have a 2.5-fold increased risk of presenting with ER in their ECG.

**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). While ER was regarded as harmless for decades, a compelling body of evidence has recently associated J-point elevation in leads other than V1-3 with electrical 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 pathophysiologic mechanisms underlying ER are not yet understood. Experimental data suggest alterations in cardiac transmembrane ion currents leading to transmural electrical 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 inter-individual 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.

**Methods**

**Subjects**

Analyses were performed in the GRAPHIC (Genetic Regulation of Arterial Pressure of Humans in the Community) cohort that has been previously described in detail.\(^12\)\(^,\)\(^13\) Briefly, the GRAPHIC study recruited nuclear families from the general population in Leicestershire, UK, by writing to women aged 40 to 69 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 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 >120ms). 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/sec) were independently read by two experienced clinicians, who were blinded with
respect to age, gender and family structure. ER was defined by the criteria proposed by
Haïssaguerre and colleagues,¹ i.e. the presence of J-point elevation ≥0.1 mV in at least two
adjacent leads in inferior (II, III, aVF) or antero-lateral leads (I, aVL, V4-6). J-point elevation
was measured by ruler-based visual inspection using Spacelab© magnifying glasses for ECG
diagnostics. Leads V1-3 were excluded from the analysis to avoid confusion with Brugada
syndrome and right ventricular dysplasia. Presence or absence of ST segment elevation in
addition to J-point elevation was not taken into account. Non-specific intraventricular
conduction delay was excluded. ER was specified by localization (inferior, antero-lateral or
both), being coded as present in both inferior and antero-lateral leads if at least two adjacent
leads in one region and at least one 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 two interpreters (kappa 0.61, proportion agreement 95%). In case of disagreement, ECGs were jointly re-assessed by the two 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. \textsuperscript{14} QT interval was corrected for heart rate using two approaches, the Framingham formula and the Bazett formula. \textsuperscript{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 (GEE) 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, age\textsuperscript{2} and gender. 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 non-additive effect of alleles (dominant effect -the source of deviation from the slope). The likelihood of presence of ER in at least one offspring of affected parents was calculated using logistic regression, conditioned on the presence of ER in any or either of the parents.

Results

Prevalence of ER and Baseline Characteristics of the Study Population

ER was present in 145 individuals (7.7%) with significant male predominance (Table 1). In the whole cohort prevalence of ER in men was 11.7% as compared to 3.7% in women
(p=4.4*10^{-9}). Parents had a lower ER prevalence as compared to the offspring generation (5.9% vs. 9.6%; p=3.3*10^{-3}). In those with ER, it was present in inferior leads only in 37.9% of subjects, antero-lateral 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 male 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 (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 due to the lack of corresponding families. In order to assess potential confounding by the use of chronotropic medication, we performed a sensitivity analysis excluding treated individuals. The results did not materially differ from our primary analyses (data not shown).
Individuals with at least one parent with ER had a 2.5-fold risk for also presenting with this ECG trait (adjusted OR, 95% confidence interval (CI) 1.33-4.84; $p=0.005$). Familial transmission was more frequent when the mother was affected (18 families; OR 3.84, CI 1.41-10.43; $p=0.008$) than when father was affected (38 families; OR 1.82, CI 0.82-4.03, $p=0.141$), although this difference was not statistically significant ($p=0.18$). As an example, Figure 1 depicts a family with presence of ER in the inferior leads of different morphology in the mother and both children.

**Discussion**

The electrocardiographic pattern of ER has been known for decades and was generally considered a benign normal variant of the surface ECG. However, recently 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 pathophysiologic mechanisms of ER are unclear. Therefore, we analyzed 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 Caucasian 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 antero-lateral occurrence of the trait seems to have a lesser genetic contribution. This observation is of importance, since a prior study by Tikannen et al. showed...
significant risk increase for cardiac mortality only for ER if present in the inferior leads,\textsuperscript{6} and 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.\textsuperscript{5} Now, the results of a relevant genetic contribution support the notion that the suspected pathophysiologic 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.\textsuperscript{1,2,4-6} Similarly, the significant male predominance with a 3-fold higher prevalence than in women is in line with published work.\textsuperscript{1,6,17} According to currently available data, the ER pattern has been associated with other demographics and ECG characteristics, such as younger age as well as lower resting heart rate, longer QRS duration, shorter QTc interval and prevalence of electrocardiographic left ventricular hypertrophy, which is also reflected in our data.\textsuperscript{5,6,17,18} The pathophysiologic mechanism underlying these relations are currently unclear. Since a lower resting heart rate and normal QTc interval generally go along with reduced cardiovascular risk,\textsuperscript{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 parental gender. Presence of the trait in the mother increases the risk in children 3.8-fold, while presence of ER in the father was associated with a non-significant 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.\textsuperscript{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 electrical heterogeneity, leading to higher susceptibility for malignant ventricular arrhythmias.\textsuperscript{7,26,27} As seen for a number of other ECG-derived traits, e.g. resting heart rate or QT interval,\textsuperscript{9-11,28} we found a significant heritable component, explaining a large part of the inter-individual 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.\textsuperscript{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 pathophysiologic principles.

Acknowledgments: We appreciate the contribution of participants of the GRAPHIC Study.

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Conflict of Interest Disclosures: None.

References:


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>

Region

<table>
<thead>
<tr>
<th>Region</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Inferior leads, n (%)</td>
<td>55 (37.9)</td>
</tr>
<tr>
<td>Antero-lateral leads, n (%)</td>
<td>40 (27.6)</td>
</tr>
<tr>
<td>Both regions, n (%)</td>
<td>50 (34.5)</td>
</tr>
</tbody>
</table>

Morphology

<table>
<thead>
<tr>
<th>Morphology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Notching morphology, n (%)</td>
<td>61 (42.1)</td>
</tr>
<tr>
<td>Slurring morphology, n (%)</td>
<td>17 (11.7)</td>
</tr>
<tr>
<td>Both morphologies, n (%)</td>
<td>67 (46.2)</td>
</tr>
</tbody>
</table>

* p-value male vs. female ER prevalence: $p=4.4*10^{-9}$
† p-value parental vs. offspring ER prevalence: $p=3.3*10^{-3}$
Table 2. Characteristics of Parental and Offspring Generation

<table>
<thead>
<tr>
<th>Demographics</th>
<th>ER positive (n=56)</th>
<th>ER negative (n=889)</th>
<th>p-value</th>
<th>ER positive (n=89)</th>
<th>ER negative (n=843)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parents</strong> (n=945)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ER positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ER negative</td>
<td></td>
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<tr>
<td><strong>Offspring</strong> (n=932)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>38 (67.9)</td>
<td>431 (48.5)</td>
<td>6.4\times10^{-3}</td>
<td>72 (80.9)</td>
<td>401 (47.6)</td>
<td>2.8\times10^{-8}</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.3 ± 3.9</td>
<td>52.8 ± 4.3</td>
<td>0.274</td>
<td>23.9 ± 4.2</td>
<td>25.6 ± 5.3</td>
<td>2.3\times10^{-3}</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4 ± 4.0</td>
<td>27.4 ± 4.3</td>
<td>0.9</td>
<td>23.2 ± 4.2</td>
<td>24.8 ± 4.6</td>
<td>2.6\times10^{-3}</td>
</tr>
<tr>
<td>Total cholesterol / HDL ratio</td>
<td>4.4 ± 1.0</td>
<td>4.2 ± 1.2</td>
<td>0.132</td>
<td>3.4 ± 0.8</td>
<td>3.5 ± 0.9</td>
<td>0.562</td>
</tr>
<tr>
<td>Past or present smoking, %</td>
<td>33 (58.9)</td>
<td>440 (49.8)</td>
<td>0.162</td>
<td>35 (40.2)</td>
<td>322 (38.3)</td>
<td>0.686</td>
</tr>
<tr>
<td>History of hypertension*, %</td>
<td>27 (48.2)</td>
<td>377 (42.7)</td>
<td>0.452</td>
<td>9 (10.3)</td>
<td>109 (13.0)</td>
<td>0.498</td>
</tr>
<tr>
<td>History of angina pectoris, %</td>
<td>0</td>
<td>7 (0.8)</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>1 (1.79)</td>
<td>16 (1.8)</td>
<td>0.021</td>
<td>0</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Chronotropic medication, %</td>
<td>6 (10.7)</td>
<td>32 (3.6)</td>
<td>-</td>
<td>0</td>
<td>6 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td><strong>ECG characteristics</strong></td>
<td></td>
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</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>63 ± 8</td>
<td>65 ± 10</td>
<td>0.098</td>
<td>63 ± 11</td>
<td>67 ± 11</td>
<td>3.9\times10^{-3}</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>92 ± 8</td>
<td>91 ± 10</td>
<td>0.397</td>
<td>95 ± 8</td>
<td>91 ± 10</td>
<td>8.6\times10^{-6}</td>
</tr>
<tr>
<td>QTc interval (Framingham)† (ms)</td>
<td>401 ± 17</td>
<td>410 ± 22</td>
<td>4.7\times10^{-4}</td>
<td>395 ± 20</td>
<td>400 ± 19</td>
<td>0.016</td>
</tr>
<tr>
<td>QTc interval (Bazett)† (ms)</td>
<td>403 ± 18</td>
<td>415 ± 23</td>
<td>6.3\times10^{-6}</td>
<td>395 ± 24</td>
<td>406 ± 22</td>
<td>2.0\times10^{-4}</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (Sokolow-Lyon Index), %</td>
<td>3 (5.4)</td>
<td>16 (1.8)</td>
<td>0.081</td>
<td>38 (42.6)</td>
<td>74 (8.8)</td>
<td>6.2\times10^{-17}</td>
</tr>
</tbody>
</table>

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

* Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg 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) / \sqrt{RR (sec)}
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><strong>Region</strong></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 antero-lateral 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><strong>Morphology</strong></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>

SE – standard error

Calculations were adjusted for age, age² and gender

* Heritability estimates for ER in both inferior + antero-lateral leads and ER of slurring morphology could not be assessed due to lack of adequate number of families with the respective phenotype in parental and offspring generation.

Figure Legend:

Figure 1. Representative Examples of ER in a GRAPHIC Nuclear Family

Figure 1 depicts a family with 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.
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