Constant ST segment elevation in leads II, III, AVF: is it a congenital heritable electrocardiographic sign.
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1. Summary (English):

Patricio Steeven Alvarez Lucin

*Title:* Constant ST segment elevation in leads II, III, AVF: is it a congenital heritable electrocardiographic sign.

*Research aim:* Evaluation of the frequency of this syndrome individually and among the family relatives

**Objectives:**
1. Selection of patients with these symptoms in their electrocardiograms.
2. Assessment of patients electrocardiograms made in different periods of life.
3. Assessment of electrocardiograms of their family relatives.
4. Comparing electrocardiograms between patients and their family relatives.
5. Evaluation of the frequency of this syndrome among family relatives.

*Methodology:* A prospective and retrospective study of a total of 2 families at first in the Outpatient Department in Kaunas City Clinical Hospital in which we collected ECG from medical history or the ECG was performed in Kaunas City Clinical Hospital during the period of this work.

*Study participants:* A total of 20 ECG were studied, 7 from the Family A and 13 from the Family B

*Research results:* The study of both families showed that may be possible that a constant ST segment elevation to be heritable. In the family A the hereditability may be zero percent, but in the other in the family, the family B, the hereditability of the syndrome may be between hundred and fifty percent.

*Conclusions:* In the individual study we observed that changes of ST segment elevation are preserved during the life time. In the family study was observed that in one family the syndrome of ST segment elevation may be heritable, but in the other family the results did not show the same results.
2. Conflicts of interest

The author reports no conflicts of interest
3. Permission issued by the Ethics Committee

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DĖL PRITARIMO TYRIMUI

LSMU Bioetikos centras, įvertinęs Patricio Álvarez Lucin pateiktus dokumentus, studento tiriamajam darbui tema „Constant ST elevation in leads II, III, AVF: is it a congenital heritable electrocardiographic sing“ pritaria*.

dr. Elmantas Pečius

* Pautaba: šis pritarimas neatliečia tiriamajį mokslinį darbą vykdančių asmenų nuo prievoles laikytis Bendrojo duomenų apsaugos reglamento nuostatų ir nuo atsakomybės gauti nacionalinio arba regioninio bioetikos komiteto leidiną, jei iešk leidiną būtinas pagal LR Biomedicininį tyrimų etikos įstatymo numatytus reikalavimus.
4. Abbreviations list

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ERS</td>
<td>Early Repolarization Syndrome</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
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<tr>
<td>KCNJ8</td>
<td>Potassium inwardly-rectifying channel, subfamily J, member 8,</td>
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<tr>
<td>CACNA1C</td>
<td>Calcium Voltage-Gated Channel Subunit Alpha1 C)</td>
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<td>CACNB2</td>
<td>Calcium Voltage-Gated Channel Auxiliary Subunit Beta 2)</td>
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<tr>
<td>CACNA2D1</td>
<td>Calcium Voltage-Gated Channel Auxiliary Subunit Alpha2delta 1</td>
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<tr>
<td>SCN5A</td>
<td>Sodium Voltage-Gated Channel Alpha Subunit 5</td>
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5. Introduction

In this prospective and retrospective study, I tried to focus in one patient per family, we chose him or her because has the most clear characteristic of the Syndrome of Early Repolarization (ERS) with ST segment elevation. Was studied the ECG of the patient which were done previously or new ECG were ordered. Most of the attention was take in the leads II, III, AVF, which represent the inferior wall of the heart. We needed to know if those changes are temporary or last during all the life time.

Also studying the family relatives of this patients will help us to get an insight whether this syndrome is frequent among the family members or not. Most of the attention was taken into the children of the patients, because here we have a direct relation for study if the syndrome is transmitted through generation to generation.
6. Aim and objectives of the thesis

Research aim:
The aim of this thesis is to evaluate the frequency of the ST segment elevation syndrome among the patient and relatives.

Objectives:
1. Selection of patients with these symptoms in their electrocardiograms.
2. Assessment of patients electrocardiograms made in different periods of life.
3. Assessment of electrocardiograms of their family relatives.
4. Comparing electrocardiograms between patients and their family relatives.
5. Evaluation of the frequency of this syndrome among family relatives.
7. Literature review

Definition of Early Repolarization

There is lack of agreement on the definition for Early Repolarization. At the beginning Early Repolarization was used for described ST segment elevation without chest pain [1-3] because it helped us to differentiate between acute myocardial infraction or pericarditis. Without chest pain, this Early Repolarization supposed to be benign [4,5]. Early Repolarization is important, because we can find it on several syndromes like, acute myocardial injury infraction, Takotsubo cardiomyopathy, pericarditis and hypothermia (Osborn waves) [6,7]. If we don't find this conditions, an Early Repolarization is a normal electrocardiographic sign, that is frequent among the population[8].

Although more recently the study of the Early Repolarization, says that the definition is complicated by the presence of several key characteristics that must be considered, including the localization and number of leads in which the ERS is present, the character of the QRS complex and J point (notching or slurring), the magnitude and duration of the J-point elevation, the elevation of the ST segment, and concomitant electrocardiographic findings such as J-wave augmentation or short coupled premature ventricular contractions [9,10].

The lack of consensus in definitions of ERS and of J-point abnormalities results in difficulty in the interpretation of the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus on the inherited arrhythmia syndromes. [11] In this document, the ERS is defined as ≥1-mm J-point elevation in ≥2 contiguous inferior or lateral leads in a standard 12 ECG leads. The authors recognize that ERS could refer to ST-segment elevation. Also says that the ERS can be diagnosed in a sudden cardiac death victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG.

Genesis of the Early Repolarization

The movement inward of sodium across the cell membrane through a specific channel produces inward current that causes depolarization. Outward movement of potassium causes repolarization. There are 8 types of Potassium currents. The plateau phase of action potential depends on balance between inward (depolarizing) and outward (repolarizing) currents.

Ventricular myocardium has actually three layers of muscles, epicardial, M cells and endocardial layer. The M cells resemble Purkinje cells. In normal state there is homogenous
genesis of action potential across the three layers, an abnormality of any layer would lead to aberration in action potential and development of ionic gradient between the layers with consequent development of slow conduction, forming a substrate for reentry in phase 2. The first phase of repolarization with a dome like small hump is due to potassium current called transient outward current. Uneven distribution with resultant gradient of transient outward current between epicardium and endocardium results in J-point elevation. Hypothermia and hypocalcemia enhance J wave development. [12]

Figure 1. Various examples of Early Repolarization Syndromes are shown

**Types of Early Repolarization**

According to Antzelevitch et al we can find 3 subtypes of Early Repolarization [13,14]:

1. Type 1: Early Repolarization pattern predominantly in the lateral precordial leads. Mostly in healthy male athletes and is rarely seen in ventricular fibrillation (VF) survivors
2. Type 2: Early Repolarization pattern predominantly in the inferior and inferolateral leads. Mostly idiopathic VF, also prevalent in healthy young males.
3. Type 3: Early Repolarization pattern globally in the inferior, lateral, and right precordial leads and is associated with the highest level of risk for development of malignant arrhythmia.
Historical perspective

The first time that was described the J-deflection presenting either in a QRS slurring or notching was in 1936 by Shilpey et al [15] and was considered a normal ECG variant.

Was in 1961, when Wasserburger et al [16] further defined Early Repolarization as a 1-4mm takeoff of the ST-segment at the end of the QRS complex with a distinct notch or slur on the downslope of the R wave in the mid to left precordial leads.

In 2000, Kalla et al provided evidence supporting above hypothesis [17] and Takagi et al [18] when they reported ventricular fibrillation in patients with prominent J-wave and ST segment elevation in inferior leads without structural heart diseases and postulated that idiopathic ventricular fibrillation with an Early Repolarization pattern in inferior leads may represent a variant of the Brugada Syndrome.

Was in 2008, when Haïssaguerre et al [19] and Nam et al[20] described a strong relationship between J-waves and many different forms of ventricular arrhythmias in the absence of known heart disease.

Prevalence

The ERS is common in hypertrophic obstructive cardiomyopathy, cocaine user, athletes and/or hypertrophy of interventricular septal defect. [21-24]

Nowadays the prevalence of ERS in our population varies between 3%-24%, depending on the methods used for ECG interpretation. The young athletes, Africans American have higher prevalence [25].

Genetic and Biological Basis of ER

Several observations have raised speculation that a genetic basis for Early Repolarization exists.

First, ERS has been reported to occur more frequently among relatives of individuals who experienced idiopathic sudden cardiac arrest than control subjects. [26]

Second, a widespread heritable basis for ERS has been reported. [27,28] Data from the Framingham study and British cohorts suggest that there is evidence of heritability of the ERS with a 2 to 3 times increased risk in siblings and offspring of subjects with inferolateral ERS.

Third, the ERS has been observed as a feature of other genetic arrhythmia syndromes such as Brugada Syndrome[29-31] and short-QT syndrome. [32] Furthermore, some genetic
variants reported to be associated with ERS have been associated with other arrhythmia syndromes. [33,34]

Also a gene mutations involve the KCNJ8, CACNA1C, CACNB2, CACNA2D1 and the SCN5A gene [35-38] Will enhance the inward–outward current imbalance responsible for accelerated epicardial

**Clinical diagnosis**

The following clinical patterns are now known: [39,40]

1. Asymptomatic and incidentally detected Early Repolarization is very common in young athletes. The prevalence and magnitude of Early Repolarization is known to increase as their training intensifies with the time.
2. Malignant variety with Idiopathic ventricular fibrillation and Sudden cardiac death.
3. Early Repolarization with Coronary artery disease (CAD) with increased risk of having ischemic ventricular fibrillation. Early Repolarization pattern recorded during ischemic event is strongest predictor of a ventricular fibrillation occurrence.
4. Early Repolarization has been linked to high cardiac death and arrhythmic death rates in vasospastic angina.
5. Idiopathic ventricular fibrillation is reported with horizontal or down-sloping ST following J-point elevation.
8. Research methodology and methods

A prospective and retrospective study of a total of 2 families at the Outpatient Department in Kaunas City Clinical Hospital in which we collected ECG from medical history or in case of an absence of an ECG, the patient was called and the ECG was performed in Kaunas City Clinical Hospital during the period of this work.

With a total of 20 ECG studied, 7 from the Family A and 13 from the Family B. For this study we checked for a constant ST segment elevation in the leads II, III and AVF. The criteria for the diagnose of the ERS with constant ST segment elevation was made by the presence of J-point elevation and ST segment elevation (at the end of J-point) ≥1 mm in ≥2 contiguous inferior leads of at least two standard 12-lead ECGs. The ECG were studied by 2 persons all the time, the student and the supervisor doctor, in this way we decreasing the margin of error or mistake.

The families were choose because we observed a pattern in which an individual has ST segment elevation without myocardial infraction, heart aneurysm or pericarditis, so we were thinking that this reason can be hereditable. Being that the reason we decided to also study the family relatives for discover if there is a pattern.
9. Results

We did a study in 2 families where was found a person with an ERS with an ST segment elevation, who we will call our main patient.

Family A
The first family we called family A, is a 5 generation family. The main patient of the family A is women in the generation 3 (G3). We chose her because we found characteristic changes of an ERS with ST segment elevation in different ECG during her lifetime in lead II, III and AVF. Is also known that she had high blood pressure during many years of her life, which made some structural changes in her heart like left ventricular hypertrophic which was diagnosed by an echocardiography in Kaunas City Clinical Hospital.

In the first and second generation of the family A was not possible to define if there are or not changes according to an ERS.

The husband of our main patient in the family A is negative for an ERS with a ST segment elevation.

Our main patient in family A has only one son (generation 4), which his ECG did not showed any changes characteristic of an ERS. Also the only grandson (generation 5) of our main patient of family A did not show changes on the ECG. This indicate that there is a zero percent of probability that the changes of ERS with ST segment elevation from the mother ECG were transmitted to the younger generation in an hereditable way.

We studied the relative of our main patient, in which the results were negative for an ERS, for example we can observe in aunt (generation 2) and the cousin (generation 3) of our main patient of family A the ECG were without the ERS.

Here we have a simplify view of the family tree of the family A in which in a red circle is our main patient.
Family B

The other family in the study is the Family B, which has 4 generations. Our main patient is a man in the generation 3. We chose him, because several of the ECG during different period of life show changes which represent an ERS with a ST segment elevation in leads II, III and AVF, and also we were able to have the ECG from his children.

In the first generation, where only found characteristic changes of an Early Repolarization in the grandmother from mother side from our main patient. She has an ST segment elevation, but this is probably is because she had an myocardial infraction maybe this is an old scar with left ventricular aneurysm.

In the second generation, the ECG of the parents of our main patient in the family B were negative for an ERS. Also we studied the ECG of three aunts of our main patient in this family, which were negative for an ERS.

In the third generation, the generation of our main patient in family B, we studied the ECG of the only brother that our main patient has, he did not have changes of ERS.
We can say at this point that fifty percent of cases from this generation express the ERS with ST segment elevation. This means that only one son of two has the syndrome, and that son is our main patient.

For our study of the fourth generation, which is the generation of the son and daughter of our main patient. We need to say that the wife of the main patient in family B did not show changes of an ERS on the ECG taken during different periods in the life. Both the son and the daughter in the fourth generation showed changes on the ECG during different periods of life, which indicate an ERS with ST segment elevation. Interesting this changes were observed in the same leads than our main patient in the family B (leads II, III and AVF). At this point we can observe that we may have a hundred percent of probability that this syndrome may be hereditary from the father, who has the same syndrome. This gives us the suspicion that this can be an hereditary syndrome.

Although we can see that our main patient has structural changes in his heart as left ventricular hypertrophy, the ECG of the his son and daughter did not show structural changes, but they do have the ERS with ST segment elevation.

Also is important to say that in the study of the brother of our main patient in the family B, the two only sons that he has, showed an negative ECG for an ERS.

Here we have a simplify view of the family tree of the family B in which in a red circle is our main patient.

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Fig 3. Family tree family B
10. Discussion

The studies provide us an insight of whether the ERS with a ST segment elevation is an hereditable condition or not. And if this condition we can predict only with an study of the ECG during different period of life.

Knowing that this syndrome is extremely rare in the population, was difficult to ask the members of the family when they are healthy for go to the doctor and do an ECG, because this people don’t go to the doctor when they are healthy, they are scared that something can be found in them. This is the reason why we only have 20 participants with the ECG.

Our study shows that in family A there is a zero percent of hereditability of the ERS into the next generation, but we need to say that she only has one child, in the case of more children we can have a better insight of this syndrome, but this is not the case.
Our study in the family B there is a hundred percent hereditability from our main patient to his son and daughter, this give us the idea that this syndrome can be hereditable to it fully.

If we take in consideration both families, in family A we do not see this syndrome being hereditable, but in the case of the family B we can see the syndrome being hereditable.

Is important to mention, that when the heart is in a high activity, for example when a sympathetic system is in action, the ECG turn out in a blurry line that does not follow any pattern, making it hard to read. In the other hand when the heart is in a slow activity, which happen when the parasympathetic nervous system is in action, the ECG follow a normal line, easy to read, making possible to give the diagnosis of an ERS.

There are some factors which affect with more frequency this syndrome, the hereditability, structural changes in the heart such a hypertrophy (for example in our main patient from both families which they have left ventricular hypertrophy), the use of androgen, African population, sport athletes and others.
11. Conclusion

In the individual study of the our main patients in both families, we observed changes of ERS with a ST segment elevation on ECG that are the same several years ago and now in the present, the changes in the leads II, III and AVF were the same, so those changes last a lifetime.

In the family study the conclusion were different in each family. In family A we noted that the mother had the ERS, but her son and grandson did not express the same syndrome, giving us a percent of zero according to hereditability. from mother to son and grandson. In the other hand, we observed in the family B that the pattern of ERS with a ST segment elevation continue through generation was noted a hundred percent from generation 4 to generation 5, but fifty percent between generation 2 to generation 3.
12. Practical recommendation

We recommend to the families affected to advice to the doctor that they have the ERS with a ST segment elevation, to avoid any wrong clinical diagnosis.
13. Literature list


