ST segment Elevation in the Brugada Syndrome: An Electrocardiographic Marker of Repolarization Heterogeneity across Ventricular Wall

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Sudden cardiac death in individuals without structural heart disease has been reported in literatures for decades.[1] Although observed worldwide, it is more common in Asian countries. In 1981, Centers for Disease Control (CDC) of United States reported 36 cases of sudden death among Asian male refugees without identified causes by autopsy.[2] Subsequently, Otto et al reported three more such cases in which ventricular fibrillation was apparently the responsible cause for sudden cardiac death, and among them one patient displayed marked ST segment elevation in the precordial leads.[3] However, a great deal of attention to this clinical entity was not paid until 1992 when Brugada and Brugada clearly and extensively defined the clinical picture of this malignant syndrome in eight patients.[4] The ECG of these patients, who had episodes of polymorphic ventricular tachycardia (VT) or fibrillation (VF), is characterized by a normal QT interval and ST segment elevation in the right precordial leads (V_1-V_3) in the absence of myocardial ischemia or defined structural heart disease.

The arrhythmogenic ECG marker of the Brugada syndrome is the ST segment elevation in right precordial leads V_1-V_3[4-6] and occasionally in inferior leads[7] that dynamically changes from time to time,[5] being influenced by heart rate,[7,8] autonomic tones,[8] and sodium channel blockers.[9,10] Obviously, the ST segment elevation associated with the Brugada syndrome can not be explained using the classic concept, i.e. so called “injury current” that flow from injured myocardium (with more positive resting membrane potential) to the uninjured (with more negative resting membrane potential) during repolarization.[11,12] Two critical questions are, therefore, naturally raised: 1) what is the mechanisms underlying the ST segment elevation in patients with the Brugada syndrome in whom there is no myocardial ischemia or apparent structural heart disease? 2) is the ST segment elevation mechanistically linked to specific arrhythmic substrates, leading to the development of polymorphic VT and ventricular fibrillation VF?

Since the ST segment corresponds temporally to plateau phase of the action potential, the difference in the plateau potentials within the ventricle may produce ST segment elevation on the ECG. In other words, heterogeneity in repolarization across the ventricular wall may generate a transmural voltage gradient that could manifest as ST segment elevation on the ECG. In a parallel to the clinical investigation by Brugada et al[4] and others,[13] a series of important basic research findings regarding electrical heterogeneity across ventricular wall and its relation to the ST segment elevation were published by Antzelevitch and his co-workers during the same

period (for reviews see references[14,15]). What they found is that epicardium and endocardium differs significantly with respect to the morphology of action potential at repolarization phases 1 and 2.[14,16] Ventricular epicardium commonly displays action potential with a prominent notch (spike and dome) largely mediated by a 4-aminopyridine-sensitive transient outward current (I_{to}), whereas the absence of a prominent notch in the endocardium is the consequence of a much smaller I_{to}. The ionic and cellular basis for the ST segment elevation in the Brugada syndrome was first suggested in 1996 to be due to an outward shift in the balance of currents (principally I_{to} and I_{Ca}) active at the end of phase 1 repolarization, preferentially resulting in the loss of action potential dome in right ventricular epicardium.[17,18] Such an outward shift of currents can accentuate the prominent action potential notch in right ventricular epicardium further to a more negative potential at which activation of L-type calcium current may be delayed, so that the action potential dome fails to develop, leading to all-or-none repolarization at the end of phase 1 and marked abbreviation of action potential duration (by 40 to 70%). A variety of pathophysiological conditions and some pharmacologic interventions, which either increase outward currents such as $I_{K\text{-}ATP}$ and I_{to} or reduce I_{Na} and I_{Ca}, can cause complete loss of action potential dome in canine right ventricular epicardium in which I_{to} is prominent.[6,14] In other words, the ST segment elevation in the Brugada syndrome is a consequence of markedly increased transmural dispersion of repolarization secondary to loss of right ventricular epicardial action potential dome.[14] The channelopathy in the Brugada syndrome that leads to an outward shift in the balance of currents in action potential phases 1 and 2 leading to ST segment elevation is due to the gene mutation in SCN5A for Na^+ channel. This is the rationale for using potent sodium channel blockers to unmask concealed form of the Brugada syndrome.[9,19]

It is well known that two prerequisites are required for the development of polymorphic VT and VF: an initiating beat that usually manifests as an “R on T” on the ECG and a functional reentrant substrate for the maintenance. Early afterdepolarization (EAD), which serves as a trigger to initiate polymorphic VT under long QT interval,[20] is unlikely to play a role in the Brugada syndrome in which “R on T” ventricular premature complexes is normally or shortly (instead of long) coupled.[4,6] A recent animal experimental study has demonstrated that phase 2 reentry, i.e. local re-excitation on epicardial surface, may provide a trigger to initiate the onset of polymorphic VT and VF in the Brugada syndrome.[14] As discussed above, I_{to}-mediated all-or-none repolarization can result in a marked abbreviation of action potential duration by 40-70%, i.e. ***complete*** loss of

action potential dome, in right ventricular epicardium.[18,21] Such a loss of epicardial action potential dome is often heterogeneous, i.e. loss of the dome may occur at some sites but not others, probably due to intrinsic differences in I_{to} in epicardium, and/or regional difference in pathophysiological alterations. Propagation of the action potential dome from sites at which it is maintained to sites at which it is lost causes phase 2 reentry, leading to the development of an R on T extrasystole. This closely coupled extrasystole is then able to initiate the onset of polymorphic VT and VF under conditions of increased transmural dispersion of repolarization.[14] Therefore, heterogeneous loss of right ventricular epicardial action potential dome provides not only a initial trigger, phase 2 reentry, but also a functional reentrant substrate, i.e. an markedly increased transmural dispersion of repolarization, for the maintenance of polymorphic VT and VF.[14]

The ST segment elevation secondary to the loss of I_{to}-mediated epicardial action potential dome may be classified into two types based on their cellular basis, shapes and arrhythmogenesis. First type of the ST segment elevation is due to the complete loss of epicardial action potential dome, i.e. all-or-none repolarization. We have recently observed that epicardial cells with phase 1 magnitude (an index reflecting the size of I_{to}) greater than 25 mV easily exhibited complete loss of epicardial dome in the presence of K_{ATP} channel opener pinacidil.[22] The shape of the ST segment elevation due to complete loss of action potential dome in epicardium but not endocardium looks like coved on the ECG, usually obscuring the downstroke of the R wave resembling to a giant J wave or RBBB as frequently seen in the Brugada syndrome.[5,6] Under conditions of heterogeneous loss of epicardial action potential dome via all-or-none repolarization, dispersion of repolarization is prominent not only transmurally but also on epicardium surface itself. This is the major reason why a coved-type ST segment elevation is more arrhythmogenic.[5] Another subtype of ST segment elevation is due to ***partial*** loss (depression) of action potential dome in epicardium but not endocardium. The ST segment elevation due to partial loss of action potential dome in epicardium is usually upward concave or saddleback like. Under such a condition, dispersion of repolarization on the epicardial surface is minimal, so that phase 2 reentry fails to occur. It should be emphasized that although a saddleback-type ST segment elevation in the early repolarization syndrome rarely evolves to a coved-type transition between two types is frequently seen in some Brugada patients. [5] This may explain why some patients with the Brugada syndrome remains asymptomatic if such a transition of ST segment elevation from a saddleback-type ST to a coved-type has never occurred. However,

the superimposition of pharmacologic interventions or pathophysiological alterations on the preexisted intrinsic anomalies may facilitate this transition, leading to the development of polymorphic VT and VF.

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