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Original Article

# Increased Prevalence of the Electrocardiographic Early Repolarization Pattern in Young Patients With Vagally Mediated Syncope: A Case-Control Study

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## ABSTRACT

**Background:** Electrocardiographic early repolarization (EER) is linked with idiopathic ventricular fibrillation in adults. It is frequently seen in children, with poorly understood significance. Some evidence suggests that it could be a vagally mediated phenomenon. A retrospective case-control study was undertaken to test the hypothesis that EER is more common among children with typical vasovagal syncope (VVS) than among their peers with nonvagal syncope (NVS) or with no syncope.

**Methods:** Patients aged 4-18 years with syncope were identified by a single-centre database search followed by a review of history for features of VVS (n = 150) or NVS (n = 84). The first available electrocardiogram (ECG) for VVS or for NVS was retrieved. Age- and sex-matched children with no known syncope or heart disease were then identified (n = 216). ECGs were assessed separately for EER based on published criteria by 2 observers blinded to patients' clinical status.

**Results:** Mean age was 12.3 ± 3.2 years, and heart rate was 74.2 ± 16.5 beats/min. EER was more prevalent in VVS (33.3%) than among patients with NVS (19.1%; odds ratio: 2.29; confidence interval:

## RÉSUMÉ

**Contexte :** La repolarisation précoce (RP) à l'électrocardiogramme (ECG) est liée à une fibrillation ventriculaire idiopathique chez les adultes. Fréquente chez les enfants, sa signification est toutefois nébuleuse. Certaines données laissent penser qu'il pourrait s'agir d'un phénomène d'origine vagale. Une étude rétrospective cas-témoins a donc été réalisée dans le but de vérifier l'hypothèse selon laquelle la RP à l'ECG est plus courante chez les enfants atteints de syncope vasovagale (SVV) typique que chez leurs pairs atteints de syncope non vagale (SNV) ou non atteints de syncope.

**Méthodologie :** Des patients de 4 à 18 ans atteints de syncope ont été recensés au moyen d'une recherche dans la base de données d'un centre, suivie d'un examen des antécédents visant à retracer des manifestations de SVV (n = 150) ou de SNV (n = 84). Le premier ECG disponible traduisant une SVV ou une SNV a été récupéré. Un appariement selon l'âge et le sexe entre les sujets atteints et des enfants qui n'étaient pas atteints de syncope ni de maladie cardiaque (n = 216) a ensuite été effectué. Deux observateurs qui ne connaissaient

Early repolarization, once considered a benign electrocardiographic (ECG) finding, has found new attention, as it is associated with a higher risk of idiopathic ventricular fibrillation in an otherwise healthy adult population.[1–3] It is seen in up to 5% of presumably healthy adults,[4] up to 10% of healthy children with male predominance,[5] and in 50%-80% of resting ECGs of highly trained athletes, but it disappears or diminishes during deconditioning. The significance of early repolarization in children remains largely unknown. There are case reports of the early repolarization pattern on ECG associated with syncope of unknown cause in the young.[6,7]

A number of features of early repolarization, including mitigation on exercise and with atropine, presence in more than 50% of well-trained athletes, and resolution with deconditioning, suggest that vagal tone might play an important role in this ECG manifestation.[8,9] As vasovagal syncope (VVS) is the most common cause of syncope in children,[10] we hypothesized that early repolarization would be

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1.32-5.50) or among those with no syncope (12.5%; odds ratio: 3.14; confidence interval: 1.81-5.46). Heart rates were significantly lower in VVS and NVS (heart rate: 70.1 ± 13.8 and 70.7 ± 12.4 beats/min, respectively) compared with children with no syncope (heart rate: 78.2 ± 18.0 beats/min), both $P < 0.001$.

**Conclusions:** EER is more common in paediatric patients with VVS than those with NVS or without syncope, consistent with a possible vagal contribution to the ECG finding.

pas l'état clinique des enfants ont évalué les ECG séparément, à la recherche d'une RP, en se basant sur les critères publiés.

**Résultats :** L'âge moyen des sujets était de 12,3 ± 3,2 ans et la fréquence cardiaque moyenne, de 74,2 ± 16,5 battements/minute. La prévalence de la RP à l'ECG était plus élevée chez les patients atteints de SVV (33,3 %) que chez les patients atteints de SNV (19,1 %; rapport de cotes [RC] : 2,29; intervalle de confiance [IC] : 1,32-5,50) ou les enfants non atteints de syncope (12,5 %; RC : 3,14; IC : 1,81-5,46). La fréquence cardiaque (FC) était significativement plus faible chez les sujets atteints de SVV ou de SNV (FC : 70,1 ± 13,8 et 70,7 ± 12,4 battements/minute, respectivement), en comparaison des enfants non atteints de syncope (FC : 78,2 ± 18,0 battements/minute); $p <$ 0,001 dans les deux cas.

**Conclusion :** La repolarisation précoce à l'ECG est plus courante chez les enfants atteints de syncope vasovagale que chez les enfants atteints de syncope non vagale ou non atteints de syncope, ce qui concorde avec une possible composante vagale dans le tracé de l'ECG.

more prevalent among patients with VVS than among those with nonvagal syncope (NVS) or syncope-free controls.

## Methods

The research ethics board at the Hospital for Sick Children, Toronto, approved this study. This was a retrospective, single-centre case-control chart review.

### Study population—cases

Patients were between the ages of 4 and 18 years and presented with a chief complaint of syncope to our hospital from 2000 to 2010. Patients with syncope were selected from our hospital's cardiology database based on the diagnostic coding. The clinical histories of patients identified were reviewed, and those who met the inclusion criteria were included in the study (Table 1). Based on the clinical history, the patients were divided into VVS and NVS. All these patients had ECGs performed.

### Syncope: vasovagal and nonvagal

Syncope was defined as a transient loss of consciousness characterized by rapid onset, short duration, and spontaneous full recovery.[11] Syncope patients with features listed under the inclusion criteria in Table 1 were categorized as VVS.

### Controls: no syncope

The patients in the control group had routine ECGs performed for noncardiac complaints at various locations in the hospital. The medical records of this group were also reviewed to meet the inclusion and exclusion criteria (Table 1).

### Matching

We designed a case-control study with 1:1:1 matching where each case with VVS was age- and sex-matched to an NVS and a nonsyncope child, but there were insufficient NVS children to match with VVS. For the first 84 patients with VVS, we were able to achieve full matching as proposed. The remaining 66 patients with VVS were each age- and sex-matched to 2 nonsyncope patients, that is, 1:2 matching. Hence, each VVS case had 2 matched controls. We then analysed our results using an unadjusted model and followed this by analysing it again with an adjusted model, which adjusts for age, sex, and heart rate.

### ECG reading

The earliest clearly interpretable resting ECG that was available in the context of syncope was considered for the purpose of this study. The readers (MS and GJG) were blinded to the patient's clinical status, and a unique identification number was assigned to each patient. Each ECG was independently interpreted by GJG and MS, and in case of disagreement, it was reviewed together by both readers for resolution in 37 instances.

### ECG analysis

Electrocardiographic early repolarization (EER) was defined as an elevation of the QRS-ST junction (J point) in at least 2 leads. The amplitude of J-point elevation was at least 1 mm (0.1 mV) above the baseline level in the inferior leads (II, III, and aVF), lateral leads (I, aVL, and V4 to V6), or both.[12]. The different morphologies of EER, that is, marked, notched, slurred, and discrete, notched with ST segment elevation were considered.[12] The EER result was described as inferior (II, III, and aVF) or lateral (aVL, I, V5, and V6) leads, or both (inferolateral) or neither. In cases of persistent uncertainty, the ECG was labelled as "borderline EER" in 24 (13 with syncope and 11 with no syncope) instances, and these were included in EER positive.

### Data collection

Birth date, date of ECG, age, sex, heart rate, and clinical diagnosis for ECG were recorded from the MUSE ECG software (version 8.01.12445; GE, Boston, MA). The clinical diagnosis was recorded from the clinical letters or discharge reports in the patient chart.

### Statistical analysis

Characteristics of the study cohort were assessed using descriptive statistics. Data are described as frequencies, medians with range, and means with standard deviation as

**Table 1.** Inclusion and exclusion criteria

| |
|---|
| Inclusion criteria used for the vasovagal syncope group[14] |
| 1. Any emotional or orthostatic stress associated with prodromal symptoms of autonomic activation (sweating, pallor, nausea, and visual alterations) |
| 2. Situational syncope—syncope associated with some specific circumstances, for example, micturition, stool, cough, etc |
| 3. Syncope within 15 minutes after the end of physical activity |
| 4. Syncopal episode within 30 seconds of standing and syncope triggered by prolonged standing (3-45 minutes) |
| Exclusion criteria for syncope |
| 1. Channelopathies (long-QT syndrome, short-QT syndrome, and Brugada syndrome) |
| 2. Arrhythmogenic right ventricular cardiomyopathy (ARVC)/ACM |
| 3. Hypertension, myocardial ischemia, and previous diagnosis of Kawasaki's disease |
| 4. Metabolic: hypoglycaemia and electrolyte abnormality |
| 5. Congenital heart disease, cardiac conduction defects, previously known dysrhythmia or patients with transient chest pain with palpitations before the syncope (suspected arrhythmia), or syncope during activity |
| 6. Psychiatric illness (known or suspected) |
| 7. Seizure disorder or seizure followed by syncope |

ACM, arrhythmogenic cardiomyopathy.

appropriate. The relationship between demographics, clinical characteristics, and outcomes was assessed using the Student *t* test, $\chi^2$ test, and linear regression, as appropriate. Linear regression analysis accounting for the matched design was used to determine significant differences between the groups (cases and controls) for continuous outcome variables. Conditional logistic regression analysis was used for binary outcome variables. All statistical analysis was performed with the SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC). A *P* value of <0.05 was considered significant.

## Results

Our hospital cardiology database search initially yielded 362 syncope cases, and their medical records were reviewed. Of these, 167 were identified as VVS and 145 as NVS. Of 167 VVS cases, 150 were finally part of the study and 8 VVS cases were excluded as follows: 1 patient had sudden cardiac death requiring resuscitation and subsequent defibrillator (implantable cardioverter defibrillator) implantation, 1 had a pacemaker implanted for recurrent bradycardic syncope, 2 had persistent bradycardia and low atrial rhythm, and 1 each had unclear psychiatric history, left ventricular noncompaction, and small coronary artery fistula. A total of 9 additional patients with VVS were excluded because of nonavailability of appropriate matching. Of 145 identified NVS cases, 61 were excluded because of lack of appropriate matching VVS patients, and 84 were matched by age and gender to patients with VVS and included.

The nonsyncope controls were identified from 1477 ECGs obtained during the time period covered by the study from the following clinical sources: Child Development Clinic (36), General Pediatrics (259), Gastroenterology (96), Hematology and Oncology (260), and Adolescent Medicine (826). After a clinical chart review and based on age and sex matching criteria, 216 nonsyncopal patients were selected for the study. Of all the VVS cases (n = 150), the first 84 were each matched to 1 patient with NVS and 1 nonsyncopal control; the remaining 66 VVS cases were each matched to 2 nonsyncopal controls. The demographics and average heart rates of the study population are listed in Table 2.

### Early repolarization: syncope, sex, and age

In our study, we found that among all children with syncope, the proportion of early repolarization was significantly higher than that in nonsyncopal patients (66/234, 28.2% vs 27/216, 12.5%; odds ratio [OR] = 2.6, 95% confidence interval [CI]: 1.6-4.3; $P < 0.0001$). After adjusting for age, sex, and heart rate, the proportion of early repolarization remained significantly higher in syncopal patients than in nonsyncopal patients (OR = 2.2, 95% CI: 1.3-3.7; $P < 0.0002$).

Further analysis revealed that this was predominantly due to the proportion of EER in the VVS group; EER was present in 50 of 150 (33.3%) VVS and 16 of 84 (19.1%) NVS, and when we considered the proportion of early repolarization between children who had VVS and NVS vs controls, we found that the OR of early repolarization was 2.2 (95% CI: 1.1-4.1; $P < 0.0001$) in children with VVS compared with NVS, 3.3 (95% CI: 2.0-5.6; $P < 0.0001$) in children with VVS compared with controls, and 1.6 (95% CI: 0.8-3.1; $P < 0.0001$) in children with NVS compared with controls.

After adjusting for age, sex, and heart rate, the OR of early repolarization remained significant at 2.1 (95% CI: 1.1-4.0; $P < 0.0005$) in children with VVS compared with NVS. Similarly, it was significant at 2.9 (95% CI: 1.6-4.8;

**Table 2.** Demographics of the cases and control group

| Demographic | Syncope | VVS | NVS | No syncope |
|---|---|---|---|---|
| Age 4-18 y | | | | |
| N | 234 | 150 | 84 | 216 |
| Males, n (%) | 114 (48.7) | 76 (50.7) | 38 (45.2) | 114 (52.8) |
| Age, mean ± SD (y) | 12.4 ± 3.2 | 12.3 ± 3.2 | 12.4 ± 3.2 | 12.3 ± 3.2 |
| HR, mean ± SD (bpm) | 70.3 ± 13.3 | 70.1 ± 13.8 | 70.7 ± 12.4 | 78.2 ± 18.0 |
| Age >14 y | | | | |
| N | 98 | 62 | 36 | 88 |
| Males, n (%) | 48 (48.9) | 32 (51.6) | 16 (44.4) | 48 (54.5) |
| Age, mean ± SD (y) | 15.3 ± 1.2 | 15.3 ± 1.1 | 15.3 ± 1.0 | 15.3 ± 1.1 |
| HR, mean ± SD (bpm) | 64.1 ± 10.7 | 63.4 ± 11.5 | 65.2 ± 9.2 | 69.4 ± 14.3 |
| Age 4-14 y | | | | |
| N | 136 | 88 | 48 | 128 |
| Males, n (%) | 66 (48.5) | 44 (50.0) | 22 (45.8) | 66 (51.5) |
| Age, mean ± SD (y) | 10.2 ± 2.5 | 10.2 ± 2.6 | 10.1 ± 2.4 | 10.4 ± 2.6 |
| HR, mean ± SD (bpm) | 74.9 ± 13.2 | 74.7 ± 13.3 | 75.2 ± 13.0 | 84.0 ± 17.9 |

HR, heart rate; NVS, nonvagal syncope; SD, standard deviation; VVS, vasovagal syncope.

**Table 3.** Distribution and localization of early repolarization in the cohort population by syncope status

| | Syncope (n = 234) | | | VVS (n = 150) | | | NVS (n = 84) | | | No syncope (n = 216) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EER status | Total, n (%) | F | M | Total, n (%) | F | M | Total, n (%) | F | M | Total, n (%) | F | M |
| No EER | 168 (71.7) | 93 | 75 | 100 (66.7) | 53 | 47 | 68 (80.9) | 40 | 28 | 189 (87.5) | 89 | 100 |
| EER | 66 (28.2) | | | 50 (33.3) | | | 16 (19.1) | | | 27 (12.5) | | |
| Leads affected with EER | | | | | | | | | | | | |
| Inferior | 14 (6.0) | 6 | 8 | 11 (7.4) | 5 | 6 | 3 (3.6) | 1 | 2 | 8 (3.8) | 1 | 7 |
| Lateral | 18 (7.7) | 5 | 13 | 15 (10.1) | 5 | 10 | 3 (3.6) | 0 | 3 | 2 (0.1) | 1 | 1 |
| Inferolateral | 21 (9.0) | 10 | 11 | 16 (10.7) | 8 | 8 | 5 (6.0) | 2 | 3 | 6 (2.8) | 3 | 3 |
| Borderline | 13 (5.6) | 6 | 7 | 8 (5.4) | 3 | 5 | 5 (6.0) | 3 | 2 | 11 (5.2) | 7 | 4 |

EER, electrocardiographic early repolarization; NVS, nonvagal syncope; VVS, vasovagal syncope.

$P < 0.0005$) in children with VVS compared with controls. Finally, the OR of early repolarization was nonsignificant at 1.3 (95% CI: 0.7-2.7; $P$ = nonsignificant) in children with NVS compared with controls.

In our total cohort (both syncope and nonsyncope groups) with EER (n = 93), there was an observed preponderance of early repolarization among males who did not reach statistical significance (54, 58.1% vs 39, 41.9%, male and female, respectively).

### Early repolarization: syncope and heart rate

The average heart rate was significantly lower in our total cohort with EER than those without EER (68.1 ± 14 beats/min vs 75.6 ± 16.3 beats/min; $P = 0.004$). When comparing the OR of syncope vs nonsyncope groups, heart rate had a significant effect on the odds of having EER (OR = 0.97, 95% CI: 0.95-0.99; $P < 0.002$). The average heart rate of children with syncope (70.3 ± 13.3 beats/min) was significantly lower than that of controls (78.2 ± 18.0 beats/min; $P < 0.001$).

### Early repolarization: patient age and ECG localization

In children older than 14 years, EER was more prevalent (43/186, 23.1%) than in those less than 14 years old (50/264, 18.9%), but this comparison was not statistically significant (Table 3).

The prevalence of lateral lead early repolarization on ECG was more prominent in males, but not to a statistically significant degree. Also, in children less than 14 years of age, inferior and inferolateral EER were more common, but this trend did not reach statistical significance. Inferior, lateral, and inferolateral EER were all seen in higher proportion in syncopal patients than in controls.

### Multivariable model

A multivariable logistic model was used to assess the significant relationships between EER with syncope and heart rate to assess whether heart rate could be acting as a confounding variable. The model was found to be significant (likelihood ratio $\chi^2$ of 19.144, degrees of freedom = 2; $P < 0.0001$), and the effects of syncope and heart rate were found to be independent with an OR of 1.8 (95% CI: 1.02-3.2; $P = 0.044$) for children with syncope and an OR of 0.97 (95% CI: 0.94-0.99; $P = 0.007$) for every unit of heart rate (beats/min) increase.

## Discussion

EER was long considered a harmless physiologic variant until the publication of 2 groundbreaking studies by Haïssaguerre et al.[1] and Tikkanen et al[2] showing a significant association between EER and mortality risk in adults. Subsequent publications showing high EER prevalence rates in healthy children, and especially in highly conditioned young athletes, suggested that the EER-associated risks identified in older adults might not be applicable to young individuals.[4,13]

The results of our blinded case-control study provide convincing, albeit indirect, support for the notion that EER is at least partly a manifestation of vagal tone independent from heart rate. Our blinded ECG analysis identified EER in 33.3% of children with classic VVS vs 19.1% of NVS and 12.5% of nonsyncopal patients, consistent with the notion that vagal tone could be an important determinant of EER in otherwise healthy young individuals.

There are many recorded cases of early repolarization associated with heightened risk of ventricular fibrillation or sudden death in young adults.[6,7] Currently, there are no longitudinal data addressing the prognostic significance of early repolarization in children. In adults, inferior and inferolateral EER are associated with worse prognosis than lateral EER,[13] but in young individuals, the significance of EER localization is not known.[12] We observed that inferior, lateral, and inferolateral repolarization patterns were more common in children with VVS than in those with NVS or in nonsyncopal controls, but the relatively small numbers of patients in each group did not allow these differences to reach statistical significance.

Adlakha et al.[14] demonstrated that children with VVS were more likely to have systolic blood pressure lower than 10th percentile compared with controls, but they found no difference in the baseline heart rate. In our work, we demonstrated that children with syncope have lower heart rates, but there is no difference between vagal and NVS heart rates. Also, in our cohort, we found that heart rate was lower among patients with EER than those without EER. This further supports the vagal nature of EER, especially in those who had syncope. HR of each subgroup (syncope, VVS, NVS, and controls) was lower in the children who had early repolarization on ECG ($P = 0.004$). This further supports that EER is likely to be a vagal phenomenon. VVS is the most common type of syncope in general population, including among repaired congenital heart disease and athletes.

There was only 1 small case series (n = 29) from Sweden comparing the ECGs of children with syncope with those with chest pain, presumed controls in the study.[15] They found that 13 of 29 (45%) children with syncope had EER compared with 24% of chest pain controls. Those investigators study also demonstrated some trend towards EER being more common in male children. Interestingly, we had similar findings in our retrospective case-control study.

### Study limitations

The limitations of the study are related to the lack of perfect matching due to inadequate numbers of patients with NVS. Although no evidence of syncopal events was identified in our review of control patients' records, we cannot categorically exclude the possibility of lifetime freedom from syncope, as fainting is common in childhood and first-hand histories were not obtained; importantly, however, ECGs in this group were not obtained in the context of investigation of syncope, as was the case for the patients with VVS and NVS. We did not analyse the specific pattern of EER (upsloping vs flat or downsloping ST segment), identified as having prognostic significance in some adult studies.[16] We did not consider patients' racial origin, widely recognized in previous studies as influencing the prevalence of early repolarization.[17]

## Conclusions

This study highlights the prevalence of early repolarization on ECG and its clinical correlation with vasovagal symptoms in children. These children with VVS and EER also have lower heart rates than their nonsyncopal counterparts. Our observations suggest that EER is a common finding in young individuals with a clinical history suggestive of VVS, and is likely consistent with the increased vagal tone that is thought to underlie their predisposition to faint in recognized situations.

## Ethics Statement

This study received ethical approval from the Hospital for Sick Children Research Ethics Board (Study #1000020103) on August 17, 2010.

## Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a REB-approved retrospective case report using de-identified data; therefore, the institutional review board did not require consent from the patient.

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## Disclosures

The authors have no conflicts of interest to disclose.

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