

***The prevalence and significance of the Early Repolarization pattern in Sudden Arrhythmic Death Syndrome (SADS) families***

***Running title: SADS ER***

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## Abstract

### 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 to family-clustered controls. ER was more common in SADS family members than in controls (21% vs. 8%, OR 5.14, 95% CI 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.

Key Words: Early Repolarization  
Sudden Arrhythmic Death Syndrome  
Signal averaged ECG  
Ajmaline  
Exercise Test

## **Introduction**

The early repolarization (ER) pattern was long thought to be benign and of little clinical significance<sup>1</sup>. More recently ER, defined by J-point elevation in the inferior and/or lateral leads, has been associated with idiopathic ventricular fibrillation<sup>2</sup> leading to recognition of Early Repolarization Syndrome (ERS) as a novel arrhythmia syndrome<sup>3</sup>. 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<sup>4,5</sup>. Several studies have suggested the ER pattern is a heritable phenotype<sup>6,7</sup> and variants in genes encoding cardiac ion channels<sup>8-10</sup> have been identified in individuals and families with ERS.

Sudden arrhythmic death syndrome (SADS) is defined as a sudden unexplained death where post-mortem examination reveals a structurally normal heart and toxicological analysis is negative<sup>11</sup>. Familial assessment of SADS relatives is recommended and may reveal evidence of an inherited cardiac condition in 22-53% of families<sup>12-15</sup> with ion channel disease the principal finding.

ER has previously been shown to be more common in SADS relatives<sup>16</sup>; however there was no differentiation by ST-segment morphology which has since been shown to distinguish between high and low risk forms<sup>17</sup>. Furthermore association with signal-averaged ECG 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 to 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.

## **Method**

### *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 between 2002 and 2014 (See figure 1). Of 526 first-degree relatives, 401 (76%) were included in the study. Relatives aged  $\leq 16$  at the time of first assessment were excluded as they were typically assessed through a separate paediatric service. The investigation of families and diagnosis of relatives was as per contemporary accepted guidelines<sup>3</sup> and has been described in detail previously<sup>14</sup>. 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. Non-Caucasian 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 GRAPHIC (Genetic Regulation of Arterial Pressure of Humans in the Community) cohort, which has been previously described in detail<sup>18,19</sup>. Briefly, the GRAPHIC study recruited Caucasian nuclear families from the UK general population. Families were included if both parents were aged 40-60 years with 2 offspring >18 years of age. Assessment

included a medical history, clinical examination and 12-lead ECG. All GRAPHIC subjects where 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 (GM) and borderline cases were adjudicated by consensus with a senior cardiologist (ERB). ER was defined as  $\geq 0.1$  mV J-point elevation in 2 contiguous leads in the inferior and/or lateral leads as per accepted modern criteria<sup>2,20,21</sup> (see figure 2). 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 100ms after the peak of the J point, or horizontal/descending otherwise. While this definition differs slightly from a very recent consensus document<sup>21</sup> it is in keeping with that used by Tikkanen et. al. when first demonstrating the prognostic benefit of ST segment gradient<sup>17</sup>. Similar criteria, described previously<sup>6</sup>, were used for the control population. J-point amplitude was categorized in 0.1 mV increments (i.e. 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 LVH. The Brugada type 1 ECG pattern was defined as per accepted definitions<sup>22</sup>.

### *Ajmaline provocation testing*

Ajmaline (1 mg/kg) was administered intravenously over 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 duration). J-point amplitude was categorized in 0.1mV increments as described above. The J-point response was classified as 'reduced' if the J-point amplitude reduced by  $\geq 0.1\text{mV}$  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  $\geq 0.1\text{mV}$  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 ETT 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 minutes 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 either: multifocal ectopics; ventricular ectopy increasing with exercise or occurring as couplets or non-sustained VT. The response to exercise was classified as 'suppressed' if ER was no longer present at peak exercise. Otherwise the response was classified as 'persistent'.

### *Signal-Averaged ECG Analysis*

Signal-averaged ECG (SAECG) analysis was performed in the study population group with acquisition of at least 300 cardiac cycles (filter setting 40-250Hz). Late potentials were defined by  $\geq 2$  of the following parameters being abnormal: filtered



QRS duration (fQRS)  $\geq 114\text{ms}$ ; duration of low amplitude signals ( $<40\mu\text{V}$ ) in the terminal filtered QRS complex ( $\text{LAS}_{40}$ )  $\geq 38\text{ms}$ ; root-mean-square voltage of terminal 40ms of filtered QRS complex ( $\text{RMS}_{40}$ )  $\leq 20\mu\text{V}$ <sup>23</sup>.

### *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 two-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 group against all controls.

Sub-group 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. 6% were non-Caucasian. The median number of relatives assessed per family was 2 (range 1-8). The cohort comprised 194 (48%) siblings, 157 (39%) parents and 50 (12%) children of SADS victims. An ICC was diagnosed in 108 individuals from 75 families with Brugada syndrome, BrS, (89 individuals from 60 families) the most frequent diagnosis (See figure 3). The control cohort was a Caucasian population with

a mean age of 39.3 where 951 (51%) were male. Information on Brugada syndrome 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 (OR 5.14, 3.37-7.34). ER appeared more common in males (28.9% vs. 12.1%) and in younger individuals with a significant interaction ( $P = 0.003$ ) between age and sex observed. Both ascending (9.7% vs. 4.5%; OR=4.34, 2.55-7.37) and horizontal (11.0% vs. 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 where no diagnosis was made (OR 0.206, 0.072-0.590, see figure 3). Results are summarized in table 2 and further in supplementary data.

#### *Ajmaline Provocation*

Ajmaline provocation was performed in 332 family members from 159 families and was positive in 86 (26%). ER was present on the index ECG in 69 cases (21%) and was more common where the test was negative (29% vs. 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;  $p$ , QRSd=0.31). Results are summarized in the supplementary data.

### *Exercise ECG*

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

Ventricular ectopy was seen during exercise in 52 (17%). Complex ectopy was more common in patients with horizontal ER (OR=4.2, 1.2 – 14.4) compared to 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 (27%) of cases (figure 4). Horizontal ER also persisted at peak exercise more frequently than ascending ER (34.6% vs. 8.0%,  $p=0.032$ ). Persistence at peak exercise was not associated with prior syncope ( $p=0.925$ ). There were no cases of ER augmentation with exercise. Results are summarized in the supplementary data.

### *Signal-averaged ECG*

SAECG was performed in 123 family members. The noise level was unacceptably high in 5 cases. Analysis was therefore carried out in 118 from 64 families. ER was present in 26 (22%; 11 ascending, 15 horizontal). The SAECG was abnormal in 23% of cases with no difference between individuals with and without ER ( $p=0.132$ ). However, individuals with ER demonstrated a longer mean fQRS ( $115\pm 12\text{ms}$  vs.  $109\pm 9\text{ms}$ ,  $p=0.021$ ), lower mean RMS<sub>40</sub> ( $29\pm 13\mu\text{V}$  vs.  $39\pm 21\mu\text{V}$ ,  $p=0.034$ ) and a trend toward longer mean LAS<sub>40</sub> ( $36\pm 10\text{ms}$  vs.  $32\pm 8\text{ms}$ ,  $p=0.055$ ). Ascending ER was

associated with a longer mean fQRS ( $p=0.032$ ) whereas there was a trend toward LAS<sub>40</sub> and RMS<sub>40</sub> being longer ( $p=0.073$ ) and lower ( $p=0.059$ ) respectively in those with horizontal ER. Results are summarized in the supplementary data.

## Discussion

We have shown that the ER pattern is more common in first-degree SADS relatives than in the general population. Nunn et al. previously found ER was present in 23% of SADS family members compared to 11% of controls. However, the control cohort used was small (matched 1:1) and comprised of 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<sup>4</sup> and long QT syndrome<sup>5</sup>.

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 as 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 while ER in the lateral leads or with a rapidly ascending ST segment is benign<sup>17</sup>. 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 VF and ERS. The

prevalence of ER in idiopathic VF has been reported between 23% and 42%<sup>2,24,25</sup>.

Only Rosso et al. have presented an analysis of data in idiopathic VF survivors stratified by ST segment and while they found that the association with IVF was strongest for horizontal ER, 30% of idiopathic VF cases with ER had the rapidly ascending form<sup>26</sup>. 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 abnormal SAECG results are uncommon in ERS patients<sup>2,27</sup> or at least in proportions similar to idiopathic VF survivors without ER<sup>25</sup>. However, Roten et al. showed that 39% of IVF survivors with ER had an abnormal SAECG<sup>28</sup> with a higher proportion where the ER pattern persisted during isoproterenol infusion. In addition, Abe et al. used 24 hour continuous signal averaged ECG monitoring and found the incidence of late potentials was higher in IVF survivors with ER than without with no difference in repolarisation markers between the two groups<sup>29</sup>. We found ER was associated with longer mean fQRS, LAS<sub>40</sub> and lower mean RMS<sub>40</sub>. 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 in at least 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. Haissaguerre et al. commented that exercise “consistently reduced or eliminated ER”<sup>2</sup> in ERS while Letsas et al. also showed that ER disappeared at peak exercise in 44/47 healthy individuals with ER<sup>30</sup> 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 prior syncope<sup>31</sup>. 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<sup>32,33</sup> the J-point was suppressed or remain unchanged with ajmaline provocation in the majority of cases. Suppression of ER may be due in part to the ajmaline-induced increase in QRS duration obscuring the J wave or to the increase in heart rate<sup>28</sup> 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’<sup>34</sup>. ER which augments with ajmaline may therefore represent such a syndrome. However, ER 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 male in keeping with previous studies<sup>17</sup>. Ascending ER was associated with longer fQRS durations ( $p=0.03$ ) and suppressed during exercise ( $p=0.02$ ). In contrast horizontal ER was associated with a lower RMS<sub>40</sub> ( $p=0.06$ ) and was more likely to persist at peak exercise ( $p=0.02$ ) accompanied by complex ventricular ectopy during exertion. In addition, three of the four 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 SAEKG 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 SAEKG parameters. The control population consisted only of Caucasian individuals, the majority of whom were of British heritage ( $n=365$ , 91%). Therefore results of this study may not be applicable to other populations due to underlying ethnic differences in ER prevalence and subtypes. Due to the retrospective nature of the study, molecular autopsy was not available for the vast majority of the cohort and genetic testing was carried out in only a proportion of

phenotype positive individuals. Therefore no suitable analysis based upon genotype was possible.

## Conclusion

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

None.

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				SADS relatives*			Control Population		
	SADS relatives*	Control Population	P	No ER	ER	P	No ER	ER	P
n	377	1884	-	297 (79)	80 (21)	-	1733 (92)	151 (8)	-
Age, years	39.6 (15)	39.3 (15)	0.638	40.0 (15)	38.4 (16)	0.429	39.6 (15)	34.8 (14)	<0.001
Male sex	163 (43)	951 (51)	0.010	116 (39)	47 (59)	0.002	837 (48)	114 (76)	<0.001
Heart rate, min <sup>-1</sup>	72 (14)	65 (10)	<0.001	73 (14)	70 (13)	0.113	66 (10)	63 (10)	0.002
PR interval, ms	156 (26)	155 (23)	0.766	153 (23)	166 (33)	<0.001	155 (23)	155 (22)	0.871
QRS duration, ms	92 (13)	93 (10)	0.090	92 (13)	91 (10)	0.382	93 (11)	96 (9)	0.002
QTc, ms	415 (27)	410 (20)	<0.001	418 (26)	405 (28)	<0.001	411 (20)	404 (17)	<0.001
LVH †	14 (4)	57 (3)	0.628	6 (2)	8 (10)	0.002	44 (3)	13 (11)	<0.001

Table 1. Baseline characteristics of SADS relatives and control populations with comparisons between those with and without ER. Continuous variables are expressed as mean (SD), categorical variables are expressed as n (%). *LVH= isolated voltage criteria for left ventricular hypertrophy (Sokolow-Lyon); ms=milliseconds.* \* Data only listed for Caucasian relatives † LVH data missing for 104 controls

	All SADS relatives			Families with ICC diagnosis			Families with no diagnosis		
ER Type	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
All ER	5.14	3.37-7.84	<0.001	4.86	2.73-8.65	<0.001	6.12	3.49-10.73	<0.001
Ascending ER	4.34	2.55-7.37	<0.001	4.38	2.26-8.46	<0.001	4.72	2.25-9.90	<0.001
Horizontal ER	3.64	2.26-5.84	<0.001	3.28	1.69-6.36	<0.001	4.36	2.33-8.16	<0.001
Notched ER	2.60	1.55-4.34	<0.001	1.65	0.77-3.51	0.197	3.94	2.05-7.58	<0.001
Slurred ER	3.17	1.95-5.15	<0.001	3.87	2.05-7.29	<0.001	2.67	1.34-5.31	0.005
Inferior ER	4.86	2.59-9.14	<0.001	5.17	2.29-11.71	<0.001	4.77	2.09-10.87	<0.001
Lateral ER	4.07	2.28-7.26	<0.001	3.86	1.76-8.47	0.001	4.63	2.15-9.98	<0.001
Inf-lat ER	2.40	1.10-5.23	0.027	1.45	0.46-4.50	0.524	3.87	1.48-10.11	0.006

Table 2. Odds ratios for presence of ER compared to control population stratified by ER subtype and presence of familial ICC diagnosis in SADS relatives. Multivariable analysis corrects for age, sex, ethnicity, familial clustering, and QTc interval and voltage criteria for LVH.

*OR=Odds Ratio, ER=Early Repolarisation, ICC=Inherited cardiac condition*

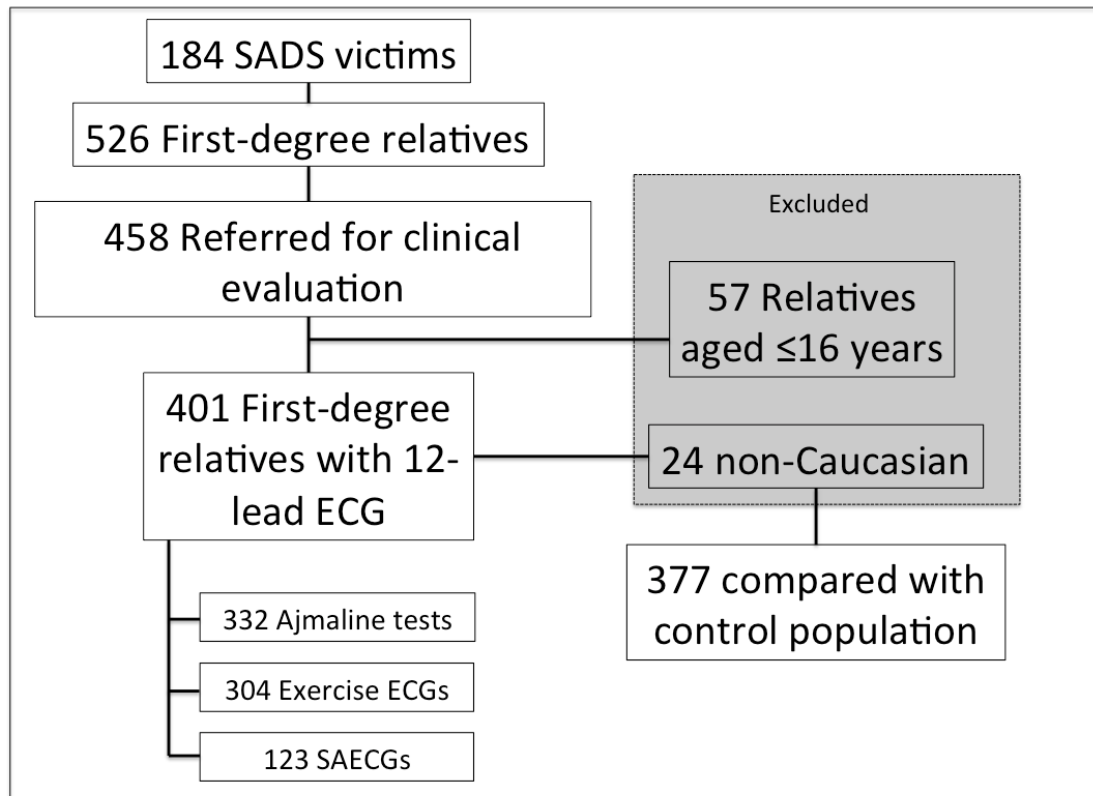


Figure 1. Study Population. 401 First-degree relatives underwent 12-lead ECG. The majority also had exercise and ajmaline tests. Approximately 30% also underwent a signal-averaged ECG. Since the control population contained Caucasian individuals only, non-Caucasians were excluded from this comparison. *SAECG=Signal-averaged ECG*.

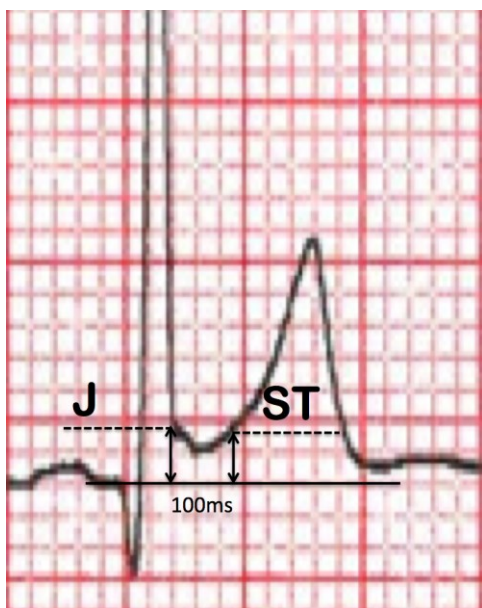


Figure 2. ECG example of rapidly ascending ER. ‘J’ denotes the J-point amplitude. J-point  $\geq 0.1\text{mV}$  in two consecutive leads was considered positive. ‘ST’ denotes the ST segment amplitude 100ms after the J-point. ST elevation  $\geq 0.1\text{mV}$  was classified as rapidly ascending. Otherwise ER was classified as horizontal/descending.

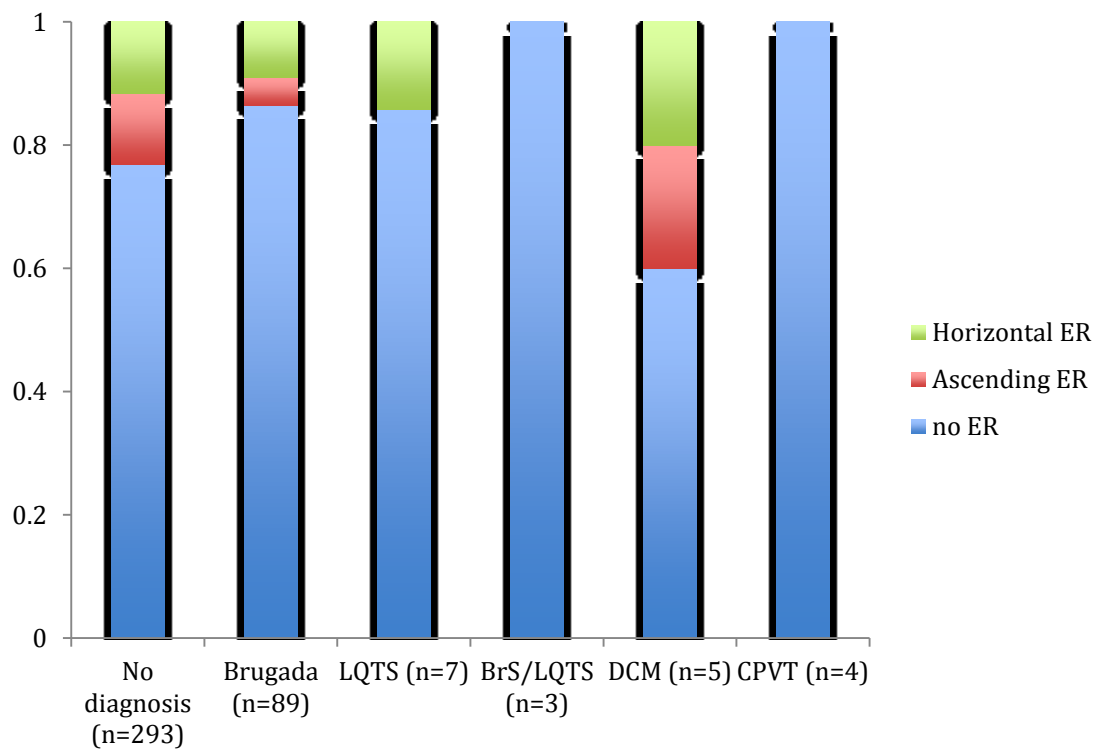
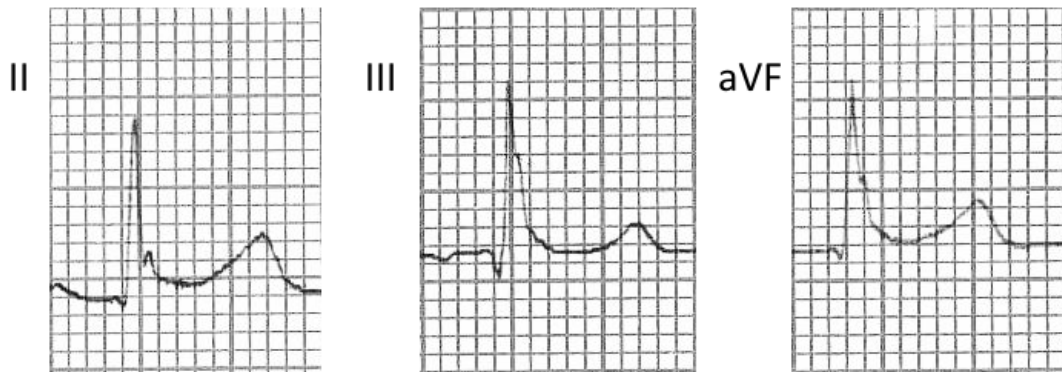


Figure 3. Summary of ICC diagnoses with ER proportions. ER was less common in relatives diagnosed with BrS than where no diagnosis was made (OR 0.206, 0.072-0.590,  $p=0.003$ ) *LQTS=Long QT Syndrome, BrS/LQTS=Brugada and Long QT overlap syndrome, DCM=Dilated Cardiomyopathy, CPVT=Catecholaminergic Polymorphic Ventricular Tachycardia*



## Baseline



## Peak Exercise

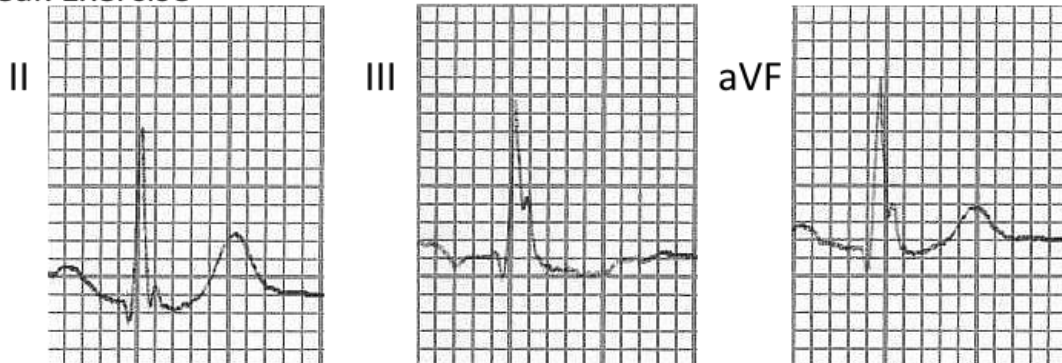


Figure 4. ER persisting with exercise. The inferior leads of ECGs from a single individual are shown. ECGs are recorded at rest, pre-exercise and at time of peak exercise. ER with a notched J-point and horizontal ST segment is seen in all inferior leads at rest. The J-point notching persists, with minimal reduction in amplitude at peak exercise.