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Early Repolarization Syndrome- to Be or Not to Be Benign

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ABSTRACT

The early repolarization syndrome, particular electrocardiographic aspect defined as J point and concave ST segment elevation, interpreted by electrophysiologists as benign for over five decades, caused over the past three years many controversies. The trigger for controversy were the results of several, mostly retrospective, studies concluding that individuals with early repolarization syndrome in inferolateral leads are at higher risk of developing malignant ventricular arrhythmia and death of cardiovascular cause. Although there is more to be said and investigate about this phenomenon, it potential malignant nature can not be neglected. The purpose of this article is to present data regarding early repolarization epidemiology and pathogenesis, data resulting from the most important studies regarding arrhythmic risk and evaluation of individuals with early repolarization syndrome.

As many times in life, things once thought to be benign, prove to produce more harm than expected. This may be the case of early repolarization syndrome (ERS), an electrocardiographic variant described more than a half century ago. Grant et al. were the first to name this phenomenon early repolarization and to consider it benign in 1951. This idiopathic syndrome is defined as: J point elevation manifested either as QRS slurring (transition from the QRS segment to the ST segment) or notching (positive deflection on terminal S wave), upper concavity ST segment elevation for more than 0.1mV and prominent T waves in at least 2 contiguous leads (1,2). Other accompanying features are vertical axis, shorter and depressed PR interval, abrupt transition, counterclockwise rotation, presence of U waves, and sinus bradycardia. (2). Epidemiology data shows higher prevalence in young adults, especially males, darker skinned persons and athletes (2). Even though it was described initially in 1-5% of the population, recently, higher incidences (over 10%) resulted from large population studies (3, 4). The incidence and degree of ERS decreases with age and isoproterenol and exercise may normalize ST segment. Similar electrocardiographic aspects may be identified in cocaine users, hypothermia, defects and/or hypertrophy of the interventricular septum and obstructive cardiomyopathy (2).

Little is known about ERS pathogenesis, most of the data emerging from in vitro animal

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studies, as *in vivo* studies are limited by anesthetic use. Ventricular repolarization occurs when depolarization ends, the transition from the latter (J point on ECG) lasting less than 10 miliseconds; any factor interfering with excitation wave propagation or cellular excitability recovery reduces or increases duration. Many electrophysiological studies have identified the voltage-gated inward and outward currents involved in repolarization: Ca, Na, Cl and most important K currents. Numerous types of channels modulate these currents, changes in their dispersion or structure directly influencing repolarization. For example long QT syndrome or Brugada syndrome underlying causes are represented by genetic changes in ion channels structure and consecutively function. The relatively small currents that determine the plateau phase of action potential alterations induce major changes in repolarization process. What is to be remembered in order to better understand ERS, is the fact that experimental studies have demonstrated that functional expression of ion channels in ventricles changes during normal development of the heart as well as in varios pathological or non pathological situations that influence cardiac activity. Little is known about the underlying mechanism (5).

J point elevation and ST segment elevation are the key features of ERS. ST segment corresponds temporally to plateau phase, the normal ECG ST segment aspect indicating the absence of a significant voltage gradient during ventricular repolarization (5). Pathological ST elevation is a marker of myocardial injury, as a result of voltage gradient among different myocardial layers due to ischemia, but this is not the case in a normal heart.

The most discussed hypothesis incriminates a voltage gradient across the ventricular wall during repolarization generated by Ito channels heterogeneity (Ito current is the most important determinant of ST segment behavior). The difference in Ito-mediated action potential spike and dome between ventricular epicardium and endocardium produces a transmural voltage gradient during early repolarization that may generate J wave elevation. Another opinion regarding the underlying mechanism speculates involvement of localized depolarization abnormalities with repolarization anomalies derived from the first (as in type 1 Brugada syndrome). Nevertheless there is a possibility that both mechanisms are responsible for ERS, but further information is required based on molecular techniques, morphologic imaging, voltage mapping, genetic profiling in familial cases, autopsy studies of the ventricular area corresponding to the electrocardiographic changes. Genetic changes in ionic channel properties were incriminated, but no sustained genetic profiling was ever performed. Recently a mutation of gene KCNJ8 responsible for the pore-forming subunit Kir6.1 of the IK_{ATP} channel was identified in individuals with idiopathic ventricular fibrillation (2, 4, 6, 7). Other possible explanations are related to anatomic nervous system disturbances in favor of vagotonia and acceleration of conduction in cardiac by pass tracts (4).

Often misdiagnosed as myocardial infarction, pericarditis or other diseases that involve ST segment elevation, ERS was considered as not having any clinical implication, until several clinical population studies "cast a spell" on its innocence. Experimental studies, case reports and clinical studies have shown ERS potential arrhythmogenic effect. In 2000, based on preclinical experimental work, Antzelevitch suggested that ERS should not be considered as normal or benign ECG abnormality, unless otherwise proven, as under certain conditions known to predispose to ST-segment elevation, patients with ERS may be at higher arrhythmogenic risk (4).

Until 2008 most of the clinical data came from case reports primarily involving Asian individuals with idiopathic arrhythmia and ERS.

In 2008, Haissaguerre et al. reported higher incidence of recurrent ventricular fibrillation in subjects with repolarization abnormality than in those without by reviewing data of 206 subjects resuscitated after cardiac arrest due to idiopathic ventricular fibrillation. Data was collected from centers in 22 countries, subjects less than 60 years were enrolled (for avoiding higher incidence of cardiac structural disease) and was compared to that of a control group (412 subjects matched as age, sex, race and physical activity). Information about history of syncope (personal and familial), level of physical activity, results on signal-averaged electrocardiography and pharmacological testing (at baseline, 6 and 12 months) was corroborated with results on electrophysiological testing with the use of multielectrode catheters. ERS occurred in 64 case subjects 31%, of case subject as compared with 5%, control subjects ($p<0.001$)

with a greater magnitude in case subjects than in control subjects ($p<0.001$) and more frequently in inferior and lateral leads. Ectopy had a positive QRS morphologic pattern in leads V_1 to V_2, indicating origin from the left ventricle and a short coupling interval initiating ventricular fibrillation. Ectopy induced in electrophysiological testing originated from the inferior leads in subjects with inferior ERS and from multiple sites in inferolateral ERS. During follow up subjects with highest elevation were proned to more frequent episodes of ventricular fibrillation (8).

In the same year a study from Rosso et al. evaluated 45 patients less than 69 years with idiopathic ventricular fibrillation (two of them were eventually diagnosed with Brugada syndrome) and two control groups (a match control and young athlete group) by a protocol similar to the previous study. ERS was more frequent among patients with idiopathic VF (42% vs. 13%, $p=0.001$), with the same topography (inferolateral leads) and greater magnitude. Results in young athlete group showed intermediate values as compared to patients and match control group regarding frequency of ERS and similar results compared to match control group regarding topography. Taking in account that the risk of ventricular fibrillation in general population (mean age 35 to 45 years) is 3.4 of 100,000 individuals, according to the Bayes formula of conditional probabilities, ERS in the ECG rise the chances to only 11 of 100,000 (9).

More data reinforced previous results in 2009, when Tikkanen et al. enrolled over 10,000 (mean age 44 years) subjects from the general population in order to asses the prevalence and prognostic significance of ERS in inferior and lateral leads in this Finnish population. The primary endpoint (death of cardiac cause) was investigated for a 30 year follow up period. Incidence of ERS was 5.8%. Subjects with ERS in the inferior leads had a higher risk of death from cardiac causes (ARR=1.28, CI=1.04-1.59; $p = 0.03$) and from arrhythmia (ARR=1.43; CI=1.06-1.94; $p = 0.03$), this risk increasing with the magnitude of elevation (10).

In 2010 Kaab et al. investigated a population of 6213 individuals (from MONICA/KORA groups) with ages ranging from 35 to 75 years for a follow up period of approximately 19 years. Results indicated a striking higher prevalence of ERS (13.1%), but with approximately the same results as previous trials regarding higher risk of arrhythmic death in population with inferior ERS (11).

In all cases there were several characteristics of ERS and sudden cardiac death: the risk is higher in male individuals, at lower baseline heart rates and decreases with age (8-11).

A certain degree of controversy risen from these studies and there were voices questioning the validity of these results. But we should take in consideration that in validated cases electrocardiograms before cardiac arrest were available, so that there is no doubt about a ERS like syndrome induced post resuscitation or pharmacological treatment. Heterogeneity of studied population avoided influences from ethnic groups with higher incidence of ERS. Moreover the incidence of arrhythmia was significantly higher in the follow up period in these individuals (8-11).

Because clinical features are similar to those of Brugada syndrome, several authors considered that those forms of ERS with higher arrhythmogenic risk are in fact incomplete forms of Brugada syndrome, also taking in account that under pharmacologic influence ERS can be converted to Brugada syndrome (12,13).

A more important fact should be considered, that once these results were published a closer attention was paid to this „benign" phenomenon. This is the case of several articles/ original papers published. For example in 2010 Tikkanen et al. raised the hypothesis that the ST-segment characteristics after the ER waveforms may have prognostic importance. A group of 10,864 middle-aged subjects and one of 565 young athletes from Finland and United States were enrolled. By analyzing ERS patterns on electrocardiograms, came the conclusion that ST-segment morphology associated with ER separates subjects with and without an increased risk of arrhythmic death in middle-aged subjects. In higher amplitude ERS (>0.2 mV) in inferior leads and horizontal/descending ST-segment, the hazard ratio of arrhythmic death increased to 3.14 but in subjects with ascending ST variant, the relative risk for arrhythmic death was not increased (14).

There is little data regarding cardiac structure and function in ERS individuals, echocardiographic studies during the last decade concluding that ERS heart has at his most several characteristics with the athlete heart (higher

end diastolic volume and better diastolic performance). In 2011 a paper evaluating cardiac function parameters and synchrony revealed in a group of 18 young subjects with inferior ERS that subjects with inferolateral ERS have significant intraventricular dyssynchrony due to a prolonged electromechanical activation into the segments with ERS. These subtle changes, suggesting particular properties of the action potential in these segments, are not associated with any other structural or functional changes, however, on a long-term, this regional dyssynchrony might affect LV function and might induce arrhythmias (15).

Integrating all of the above is it or is it not benign and why is it so important to know? First of all, we should take in consideration that sudden cardiac death is not at all a neglectable cause of death; the majority of such sudden cardiac arrests are caused by ventricular tachyarrhythmias, which occur in persons without structural heart disease in 6 to 14% of cases, so any tool of identifying population at risk is important. Probably being the devil advocate, taking in account that a) ST elevation during myocardial infarction in women is less higher than in men, and women have a four fold lower risk of cardiac death than men, b) sodium channels blockers used to unmask Brugada syndrome generate a ST elevation similar to that in inferior myocardial infarction, c) Ito channel incriminated in ERS is more prominent in men has a greater heterogeneity in the inferior wall, I think arrhythmogenic potential of ERS should not be underestimated (2-4,16). Of course, there are opinions in favor of its benign nature, which emphasize the fact that the results of the available studies can not be generalized as they involved selected population, but let's accept that there is no single large clinical trial certifying ERS benign prognostic. Until prospective population data are available, careful attention should be paid to ERS especially in case idiopathic arrhythmias or family history of unexplained sudden death. Holter monitoring or telemetry, eventually electrophysiological studies are useful tools for evaluating individuals with ERS on ECG and syncope (17-19). No specific treatment is available for this entity, taking in consideration that it pathological nature is not well established. As Haissaguerre pointed out in 2008, it is difficult to identify the ERS population at risk of VF. There is a speculation that Brugada syndrome treatment (quinidinde) may be an option for inferolateral ERS and that research in order to identify outward current blockers drugs would be an option for treatment for those at risk. Clinicians should also have in mind the possible relation with Brugada syndrome, Na channels blockers being a useful tool for unmasking the last one (20-22).

Not knowing what exactly causes this phenomenon, it is difficult to declare its benign nature. Even though no data is available, it is of great interest if inferolateral ERS may be an individual syndrome differentiated from anterior ERS, with another pathogeny and therefore different prognosis (23).

I would like to end considering that as in war, when you do not know well your enemy, it is better to maintain a constant precaution and to look for as many information as possible in order to avoid defeat.

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