The Prevalence and Significance of the Early Repolarization Pattern in Sudden Arrhythmic Death Syndrome Families

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Background—The early repolarization (ER) pattern is associated with sudden death and has been shown to be heritable. Its significance when identified in families affected by sudden arrhythmic death syndrome (SADS) remains unclear.

Methods and Results—We analyzed 12-lead ECGs of 401 first-degree relatives of individuals who had died from SADS. The prevalence of ER patterns was compared with family-clustered controls. ER was more common in SADS family members than in controls (21% versus 8%; odds ratio: 5.14; 95% confidence interval, 3.37–7.84) independent of the presence of a familial cardiac diagnosis. Both ascending and horizontal ER patterns were more common. In addition, ER was investigated for associations with findings from ajmaline provocation (n=332), exercise ECG (n=304), and signal-averaged ECG (n=118) when performed. ER was associated with a trend toward late depolarization, in general was suppressed with exercise and was unaffected by ajmaline. Inferior and horizontal patterns were, however, more likely to persist during exercise. Augmentation of ER with ajmaline was rare.

Conclusions—The ER pattern is more common in SADS family members than controls adjusted in particular for relatedness. The increased prevalence is irrespective of ER subtype and the presence of other inherited arrhythmia syndromes. ER may therefore represent an underlying heritable arrhythmia syndrome or risk factor for sudden death in the context of other cardiac pathology. The differing response of ER subtypes to exercise and ajmaline provocation suggests underlying mechanisms of both abnormal repolarization and depolarization. (Circ Arrhythm Electrophysiol. 2016;9:e003960. DOI: 10.1161/CIRCEP.116.003960.)

Key Words: ajmaline ■ death, sudden ■ electrocardiography

The early repolarization (ER) pattern was long thought to be benign and of little clinical significance.1 More recently, ER, defined by J-point elevation in the inferior or lateral leads, has been associated with idiopathic ventricular fibrillation2 leading to recognition of early repolarization syndrome (ERS) as a novel arrhythmia syndrome.3 In addition, there is increasing evidence for the role of ER as a risk factor for arrhythmic events in the context of other inherited arrhythmia syndromes.4,5 Several studies have suggested the ER pattern is a heritable phenotype6,7 and variants in genes encoding cardiac ion channels8–10 have been identified in individuals and families with ERS.

Sudden arrhythmic death syndrome (SADS) is defined as a sudden unexplained death where postmortem examination reveals a structurally normal heart, and toxicological analysis is negative.11 Familial assessment of SADS relatives is recommended and may reveal evidence of an inherited cardiac condition in 22% to 53% of families12–15 with ion channel disease as the principal finding.

ER has previously been shown to be more common in SADS relatives16; however, there was no differentiation by ST-segment morphology which has since been shown to distinguish between high- and low-risk forms.17 Furthermore, association with signal-averaged ECG (SAECG) findings and the response of the ER pattern to exercise and sodium channel provocation have not been investigated in the setting of familial SADS.

We therefore examined the prevalence of ER in SADS relatives compared with a family-clustered control population, analyzing ascending and horizontal forms, and characterized the behavior of ER in investigations commonly used in assessment of SADS families.
Methods

Study Population

We studied first-degree relatives of 184 individuals who died from SADS referred consecutively to the inherited cardiac conditions (ICC) clinics at St. George’s Hospital, London, and University Hospital Lewisham, London, between 2002 and 2014 (Figure 1). Of 526 first-degree relatives, 401 (76%) were included in the study. Relatives aged \( \leq 16 \) years at the time of first assessment were excluded because they were typically assessed through a separate pediatric service. The investigation of families and diagnosis of relatives were as per contemporary accepted guidelines and have been described in detail previously. All individuals had a 12-lead ECG. Further investigations were arranged at the discretion of the attending physician and in view of previous findings. All participants gave written consent. Nonwhite individuals (n=24) were excluded from comparison with the control population. The local institutional review committee approved the study. All individuals gave informed consent.

Control Population

Controls (n=1884 from 505 families) were taken from the Genetic Regulation of Arterial Pressure of Humans in the Community (GRAPHIC) cohort, which has been previously described in detail. Briefly, the GRAPHIC study recruited white nuclear families from the UK general population. Families were included if both parents were aged 40 to 60 years with 2 offspring \( >18 \) years of age. Assessment included a medical history, clinical examination, and 12-lead ECG. All GRAPHIC subjects for whom ER information was available were included in the control group.

ECG Analysis

The resting 12-lead ECG performed at the initial clinic visit for SADS relatives and at recruitment for GRAPHIC controls was used for analysis. Baseline automated ECG measurements were taken with manual verification of values outside accepted normal ranges. For SADS families, ER was reported manually by a single cardiologist (G.M.), and borderline cases were adjudicated by consensus with a senior cardiologist (E.R.B.). ER was defined as \( \geq 0.1 \) mV J-point elevation in 2 contiguous leads in the inferior or lateral leads as per accepted modern criteria. ER was classified as notched if there was a positive upstroke in the terminal R wave. Otherwise, it was described as slurred. The associated ST segment was classified as rapidly ascending if there was \( \geq 0.1 \) mV ST elevation 100 ms after the peak of the J point or horizontal/descending otherwise. Although this definition differs slightly from a recent consensus document, it is in keeping with that used by Tikkanen et al when first demonstrating the prognostic benefit of ST-segment gradient. Similar criteria, described previously, were used for the control population. J-point amplitude was categorized in 0.1 mV increments (ie, 0.10–0.19 mV; 0.20–0.29 mV, etc) and considered high amplitude if \( \geq 0.2 \) mV. Sokolow-Lyon isolated voltage criteria >35 mm were used to denote left ventricular hypertrophy. The Brugada type 1 ECG pattern was defined as per accepted definitions.

Ajmaline Provocation Testing

Ajmaline (1 mg/kg) was administered intravenously for 5 minutes. Standard and high precordial leads were examined. The test was classed positive if a type 1 Brugada ECG pattern was induced in at least one precordial lead. Heart rate, QRS duration, and J-point amplitude in the inferior and lateral leads were measured at baseline and at the time of peak effect of ajmaline (defined by maximal QRS

**WHAT IS KNOWN**

- The early repolarization (ER) ECG pattern is associated with an increased risk of sudden cardiac death.
- The ER pattern is heritable.

**WHAT THE STUDY ADDS**

- The ER pattern is over-represented in first-degree relatives of individuals who died due to sudden arrhythmic death syndrome (SADS relatives) compared to a family-clustered control population.
- Both the ascending ER and horizontal ER types are increased in SADS relatives.
- Results from signal-averaged ECG, exercise testing, and ajmaline provocation suggest there may be contrasting physiological mechanisms underlying ascending and horizontal ER.

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duration). J-point amplitude was categorized in 0.1 mV increments as described above. The J-point response was classified as reduced if the J-point amplitude reduced by $\geq 0.1$ mV or was not present at peak ajmaline effect in either inferior or lateral territory; unchanged if the amplitude remained the same or; augmented if the amplitude increased by $\geq 0.1$ mV in either inferior or lateral territory.

**Exercise ECG**

Exercise testing was performed using the full Bruce protocol. Heart rate and J-point amplitude in the inferior and lateral leads were measured at rest, peak exercise, and 1, 3, and 5 minutes into recovery. In cases where ER was present on the exercise tolerance test but not the index ECG, J-point amplitude was not analyzed. Heart rate recovery was defined as the change in heart rate from peak exercise to 5-minute recovery. Ventricular ectopy, where present, was recorded as simple if there were isolated ventricular ectopics occurring early in exercise or in recovery only. Complex ectopy was defined as multifocal ectopics, ventricular ectopy increasing with exercise or occurring as couplets, or nonsustained ventricular tachycardia. The response to exercise was classified as suppressed if ER was no longer present at peak exercise. Otherwise, the response was classified as persistent.

**SAECG Analysis**

SAECG analysis was performed in the study population with acquisition of at least 300 cardiac cycles (filter setting: 40–250 Hz). Late potentials were defined by $\geq 2$ of the following parameters being abnormal: filtered QRS duration ($\text{fQRS} \geq 114$ ms), duration of low amplitude signals ($\text{LAS}_{40} \geq 38$ ms), and root mean-square voltage of terminal 40 ms of filtered QRS complex ($\text{RMS}_{40} \leq 20$ μV).23

**Statistical Methods**

Study characteristics were compared between the case and control groups using mixed models adjusting for family structure as a random effect. A logistic regression was performed in a mixed model on ER status adjusting for family as a random effect and family history of SADS as the covariate of interest. Further covariates were assessed as fixed effects, and 2-way interactions were investigated with covariates retained in the model if found to significantly improve the model fit. All models therefore included adjustments for age, sex, age and sex interaction, LVH, and QTc interval as fixed effects. Subtypes of ER were assessed in the same way. Subgroup analyses were performed in families with and without a familial ICC diagnosis in the study population against all controls. Subgroup analyses of ajmaline provocation, exercise ECG, and SAECG traits were conducted using a univariate mixed model accounting for family as a random effect.

**Results**

The mean age of the SADS relatives was 39.5 years and 173 (43%) were male. Six percent were nonwhite. The median number of relatives assessed per family was 2 (range: 1–8). The cohort comprised 194 siblings (48%), 157 parents (39%), and 50 children (12%) of SADS victims. An ICC was diagnosed in 108 individuals from 75 families with Brugada syndrome (BrS; 89 individuals from 60 families) as the most frequent diagnosis (Figure 3). The control cohort was a white population with a mean age of 39.3 years where 951 (51%) were male. Information on BrS and ICC diagnoses were not available in the control cohort. Clinical characteristics and ECG findings of SADS relatives and controls are summarized in Table 1.

**Prevalence and Associations of ER**

The ER pattern was seen in 20.7% of SADS relatives and in 8.1% of the control population (odds ratio [OR]=5.14, 3.37–7.34). ER appeared more common in males (28.9% versus 12.1%) and in younger individuals with a significant interaction ($p=0.003$) between age and sex observed. Both ascending (9.7% versus 4.5%; OR=4.34, 2.55–7.37) and horizontal (11.0% versus 3.8%; OR=3.64, 2.27–5.84) ER were more common in SADS relatives than in controls, as was ER in either the inferior or lateral leads (OR=4.86, 2.59–9.14 and OR=4.07, 2.28–7.26, respectively). ER was more common in SADS relatives regardless of whether an ICC was diagnosed (OR=4.86, 2.73–8.65) or not (OR=6.12, 3.45–10.73). However, ER was less common in individuals diagnosed with BrS than in those for whom no
Mellor et al  SADS ER

diagnosis was made (OR 0.206, 0.072–0.590; Figure 3). Results are summarized in Table 2 and further in the Data Supplement.

Ajmaline Provocation
Ajmaline provocation was performed in 332 family members from 159 families and was positive in 86 members (26%). ER was present on the index ECG in 69 cases (21%) and was more common where the test was negative (29% versus 14%; P=0.02). At peak ajmaline effect, the J-point was reduced in 56%, unchanged in 38%, and augmented in 6%. J-point augmentation was associated with a positive ajmaline result (P<0.001). Responses were similar in inferior and lateral leads (P=0.62). The heart rate and QRS duration increase seen at peak ajmaline effect was similar in the reduced, persistent, and augmented groups (P, heart rate=0.17; P, QRS duration=0.31). Results are summarized in the Data Supplement.

Exercise ECG
An exercise ECG was performed in 304 family members from 151 families. ER was present on the resting ECG in 66 members (22%; 10% ascending and 12% horizontal). Of these 66 members, ER was seen on the pretest ECG at the time of exercise in 51 members.

Ventricular ectopy was seen during exercise in 52 members (17%). Complex ectopy was more common in patients with horizontal ER (OR=4.2, 1.2–14.4) compared with those with either ascending or no ER.

The majority of ER was suppressed at peak exercise. ER in the lateral leads (n=25) was suppressed in all cases. ER in the inferior leads persisted at peak exercise in 11 cases (27%; Figure 4). Horizontal ER also persisted at peak exercise more frequently than ascending ER (34.6% versus 8.0%; P=0.032). Persistence at peak exercise was not associated with previous syncope (P=0.925). There were no cases of ER augmentation with exercise. Results are summarized in the Data Supplement.

Signal-Averaged ECG
SAECG was performed in 123 family members. The noise level was unacceptably high in 5 cases. Analysis was therefore performed in 118 members from 64 families. ER was

Table 1. Baseline Characteristics of SADS Relatives and Control Populations With Comparisons Between Those With and Without ER

<table>
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<tr>
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<td>n</td>
<td>377</td>
<td>1884</td>
<td>…</td>
<td>297 (79)</td>
<td>80 (21)</td>
<td>…</td>
<td>1733 (92)</td>
<td>151 (8)</td>
<td>…</td>
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<tr>
<td>Age, y</td>
<td>39.6 (15)</td>
<td>39.3 (15)</td>
<td>0.638</td>
<td>40.0 (15)</td>
<td>38.4 (16)</td>
<td>0.429</td>
<td>39.6 (15)</td>
<td>34.8 (14)</td>
<td>&lt;0.001</td>
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<td>Male sex</td>
<td>163 (43)</td>
<td>951 (51)</td>
<td>0.010</td>
<td>116 (39)</td>
<td>47 (59)</td>
<td>0.002</td>
<td>837 (48)</td>
<td>114 (76)</td>
<td>&lt;0.001</td>
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<tr>
<td>Heart rate, min⁻¹</td>
<td>72 (14)</td>
<td>65 (10)</td>
<td>&lt;0.001</td>
<td>73 (14)</td>
<td>70 (13)</td>
<td>0.113</td>
<td>66 (10)</td>
<td>63 (10)</td>
<td>0.002</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>156 (26)</td>
<td>155 (23)</td>
<td>0.766</td>
<td>153 (23)</td>
<td>166 (33)</td>
<td>&lt;0.001</td>
<td>155 (23)</td>
<td>155 (22)</td>
<td>0.871</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>92 (13)</td>
<td>93 (10)</td>
<td>0.090</td>
<td>92 (13)</td>
<td>91 (10)</td>
<td>0.382</td>
<td>93 (11)</td>
<td>96 (9)</td>
<td>0.002</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>415 (27)</td>
<td>410 (20)</td>
<td>&lt;0.001</td>
<td>418 (26)</td>
<td>405 (28)</td>
<td>&lt;0.001</td>
<td>411 (20)</td>
<td>404 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH†</td>
<td>14 (4)</td>
<td>57 (3)</td>
<td>0.628</td>
<td>6 (2)</td>
<td>8 (10)</td>
<td>0.002</td>
<td>44 (3)</td>
<td>13 (11)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean (SD), and categorical variables are expressed as n (%). ER indicates early repolarization; LVH isolated voltage criteria for left ventricular hypertrophy (Sokolow-Lyon); and SADS, sudden arrhythmic death syndrome.

*Data only listed for white relatives.
†LVH data missing for 104 controls.

Table 2. Odds Ratios for Presence of ER Compared With Control Population Stratified by ER Subtype and Presence of Familial ICC Diagnosis in SADS Relatives

<table>
<thead>
<tr>
<th>ER Type</th>
<th>All SADS Relatives</th>
<th>Families With ICC Diagnosis</th>
<th>Families With No Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>P Value</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>All ER</td>
<td>5.14 3.37–7.84</td>
<td>&lt;0.001</td>
<td>4.86 2.73–8.65</td>
</tr>
<tr>
<td>Ascending ER</td>
<td>4.34 2.55–7.37</td>
<td>&lt;0.001</td>
<td>4.38 2.26–8.46</td>
</tr>
<tr>
<td>Horizontal ER</td>
<td>3.64 2.26–5.84</td>
<td>&lt;0.001</td>
<td>3.28 1.69–6.36</td>
</tr>
<tr>
<td>Notched ER</td>
<td>2.60 1.55–4.34</td>
<td>&lt;0.001</td>
<td>1.65 0.77–3.51</td>
</tr>
<tr>
<td>Slurred ER</td>
<td>3.17 1.95–5.15</td>
<td>&lt;0.001</td>
<td>3.87 2.05–7.29</td>
</tr>
<tr>
<td>Inferior ER</td>
<td>4.86 2.59–9.14</td>
<td>&lt;0.001</td>
<td>5.17 2.29–11.71</td>
</tr>
<tr>
<td>Lateral ER</td>
<td>4.07 2.28–7.26</td>
<td>&lt;0.001</td>
<td>3.86 1.76–8.47</td>
</tr>
<tr>
<td>Inf-lat ER</td>
<td>2.40 1.10–5.23</td>
<td>0.027</td>
<td>1.45 0.46–4.50</td>
</tr>
</tbody>
</table>

Multivariable analysis corrects for age, sex, ethnicity, familial clustering, and QTc interval and voltage criteria for LVH. CI indicates confidence interval; ER, early repolarization; ICC, inherited cardiac condition; LVH, left ventricular hypertrophy; OR, odds ratio; and SADS, sudden arrhythmic death syndrome.
Discussion

We have shown that the ER pattern is more common in first-degree SADS relatives than in the general population. Num et al previously found that ER was present in 23% of SADS family members compared with 11% of controls. However, the control cohort used was small (matched 1:1) and comprised unrelated individuals. The use of a family-based control population in this study and controlling for the effect of relationships within families improves the accuracy of the comparison, and therefore, our findings support and extend this previous work. The prevalence of ER was increased irrespective of the presence or not of an ICC being diagnosed in the family supporting ERS both as a primary heritable arrhythmia syndrome and as a marker of increased risk in the context of other inherited arrhythmia syndromes, notably BrS and long-QT syndrome.5

We have also shown for the first time that this increase in prevalence is not driven by one particular subtype of ER; the prevalence of ER in SADS relatives was increased irrespective of ST-segment morphology and ECG territory. This was unexpected because it has been shown in large general population cohorts that ER in the inferior leads and ER with a horizontal ST segment confer an increased risk of sudden death, whereas ER in the lateral leads or with a rapidly ascending ST segment is benign.17 However, SADS relatives represent a different population with a high prevalence of genetic cardiac disease and a proven malignant course in family members. It is therefore more appropriate to compare this population to studies of idiopathic ventricular fibrillation (VF) and ERS. The prevalence of ER in idiopathic VF has been reported between 23% and 42%,24,25 Only Rosso et al26 have presented an analysis of data in idiopathic VF survivors stratified by ST segment and although they found that the association with idiopathic VF was strongest for horizontal ER, 30% of idiopathic VF cases with ER had the rapidly ascending form. The distinction in prognosis between ascending and horizontal ER made in the general population may not therefore translate into higher risk groups such as SADS families and highlights the likely heterogeneity within the ER phenotype.

The physiological mechanisms underlying ER remain unclear. The presence of late potentials and the response of ER to exercise and ajmaline provocation may, however, give insight into such mechanisms.

SAECG and Late Potentials

The majority of individuals with ER in our study had SAECG recordings within normal limits. Several previous studies have also shown that abnormal SAECG results are uncommon in ERS patients27–29 or at least in proportions similar to idiopathic VF survivors without ER.30 However, Roten et al28 showed that 39% of idiopathic VF survivors with ER had an abnormal SAECG with a higher proportion where the ER pattern persisted during isoproterenol infusion. In addition, Abe et al29 used 24-hour continuous SAECG monitoring and found that the incidence of late potentials was higher in idiopathic VF survivors with ER than those without ER, with no difference in repolarization markers between the 2 groups. We found that ER was associated with longer mean fQRS, LAS40, and lower RMS40. The interpretation of SAECG findings, particularly where the ER pattern is manifest in the X, Y, or Z leads, is unclear, and the significance of abnormal results has not been validated. However, taken in line with interpretation in previous studies, delayed depolarization may contribute to the ER phenotype at least in a proportion of cases.

Exercise ECG

ER in the lateral leads or ER with an ascending ST segment universally suppressed with increased heart rates during exercise. In contrast, horizontal ER in the inferior leads persisted in 29% of cases. Haïssaguerre et al commented that exercise consistently reduced or eliminated ER2 in ERS, whereas Letsas et al30 also showed that ER disappeared at peak exercise in 44 out of 47 healthy individuals with ER but neither commented on differences between ascending and horizontal ER. Our group has previously shown that horizontal ER is more likely to persist during exercise and was also associated with a history of syncope.31 The number of individuals with syncope in this study was small, and we did not see such an association.

Ajmaline Provocation

Similarly to previous studies,22,33 the J-point was suppressed or remain unchanged with ajmaline provocation in the
majority of cases. Suppression of ER may in part be because of the ajmaline-induced increase in QRS duration obscuring the J wave or because of the increase in heart rate seen at peak ajmaline effect. Augmentation of ER in response to ajmaline was uncommon (n=4), and BrS was diagnosed in 3 such cases. It has previously been suggested that ERS and BrS are closely related and should be considered as a spectrum of J-wave syndromes. ER that augments with ajmaline-induced increase in QRS duration obscuring the J wave or because of the increase in heart rate seen at peak ajmaline effect. Augmentation was less common in those diagnosed with BrS, and J-point augmentation occurred in only a small minority. Therefore, a common mechanism underlying ER and BrS is unlikely in the majority of our cases.

Horizontal Versus Ascending ER

Ascending and horizontal ER were both seen more commonly in SADS relatives than in controls, with odds ratios of similar magnitude. Individuals with ascending ER were younger and more often men in keeping with previous studies. Ascending ER was associated with longer IQRS durations (P=0.03) and suppressed during exercise (P=0.02). In contrast, horizontal ER was associated with a lower RMS40 (P=0.06) and was more likely to persist at peak exercise (P=0.02) accompanied by complex ventricular ectopy during exertion. In addition, 3 out of the 4 cases of ER augmentation with ajmaline had horizontal ER although the differences in ajmaline response were not significant (P=0.49).

The contrasting demographic associations SAECG features and acute response to exercise between ascending and horizontal ER can be taken as further evidence of phenotypic heterogeneity within ER. There are likely to be distinct underlying mechanisms with horizontal ER involving a greater degree of depolarization abnormality.

Limitations

The study was a retrospective analysis and therefore may be susceptible to bias. Small cohort size limits the analysis of SAECG parameters. The control population consisted only of white individuals, the majority of whom were of British heritage (n=365, 91%). Therefore, results of this study may not be generalizable to other populations because of underlying ethnic differences in ER prevalence and subtypes. Because of the retrospective nature of the study, molecular autopsy was not available for the vast majority of the cohort, and genetic testing was performed in only a proportion of phenotype-positive individuals. Therefore, no suitable analysis based on genotype was possible.

Conclusions

The ER pattern is more common in first-degree SADS relatives than in family-clustered controls regardless of the presence of an ICC diagnosis. Both ascending and horizontal patterns are seen more frequently. ER of both subtypes may therefore represent a primary heritable arrhythmia syndrome or a risk factor for sudden death in the young. Investigation with SAECG, exercise testing, and ajmaline provocation suggests phenotypic heterogeneity within ER with differing physiological mechanisms that may include delayed depolarization.

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Disclosures

N.J. Samani is a National Institute for Health Research Senior Investigator. The other authors report no conflicts.

References


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<th>Total</th>
<th>No ER</th>
<th>Any ER</th>
<th>Ascend. ER</th>
<th>Horiz. ER</th>
<th>ER vs. None</th>
<th>Ascend. vs. None</th>
<th>Horiz. vs. None</th>
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<td></td>
<td>118</td>
<td>92</td>
<td>26</td>
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<td>15</td>
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<td>&lt;0.001</td>
<td>0.003</td>
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<td>Male</td>
<td></td>
<td>56 (47)</td>
<td>39 (45)</td>
<td>15 (58)</td>
<td>10 (91)</td>
<td>5 (33)</td>
<td>0.001</td>
<td>&lt;0.001</td>
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<td>Abnormal SAECG</td>
<td></td>
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<td>18 (20)</td>
<td>9 (35)</td>
<td>4 (36)</td>
<td>5 (33)</td>
<td>0.132</td>
<td>0.272</td>
<td>0.308</td>
</tr>
<tr>
<td>- abnormal fQRS</td>
<td></td>
<td>34 (29)</td>
<td>23 (25)</td>
<td>11 (42)</td>
<td>6 (55)</td>
<td>5 (33)</td>
<td>0.111</td>
<td>0.058</td>
<td>0.680</td>
</tr>
<tr>
<td>- abnormal LAS$_{40}$</td>
<td></td>
<td>28 (24)</td>
<td>19 (21)</td>
<td>9 (35)</td>
<td>4 (36)</td>
<td>5 (33)</td>
<td>0.173</td>
<td>0.308</td>
<td>0.354</td>
</tr>
<tr>
<td>- abnormal RMS$_{40}$</td>
<td></td>
<td>25 (21)</td>
<td>16 (17)</td>
<td>9 (35)</td>
<td>3 (27)</td>
<td>6 (40)</td>
<td>0.084</td>
<td>0.606</td>
<td>0.065</td>
</tr>
<tr>
<td>Mean fQRS</td>
<td></td>
<td>110 (10)</td>
<td>109 (9)</td>
<td>115 (12)</td>
<td>117 (11)</td>
<td>113 (13)</td>
<td>0.021</td>
<td>0.032</td>
<td>0.338</td>
</tr>
<tr>
<td>Mean LAS$_{40}$</td>
<td></td>
<td>33 (9)</td>
<td>32 (8)</td>
<td>36 (10)</td>
<td>35 (7)</td>
<td>36 (11)</td>
<td>0.055</td>
<td>0.401</td>
<td>0.073</td>
</tr>
<tr>
<td>Mean RMS$_{40}$</td>
<td></td>
<td>37 (20)</td>
<td>39 (21)</td>
<td>29 (13)</td>
<td>32 (14)</td>
<td>28 (14)</td>
<td>0.034</td>
<td>0.337</td>
<td>0.059</td>
</tr>
</tbody>
</table>
Table S1. Signal-averaged ECG findings. Continuous variables are expressed as mean (SD), categorical variables are expressed as n (%).

*ER* = Early Repolarisation; *fQRS* = filtered QRS duration; *LAS*<sub>40</sub> = duration of low amplitude signals (<40μV) in the terminal filtered QRS complex; *RMS*<sub>40</sub> = root-mean-square voltage of terminal 40ms of filtered QRS complex.

<table>
<thead>
<tr>
<th>ER Type</th>
<th>Controls, n=1884</th>
<th>All Relatives, n=377</th>
<th>Relatives of families with ICC diagnosis, n=178</th>
<th>Relatives of families with no diagnosis, n=199</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ER</td>
<td>151 (8)</td>
<td>80 (21)</td>
<td>40 (20)</td>
<td>40 (22)</td>
</tr>
<tr>
<td>Ascending ER</td>
<td>82 (4)</td>
<td>38 (10)</td>
<td>20 (10)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Horizontal ER</td>
<td>69 (4)</td>
<td>42 (11)</td>
<td>20 (10)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Notched ER</td>
<td>132 (7)</td>
<td>42 (11)</td>
<td>17 (9)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Slurred ER</td>
<td>89 (5)</td>
<td>38 (10)</td>
<td>23 (12)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Inferior ER</td>
<td>54 (3)</td>
<td>37 (10)</td>
<td>20 (10)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Lateral ER</td>
<td>48 (3)</td>
<td>29 (8)</td>
<td>15 (8)</td>
<td>14 (8)</td>
</tr>
</tbody>
</table>

Table S2. Prevalence of ER subtypes in SADS relatives and control population. Prevalence in SADS relatives are also presented for families in which an ICC diagnosis was made and those families where no diagnosis was made. *ER=Early Repolarization*
P-values are compared to no ER.

Table S3. ER response to exercise. Continuous variables are expressed as mean (SD), categorical variables are expressed as n (%).

*Response to exercise data is limited to 51/66 individuals with ER at the time of exercise testing. **p (Suppressed vs. Persistent). ER= Early Repolarisation, VE= Ventricular ectopy during exercise test, HR= Heart Rate, HRR= Heart Rate Recovery
<table>
<thead>
<tr>
<th></th>
<th>Reduced</th>
<th>Unchanged</th>
<th>Augmented</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>24</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>37.2 (13.8)</td>
<td>37.4 (15.8)</td>
<td>47.3 (16.4)</td>
<td>0.350</td>
</tr>
<tr>
<td>Male</td>
<td>21 (58)</td>
<td>14 (58)</td>
<td>2 (50)</td>
<td>0.950</td>
</tr>
<tr>
<td>Baseline HR</td>
<td>75.2 (11.9)</td>
<td>71.2 (14.6)</td>
<td>62.3 (15.7)</td>
<td>0.056</td>
</tr>
<tr>
<td>Baseline QRSd</td>
<td>94.0 (11.4)</td>
<td>89.4 (20.4)</td>
<td>102.5 (16.4)</td>
<td>0.172</td>
</tr>
<tr>
<td>Peak effect HR</td>
<td>82.6 (11.3)</td>
<td>82.3 (11.7)</td>
<td>68.3 (9.1)</td>
<td>0.022</td>
</tr>
<tr>
<td>Peak effect QRSd</td>
<td>124.6 (17.2)</td>
<td>129.0 (16.7)</td>
<td>149.0 (38.0)</td>
<td>0.064</td>
</tr>
<tr>
<td>Change in HR</td>
<td>7.4 (8.9)</td>
<td>11.1 (9.0)</td>
<td>6.0 (9.1)</td>
<td>0.183</td>
</tr>
<tr>
<td>Change in QRSd</td>
<td>30.6 (11.6)</td>
<td>39.5 (24.9)</td>
<td>46.5 (29.7)</td>
<td>0.131</td>
</tr>
<tr>
<td>Positive test</td>
<td>4 (11)</td>
<td>2 (8)</td>
<td>3 (75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascending ER</td>
<td>19 (53)</td>
<td>12 (50)</td>
<td>1 (25)</td>
<td>0.490</td>
</tr>
<tr>
<td>Horizontal ER</td>
<td>17 (47)</td>
<td>12 (50)</td>
<td>3 (75)</td>
<td></td>
</tr>
<tr>
<td>Notched J-point</td>
<td>23 (64)</td>
<td>9 (38)</td>
<td>1 (25)</td>
<td>0.072</td>
</tr>
<tr>
<td>Slurred J-point</td>
<td>13 (36)</td>
<td>15 (63)</td>
<td>3 (75)</td>
<td></td>
</tr>
<tr>
<td>Inferior ER</td>
<td>18 (50)</td>
<td>12 (50)</td>
<td>3 (75)</td>
<td></td>
</tr>
<tr>
<td>Lateral ER</td>
<td>12 (33)</td>
<td>9 (38)</td>
<td>1 (25)</td>
<td>0.877</td>
</tr>
<tr>
<td>Infero-lateral ER</td>
<td>6 (17)</td>
<td>3 (13)</td>
<td>0 (0)</td>
<td>0.646</td>
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<tr>
<td>Low amplitude ER</td>
<td>28 (78)</td>
<td>22 (92)</td>
<td>3 (75)</td>
<td>0.349</td>
</tr>
<tr>
<td>High amplitude ER</td>
<td>8 (22)</td>
<td>2 (8)</td>
<td>1 (25)</td>
<td>0.349</td>
</tr>
</tbody>
</table>

Table S4. ER response in ajmaline provocation. Continuous variables are expressed as mean (SD), categorical variables are expressed as n (%). ER= Early Repolarisation, Positive test = Type 1 Brugada Syndrome pattern. HR=heart rate, QRSd=QRS duration. p value obtained from a univariate mixed model adjusting for family as a random-effect. *from a Fishers exact test.