EDITORIAL COMMENTARY

# Early repolarization patterns: The good, the bad, and the ugly?

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The innocence of the electrocardiographic (ECG) pattern of early repolarization (ER) has been challenged by the recent association of the ER pattern in inferolateral leads with idiopathic ventricular fibrillation (VF).[1] Until then, the ER pattern was considered a benign finding occurring in the absence of heart disease[2] and especially in athletes.[3] As the ER pattern in inferolateral leads is a common finding, occurring in approximately 5% of apparently healthy individuals,[1,4] the question arises whether these individuals are at increased risk of cardiac arrest and whether further risk stratification can be performed to identify patients eligible for primary prevention.

Recently, analysis of ER pattern morphologies in a large population of middle-aged subjects established that the ER pattern with a horizontal or descending ST segment was associated with sudden cardiac death during follow-up while the ER pattern with an ascending ST segment was not.[4] In this issue of Heart*Rhythm*, Rosso et al[5] expand this observation to idiopathic VF. The ER pattern followed by a horizontal or descending ST segment was the most common ER pattern in patients with idiopathic VF (13 of 19) in this study, whereas this morphology made up a minority of ER pattern in matched controls (4 of 16) or in young athletes (4 of 28).

In line with previous publications,[4] the ER pattern with horizontal or descending ST segments occurred in approximately 3% of control patients.[5] As the authors acknowledge, this hinders the use of the ER pattern morphology for the attribution of primary prevention strategies because idiopathic VF is rare.[6] However, the rigorous exclusion of underlying cardiovascular disease in this study strengthens the concept that the mechanism underlying the ER pattern directly facilitates VF and that the association with VF is not merely by proxy via another mechanism (eg, latent coronary artery disease). Hence, the distinction of ER pattern morphologies in patients with idiopathic VF may help focus research on its underlying cause, association with idiopathic VF and sudden cardiac death in the general population.

Several nonexclusive options exist by which the ER pattern can be associated with VF. First of all, the mechanism causing the ER pattern may be the same as that causing VF by providing a trigger and/or substrate for VF. The early phase of repolarization (the "notch" in the cardiac action potential) has been suggested to underlie the ER pattern in both healthy individuals and patients with idiopathic VF.[1] If the "notch" increases in amplitude it may regionally cause loss of the action potential dome. It has been reasoned that the resulting heterogeneity in repolarization leads to a current flowing from the normal myocardium toward the area with the short action potential. This current supposedly can initiate extrasystoles in areas with early repolarization (by so-called phase-2 reentry) and may subsequently initiate reentrant arrhythmias.[7] It is unclear why such a strong electrotonic current during phase 2 of the action potential does not lead to equilibration of the action potential duration as expected, unless intercellular coupling is decreased (thus opposing current flow).[8] In addition, this does not explain why idiopathic VF is such a rare condition if such currents are present in approximately 3% of healthy individuals.[4,5]

Another mechanism by which heterogeneity of repolarization provides the conditions for unidirectional block is after an appropriate premature beat from the area with the short action potential. The mechanism of the premature beat may be unrelated to the mechanism of ER.[9]

Second, the mechanism underlying the ER pattern may predispose patients to VF without itself initiating VF. The presence of the ER pattern may identify patients with a deep "notch" in the action potential. Such a deep "notch" can hypothetically predispose patients to develop unidirectional block, which is a prerequisite for the development of reentry arrhythmias. The amplitude of the "notch" is the result of balance between repolarizing and depolarizing currents in the early phases of the action potential.[10] A deeper "notch" indicates a shift of this balance toward more repolarizing current.[10] This means that less depolarizing current is avail-

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able for depolarizing neighboring myocytes and hence for conduction at this point of the action potential. Under normal conditions, such a reduction in depolarizing current during phase 1 of the action potential will not impair conduction. However, in conditions of reduced excitability[11] or in structurally discontinuous myocardium,[12,13] it may mean the difference between successful conduction and conduction block. This hypothesized increased susceptibility to unidirectional block and VF during arrhythmogenic conditions such as myocardial infarction may explain the association between the ER pattern and VF on a population level. Moreover, it suggests that another arrhythmogenic mechanism is present but unidentified in patients with idiopathic VF with the ER pattern.

Third, the ER pattern in patients with VF may only mimic the early repolarization pattern in healthy individuals and reflect activation abnormalities. A similarity with the Brugada ECG pattern comes to mind. The Brugada syndrome has previously been attributed to heterogeneity in repolarization.[7] Recent studies have questioned whether this attribution was correct. In an epicardial mapping and ablation study, fragmented unipolar electrograms with ST-segment elevation were identified in patients with Brugada syndrome. Subsequent ablation of these sites abolished the Brugada ECG pattern and arrhythmias during follow-up.[14] Similar unipolar electrograms were induced by sodium-channel blockers in the explanted heart of a sodium channel mutation carrier at sites containing fatty infiltration and fibrosis.[15] These studies suggest that conduction abnormalities in structurally discontinuous myocardium underlie ST-T segment abnormalities and arrhythmias in the Brugada syndrome. Differentiation of these mechanisms by the modulation of the ECG pattern and arrhythmias by quinidine or isoproterenol is not possible because these drugs can affect both repolarization[7] and conduction.[12] The main difference between the ER and Brugada ECG pattern is, however, that sodium-channel blockade, the most potent inducer of the Brugada ECG pattern, attenuates the ER pattern in patients with idiopathic VF[16,17] and provokes more QRS widening in patients with Brugada syndrome than in patients with the ER pattern or controls.[16] These finding argue against the idea that the mechanisms of the Brugada ECG pattern and the ER pattern are the same.

The challenge ahead of us is to determine the mechanism(s) of the initiation of VF in survivors of sudden cardiac death with an ER pattern and to clarify its relationship with the ER pattern.

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