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Early repolarization syndrome in modern interpretation

T. V. Ashcheulova[A-F], N. M. Herasymchuk*[A-F], I. V. Sytina[A-F]

Kharkiv National Medical University, Ukraine

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Key words: early repolarization syndrome, ventricular fibrillation, sudden cardiac death.

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***E-mail:** nino.gerasimchuk@gmail.com

Relevance of the study of early repolarization syndrome is associated with a high degree of its occurrence among the general population, namely among young people and people doing sports.

Objective is to generalize the data of experimental and clinical studies which have found that the early repolarization syndrome is an idiopathic electrocardiographic phenomenon, which is considered by various specialists ambiguously; to assess the state of the cardiovascular system in the subjects, both adults and children with early repolarization syndrome, and to propose a diagnostic algorithm for detecting this phenomenon on the ECG when admitting to physical exercise and sports.

The history of the development of early repolarization syndrome has been shown since 1936 to present time, which was first described by R. Shipley and W. Halleran. Clinical interest in ERS appeared as a result of a clinically established relationship with lethal arrhythmias in healthy people without structural changes in the heart. According to existing recommendations, the opinions of leading experts, incluеding members of Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), the Asia-Pacific Society for Heart Rhythm (2015), it should be distinguished between the pattern and the syndrome of early ventricular repolarization. The Shanghai scale for the diagnosis of early repolarization syndrome, as well as the etiology, electrophysiology of early repolarization syndrome, its modern classification and electrocardiographic signs are presented. The features of early repolarization syndrome in athletes and in children, as well as the features of its treatment and prevention are shown.

Conclusions. Thus, the early repolarization syndrome is an important cardiac problem. Future clinical and experimental studies should focus on finding out the exact causes and mechanisms for the development of the early repolarization syndrome and, ultimately, on developing strategies to prevent premature death from cardiac causes in individuals with this electrocardiogram disorder.

Ключові слова: синдром ранньої реполяризації шлуночків, фібриляція шлуночків, раптова серцева смерть.

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Синдром ранньої реполяризації шлуночків у сучасній інтерпретації

Т. В. Ащеулова, Н. М. Герасимчук, І. В. Ситіна

Вивчення синдрому ранньої реполяризації шлуночків (СРРШ) пов'язано з чималим його поширенням у загальній популяції населення, зокрема серед молодих осіб та осіб, які займаються спортом.

Мета роботи – узагальнення даних експериментальних і клінічних досліджень, якими встановлено, що синдром ранньої реполяризації шлуночків – це ідіопатичний електрокардіографічний феномен, до якого різні фахівці ставляться неоднозначно. Оцінити стан серцево-судинної системи в обстежуваних і дорослих, і дітей із синдромом ранньої реполяризації шлуночків, а також запропонувати діагностичний алгоритм, якщо цей феномен виявлений на ЕКГ при допуску до фізичних навантажень і занять спортом.

Показано історію розвитку синдрому ранньої реполяризації шлуночків (СРРШ), який уперше був описаний R. Shipley і W. Halleran, з 1936 р. і донині. Клінічний інтерес до СРРШ виник унаслідок клінічно встановленого взаємозв'язку з летальними аритміями у здорових людей без структурних змін у серці. За чинними рекомендаціями провідних експертів, зокрема членів Товариства серцевого ритму (HRS), Європейської асоціації серцевого ритму (EHRA), Азіатсько-Тихоокеанського товариства серцевого ритму (2015), слід розрізняти феномен і синдром ранньої реполяризації шлуночків. Наведено Шанхайську шкалу для діагностики синдрому ранньої реполяризації шлуночків, а також етіологію, електрофізіологію під час СРРШ, його сучасну класифікацію та електрокардіографічні ознаки. Показано особливості СРРШ у спортсменів і в дітей, а також особливості його лікування і профілактики.

Висновки. Синдром ранньої реполяризації шлуночків – важлива кардіологічна проблема. Майбутні клінічні та експериментальні дослідження мають зосередитися на з'ясуванні точних причин і механізмів розвитку синдрому ранньої реполяризації шлуночків, а також на розробленні стратегій профілактики передчасної смерті від серцевих причин в осіб із цими порушеннями електрокардіографічних ознак.

Ключевые слова: синдром ранней реполяризации желудочков, фибрилляция желудочков, внезапная сердечная смерть.

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Синдром ранней реполяризации желудочков в современной интерпретации

Т. В. Ащеулова, Н. Н. Герасимчук, И. В. Сытина

Изучение синдрома ранней реполяризации желудочков (СРРЖ) связано с высокой степенью его распространения в общей популяции населения, и в частности среди молодых лиц и лиц, занимающихся спортом.

Цель работы – обобщение данных экспериментальных и клинических исследований, которыми установлено, что синдром ранней реполяризации желудочков – это идиопатический электрокардиографический феномен, к которому специалисты относятся неоднозначно. Оценить состояние сердечно-сосудистой системы у обследуемых и взрослых,

и детей с синдромом ранней реполяризации желудочков, а также предложить диагностический алгоритм при обнаружении данного феномена на ЭКГ при допуске к физическим нагрузкам и занятиям спортом.

Показана история развития синдрома ранней реполяризации желудочков (СРРЖ), который впервые был описан R. Shipley и W. Halleran, с 1936 г. и до настоящего времени. Клинический интерес к СРРЖ возник вследствие клинически установленной взаимосвязи с летальными аритмиями у здоровых людей без структурных изменений в сердце. Согласно имеющимся рекомендациям ведущих экспертов, а именно членов Общества сердечного ритма (HRS), Европейской ассоциации сердечного ритма (EHRA), Азиатско-Тихоокеанского общества сердечного ритм (2015), следует различать феномен и синдром ранней реполяризации желудочков. Представлены Шанхайская шкала для диагностики синдрома ранней реполяризации желудочков, а также этиология, электрофизиология при СРРЖ, его современная классификация и электрокардиографические признаки. Показаны особенности СРРЖ у спортсменов и у детей, а также особенности его лечения и профилактики.

Выводы. Синдром ранней реполяризации желудочков представляет собой важную кардиологическую проблему. Будущие клинические и экспериментальные исследования должны сосредоточиться на выяснении точных причин и механизмов развития синдрома ранней реполяризации желудочков и в итоге – на разработке стратегий профилактики преждевременной смерти от сердечных причин у лиц с этими нарушениями электрокардиографических признаков.

The syndrome of early ventricular repolarization (ERS) was first described by R. Shipley and W. Halleran in 1936 and has long been considered as a variant of the norm. Only in the late 70s of the twentieth century, this syndrome attracted the attention of researchers again. The subject of study was its clinical course, mechanisms of occurrence, as well as the specification of electrocardiographic (ECG) signs. For a long time, such disturbances of repolarization were considered benign, but since the publication of C. Otto et al. in 1984, attitude toward this ECG phenomenon has changed. These researchers first described cases of ventricular fibrillation (VF) in three young people with a J-wave on an ECG without structural myocardial pathology.

The relevance of the study of ERS is associated with a high degree of its occurrence among the general population, as well as among patients with and without cardiac complaints. The prevalence of ERS, according to different authors, ranges from 2.0 to 31.0 %, and is most often recorded among young people and people doing sports. In men younger than 40 years old, with a higher level of physical activity ERS occurs 2–3 times more frequently than in women, especially those leading a sedentary lifestyle. It is more commonly seen in black people and African Americans [1,2]. In patients older than 70 years old ERS is very rare.

The relevance of studying ERS is explained by the complexity of conducting differential diagnosis between acute coronary syndrome, pericarditis, which in some cases can cause expensive and not always safe methods of examination and inadequate prescription of drugs, as well as cause unreasonable disability of this group of patients [3,4].

Clinical interest in ERS appeared as a result of a clinically established relationship with lethal arrhythmias in healthy people without structural changes in the heart. On the whole, ERS was detected in 1–9 % of individuals in the general population during an ECG study. With an increase in age, the frequency of ERS detection decreases, which is most likely due to the fact that this syndrome may be masked by acquired repolarization disorders. According to the results of the CASPER (2009) study, among those surveyed who survived after an unexplained cardiac arrest in the absence of organic cardiac diseases, the prevalence of ERS reaches 8 %. In patients with a shortened QT interval, ECG signs of early repolarization occur in 65 % of cases (H. Watanabe, T. Makiyama, T. Koyama et al., 2010), and their presence is considered a risk factor for the development of arrhythmic episodes [5]. ERS is an idiopathic ECG phenomenon, which is considered by various specialists ambiguously. According to the research of 2008–2010 it was concluded that people with ERS have a higher risk of developing sudden cardiac death (SCD).

Disputes about the prognostic significance of this ECG phenomenon, the criteria for its determination, the mechanisms of its occurrence (including the cellular and molecular levels) led to the creation of two important agreement documents: “Early repolarization pattern: consensus paper”, P. W. Macfarlane, C. Antzelevitch and et al., 2014 [6], devoted to a greater extent to the methodological aspects of the definition of early repolarization and “J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge” 2016, C. Antzelevitch, G. X. Yan, Michael J. et al., 2016 [7], which contains the opinions of leading experts, including members of Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), the Asia-Pacific Society for Heart Rhythm, etc. about the mechanisms of occurrence and prognostic value of the early repolarization pattern (ERP).

It is devoted to the compilation of available information on the ERS.

Aim

The objective is to assess the state of the cardiovascular system in the subjects, both adults and children with early ventricular repolarization syndrome, and to propose a diagnostic algorithm for detecting this phenomenon on the ECG when admitting to physical exercise and sports.

Terminology

According to existing recommendations, one should distinguish between the pattern and the syndrome of early ventricular repolarization. The availability of just characteristic electrocardiographic changes in the absence of clinical death, ventricular tachycardia (VT) or ventricular fibrillation (VF) in the history should be referred to as ERP (in the English-language literature such terms as the J-pattern and J-wave are encountered). The J-pattern can also be considered as a marker of conduction disturbance due to fibrotic changes in

Table 1. Shanghai scale for the diagnosis of early repolarization syndrome [7]

I. Anamnesis of the disease	
A. Unexplained cardiac arrest, documented VF or polymorphic VT;	3
B. Syncope of unclear mechanism/unclear etiology;	2
C. Syncopes of unclear genesis / unclear etiology;	1
* Points are awarded only once in this category for the item with the maximum number of points.	
II. 12-lead ECG	
A. Early repolarization ≥0.2 mV inferior and/or lateral leads with a horizontal descending ST segment;	2
B. Dynamic J-point elevation (≥0.1 mV) ≥2 inferior and/or lateral leads;	1.5
C. J-point elevation ≥0.1 mV in at least 2 inferior and/or lateral leads;	1
* Points are awarded only once in this category for the item with the maximum number of points	
III. ECG Holter Monitoring	
A. Premature ventricular contraction; with a short adhesion interval ((R to T) R on the upward part or T peak);	2
IV. Family history	
A. Relatives with established ERS;	2
B. ≥2 first-degree relatives with ECG signs of ERP;	2
C. First-degree relatives with II.A. ECG signs of ERP;	1
D. Unexplained sudden death in persons younger than 45 years old among first- or second- degree relatives;	0.5
* Points are awarded only once in this category for the item with the maximum number of points	
V. The result of genetic testing	
A. Probable pathogenetic mutations associated with ERS;	0.5

Scoring (requires at least 1 ECG finding):
≥5 points: Probable/definite ERS; **3.0–4.5 points:** possible ERS; **<3 points:** not diagnosed

the myocardium, which is interpreted in the analysis of ECG as an intraventricular conduction disturbance. The combination of ECG criteria of ERP and life-threatening arrhythmias or cardiac arrest without structural myocardial pathology in patients should be regarded as ERS [1,6,7]. For the diagnosis of ERS in 2015, the Shanghai Diagnostic Model for ERS was proposed (*Table 1*), taking into account the data of arrhythmic and family history, Holter monitoring, ECG and genetic test. The term "J-wave syndromes" (JWSs) was proposed not so long ago, combining two syndromes based on a number of common characteristics – Brugada syndrome (BrS) and early repolarization syndrome (ERS).

Etiology, electrophysiology with ERS

Since ERS is detected both in healthy individuals and in people with various diseases, today there is no unequivocal opinion about its origin.

It is known that ERS can be caused by:

– long-term administration or overdose with drugs of the adrenomimetic group, for example, α_2-adrenomimetic (hemiton, clofelin, catapresan, clonidine);

– cocaine consumption;

– some physical factors (for example, both hyperthermia and hypothermia, excessive exercise);

– the conditions associated with the appearance of the J-pattern on the ECG are recorded in certain diseases and pathological conditions;

– familial hyperlipidemia (congenital elevated levels of low-density lipoproteins (LDL) and insufficient levels of high-density lipoproteins (HDL) in the blood), which results in atherosclerotic heart disease [3,4];

– hypertrophic cardiomyopathy [3,8,9]; J. P. Guillem, M. Haissaguerre and co-authors back in 1988 suggested the correlation of ERS with borderline forms of obstructive hypertrophic cardiomyopathy (HCM) on the basis of similar echocardiographic signs (the state of the basal interventricular septum, ventricular hyperkinesia, the movement of the anterior mitral valve, reduction of the area of the outgoing LV tract);

– with congenital and acquired heart defects [10];

– connective tissue disorders (CTD) in the form of the appearance of longitudinal, oblique and transverse additional chords in the ventricular cavity of the heart. According to S. N. Shulenin et al. [11], in patients with ERS some isolated signs of CTD (dolichomorphy, hypermobility of joints, arachnodactyly, the presence of abnormal chords and mitral valve prolapse) were significantly more often revealed (51 %) than in individuals without this phenomenon (41 %).

Surawicz et al. (2002) noted hormonal hypothesis after an ECG evaluation of 529 men aged 5 to 96 years old. They noted that the prevalence of ERS increased with a rise in testosterone levels during puberty. However, in older men, when testosterone levels decrease, the prevalence of ERS decreases [12].

In recent years, suggestions have been made about the genetic nature of this syndrome and the presence of specific genes responsible for its evidence. ERS is associated with mutations in the genes encoding proteins that form subunits of ion channels. Currently there are 7 genes which are known: *KCNJ8, Kir6.1*, (locus 12p11.23); *CACNA1C, Cav1.2* (locus 12p13.3); *CACNB2b, Cavß2b* (locus 10p12.33); *CACNA2D1, Cava2δ* (locus 17q21.11); *ABCC9, SUR2A* (locus 12p12.1); *SCN5A, Nav1.5 3* (locus p21); *SCN10A, Nav1.8* (locus 3p22.2). A number of these genes are similar to genes associated with Brugada syndrome (BrS) [6]. According to the recommendations of the American Heart Association 2017 genetic testing is not recommended for the diagnosis of early repolarization syndrome [13].

In ERS, repolarization processes accelerate sharply in the subepicardial layers of the myocardium. ERS is based on congenital individual features of electrophysiological processes in the myocardium, leading to early repolarization of its subepicardial layers.

1. Additional conduction paths.

It is believed that this phenomenon is a manifestation of anomaly of the atrioventricular conduction with the functioning of additional atrioventricular or paradoxical pathways with a sufficiently wide diameter and pronounced antegrade impulse conduction [14]. There is an opinion that the appearance of a notching in the final part of the QRS complex is nothing more than a delayed delta wave.

2. The irregularity of the processes of de- and repolarization of the ventricles.

The basis for the occurrence of ERS is the imbalance in the electrophysiological mechanism of changing the processes of repolarization and depolarization in individual myocardial structures localized at the cardiac apex and in its basal parts.

– ERS occurs as a result of excessive overlapping of depolarization and repolarization processes due to their delay, but to different degrees, or the predominance of one of them.

– ERS occurs as a simultaneous excitation of a part of the ventricular myocardium from different directions along the so-called ventricular depolarization pathways.

The elevation of the ST segment in the chest leads in case of ERS reflects the forward directional displacement of the ST segment vector as a result of delayed repolarization in the subendocardial zone, or premature (early) repolarization of the subepicardial zone of the heart. Such point of view is recognized by most authors, fully justifying the term "early ventricular repolarization".

It was found that the earliest electrocardiographic manifestation of ERS is the primary disorder of the process of ultimate depolarization of the ventricles in the form of a sharp slowdown in the decline of the positive potential on the downward bend of the R- wave and the absence of the S-wave on the ECG. Such a situation is possible only if the physiological asynchronism of depolarization in different parts of the heart muscle is impaired as a result of either earlier activation of the posterior basal regions of the heart, or (more often) late depolarization of the myocardium of the anterior wall of the ventricles. In both cases, the vector of late depolarization of the ventricles, as well as the initial vector of the ST segment, are directed forward, towards the active electrodes of the thoracic leads, which leads to the changes described above on the downward bend of the R-wave and ST segment [11].

Existing hypotheses explain early repolarization by the presence of three types of cells with different electrophysiological potentials. They are named for the location in the layers of the heart wall: epicardial, endocardial, M-cells. These three types of cells differ in their repolarization characteristics in the first and third phases of the action potential (AP). The epicardial and M-cells mainly have pronounced 1st phase, which is caused by the outgoing current (Ito), which is sensitive to 4-aminopyridine (4-AP), as a result of which the action potential takes the form of a "peak" and an "arch" or a notching. This regional difference of Ito was detected in the ventricular myocytes of dogs, cats, rabbits, rats and in humans. An experimental study of the myocardium of the left ventricle (LV) in the syndrome of short QT interval confirmed the hypothesis that an increase in the outgoing repolarizing current can shorten AP primarily in M-cells, thereby increasing the dispersion of cells and generating a substrate for the re-entry mechanism [15,16].

3. Dysfunction of the autonomic nervous system (ANS).

There is evidence that ERS occurs when both the parasympathetic and sympathetic ANS prevail. A test with physical stress [11], in which the symptoms of the syndrome are minimized, proves vagal genesis of ERS: the ST segment, despite the isoelectricity achieved, retains a characteristic trough-shaped concavity, the T-wave is absent or slightly deepens, in all cases the J-point or wave J is identified. Arrhythmic activity was suppressed by isoproterenol in an experimental model of ERS [17]. After administration of novocainamide or propranolol, and during the nighttime sleep, which is detected during daily monitoring of ECG, the severity of symptoms of ERS, on the contrary, increased [15].

F. A. Kralios et al. (1975) suggested that ECG of ERS manifestations are due to local disorders of the sympathetic innervation of the heart in various disorders of the central nervous system. The segmental nature of sympathetic innervation of the heart revealed by some researchers makes it possible to explain the hypothesis about the role of impaired physiological asynchronism of excitation in the genesis of ERS. Currently, it is considered that ANS dysfunction contributes to the manifestation of symptoms of the syndrome, but does not determine their genesis.

The role of the nerve endings of the autonomic nervous system in early repolarization (fibers of the sympathetic and vagus nerve) is not excluded. An activating effect of the sympathetic nerve on the repolarization of the anterior wall and apex zones has been shown [18].

4. Electrolyte disturbances (theory).

In general, the primary changes in electrolyte balance as the cause of the occurrence of ERS are considered by the majority of authors an untenable hypothesis, since no deviation of electrolyte content from the norm was detected in patients with "pure" ERS. Probably, electrolyte disturbances can only explain ECG dynamics of some signs of the syndrome, for example, a change in the polarity of the T-wave or the duration of the ECG intervals.

Classification of early repolarization syndrome

According to the classification of C. Antzelevich, G.X. Yan (2010) three types of ERS are distinguished: Type I lateral – specific ECG-signs of the syndrome, revealed mainly in the lateral precardiac leads (V_5, V_6) (this option prevails in athletic developed men and has a favorable course) (*Fig. 1*); Type II inferolateral – ECG changes are determined in the inferior (II, III, aVF) and lateral precordial leads (it is associated with higher cardiovascular risk) (*Fig. 2*); Type III is global – when, in addition to changes in the inferolateral region, signs of ERS are detected and anterior (right precordial) leads (*Fig. 3*). Type III of ERS with a high amplitude of J waves is considered to be the most arrhythmogenic, followed by BrS, Type I and II of ERS.

ECG registration with J-waves appearing as notching on the positive R-wave descending limb in $V_{4–6}$ leads and ascending ST segment.

Malignant early repolarization: J-point elevation in the inferior and lateral leads and ascending ST segment in most leads.

J waves are apparent in the inferior, lateral, and anterior (right precordial) leads.

The clinical significance of the syndrome

Early repolarization syndrome is the cause of numerous diagnostic errors. The elevation of the ST segment on the ECG is the reason for the differential diagnosis with left ventricular hypertrophy, left bundle-branch block, pericarditis, pulmonary embolism, intoxication with digitalis preparations, acute myocardial infarction, BrS and others.

Electrocardiographic signs of early repolarization syndrome

For a long time, there was no generally accepted definition of early repolarization: different researchers used different ECG criteria for diagnostics of early repolarization. According to a 1976 study by H. Kambara and J. Phillips, based on the findings of R. H. Wasserburger et al., 1961, according to the results of a study by

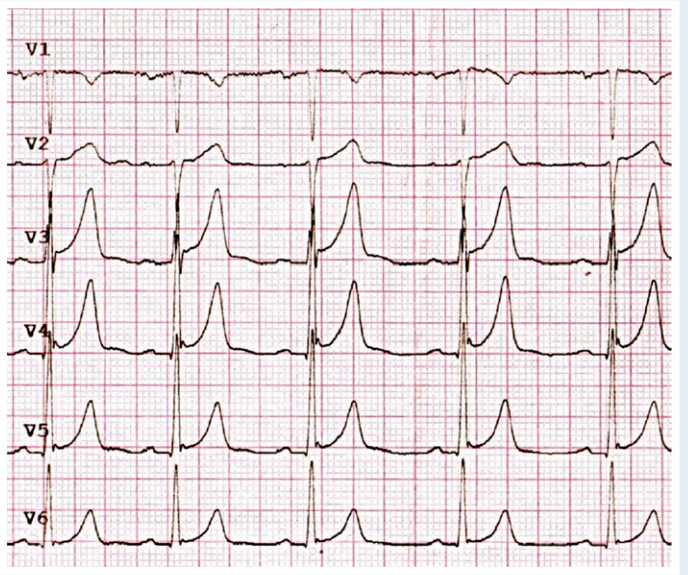


Fig. 1. Type I lateral of ERS (adapted from [http://therapy.odmu.edu.ua/ru/component/phocagallery/1-ecg/detail/125-athletic-heart1?Itemid=0]).

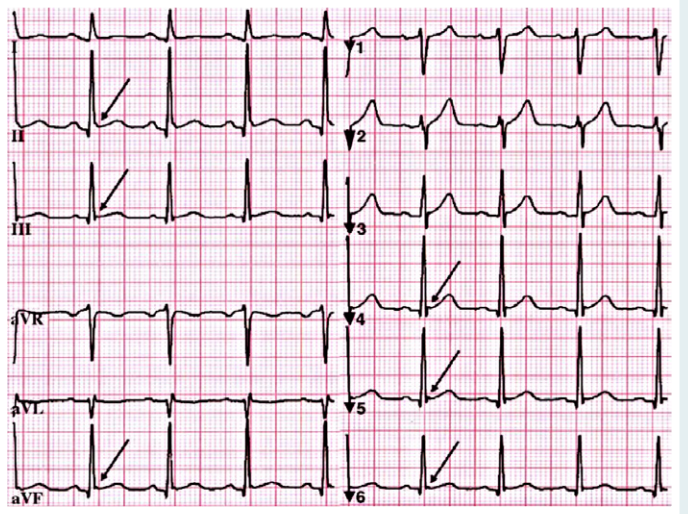


Fig. 2. Type II inferolateral of ERS (adapted from [16]).

M. Haissaguerre et al., 2008, according to which the ECG criteria of the ERP should be considered:

1. The elevation of the ST segment above isoline is concave upward. Usually it does not have a strictly horizontal direction and smoothly passes into the ascending bend of the T wave. The ST segment has a peculiar shape: in the form of a scapha, a fishing hook. The ST segment displacement may be small (1–3 mm) or significant (4–7 mm) in the chest leads and in leads from the extremities to 0.5 mm. The detected ST elevation does not change with time: it is present on the archived ECG and does not change when the ECG is repeated after 15–30–60 minutes.

With an increase in rhythm, the ST-segment displacement decreases (for example, during exercise), and with a decrease in rhythm it increases. In this case there is absence of reciprocal ST depression in the "mirror" leads.

A sharp rise indicates the process of necrosis in infarction, pronounced dystrophy, digitalis intoxication, and pericarditis.

2. The characteristic notching ("wave transition", J-wave) on the descending bend of the R wave or at the top of the ascending bend of the S-wave, imitating the r'wave (pseudo r'wave). Instead of a notching at the end of the QRS complex, there may be a line thickening at the transition of the R-wave (or S) into the ST segment – a junction point (j-point).

3. It is characterized by a high-amplitude, pointed, symmetrical with a wide base T wave (sometimes inverted). Two variants of changes in the ST segment and T-wave in case of ERS are described: T-positive and T-negative. In the T (+) variant of ERS, the ST segment shifted upwards has a concavity and passes into a high positive T-wave. In a T (-) variant, the ST segment shifted upwards has a slightly convex shape and passes into a negative, sometimes deep T-wave.

The main criterion of the syndrome – the J-wave in the literature has different names: "camel hump sign", "Osborne wave" (T. C. Chou, 1979), "late delta wave" (S. H. Litovsky, C. Antzelevith, 1989), "a hathook junction", "hypothermic wave" or "hypothermic hump", "J point wave", "K wave ", "H wave" and "injury current" (M. R. Sridharan, L. G. Horan, 1984; A. Solomon et al., 1989; N. Hugo et al., 1988).

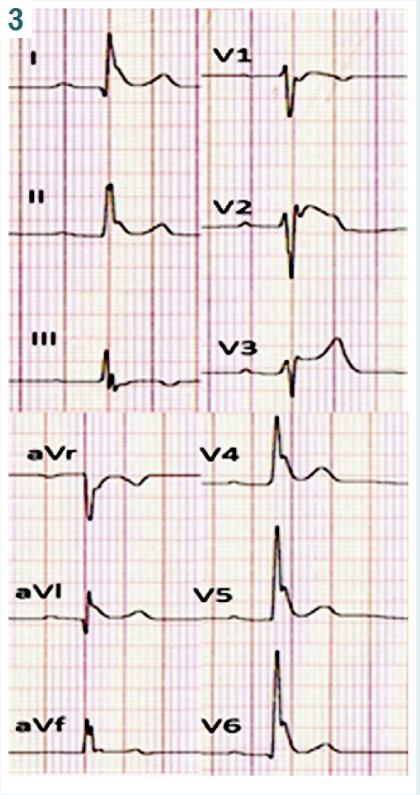
In 2015, new criteria on the ERP were published, according to which the presence of a notching or wave at the end of the QRS complex on the descending bend of the R-wave above the isoline should be considered as the ERP on ECG. Peak J must be greater or equal to 0.1 mV in two or more adjacent leads, with the exception of leads from V_1–V_3. It is important to note that the J-phenomenon can be assessed only in complexes with a duration <120 ms [6].

It is also recommended to evaluate changes in the ST segment. If it has an oblique ascending tilt the ECG phenomenon should be described as "early repolarization with the ascending ST segment". If the ST segment has a horizontal or oblique descending depression, the ECG phenomenon should be described as "early repolarization with a horizontal or descending ST depression". If the elevation of the ST segment is observed in at least two leads corresponding to one blood supply zone, and there is also a horizontal or oblique descending depression in one lead, then this should be described as a ST elevation. If the ST segment is horizontal in the lower leads and ascending in the lateral leads, the final interpretation will depend on where early repolarization is most pronounced: the more leads, the largest wave or notching amplitude [6].

Isolated ST segment elevation without a wave or notching should not be considered as early repolarization [6]. Thus, in order to diagnose EVR, it is necessary to have a wave or notching at the end of the QRS-complex (*Fig. 4*).

However, this "notching" for making a diagnosis of ERP must meet several requirements. First of all, it concerns those ECG leads in which it is recorded.

It is authorized to identify it in the leads from the limb (with the exception of the lead aVR) and left chest leads. The right chest leads (V_1–V_3) are not involved in the diagnosis of ERP. The amplitude of the "notching", measured



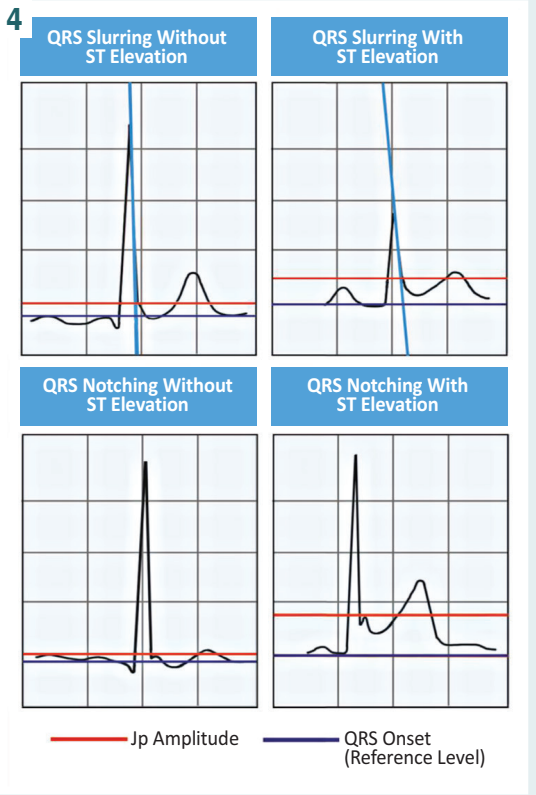


Fig. 3. Type III global of ERS (adapted from [7]).

Fig. 4. Types of possible variants of early repolarization pattern (adapted from [6]).

from the isoline to the peak, must be at least 0.1 mV. The duration of the QRS complex should not exceed 120 ms, and the "notching" should be located in the lower half of the descending bend of the R-wave. Obviously, the latter requirements regarding the width of the QRS complex and the location of the "notching" are necessary to exclude such ECG changes associated with disorders of intraventricular conduction. Finally, it must be emphasized that in order to make a diagnosis of ERP, a "notching" should be identified in two or more consecutive leads.

Identifying a "notching" on the descending bend of the R-wave involves identifying a series of points, measuring amplitudes and durations (*Fig. 5A*). There are points Jo (onset), Jp (peak) Jt (termination). The amplitude Jp (relative to the isoline) of the "notching" is measured, which should be at least 0.1 mV, and the intervals Jo-Jp and Jo-Jt, which are recommended to be denoted as D_1 and D_2, respectively. To determine the nature of the ST segment (ascending, horizontal or descending), the position of the point Jt and the point on the ST segment separated from it by 100 ms is compared.

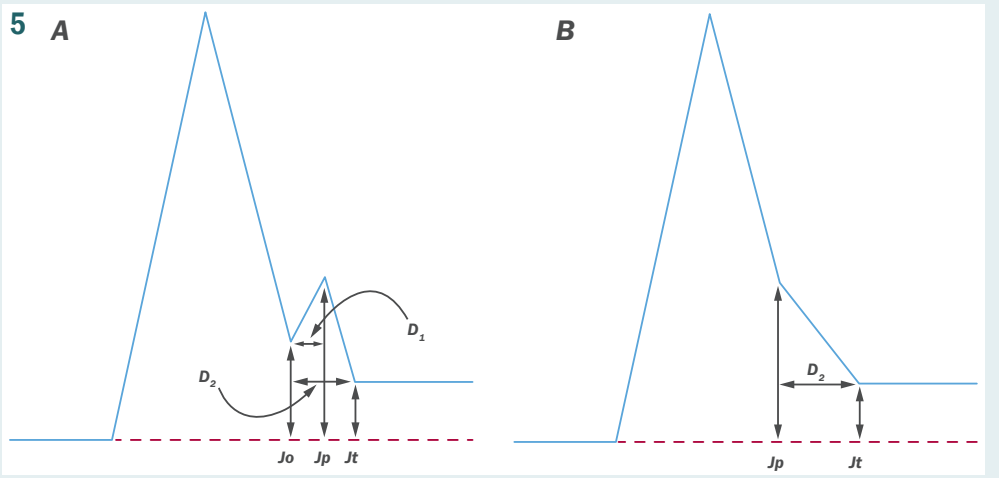
A similar approach is applied to the description of the "slurred" part of the descending bend of the R-wave (slur) (*Fig. 5B*). "Slurring" can be detected in the same leads in the lower half of the R wave with a QRS complex with duration of no more than 120 ms.

A quantitative criterion is also proposed – the angle between the upper and "slurred" parts of the R-wave must be at least 10° (*Fig. 5B*). In practice "slurring" is not a straight line, but a curve (arc). Therefore, the angle described varies in magnitude. The consensus proposes to determine the Jp point at the moment when the angle reaches 10° (at a tape speed of 25 mm / s and an amplification of 1 mV / 1 cm).

The inclination of the ST segment should be measured from the J end (*Fig. 6*). The inclination of the ST segment should be considered as horizontal or oblique ascending if the amplitude of the ST segment 100 ms after the end of J (interval M) is less or equal to the amplitude of the end of the point J. The inclination of the ST segment should be considered as oblique ascending if the amplitude of the ST segment 100 ms after the end of J (interval M) is greater than the amplitude of the end of J. If the Jt point was not used when measuring the inclination during evaluation of the J-sign on ECG, it should be indicated whether the interval of 100 ms was used at such points as K, L, M (*Fig. 6*). It is these approaches to the evaluation of the J-sign that are the most reasonable and recommended for use nowadays [6,7]. The horizontal or descending ST segment is currently considered to be more "malignant" [19].

The width of the QRS complex should be estimated according to special rules, since with the ERP its final part reflects not the depolarization processes, but early repolarization. Therefore, when determining the duration of QRS, leads in which signs of ERP are recorded, as indicated in the consensus, should be excluded from the analysis.

The other ECG features in the syndrome are: double-horned P-wave of normal duration and amplitude; shortening the PQ, PR and QT intervals; a rapid and sharp increase in the amplitude of the R-wave in the chest leads with a simultaneous decrease and disappearance



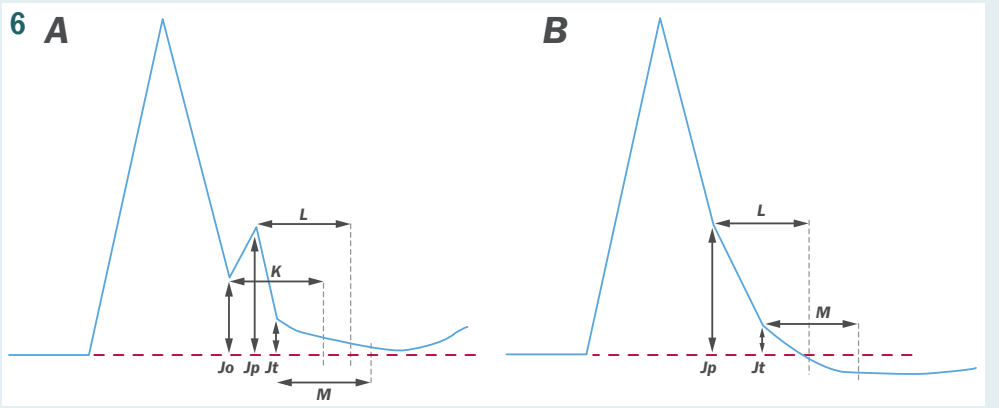


Fig. 5. Evaluation of notching (A) and slurring (B) of the final part of the QRS (adapted from [6]).

Fig. 6. Scheme for determining the inclination of the ST segment (adapted from [6]).

L: 100 ms interval from Jp;
K: 100 ms interval from Jo;
M: 100 ms interval from Jt.

of the S-wave, which leads to a displacement of the transition zone (R/S = 1 or R = S) to the right to V_2, V_1 or to its disappearance; rotation of the electrical axis of the heart counterclockwise along the longitudinal axis.

Detection of Early Repolarization Syndrome during electrocardiographic examination requires the implementation of the diagnostic algorithm:

1. Conducting an inquiry and physical examination in order to reveal cases of sudden coronary death at a young age in relatives, as well as to confirm / exclude signs of cardiac rhythm disturbances, syncopal states.

2. Phenotypic examination of the patient in order to identify external stigmas of undifferentiated connective tissue dysplasia, assessment of the manifestation of dysplasia.

3. Evaluation of the degree of manifestation of early repolarization syndrome. When identifying the ERP, it is necessary to describe in which leads the "notching" and / or "slurring" are noted, to evaluate their manifestation (the position of the Jp points) and the presence of an elevation, as well as the shape of the ST segment, ascending, horizontal or descending. All these signs can determine the degree of "malignancy" of ERP. It is shown that an increase in the amplitude of "notching" and/or "slurring" may precede the development of arrhythmic events. On the other hand, the consensus clearly defines that the presence of ST segment elevation in the absence of "notching" and/or "slurring" cannot be considered as a sign of ERP.

4. Conducting daily monitoring of the electrical activity of the heart (Holter monitor) to find out how the ECG changes throughout the day in the usual conditions for the patient, in order to exclude paroxysmal cardiac rhythm.

Daily monitoring allows conducting test with some drugs (procainamide test, test with potassium drugs), which enhance the manifestations of ERS, as well as to record the increased signs of this disease when the patient is sleeping [20].

5. Carrying out an echocardiography at rest in order to exclude latent systolic and diastolic dysfunction of the myocardium, the presence of remodeling of the left ventricle.

6. Carrying out stress echocardiography to identify signs of systolic dysfunction during physical activity in individuals with moderate and maximum manifestation of ERS with normal echogram indices at rest.

Tests with medicines can trigger or eliminate typical ECG changes. They are carried out only in the hospital under the supervision of the attending physician. The most acceptable test for ambulance station is physical activity. It is prescribed to detect latent pathology and the degree of adaptability of the heart. As noted earlier, with exercise and an increase in heart rate, manifestations of ERS disappear. Squats, treadmills, walking on stairs, bicycle ergometry are used.

It is very important to conduct several types of investigations, including echocardiography, blood biochemistry with the determination of electrolytes, lipidograms, creatine phosphokinase and lactate dehydrogenase, in order to exclude other pathologies (pericarditis, hyperkalemia, diffuse cardiosclerosis, and others).

It is obvious that such an assessment system is aimed at identifying the "malignant" nature of ERS for the subsequent determination of treatment tactics.

Features of early repolarization syndrome in athletes

This issue is particularly relevant due to a whole series of deaths of young athletes in sports arenas, which drew close attention to sports cardiology.

Interesting data were obtained, indicating a definite clinical significance of ERS among athletes. For many decades, it has been known that the benign model of ERS is common in athletes and ranges from 10 to 90 %, which is several times higher than among the general population [21]. It is believed that this type of ERS is a result of a higher vagal nerve tone and is associated with exercise. This concept is quite controversial among specialists in sports cardiology. The malignant model of ERS is also common in athletes. Estimates of prevalence range from 8 to 44 %, which is significantly higher than in the general population [22–24]. Noseworthy et al. (2011) demonstrated that exercise with physical activity can cause both benign and malignant ERS model. For college athletes who returned to intense training, ERS was present in 37 % before and 53 % after an intensive 90-day training period ($P < 0.01$). It should be noted that the increase in the prevalence of ERS after the 90-day training period was caused by an increase in endurance (rowers), while the prevalence of ERS remained stable in soccer players, suggesting that endurance training is a more powerful inducer of ERS than strength training.

Since rhythm disturbances are a very frequent cause of sudden coronary death in athletes, the study of ERS as a factor of arrhythmogenicity in the sport of higher achievements is especially important. The causes of arrhythmogenicity in ERS can be either congenital anomalies of the structure of the cardiac conduction system, or an increased tone of the parasympathetic division of the autonomic nervous system, which has a direct effect on the occurrence of fatal arrhythmias. In sportsmen, diagnostic signs associated with CTD are often detected. This makes this problem particularly relevant among professional athletes, given the high percentage of potentially dangerous arrhythmias and sudden cardiac death in sports [3].

When considering ERS as a manifestation of heart CTD syndrome, the prognostic value of the combination of ERS and additional LV chords is very important. It is believed that the most clinically significant are the transverse basal and multiple chords, which lead to impaired intracardiac hemodynamics, diastolic function of the heart and contribute to the occurrence of cardiac arrhythmias. The frequency offers ERS is closely related to the presence of signs of CTD – more than a third of individuals with the presence of the syndrome have oblique additional LV chords that can cause hemodynamic disturbances [11]. Such disturbances are most often manifested by a deterioration of the diastolic function of the left ventricle, arising from the opposition to relaxation with a high position of oblique chords. An increase in myocardial stiffness can also occur due to the deterioration of intramural blood flow that occurs when the chord is stretched, and the location of the chord in the heart cavity by 33.6 % determines the magnitude of ST segment elevation on an ECG. At the same time, oblique basal-median chords are accompanied by maximal elevation of the ST segment. Considering the theory of the association of ERS with the presence of additional LV chords, we believe that the oblique basal-median chord provides the most rapid conduction of an electrical impulse to the myocardium of the lower and lateral wall of the left ventricle (the area of the most often identified signs of the syndrome of early ventricular repolarization in athletes), causing earlier repolarization in these zones. It is shown that additional chords with their basal location can lead to a decrease in tolerance to physical activities [11], therefore, the presence of ERS in athletes necessarily requires additional diagnostics and careful observation in each individual case.

Due to the relatively high frequency of identifying this syndrome in highly skilled athletes, ERS in sports, in our opinion, should be considered a borderline variant of the norm, requiring close attention and in-depth diagnostic studies. Careful control of the sports cardiologist over each athlete with ERS will help to coordinate the training program, to appoint, if necessary, drug therapy and, thus, to prevent possible sudden coronary death during training and competition.

Early repolarization syndrome in children

Recently, cardiologists have noted a tendency to an increase in the prevalence of ERS among children, which can most often be found in a child during an ECG. It is believed that this process is caused by the lability of the nervous system in children with increased fatigue and anxiety. Some experts associate this condition with the influence of catecholamines, because the heart cells of the child are very sensitive to their minor fluctuations or physical fatigue. T. B. Ignatova (2015) determines that the majority (57.9 %) of the surveyed 169 children of primary school age with ERS, recorded on ECG, had autonomic dysfunction syndrome. In most children, this syndrome was recorded continuously (58.9 % of children) and was accompanied by various cardiac arrhythmias (54.6 %). In children with this syndrome, the values of triglycerides and VLDL were significantly higher, which led to an increase in atherogenicity. The concentration of HDL was significantly lower in children with the above syndrome [4].

Eitan Nahshoni, M. Sc at al. (2009) determined that in ECG examinations of 50 children (aged 8.7 ± 1.4 years old; 12 girls, 44 boys) the frequency of patterns was significantly higher in children with attention deficit hyperactivity syndrome (ADHD) compared with the control group (32 % vs 13 %, respectively, $P = 0.012$; relative risk [RR] = 1.68; 95 % meeting the confidence interval [CI] 1.16–2.44), regardless of the treatment and gender of the child [25].

R. Safa, R. Thomas, Peter P. Karpawich (2016) conducted a one-year retrospective review of three hundred and one ECG, where ERS was detected in 177 (59 %) patients (age 11.7 ± 4.3 years old); 54 % were male; 46 % female. Of these, 6 people had a history of sudden cardiac death (SCD) among relatives. Arrhythmias were observed in 72 % of patients, while only 3 patients had ventricular arrhythmias. Ascending ST segment and increased J-point were observed in 77 % and 51 % of patients with and without arrhythmias, respectively [26].

The manifestation of the syndrome of early repolarization was also noted in children with intrauterine developmental pathology, in children with problems with placental circulation during pregnancy, in adolescence with active puberty of the child, congenital malformations. The absence of any effects of the syndrome of premature repolarization of the pregnant mother on the development of the fetus and the gestation process has been proven, unless other serious arrhythmias appear.

It is important to understand the causes and signs of ERS in the child, as well as remember the measures to prevent its occurrence. If a child is diagnosed with ERS, this should not be considered as a sentence. Repeated ECG may not show such a picture.

The pattern itself does not cause pronounced cardiac disorders. The tactics of a pediatrician and a pediatric cardiologist, after detecting ERS on the ECG, should be determined on the basis of the results of clinical and functional diagnostic examinations when children are admitted to physical education and sports [20]. All children with ERS must pass: a clinical study of blood and urine, a study of the blood lipid spectrum, electrocardiography, 24-hour monitoring of electrocardiography, assessment of vegetative homeostasis using cardiointervalography, echocardiography, in order to determine the possible cause of the disease and associated diseases.

If a child has an "isolated early repolarization syndrome", that is, not accompanied by another cardiac pathology, then it is not advisable for these patients to use drug therapy, but rather normalize eating behavior (balance nutrition and enrich the child's menu with products containing beneficial microelements for the body), limit excessive physical activity and eliminate the effects of stressful situations. The preventive ultrasound investigation of the heart and an ECG 2 times per year is obligatory and, if necessary, the correction of drug treatment by a cardiologist. It is advisable to prescribe antiarrhythmic drugs only when the cardiac rhythm disturbances are confirmed during an ECG study. For prophylactic purposes, children are recommended to use drugs which include magnesium.

Clinical manifestations of early repolarization syndrome

The first group includes those patients in whom this syndrome leads to complications – syncope and cardiac arrest. The syncope develops owing to deterioration in blood supply of a brain. With ERS, the most common cause of syncope is a violation of the rhythm of ventricular contractions of the heart.

In case of ERS, cardiac arrest is caused by ventricular fibrillation [27]. Ventricular fibrillation is the most dangerous heart rhythm disorder, which is characterized by rapid, irregular and uncoordinated contractions of ventricular cardiomyocytes. Within a few seconds of the onset of ventricular fibrillation, the patient usually loses consciousness, then his pulse and breathing disappear. Without the necessary assistance, the person most often dies.

The second (and largest) group of patients with ERS has no symptoms. Early ventricular repolarization on an ECG is detected by chance. This group is less likely to develop complications and is characterized by a benign course of this syndrome. Until the development of complications, pathology does not limit the activity and functioning of a person.

Treatment of patients with early repolarization syndrome

Disease therapy is aimed at preventing the development of serious complications from cardiac activity. In identifying life-threatening arrhythmias or other pathologies, the patient is administered medication therapy, and in some cases surgery.

The correction of the patient's lifestyle recommended by the attending physician is important. A patient with early repolarization is indicated to limit physical activity and psycho-emotional stress. It is necessary to give up bad habits (smoking, drinking alcohol) and patient's compliance with a special diet, regular monitoring by a cardiologist.

The patient's eating behavior is corrected in order to balance their daily diet and enrich them with B vitamins and trace elements such as magnesium and potassium. It is necessary to eat more raw vegetables and fruits, it is necessary to enter into the menu sea fish and seafood, liver, beans and cereals, different types of nuts, fresh potherbs, soy products. Surgical treatment is used only in severe cases of arrhythmias contributing to heart failure.

Drugs of the following pharmacological groups may be prescribed:

– in the presence of cardiac pathology (coronarolytics, antihypertensive drugs, β-blockers);

– antiarrhythmic drugs: Etmozin (100 mg 3 times a day), quinidine sulfate (200 mg three times a day), Novocainamide (0.25 mg every 6 hours), which slow down the repolarization, if rhythm disturbances are accompanied;

– energotropic drugs: Neurovitan (1 tablet per day), Kudesan (adult dosage – 2 mg per kilogram of weight), Carnitine (500 mg twice a day), you should pay attention to the fact that these drugs do not have a clear evidence base, confirming effectiveness;

– vitamins of group B are recommended as coenzymes in the processes of restoring the balance of electrical activity and impulse transmission.

According to the indications the following operations are assigned:

Radiofrequency ablation (if additional conductive pathways or severe arrhythmia are detected). The elimination of an additional bundle helps eliminate arrhythmic disorders. Heart pacemaker implantation (in the presence of life-threatening cardiac arrhythmias). Implantation of a cardioverter defibrillator (for ventricular fibrillation). A small device is placed under the skin on the chest, from which electrodes are inserted into the heart cavity. At the time of arrhythmia, the device transmits an accelerated electrical impulse through them, due to which normalization of the heart and restoration of the heart rate occur (*Table 2*) [7].

Prevention and prognosis

The prognosis for most patients with ERS is favorable. In some cases, the disease may threaten the emergence of a critical situation for the patient's life. The task of the doctor is to timely determine such a probability and minimize the dangerous consequences of a heart rhythm

Table 2. Consensus recommendations of experts on early repolarization therapy (adapted from [7])

Class I	1	ICD (implantable cardioverter-defibrillator) implantation is recommended for patients with a diagnosis of ERS syndrome who have experienced cardiac arrest
Class IIa	2	Isoproterenol infusion may be helpful in suppressing electrical storms in patients diagnosed with ERS syndrome.
	3	Quinidine in addition to ICD may be useful for secondary prophylaxis of VF in patients diagnosed with ERS syndrome.
Class IIb	4	ICD implantation may be considered in symptomatic family members of patients with ERS syndrome in a history, having a ST segment elevation >1 mm in 2 or more lower or lateral leads.
	5	ICD implantation can be considered in asymptomatic people who demonstrate high-risk ECGs (high J-wave amplitude, horizontal/descending ST segment) with a strong family history of juvenile unexplained sudden death with or without pathogenic mutation.
Class III	6	ICD implantation is not recommended for patients with asymptomatic course and an isolated ECG pattern.

disorder, to identify these patients before the first episode of the syncopal state of arrhythmic origin or unexplained cardiac arrest occurs.

Differentiated diagnostics of early repolarization syndrome

Considering the frequency of occurrence and the risk of cardiovascular events, including fatal events, we will consider on the differential diagnosis between ERS and acute myocardial infarction, acute pericarditis and Brugada syndrome.

Acute myocardial infarction (AMI) with ST segment elevation.

ECG criteria for AMI depend on the stage and location of myocardial damage.

In its development, AMI undergoes a series of stages: the first is ischemia (up to 3 hours) when there is a high-amplitude, symmetrical, "coronary" T-wave in at least two adjacent leads, the second is damage (up to 3 days) accompanied by an ST segment elevation with concavity upwards over time, the ST segment approaches the isoline and a negative T-wave forms, the next stage is the formation of a necrosis zone with the occurrence of an abnormal Q-wave on the ECG, i.e. this is a dynamic process that changes over the course of several minutes, hours, days. It is characteristic of ERS that for many years the ECG does not undergo changes and, in the presence of ST segment elevation, as noted above, concavity downwards remains and is characterized by a lack of reciprocity, which is often observed in AMI.

According to ESC / ACC / AHA / WHF (2018) [28], ECG signs of acute coronary ischemia are: in V_{2-3} elevation of the ST segment at point j in two adjacent leads >2mm in men ≥40 years old and ≥2.5 mm in men <40 years old or >1.5 mm in women regardless of age; for other leads, the elevation should be >1 mm, appeared ST depression in two adjacent leads >0.5mm and/or T-wave inversion >1mm in two adjacent leads with a pronounced R wave or R/S ratio >1.

In addition to ECG criteria, for the diagnosis of ACS, it is important to take into account the clinical picture, with characteristic cardiac symptoms, the identification of markers of myocardial damage (troponins, myoglobins), as well as visualization methods: echocardiography, radionuclide methods, MRI of the heart, computed tomographic coronography.

An interesting and quite simple method for identifying ERS was proposed by a group of researchers. Using multivariate modeling of logistic regression they derived an equation based on 3 criteria (ST elevation, R-wave amplitude in lead V_4 and QTc) and showed independent and reliable criterion for the diagnosis of AMI with ST segment elevation.

$$\text{Index} = [1.196 \times STE] + [0{,}059 \times QTc] - [0{,}326 \times RV_4],$$

where STE – exceeding the ST segment 60 ms after point J in the lead V_3 in mm, QTc – in ms.R_{V4} – R-wave amplitude in V_4 lead in mm.

Index ≥23.4 with high sensitivity, specificity and accuracy indicates AMI with ST segment elevation, if ≤ 23.4 – ERS.

In 2017, they improved the formula by adding the 4th criterion – the voltage of the QRS complex in V_2 and the formula got the following form:

$$\text{Index} = 0.052 \times QTc - 0.151 \times QRSV_2 - 0.268 \times RV_4 + 1.062 \times STE60V_3,$$

an index value of ≥18.2 indicates the presence of AMI with elevation of the ST segment [29].

ERS vs acute pericarditis. The ECG is characterized by a certain staging. In the first stage (duration from several days to one or two weeks), diffuse elevation of ST segment with upward convexity with depression in leads aVR, V_1, sometimes V_2 was observed.

ECG changes characteristic of the first stage are found in more than 80 % of patients with pericarditis. In the second stage of ECG changes (duration from several days to several weeks), a return of the ST and PR segments to the isolines is noted, and the T-wave may be biphasic. In the third stage (the duration varies from several weeks to 1–2 months) the T-wave becomes inverted in many leads, followed by recovery in the fourth stage (within 2–3 months). These changes on the ECG are recorded in most standard, reinforced from the limb and chest leads. And the fourth stage is the return of the ECG to the original-normal picture.

One of the differential diagnostic symptoms, pericarditis, on an ECG, can be the ratio of the amplitude of ST/T in V_5 or V_6. The diagnosis of acute pericarditis is more likely when the ratio index is >0.25, a smaller value is in favor of ERS. The authors indicate that this ratio becomes more informative when the amplitude of the T-wave V_6 is <0.3 mm.

In ERS there is no characteristic dynamics as for acute pericarditis. Also, when diagnosing of pericarditis (unlike ERS), it is necessary to take into account the classical clinical findings: chest pain, typical acute, relief comes from sitting with the torso forward, friction

pericardial noise during auscultation, with a maximum near the left sternum, and also methods of visualization of pericardial damage, including the presence of effusion, increased markers of inflammation in laboratory studies [30].

Distinctive changes on the ECG were first described and studied by the brothers, cardiologists Josep and Pedro Brugada, and subsequently their surname was firmly entrenched in the clinical and instrumental syndrome. Brugada syndrome is a hereditary disease caused by a mutation of the *SCN5A* gene located on the shoulder p of the third chromosome, which is responsible for encoding the biosynthesis of the protein subunits of the sodium channel of cardiomyocytes. This syndrome is characterized by the presence of infarct-like ST segment elevation in leads V_{1-3}, pseudo-blockade of the left bundle-branch, with frequent grade 1 AV block, combined with documented episodes of persistent ventricular tachycardia or ventricular fibrillation and is associated with a high risk of sudden cardiac death. Men are more likely to suffer, the average age of sudden death is 41 ± 15 years old [31,32].

Three types of ECG changes are described: the first type (classic) is a "dome-shaped" pseudo-infarction elevation of the ST segment ≥2 mm (0.2 mV), with a negative T-wave. The second type is characterized by a "saddle-shaped" ST segment elevation ≥2 mm with a positive or two-phase T-wave. The third type also has a "saddle" ST segment elevation, but it is <1 mm. There are also characteristic some prolongation of the QT and PQ interval.

Pharmacological tests (administration of class 1 antiarrhythmic drugs) help in the diagnosis of this pattern during continuous ECG recording. The diagnosis is considered to be confirmed, in the case of ECG conversion by type Brugada 1, when ST segment elevation more than 2 mm occurs, arrhythmias develop or the QRS complex is broadened to ≥130 % of the initial level. With ERS, similar pharmacological tests provoke masking or full leveling of ECG signs of ERS (J waves) [31].

The differential diagnosis includes the localization of ECG changes: with Brugada, the pattern is the lead of V_{1-3}, with ERS it is mainly V_{5-6}, less often II, III, aVF. The European Society of Cardiology has proposed the "Corrado index" which is based on the measurement of elevation height at the beginning of the ST segment (point J) – STJ and 80 ms after the beginning of the ST segment (ST80) – with type 1 Brugada syndrome, this index is >1, and in case of ERS <1 [33,34].

Thus, conducting a differential diagnosis of ERS should include not only the registration of 12 standard ECG leads, but also a deep comprehensive analysis in close connection with the clinical picture of the disease, laboratory and genetic studies, as well as various imaging methods (echocardiography, MRI, radionuclide methods, etc.) and the use of auxiliary formulas of mathematical calculation.

Conclusions

1. Thus, the early repolarization syndrome is an important cardiovascular problem. According to experimental data, the third type of early repolarization pattern with high amplitude of J waves in the inferolateral area in combination with the localization of the latter in the front or right leads and the horizontal or descending ST segment is considered to be the most arrhythmogenic.

2. Future clinical and experimental investigations should focus on identifying the exact causes and mechanisms for the development of the early ventricular repolarization syndrome and, ultimately, on developing strategies to prevent premature death from cardiac causes in individuals with this electrocardiogram disorder.

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Information about authors:
Ashcheulova T. V., MD, PhD, DSc, Professor, Head of the Department of Propedeutics to Internal medicine No 1, the Basics of Bioethics and Biosafety, Kharkiv National Medical University, Ukraine.
ORCID ID: 0000-0002-8860-652X
Herasymchuk N. M., MD, PhD, Associate Professor, Department of Propedeutics to Internal medicine No 1, the Basics of Bioethics and Biosafety, Kharkiv National Medical University, Ukraine.
ORCID ID: 0000-0002-3172-6491
Sytina I. V., MD, PhD, Assistant of the Department of Propedeutics to Internal medicine No 1, the Basics of Bioethics and Biosafety, Kharkiv National Medical University, Ukraine.
ORCID ID: 0000-0001-5232-7230

Відомості про авторів:
Ащеулова Т. В., д-р мед. наук, професор, зав. каф. пропедевтики внутрішньої медицини № 1, основ біоетики та біобезпеки, Харківський національний медичний університет, Україна.
Герасимчук Н. М., канд. мед. наук, доцент каф. пропедевтики внутрішньої медицини № 1, основ біоетики та біобезпеки, Харківський національний медичний університет, Україна.
Ситіна І. В., канд. мед. наук, асистент каф. пропедевтики внутрішньої медицини № 1, основ біоетики та біобезпеки, Харківський національний медичний університет, Україна.

Сведения об авторах:
Ащеулова Т. В., д-р мед. наук, профессор, зав. каф. пропедевтики внутренней медицины № 1, основ биоэтики и биобезопасности, Харьковский национальный медицинский университет, Украина.
Герасимчук Н. Н., канд. мед. наук, доцент каф. пропедевтики внутренней медицины № 1, основ биоэтики и биобезопасности, Харьковский национальный медицинский университет, Украина.
Сытина И. В., канд. мед. наук, ассистент каф. пропедевтики внутренней медицины № 1, основ биоэтики и биобезопасности, Харьковский национальный медицинский университет, Украина.

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