The differential diagnosis of Brugada syndrome with early repolarization variant - 2008

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Early repolarization variant (ERV) is a well-recognized idiopathic electrocardiographic phenomenon considered to be present when at least two adjacent precordial leads show elevation of the ST segment, with values equal or higher than 1mm. The variant is characterized by a diffuse elevation of the ST segment of upper concavity, ending in a positive T wave of V_2 to V_4 or V_5[1] and prominent J wave and ST-segment elevation predominantly in left precordial leads.

The phenomenon constitutes a normal variant; it is almost a rule in athletes (present in 89% of the cases in this universe). However, it is found in a 36% of sedentary men. The variant shares remarkable cellular, ionic, and electrocardiographic similarities with the Brugada syndrome (BrS) and idiopathic ventricular fibrillation (a variant of the Brugada syndrome with ST-segment elevation in inferior leads). Although ERV is considered a benign entity, its arrhythmogenic potential still remains unknown. (**Letsas KP, Efremidis M, Pappas LK, et al. Early repolarization syndrome: Is it always benign? Int J Cardiol. 2007; 114: 390-392.**) The ERV may not always be benign and that it can become a substrate for ventricular arrhythmias, sudden death, and hypercontractility cardiomyopathy in some subjects, including certain high-performance athletes. In addition, it is suggested that it likely represents part of a spectrum of cardiovascular anomalies related to nonischemic ST elevation including BrS, and that it may also have a molecular genetic origin of variable penetrance. (**Boineau JP. The early repolarization variant-normal or a marker of heart disease in certain subjects. J Electrocardiol. 2007; 40: 11-16**.). The mean of QRS duration in BrS e is 110 +/- 2msec. It is higher than in individuals with ERV who present a mean of QRS duration of 90 +/- 10msec (up to 100msec). Only 8% of tracings of athletes with ERV are similar to tracings of BrS. **Bianco M, Bria S, Gianfelici A, et. al. Does early repolarization in the athlete have analogies with the Brugada syndrome? Eur Heart J 2001; 22:504-510**

. These are not accompanied by positive family history for syncope or SCD.

In short, there are significant differences between the ECG for the BrS and that of ERV regarding duration of QRS, and the characteristics and location of the elevation of the J point and the ST segment[2].
In BrS, many changes in the morphology of ST are described[3].

In ERV, there exists a voltage gradient but no dispersion of APD. That is why these patients show ST elevation but do not develop arrhythmias.

ECG CRITERIA THAT SUGGEST ERV

Rhythm: Sinus bradycardia is often present;

HR: Sinus bradycardia and phasic arrhythmia

Axis: The frontal plane QRS axis and ST segment axis and T wave axis are all in the same direction.

QRS complex: Relatively deep but narrow q waves may appear in the left precordial leads; A rapid transition may occur from right oriented complexes to left oriented complexes in the precordial leads;
III, and aVF

J point: A minimally elevated J point;

ST segment: Upward concavity of the initial portion of the upsloping ST segment; and notching or slurring of the terminal QRS complex (J point) Elevated ST segments are most commonly seen in the mid-to-left precordial leads, and they are also sometimes seen in the limb leads (I, II, II, aVF and aVL) besides chest leads (V_2–V_6) with the degree of precordial lead ST segment elevation > limb lead ST segment elevation associated R waves are usually tall prominent Reduction in ST segment elevation may occur secondary to sympathomimetic influences. Relative temporal stability of the ST segment and T wave pattern. The ST elevation in ERV is usually < 2 mm (but can rarely be > 5mm) in the precordial leads and the greatest ST elevation is usually seen in the mid-to-left precordial leads; the ST segment elevation is usually < 0.5 mm in the limb leads (strongly consider an inferior AMI if the elevated segments are only seen in the inferior leads. Morphologically, the ST segment appears as if it has been evenly uplifted from the isoelectric baseline at the J point => preserving the normal concavity of the initial upsloping ST segment.
Reciprocal changes are not seen in ERS.
There are no evolutionary short-term changes in the ST segment and T waves; and Q waves do not appear. (Reciprocal changes in leads without elevated ST segments, initial up-sloping section of the ST segment that is either flat/obliquely upwards or convex upwards, constantly evolving ST segment/T wave changes, and the appearance of a new Q wave suggests an AMI.)

T waves: Symmetric, concordant T waves of large amplitude (the T waves may appear "peaked" or pointed);
—and a lateral AMI if the ST segment elevations are only seen in leads I and aVL).

ERV is felt to be a normal variant and is seen more commonly in young/middle-aged adult males and the magnitude of the ERV may diminish as the patient ages (20 - 30% of cases).

In BrS, the mutations in SCN5A reduce sodium current channel density, causing premature repolarization of the epicardial AP due to an all-or-none repolarization at the end of phase 1 (I_{to1} channel). The loss of AP dome in the epicardium but not the endocardium creates a dispersion of repolarization across the ventricular wall, resulting in the development of a vulnerable window during which phase 2 reentry can be induced (**Antzelevitch C. MOLECULAR BIOLOGY AND CELLULAR MECHANISMS OF CARDIAC ARRHYTMIAS AND SUDDEN DEATH IN INFANTS (SIDS) AND YOUNG CHILDREN. XXVIII INTERNATIONAL CONGRESS ON ELECTROCARDIOLOGY 42nd Symposium on Vectorcardiography- Guarujá – SP Brazil, 2001**.)

POSSIBLE SIMILARITIES BETWEEN ERV AND BRUGADA SYNDROME

1) Both more frequent in males

2) Both occur more frequently in young adults

3) Both occur in individuals with heart without apparent structural alterations

4) Both can influence just the V_1-V_2 leads. Occasionally, ST elevation can be observed in ERV only in the right precordial leads: V_1-V_2, or in the inferior ones[6]. When ST elevation is normal, it can reach up to 3mm in V_2-V_3, especially in young people. In those individuals over 40 years, it seldom exceeds the 2mm. Both can show incomplete RBBB patent or right bundle branch conduction disorder: in BrS, it can present atypical features, RBBB-like and of the saddle type by exclusive elevation of the J point. S wave with delay in the left leads: DI, aVL, V_5 and V_6, could be absent as it is to be expected in a classic RBBB. The elements considered as typical in BS are: 1) elevation of the terminal part of QRS (prominent J wave): 2) elevated and descending ST, not related to lesion of ischemic (idiopathic) injury; 3) negative T wave in the right precordial leads; 4) normal QTc; 5) absence of final delay in left leads as it would be expected in a classic RBBB (Gussak I., Antzelevitch C., Bjerregaard P, Towbin JA, Chaitman

BR.: The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol 1999, 33:5-15.) In ERV, when associated to athlete heart, QRS can present a moderate extension (100msec to 110msec) in 15% of the cases, which in non-athlete, normal population, in a 2.4% is called outflow tract hypertrophy. In this case r' does not exceed the 5mm and is lower than S in the same lead: rSr' (Hiss RG, Lamb LE: Electrocardiographic findings in 122.043 individuals. Circulation 1962; 25: 947-961.)

5) Both can improve repolarization during the stress test

6) Both can improve with use of isoproterenol

7) Both respond to a shortening of AP phase 2 in a part of ventricular thickness, and intensification of fast repolarization notch (phase 1) mediated by transmural dispersion of ventricular repolarization by a larger notch in the I_{to} channel (Antzelevitch Ch, Xin Yan G, Shimuzi W, et al. Electrical heterogeneity , the ECG, and Cardiac Arrhthmias. In Zipes DP, Jalife J Cardiac Electrophysiology From Cell to Bedside, Thrid Edition. W.B. Saunders Company.2000. Chaper 26 p: 222-238.)The alteration of the I_{to} and $I_{Ca^{++}\text{-}L}$ channels in Brugada Syndrome and in ERS are the electrophysiologic substrate that explains the J point and ST segment elevation, because they cause the intensified notch in phase 1 and suppression in phase 2 duration in the subepicardium and in the subendocardium of ventricular wall thickness (**Gussak I, Antzelevitch C.Early repolarization syndrome: Clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol. 2000; 33:299-309**.)

ELEMENTS FOR DIFFERENTIAL DIAGNOSIS

1) Family background

ERV: negative
BrS: frequently positive

2) Race:

ERV: predominantly Africans decedents (Grusin H. peculiarities of the African's electrocardiogram and the changes observed in serial studies. Circulation 1954; 9: 860.

BrS: predominantly yellow (58%) Nademanee KK, Veerakul G, Nimmannit, S, et.al. Arrhytmogenic marker for the sudden unexplained death syndrome in Thail men. **Circulation. 1997; 96:2595-2600**. and white.

3) Response to IC group antiarrhythmic agents:

BrS: flecainide, used in a 10mg/Kg dosage in 10 minutes, increases ST elevation and QRS duration in a more significant way in patients with BrS than in individuals without the entity, and only in those it triggers ventricular extrasystoles (**Shimizu W, Antzelevitch C, Suyama K, et al: Effect of sodium channel**

blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. *J Cardiovasc Electrophysiol* 2000; 11:1320-1329.).

ERV: it can induce a pattern similar to BrS; however, the degree of ST elevation caused by the drug is much higher in patients with BrS than in patients without the disease.

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