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A three-dimensional computed model of ST segment abnormality in type 1 Brugada Pattern: A key role of right ventricular outflow tract orientation?

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ABSTRACT

Since its first description, Brugada Syndrome is characterized by definite ECG abnormalities (J wave, elevated ST segment) confined in right precordial leads. Brugada Pattern (BP) could be found in one or more right precordial leads, at conventional or higher intercostal spaces. A recent study, conducted by our group, reported that slightly less than one half of patients with type 1 BP show a definite ST segment depression (≥0.1 mV with duration ≥ 0.08 s) in the inferior leads. With these premises, 4 distinct ST abnormalities phenotypes can be recognizable in Type 1 BP. We speculated the key role of orientation of right ventricular outflow tract in the thorax, particularly the inclination of anterior wall compared to the sternum, contributing to the determination of these various ECG phenotypes. An interactive program, ECGsim, able to simulate ECG appearance in several anatomical and electrical models, confirmed this assumption. This computed model affirmed the strict relationship between ST segment depression in the inferior leads and the ST segment elevation in right precordial leads, typical of type 1 BP. A horizontal right ventricular outflow tract, in fact, gives raise to abnormal BP vector directed both superiorly and anteriorly, explaining, at the same time, typical BP appearance in right precordial leads and ST segment depression in the inferior leads.

Introduction

Brugada Syndrome (BrS) is characterized by: 1) definite ECG abnormalities (J wave, elevated ST segment) confined to the right precordial leads, and 2) risk of sudden death due to ventricular fibrillation [1]. In the present study, we use the term "Brugada Pattern" (BP) in order to identify the presence of typical ECG abnormalities. A recent Consensus [2] distinguished 2 ECG patterns: type 1 with a coved ST-segment elevation ≥2 mm followed by negative T wave, and type 2, characterized by saddle-back ST segment elevation and positive T wave. In several subjects, the typical type 1 BP signs are invisible with the right precordial electrodes placed at the 4th intercostal space, but become evident if the electrodes are displaced 1 or 2 intercostal spaces (ics) above [3]. This has been explained assuming that the abnormal electrical activity arises from a very small area of the right ventricular outflow tract (RVOT), in such a way that only electrodes placed very close to the affected region succeed in revealing the pattern. On the other hand, in the last years, ST segment abnormalities in peripheral leads have been reported in patients with type 1 BP [4–6]. A recent study, conducted by our research group, has pointed out that slightly less than one half of patients with type 1 BP show a definite ST segment depression (≥0.1 mV, with duration ≥ 0.08 s) in the inferior leads (Fig. 1) [7]. On the basis of our previous study, we can distinguish 4 ST abnormality "phenotypes" (the term phenotype defines a specific ST segment abnormality) in Type 1 BP:

Phenotype A: type 1 BP in V1–V2 at the 4th ics, no ST segment depression in the inferior leads (Fig. 2A);

Phenotype B: type 1 BP in V1–V2 at the 4th ics, ST segment depression in the inferior leads (≥0.1 mV with duration ≥ 0.08 s) (Fig. 2B);
Phenotype C: type 1 BP only at the 3rd or 2nd ics, no ST segment depression in the inferior leads (Fig. 2C);
Phenotype D: type 1 BP only at the 3rd or 2nd ics, ST segment depression in the inferior leads (≥0.1 mV with duration ≥ 0.08 s) (Fig. 2D).

Aim of our study was to found a correlation between ST segment abnormality in BP, location of the ionic abnormality within the RVOT and orientation of this latter in the chest.

Abbreviations: BP, Brugada Pattern; BrS, Brugada Syndrome; ics, intercostal spaces; RVOT, right ventricular outflow tract.

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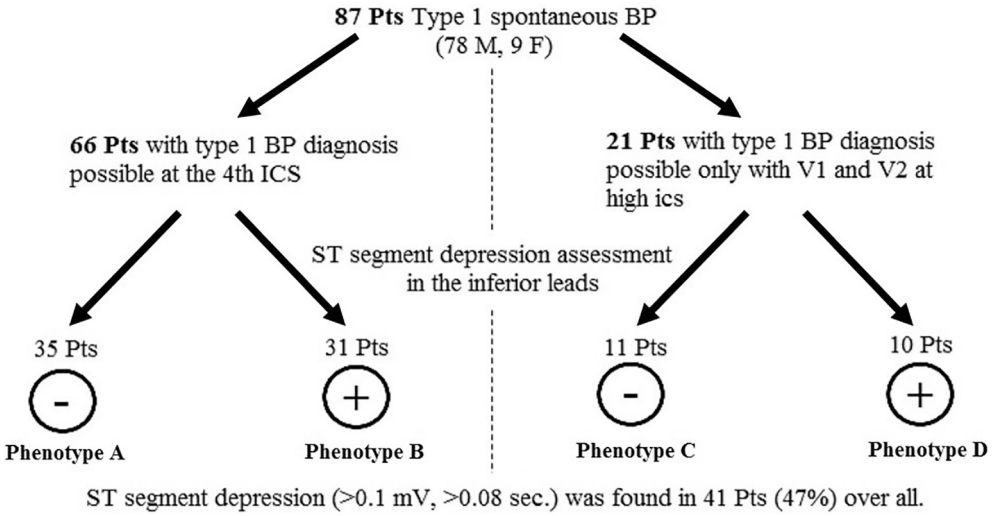

Fig. 1. Diagram reporting results of our previous study [7]. 4 distinct ECG phenotypes of type 1 BP could be identified.

Methods

We used an interactive simulation program able to assess, in a cardiothoracic three dimensional model, the relationship between the electrical cardiac currents and the resulting electrocardiographic signals (ECGSIM vers. 3.0.0) [8,9]. In this software seven parameters are used to describe the local transmembrane potential analytically: 1) the depolarization time, 2) the repolarization time, 3) the resting potential, 4) the maximum amplitude, 5) the depolarization slope, 6) the plateau slope and 7) the repolarization slope. The user may change any of these parameters at any section of the heart in the epicardial layer or transmurally; the effects of such changes on the ECG are displayed instantaneously. In a previous work, performed with the same software, shortening of action potential or activation delay applied to the epicardial aspect of right ventricular free wall and RVOT failed to obtain the ST segment elevation in type 2 BP, whereas a gradual raise of diastolic potentials in the selected region succeeded in reproducing it [10].

Using ECGSIM, we reproduced an endo-epicardial transmural gradient (Fig. 3), according to Antzelevitch's model of Brugada Syndrome [11], combining: 1) loss of action potential dome (from +15 mV to a minimum of −25 mV) in right ventricular epicardium but not in the endocardium, resulting in a transmural voltage gradient responsible for ST segment elevation; 2) prolongation of the epicardial action potential (from 350 ms to a maximum of 400 ms), in order to obtain a reversed repolarization, responsible for the negative T wave observed in type 1 BP. We created, thus, "areas of injury" in the epicardial layer of the RVOT of two 3D heart models: one with vertical RVOT orientation (called "Normal young male" in ECGSIM - Fig. 4, Model 1), and the other one with horizontal heart and horizontal RVOT (called "Normal male" in ECGSIM - Fig. 4, Model 2). The latter condition is commonly found in obesity, pregnancy, low height, etc.

Results

Model 1 (vertical RVOT)

When the "injury area" was localized in the lower section of a vertical RVOT (Fig. 5A) the simulated ECG showed a clear type 1 BP both in V1 and V2 recorded at the 4th ics and no significant ST segment depression was found in the inferior leads (phenotype A, Fig. 6A). On the

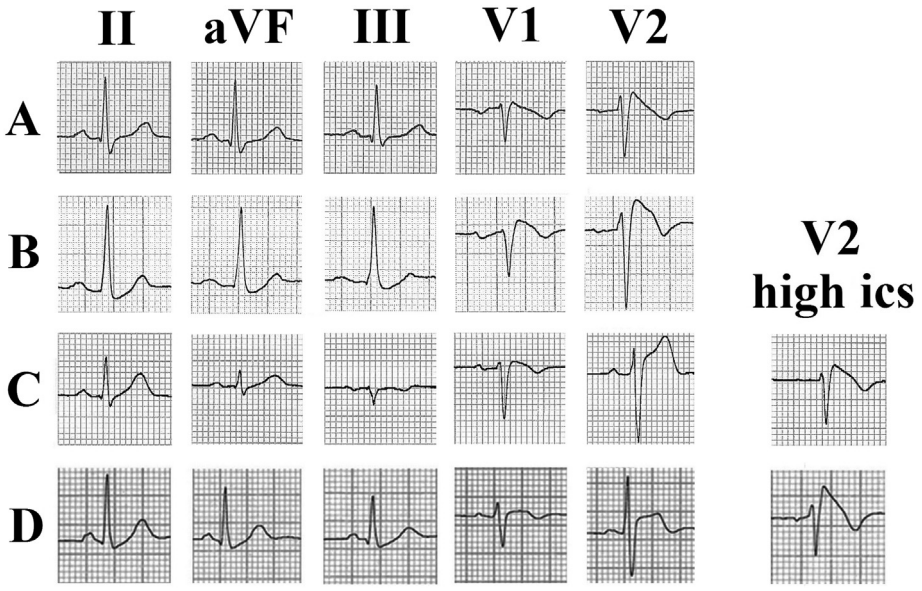

Fig. 2. The four ECG phenotypes of type 1 BP. See text.

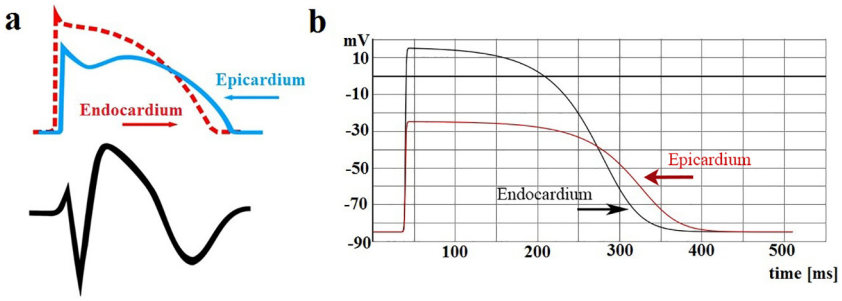

Fig. 3. a) "Antzelevitch's hypothesis" about type 1 BP genesis b) replication of transmural endo-epicardial gradient in action potential with ECGsim.

contrary, if the "injury area" was located in the upper part of a vertical RVOT (Fig. 5C), V1 and V2 recorded at the 4th ics didn't show any type 1 BP (an isolated 2 mm ST segment elevation occurred only in V2). Only evaluation of the 3rd ics revealed a typical type 1 BP (phenotype C, Fig. 6C).

Model 2 (horizontal RVOT)

An "injury area" involving the lower part of a horizontal RVOT (Fig. 5B) resulted in phenotype B with evident BP in leads V1, V2 at the 4th ics and ascending ST depression (≥0.1 mV, with duration ≥ 0.08 s) in the inferior leads. Contrariwise, if the "injury area" is localized in the middle-upper region of a horizontal RVOT (Fig. 5D), the simulated ECG shows a clear ST segment depression in inferior leads, associated with only a mild ST segment elevation in lead V2 recorded at the 4th ics. Only evaluation at the 3rd and 2nd ics reveals type 1 BP (phenotype D, Fig. 6D).

Discussion

The origin of ST segment elevation in BP is still debated [12]. One possible mechanism is RVOT epicardium abnormal repolarization. This hypothesis, introduced by Yan and Antzelevitch [13], is based on experimental data obtained with perfused wedges of canine right ventricle. Loss of action potential dome in right ventricular epicardium, but not in the endocardium, gives rise to a transmural voltage gradient responsible for ST segment elevation, similar to that observed in type 1 BP. Several studies found a correlation between RVOT anatomical location and leads showing a diagnostic type 1 Brugada Pattern. Both right ventriculography [14] and magnetic resonance imaging [15] studies support such a relationship. Savastano et al. [16] recently demonstrated with echocardiography a relationship between RVOT location and ics (4th, 3rd or 2nd) showing type 1 ECG pattern. In other words, an upper or lower position of the RVOT area with abnormal electrical activity

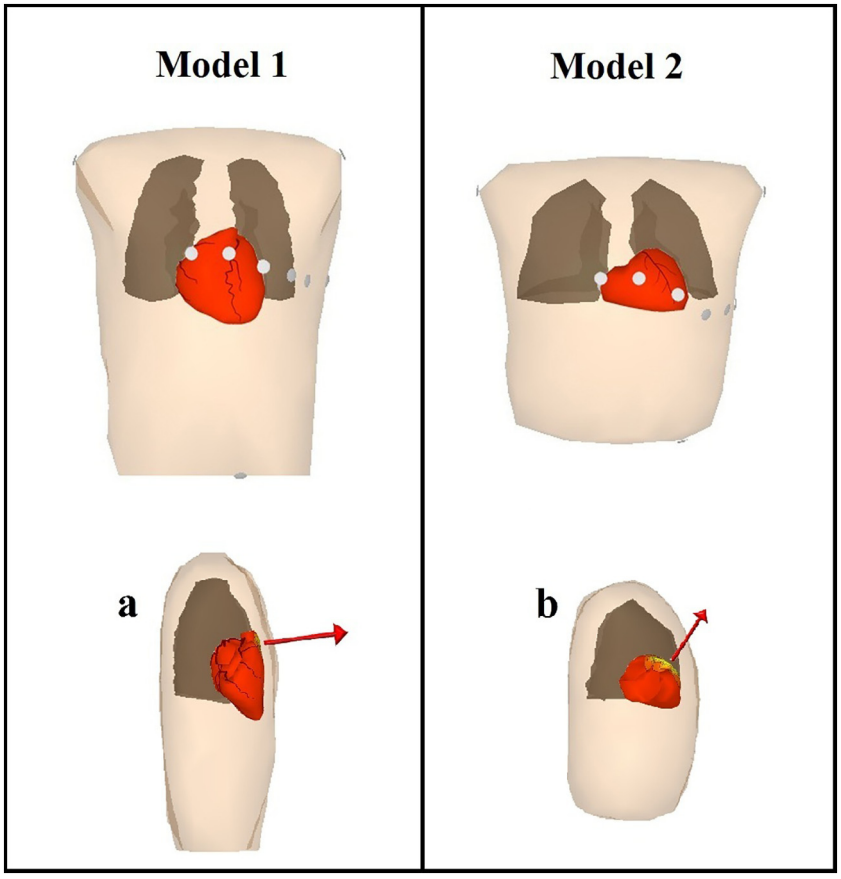

Fig. 4. The two 3d-models of heart (by ECGsim): Model 1 with is characterized by a vertical RVOT, the angle between the sternum and RVOT anterior wall is about 15°; whereas in Model 2 RVOT is horizontal, angle between the sternum and RVOT anterior wall is about 60°; BP vector direction in Model 1 (a) and Model 2 (b).

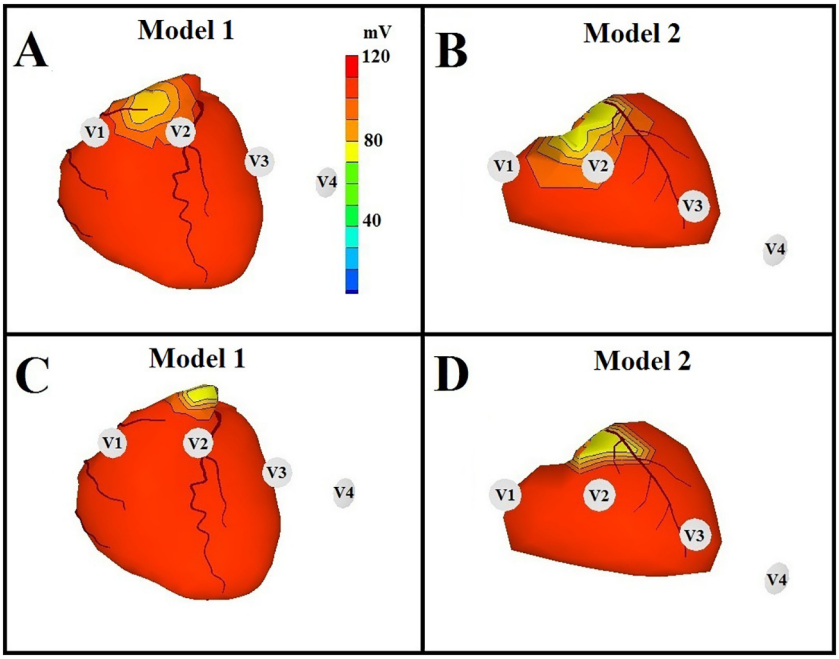

Fig. 5. Simulation of various localization of "injury area" on the two model reported in Fig. 4.

determines the ECG phenotype. Recently our group found that about half of patients with BP show ST segment depression in the inferior leads.

In the current study a 3D electrophysiological computed model suggested, for the first time, a strong correlation between RVOT orientation in the chest, particularly the inclination of anterior wall compared to the sternum, and ST segment depression in the inferior leads in BP.

In the setting of a vertical RVOT, assuming that the main electrical BP abnormality is a vector directed from the endocardium to the epicardium of RVOT anterior wall, a positive deflection is theoretically expected in leads V1 and V2. Abnormal BP vector is directed mainly anteriorly (Fig. 4a) and no ST segment depression in the inferior leads is found, despite a large ST segment elevation in the right precordial leads (phenotype A, Fig. 6A). An upper "injury area" within a vertical RVOT hampers BP recognition at the 4th ics (phenotype C, Fig. 6C). In this latter case standard 12 lead ECG can't show any suspicion of BP. Diagnosis is possible only with right precordial leads placed at 3rd or 2nd ics.

In the setting of a horizontal RVOT, instead, the abnormal BP vector is directed anteriorly and superiorly (Fig. 4b), resulting in both evident BP in leads V1, V2 at the 4th ics and a clear ascending ST depression in the inferior leads (phenotype B, Fig. 6B). An upper location of the "injury area" within a horizontal RVOT hampers BP recognition in the right precordial leads recorded at the 4th ics. However, ST segment depression in the inferior leads persists and is helpful in suspecting BP, suggesting the need for right precordial electrodes displacement at 3rd and 2nd ics (phenotype D, Fig. 6D).

Fig. 7 shows an example of BP not evident in leads V1 and V2 recorded at the 4th ics; inferior leads, however, shows a clear ascending ST segment depression, suggesting the need for recording V1 and V2 above the conventional position. The amount of inferior leads ST depression is often mild and difficult to be recognized unless a detailed analysis is performed. We have proposed to obtain an "inverted mirror image of the inferior leads" (the tracing must be "flipped", rotated upside down, and analyzed backlight) in order to simplify ST segment depression detection in subjects with BP [17]. Fig. 7 shows the striking

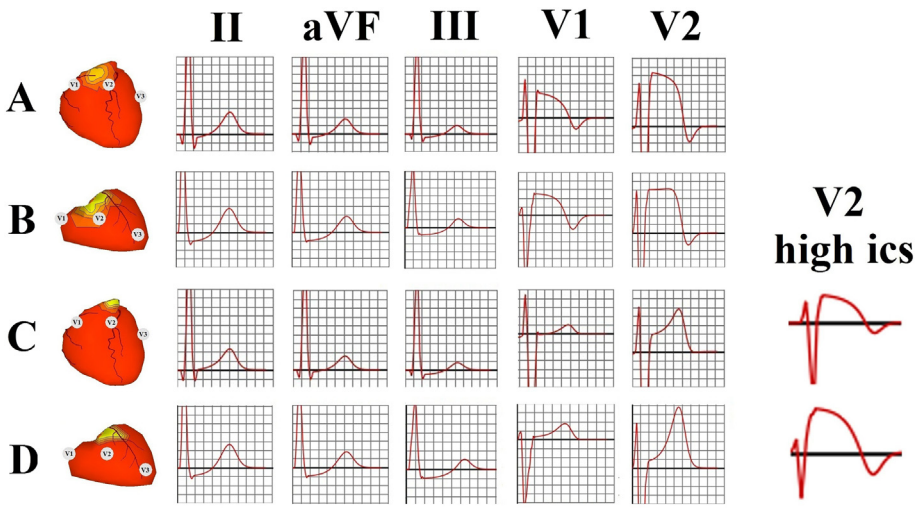

Fig. 6. Simulated ECGs (by ECGsim) reproducing the four type 1 BP phenotypes related to the "injury area" reported in Fig. 5.

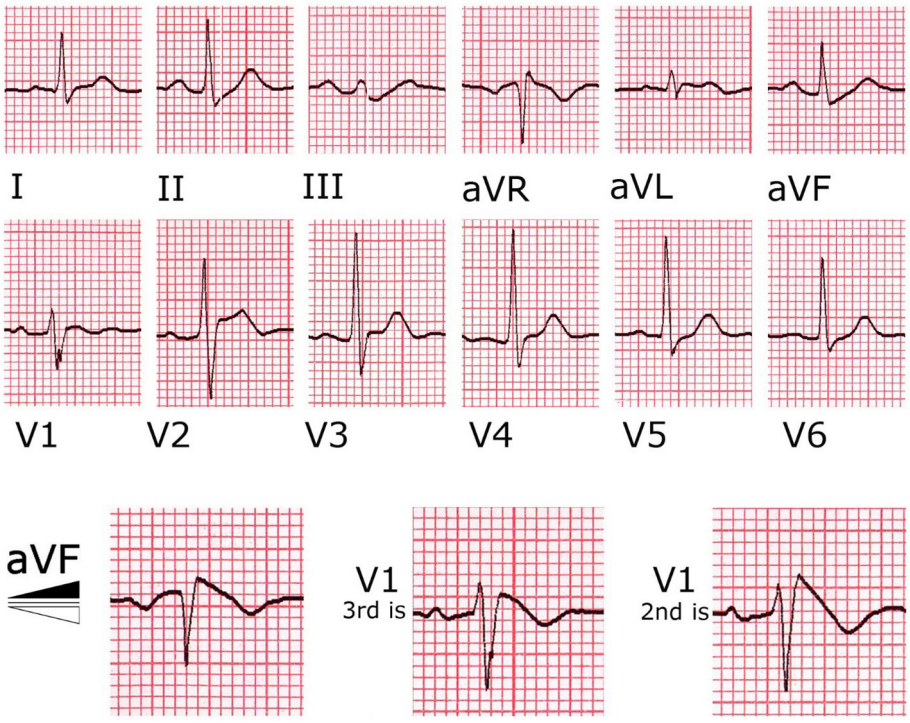

Fig. 7. Type 1 BP recognizable only at the 3rd or 2nd ics. Analysis of inferior leads shows a clear ascending ST segment depression. In addition, inverted mirror image of lead Avf (on the bottom, left side) discloses a pattern suggestive for BP.

analogy between inferior leads inverted mirror image and leads V1 and V2 recorded at the 3rd and 2nd ics.

Conclusions

Type 1 BP has several ECG phenotypes. The typical pattern (ST segment elevation and negative T waves) can be found in one or more right precordial leads, at conventional and/or high ics. Moreover, in about half of patients, standard ECG shows ST segment depression in the inferior leads. The different ECG phenotypes of type 1 BP result from the location of RVOT injury area in the chest, but also from RVOT orientation, as suggested by this 3D electrophysiological computed model of Brugada Pattern. In particular, a lower or upper position of the "injury area" conditions BP recognition at 4th or higher ics. Moreover, a horizontal RVOT gives raise to abnormal BP vector directed both superiorly and anteriorly, explaining ST segment depression in the inferior leads. Cardiac imaging, such as computed tomography and magnetic resonance could guarantee a further validation. Future studies needs to assess a possible prognostic role of various ECG phenotypes of type 1 BP.

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