Malignant ventricular arrhythmias induction by programmed electrical stimulation of the right ventricular outflow tract only during type 1 Brugada ECG maximization

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Abstract. – OBJECTIVE: The role of electrophysiology study in Brugada syndrome (BS) sudden cardiac death risk stratification remains controversial and seems to depend on the phenotypic expression of the channelopathy. Ajmaline has a key role in the diagnosis of BS. We observed that programmed electrical stimulation (PES) of the right ventricular outflow tract (RVOT), only when type 1 BS ECG is unmasked by ajmaline administration, induces ventricular arrhythmias.

CASE REPORT: We describe a case of ventricular fibrillation induction by PES of the RVOT when type 1 BS ECG is revealed by ajmaline, in a patient with a baseline dynamic intermittent type 1 and 2 BS ECG.

CONCLUSIONS: The heterogeneous clinical presentations of BS are due to the underlying mechanisms. PES of the RVOT during positive ajmaline test maximizes the channelopathy and therefore sudden cardiac death risk-stratification in BS.

Key Words: Brugada syndrome, Ventricular arrhythmias, Programmed electrical stimulation, Right ventricular outflow tract, Ajmaline.

Abbreviations

EPS = Electrophysiology study; BS = Brugada syndrome; RVOT = Right ventricular outflow tract; PES = Programmed electrical stimulation; VT = Ventricular tachycardia; VF = Ventricular fibrillation.

Introduction

Brugada syndrome (BS) is an ion channels genetic disorder characterized by typical electrocardiographic (ECG) anomalies responsible for major complications such as syncope and/or sudden cardiac death secondary to malignant ventricular arrhythmias (VAs). Among the 3 BS ECG types described, type 1 BS ECG is diagnostic and considered at higher-risk for sudden cardiac death, according to most authors, characterized by a coved ST-segment elevation (>2 mm-0.2 mV), trending downwards, followed by a negative T-wave in leads V1 and/or V2 positioned in the second, third, or fourth intercostal space, occurring intermittently or continuously, either spontaneously or after intravenous sodium-channel blockers administration, such as ajmaline and/or flecainide. Arrhythmic sudden death risk-stratification remains controversial, in particular in regards to the role of electrophysiology study (EPS) with programmed ventricular stimulation (PES), which is considered relevant if positive but is not considered risk-free if negative. Other factors such as family history of sudden death, symptoms and drug challenge affect the prognosis. EPS has a class IIB recommendation in current international guidelines, because of the low reproducibility and high variability of protocols used in various centers. It has recently been described a case of different VAs inducibility depending on the presence or absence of ECG anomalies induced by drug challenge. Also, the treatment of BS patients is not unanimous, such as the timing for internal cardioverter defibrillator (ICD) or quinidine. Epicardial ablation of the right ventricular outflow tract (RVOT) to reduce ICD discharges has recently been described, confirming the presence of a sectorial vulnerability. We report a type 1 BS patient who experienced different VAs inducibility depending on the timing of PES, with and without ajmaline administration.

We analyzed the sequence of events to manage BS in this patient in order to better understand its
dynamic mechanisms responsible for the existing controversies between centers, and for the wide spectrum of clinical presentations, including occasional fatal events.

**Case Report**

A 68-year-old man was referred for suspected BS because of the appearance of a J-wave and a convex upwards ST-segment elevation >2 mm in leads V1-V2-V3 at peak cycle ergometer stress test (Figure 1). His cardiovascular risk-factors were: male sex, age, second-degree systemic hypertension, type IIB dyslipidemia, hyperhomocysteinemia, hyperuricemia, prior smoking habits, and family history of sudden death (a 50-year-old uncle died suddenly). The patient, without structural heart disease, reported a prior syncopal episode, and episodes of persistent atrial fibrillation treated by successful electrical cardioversion. Multiple 12-lead ECGs showed sinus rhythm (SR), horizontal axis, PQ interval 160 msec, QRS interval 80 msec with a small progressive R wave in V1-V2, J-point and ST-segment variability (Figure 2).

A second cycle ergometer stress test was negative for myocardial ischemia and showed no additional ST-segment alterations compared to baseline (Figure 3). Echocardiography was normal (LVEF 0.64, normal diastolic pattern), except for a mild tricuspid valve regurgitation and a non-significant mitral valve regurgitation. Chest X-ray and hemogasanalysis were normal. The laboratory tests showed normal electrolytes, cholesterol > 250 mg/dL, triglycerides > 200 mg/dL.

The patient underwent sodium-channel blockers challenge. Baseline conditions were SR, heart rate (HR) 80 bpm, PQ 160 msec, incomplete right bundle branch block (RBBB) QRS 105 msec, J-point and ST-segment elevation of 0.14 mV in V1 and 0.18 mV in V2 concave upwards (V1-V2 in the second intercostal space) compatible with type 2 BS ECG, QTc 0.41 sec.

Diagnostic drug-challenge performed by intravenous administration of ajmaline (1 mg/kg over 10 min) unmasked an abnormal response compatible with “coved” type 1 BS ECG with SR HR 78 bpm, PR 180 msec, QRS 150 msec, complete RBBB with J-point and ST-segment elevation of 0.38 mV convex upwards and negative T-waves in
V1-V2 at the second intercostal space; J-point and ST-segment elevation of 0.14 mV in aVL, 0.1 mV in D1, QTc 0.45 sec (Figure 4).

We waited for about 40 min after ajmaline test (double of its half-life), and the ECG turned into type 2 BS with SR, HR 80 bpm, QRS 105 msec, incomplete RBBB with J-point and ST-segment elevation concave upwards of 0.14 mV in V1 and 0.18 mV in V2 at the second intercostal space, QTc 0.41 sec (Figure 4).

VAs risk stratification was, then, performed with PES from the right ventricular apex (RVA) and the RVOT by double extra-stimuli up to ventricular effective refractory period (VERP) of 500-300-210 msec and 400-350-210 msec without VAs induction (Figure 5). We, then, repeated PES after a new administration of ajmaline (0.5 mg/kg in 10 min) and during the restoration of type 1 BS ECG, from the RVA and the RVOT by double extra-stimuli up to VERP of 500-300-210 msec and 400-350-200 msec. The intervals were AH 125 msec, HV 55 msec, VERP <250 msec. PES from the RVA induced only ventricular couples, whereas PES from the RVOT induced a reproducible self-terminated symptomatic ventricular tachycardia (VT) followed by ventricular fibrillation (VF) with a cycle length of 260 msec, HR 230 bpm (Figure 6). A dual-chamber ICD was implanted, per international guidelines (1), after informed consent was obtained. The patient was discharged in good clinical conditions, and was advised to follow BS and ICD recommendations.

**Discussion**

We describe a different VAs inducibility in the same patient, during the same EPS, by PES of the RVOT without and with ajmaline administration, without and with type 1 BS ECG maximization. The active presence of the channelopathy is responsible for type 1 BS ECG pattern. This condition has been reported to ease the induction of malignant VAs at EPS.

The role of EPS in arrhythmic sudden cardiac death risk stratification remains controversial. Current international guidelines recommend EPS with class IIB. Its low reproducibility is explained by the highly variable protocols used in various centers. However, a recent study with a 20-year follow-up showed that EPS is a good predictor of outcomes in BS individuals, but not absolute. According to Makimoto et al., VAs inducibility with single or double extra-stimuli in...
patients with type 1 BS ECG is a negative prognostic indicator, compared to the protocol with triple extra-stimuli. Other known factors that affect VAs inducibility at EPS are the presence of symptoms, male sex, a conduction delay with prolonged HV interval, and first-degree AV block, supporting the hypothesis of the conduction/depolarization anomaly. We also described a case of inducible VF in a BS patient with pre-existing RBBB, supporting the role of conduction disorders as negative prognostic factors.

The conduction disturbances are associated with repolarization dispersion in BS and may worsen the prognosis.

The controversial role of EPS in risk-stratification could depend on the dynamic phenotypic channelopathy expression. International guidelines recommend provocative drug tests with

Figure 3. Ergometer stress test in hospital; it is not diagnostic for BS or ischemic heart disease.

Figure 4. Ajmaline test, it is diagnostic for BS.
intravenous administration of sodium-channel blockers in class IC, because of their diagnostic key role when BS is suspected. They can unmask BS pattern by unbalancing the transmembrane ion fluxes equilibrium in favor of the repolarizing Ito current, resulting in J-wave and ST-segment elevation in the right precordial leads. Since a negative EPS could be interpreted as a low-risk non-type 1 BS, or depend on the dynamic nature of the ECG modifications and on its unclear reproducibility, when type 1 BS is suspected drug challenge is mandatory.

In this case, VAs induction by PES occurred after maximizing type 1 BS ECG during ajmaline administration, and did not occur otherwise. PES induced VF only when type 1 BS ECG anomalies were present and maximized by ajmaline, while it failed to induce VAs in the presence of type 2

Figure 5. EPS + PES without effect ajmaline; not induce VT / VF.

Figure 6. Left: EPS+PES without effect Ajmaline not induce VT/VF. Right: EPS+PES effect of Ajmaline induces VT/VF.
BS ECG. A similar case was characterized by a different VAs inducibility in different centers depending on the presence or absence of the altered type 1 BS ECG unmasked by ajmaline\textsuperscript{4}.

In this patient, RVOT PES induced VAs during type 1 BS ECG maximization as opposed to RVA PES. RVOT is the most vulnerable area in BS\textsuperscript{14}, with electrophysiological and structural abnormalities. The electrophysiological anomalies are dispersion of repolarization and/or slow discontinuous ventricular conduction\textsuperscript{1,12} and depolarization\textsuperscript{12,16}. The repolarization anomaly involves phase 1 of the action potential in the epicardial cells of the RVOT, which has a configuration “spike and dome”, leading to an electric transmural gradient between the endocardium and the epicardium (J-wave on ECG) and predisposing to polymorphic VT that often degenerates into FV. In fact, the onset of VAs is due to phase 2 re-entry of the action potential, which develops when trans-membrane ionic fluxes alterations cause the plateau phase loss in some infundibular epicardial regions, with considerable shortening of the action potential duration and occurrence of a transmural electric gradient. Conduction disturbances are often observed in BS, suggesting the involvement of mild RVOT and conduction system structural anomalies, which are the arrhythmogenic substrate in combination with functional electrical anomalies, according to the depolarization hypothesis\textsuperscript{15}. A BS case of RVOT fibrosis associated with conduction anomalies has been described, and may explain the underlying mechanisms for reentry and VF\textsuperscript{15}. Substrate heterogeneity represents an additional risk-factor for VAs, and some mild or diffuse RVOT structural anomalies include fibrosis, reduced gap junctions, collagen deposition\textsuperscript{15}. RVOT ablation to reduce ICD discharges has been described, confirming such sectorial vulnerability\textsuperscript{5,17}.

Conclusions

PES of the most vulnerable areas such as the RVOT, and BS phenotypic expression maximization with ajmaline may induce VAs. A critical review of the induction timing and technique, in this case, allowed us to postulate that fatal events in BS may happen when two factors are combined: ventricular extra-stimuli or ectopies, and the greatest expression of the channelopathy depending on multiple factors. It is otherwise hard to induce malignant VAs. EPS poor reproducibility and non-proper risk-stratification are due to the variability of protocols used in various centers. Our observations confirm that BS phenotype heterogeneity and high variability require standardized risk-stratification protocols that may improve patient selection and timing for ICD implantation, when no history of cardiac arrest is present. Further studies are required to return to EPS its deserved prognostic value.

Conflicts of interest

The authors declare no conflicts of interest.

References


