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An update on early repolarization(ER) syndrome

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Early repolarization (ER), also known 'J-waves' or 'J-point elevation', is an electrocardiographic abnormality consistent with elevation of the junction between the end of the QRS complex and the beginning of the ST segment in 2 contiguous leads. Many studies have shown that the ER ECG pattern is a sign of increased mortality. In this issue of the EP update, we have summarized the recent research related to early repolarization (ER).

Early repolarization and mortality

Presence of early repolarization ECG pattern has been associated with increased risk of resuscitated VT/VF and sudden arrhythmic death [1,2]. The arrhythmic events usually occur at high age (>55 Years) and in absence of pre-existing cardiac disease [2]. Besides idiopathic VF, there is an increased incidence of VT/VF in presence of Coronary ischemia (Acute coronary syndrome and prinzmetal angina) [3,4]. Risk for VF during the first 48 h after myocardial infarction has been found to be higher in patients who exhibit ER patterns on the premorbid ECG [2]. However ER pattern is not associated with non-arrhythmic cardiac events, Congestive heart failure, coronary artery disease and new onset AF[2].

Benign vs malignant early repolarization pattern

A number of surface ECG characteristics have been described to differentiate between benign ER pattern (frequently observed in healthy persons) and malignant ER (clearly associated with idiopathic ventricular fibrillation). These ECG patterns include presence of J wave, magnitude of J point elevation, ST segment pattern, Localization of ER pattern, Type of ER, J wave duration and J angle. ER pattern consists of prominent J wave and ST segment elevation. Whereas prominent J wave is a significant finding in patients with idiopathic VF [5]· [6], ST segment elevation in absence of J wave is considered as benign ER [7]. Magnitude of the J-point elevation may also have prognostic implication: a slurred or notched J-point elevation ≥2 mm (0.2 mV) appears to be associated with a higher risk. Other abnormalities, such as localization of the ER pattern in inferior or infero-lateral leads, absence of other QRS complex abnormalities [2](eg: abnormal Q wave, LBBB) or extension of ER into a BrS pattern (involvement of anterior precordial lead) and associated Short QT may also represent a bad prognosis. A horizontal/descending type ST is defined as ≤0.1 mV elevation of the ST segment within 100 ms after the J point. Tikkanen et al. were first to describe that "horizontal/descending" ST pattern is potentially malignant and prognosis of persons with a rapidly ascending ST-segment was similar to that of persons without ER [8]. After that a number of case-control and population based studies have showed that horizontal ST pattern with ER has been associated with idiopathic VF and myocardial ischemia related VT/VF [3]. J wave duration is measured as the interval between the onset of J point (or Jo) and the intersection of the tangent to the J wave with the isoelectric line or the change in slope of the J wave into the ST/T wave, whichever comes first. J angle is the angle between an ideal line drawn from the J point [J_o] perpendicular to the isoelectric line and the tangent to the J wave. Cristoforetti Y et al. have demonstrated that J-wave duration of> 60 ms and a J angle > 30° are marker of malignant ER [9]. Other high risk criteria include frequent and short-coupled ventricular premature beats (VPBs) [10] and dynamicity of the J wave (Aizawa et al. reported that pause-dependent augmentation of J waves has 100% specificity and positive predictive value for idiopathic VF in ER patients [11]). Although, above ECG parameters have been demonstrated to be associated with arrhythmia risk, absolute risk conferred by each variant is small, and, in isolation, these ECG markers are of limited value as risk stratification tools in clinical practice. The role of so called high risk criteria is not clear in asymptomatic patients with ER pattern, in asymptomatic relatives with ER pattern and

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idiopathic VF and in patients with syncope without documented VT/VF because there is no way to know who would be at considerable risk when presenting with ER pattern unless they have had a cardiac arrest.

Mechanism of early repolarization

Generation of early repolarization is explained by the balance between inward Na^+ and Ca^{2+} (I_{Na}, and I_{CaL}) and outward K^+ currents (I_{to}, $I_{K\text{-}ATP}$, $I_{K\text{-}Ach}$) in the early part of repolarization of action potential of ventricular myocardium. Accentuation of outward currents or inhibition of inward currents causes more negative phase 1 of action potential and loss of dome of phase 2 [12] due failure of activation of L-type calcium current (more negative phase 1 leads to inactivation of $I_{Ca,L}$). As there is a physiological transmural gradients in ion channel distribution, Loss of the action potential dome usually is heterogeneous. This transmural electrical heterogeneity gives rise to local transmural reentry and closely coupled extra systoles (phase 2 re-entry) [10]. When the extra-systole occurs on the preceding T wave, it results in an R on T phenomenon that initiates polymorphic VT or VF. Higher intrinsic levels of the transient outward current (I_{to}) can explain greater sensitivity of the inferior LV wall to the development of VT/VF in the setting or ER [13]. Reported genetic mutations associated with early repolarization syndrome include gain of function of $I_{K\text{-}ATP}$(KCNJ8 and ABCC9 mutation) or I_{to} (KCNE5mutation and rare polymorphism in DPP10) or loss of function in $I_{Ca.L}$ (CACNA1C, CACNB2,andCACNA2D1) or I_{Na} (SCN5A and SCN10A) [14]. Opening of $I_{K\text{-}ATP}$ in presence of coronary ischemia may explain increased incidence of VF in patients of coronary ischemia and co-existent ER [3]. Activation of outward $I_{K\text{-}Ach}$ by vagal stimulation can explain pause dependent augmentation of J point elevation and precipitation of VF during high vagal tone [10] (eg; at rest or during sleep). Quinidine and phosphodiesterase-3 (PDE-3) inhibitors (isoproterenol, cilostazol, and milrinone) inhibit the I_{to} and exerts an ameliorative effect in early repolarization syndrome [14]. Cilostazol, milrinone and isoproterenol also augment I_{ca}. Isoproterenol has been clinically effective for the acute suppression of idiopathic VF. Quinidine, cilostazol, and milrinone have been found to suppress the hypothermia - induced VT/VF in a canine left ventricular model [10,14].

Role of electrophysiological studies in risk stratification in early repolarization syndrome

Although it has been demonstrated that VF in ER is precipitated by short coupled ventricular ectopic, a recent study failed to demonstrate the role of programmed ventricular stimulation in risk stratification of ER syndrome patients [15]. Despite a recent history of aborted sudden death secondary to VF, only a small proportion of ER syndrome patients were found to have inducible ventricular arrhythmias during programmed electrical stimulation and inducibility of VF during programmed stimulation did not predict risk of recurrent arrhythmic events during long-term follow-up. It has been postulated that VF is initiated by an interaction between triggering premature ventricular beats and a susceptible ventricular substrate, which is prone to transmural re-entry. The susceptibility is determined by the transmural ventricular gradient, which is likely to be dynamic. This hypothesis is strengthened by the observation that J-point elevation is augmented prior to VF episodes in ER syndrome patients. Therefore, during an EPS, the substrate is likely to be unfavorable for transmural re-entry [15].

Novel techniques in understanding the pathogenesis and risk stratification of early repolarization

Electrocardiographic imaging (ECGI) is a novel, non-invasive imaging technique that combines cardiac electrical data recorded on body surface with cardiac CT images. This technique is used to detect epicardial potential maps, epicardial electrogram, and maps of epicardial activation and repolarization. Ghosh et al. [16], by using ECGI, demonstrated abnormally short activation–recovery intervals in inferior and lateral regions in patient with ER, indicative of augmented repolarization in these regions (probably due to high density of I_{to} in this region). They also demonstrated steep repolarization gradients that may represent substrates for ventricular arrhythmia. Recently Hocini and colleagues (Personal Communication, August 2014) demonstrated that VF rotors are anchored in the inferior–lateral left ventricular wall in a patient with idiopathic VF due to ER. Monophasic action potential (MAP) is an invasive electrophysiological procedure which allows direct measurements of action potential characteristics and record regional variation in repolarization. The MAP catheter has the potential to characterize transmural repolarization gradients in detail and may allow more detailed characterization of the arrhythmogenic substrate in ER syndrome patients [10]. In future, studies with MAP catheters may be valuable in further investigating ER patients who are at intermediate or high risk of sudden death. Early repolarization syndrome is a Channelopathy characterized by malfunction of ion channels involved in early part of repolarization. Multiple mechanisms and genetic mutations could underlie ER syndrome. Till date, classic genetic techniques have identified small number of mutations. The recent advent of next-generation sequencing technology has significantly enhanced the ability to identify genetic mutations which are involved ER. Different genetic mutations may be associated with variable arrhythmogenic risk. The elucidation of the genetic substrate underlying ER may therefore have a significant impact on risk stratification [10].

Treatment of early repolarization

Most of the patients with an ER pattern are asymptomatic and these patients do not require any intervention [17]. On the other hand patients who have experienced aborted sudden cardiac death should receive implantable cardiac defibrillator. VF storm can be suppressed by isoproterenol infusion in acute setting and recurrence of VF can be prevented by quinidine

therapy [6]. Radiofrequency ablation has been limited role in VF storm [18]. There is no consensus in the management of patients with intermediate risk. These patients include patients with syncope who may have a "malignant" ER pattern and/or a strong family history of sudden death. There is a relative paucity of data regarding the management of this subset of patients.

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