

CARDIAC ARRHYTHMIA UPDATE

Brugada Syndrome

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ABSTRACT

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cardiac death; implantable cardioverter
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ABBREVIATION

BS = Brugada syndrome
ECG = electrocardiogram
EPS = electrophysiology study
ICD = implantable cardioverter
defibrillator
RBBB = right bundle branch block
SCD = sudden cardiac death
VF = ventricular fibrillation
VT = ventricular tachycardia

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The Brugada syndrome (BS) is a relative **new clinical entity characterized by complete or incomplete right bundle branch block (RBBB) and ST-segment elevation in leads V₁ through V₃ on surface electrocardiogram (ECG), the absence of structural heart disease, and a high risk of atrial fibrillation, ventricular tachycardia/ventricular fibrillation (VT/VF) and sudden cardiac death (SCD).** The syndrome is considered responsible for 4-12% of all sudden deaths and at least 20% of deaths in patients with structurally normal hearts. BS typically manifests with syncope and cardiac arrest, occurring in the third and fourth decade of life, and usually at rest or during sleep. Although the average age at time of first diagnosis or SCD is 40 years, the BS has been described in a wide range of ages. The clinical phenotype is 8 to 10 times more prevalent in males than in females. Since its initial recognition, an exceptional progress regarding the pathophysiology and management of the disease has been performed.

Several candidate genes have been identified in patients with BS. The *SCN5A* gene (chromosome 3p21) encoding for the cardiac sodium channel (*I_{Na}*) was the first gene linked to BS. Over 100 mutations of the *SCN5A* gene have been identified up to now. Loss of function of the *I_{Na}* channel resulting from changes in the functional properties (gating) of the mutant Na channels, or failure of expression in the sarcolemma (trafficking) is the major effect of *SCN5A* gene mutations. In a large family with BS phenotype where a *SCN5A* mutation was excluded as the candidate gene, a second distinct locus (chromosome 3p24) linked to the glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*) was identified. *GPD1L* mutations have been shown to result in a reduction of *I_{Na}*. The third and fourth genes associated with the BS are the α 1- (*CACNA1C*) and β - (*CACNB2b*) subunits of the L-type cardiac calcium channel. BS is a disease that manifests in adulthood with a very incomplete penetrance and a high proportion of mutation carriers remain asymptomatic, and therefore, the value of genetic analysis for reproductive counselling is less obvious than in other conditions associated with SCD.

Up to date, the diagnosis of Brugada ECG pattern is strictly based on the recommendations of the Second Consensus Conference on BS. According to this report, three types of ECG repolarization patterns in right precordial leads (V₁-V₃) have been recognized. Type 1 is diagnostic of BS and is characterized by a coved ST-segment elevation ≥ 2 mm followed by a negative T wave in more than one right precordial leads. Type 2 ST-segment elevation displays a saddleback configuration with a high takeoff ST-segment elevation of ≥ 2 mm, a trough displaying ≥ 1 mm ST elevation, and either a positive or biphasic T wave. Type 3 has either a saddleback or coved appearance with an ST-segment elevation of ≤ 1 mm. The ECG features of Brugada syndrome are often concealed requiring a pharmacological challenge (sodium channel blocking

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test) with a Class I antiarrhythmic agent (ajmaline, ajmaline, procainamide, flecainide) to unmask the characteristic ST-segment elevation in the right precordial leads. The diagnosis of BS is afterwards considered positive when the baseline type 2 or type 3 ST-segment elevation converted to the diagnostic type 1 pattern (ST-segment elevation ≥ 2 mm). Previous studies have demonstrated that ECG recordings (leads V_1 and V_2) performed at a higher intercostal space exhibit a higher sensitivity compared to the standard positions in detecting the type 1 ECG pattern of BS. Additionally, the type 1 ECG pattern recorded only at the higher intercostal space showed a similar prognostic value for subsequent cardiac events as that recorded at the standard space. In a recent report, individuals with ECGs displaying only one diagnostic right precordial lead (lead V_1 or V_2) had a similar clinical profile and arrhythmic risk as BS patients with ECGs displaying more than one diagnostic right precordial lead. Revision of the Consensus criteria should be therefore considered.

The sensitivity and specificity of sodium channel blocking test varies significantly. The sensitivity and specificity of flecainide, estimated among *SCN5A*-positive probands and their family members, were 77% and 80%, and its positive and negative predictive values 96% and 36%, respectively. In a similar study, the sensitivity, specificity, and positive and negative predictive values of ajmaline challenge among 35 genetic carriers were 80%, 94.4%, 93.3%, and 82.9%, respectively. On the contrary, procainamide exhibits a less use-dependent block of the fast I_{Na} channel, and therefore is less effective compared to all other agents. It has to be mentioned that a negative I_{Na} blocking test does not exclude the presence of a *SCN5A* mutation. Apart from the sodium channel blockers, several other conditions or drugs may uncover a Brugada-type ECG pattern including vagotonic agents, α -adrenergic agonists, β -adrenergic blockers, tricyclic antidepressants, glucose-induced insulin secretion, fever, hyperkalemia, hypokalemia, hypercalcemia, alcohol and cocaine toxicity have been shown to unmask or modulate the characteristic ST-segment elevation in right precordial leads.

BS is definitively diagnosed when a spontaneous or drug-induced type 1 ECG pattern is observed in more than one right precordial lead in combination with one or more of the following: (i) documented VF, polymorphic ventricular tachycardia (VT), (ii) family history of SCD (<45 years old), (iii) coved-type ECGs in family members, (iv) inducibility of VT with programmed electrical stimulation, and (v) syncope or nocturnal agonal respiration. The ECG features of BS are dynamic and often masked, and thus it is relatively difficult to estimate the true incidence of the disease in the general population. Furthermore, the occurrence of Brugada-type ECG pattern is strongly related to age. Previous studies have demonstrated that Brugada sign begins to appear during junior high school and increases until late adulthood. The frequency of Brugada sign varies significantly among ethnic populations

(0.012-6.1%).

The pathophysiology of the BS is only partially resolved. The seminal work by Antzelevitch and colleagues had clearly demonstrated regional heterogeneities in action potential characteristics between the right and left ventricles, as well among epicardium, mid-myocardium and endocardium. A loss of the action potential dome at the epicardium but not at the endocardium creates a transmural voltage gradient that may be responsible for the ST-segment elevation. This mechanism properly accounts for not only the ST-segment elevation but also the premature ventricular contraction (phase 2 reentry) and reentrant substrate for VF in BS. Up to now, two principal mechanisms are thought to be responsible for BS. The repolarization disorder hypothesis states that a non-uniform abbreviation of the right ventricular action potential, related to differences in expression of ion channels, causes the BS features. The depolarization disorder hypothesis states that the reduction in I_{Na} results in conduction delay in the right ventricular outflow tract action potential in respect to the right ventricle action potential. Overlap between these mechanisms may be present.

Risk stratification of subjects with BS remains problematic. Several clinical, ECG and electrophysiological parameters have been proposed to identify high risk patients with BS. Male sex is a risk factor for SCD in BS. Familial forms of the disease do not carry a worse prognosis than isolated cases. Therefore, a family history of BS does not predict a worse outcome. Several original works have showed that individuals with spontaneous type 1 ECG pattern of BS carry a worse prognosis than individuals with a sodium channel blocking test-induced ECG pattern. A spontaneously abnormal ECG carries an almost twice higher risk of developing an arrhythmic event during lifetime as compared to individuals with only drug-induced features of BS. In a recent study, a spontaneous Type 1 Brugada ECG pattern in lead V_2 (but not lead V_1) was both a prospective and retrospective independent predictor of VF episodes in Brugada syndrome. A corrected QT (QTc) >460 ms in lead V_2 has been associated with an increased risk of arrhythmic events. Larger daily fluctuations of the r-J interval (interval from QRS onset to J-point) in leads V_1 , V_2 , and V_6 have been observed in symptomatic than in asymptomatic patients with BS. A prolonged QRS duration in lead V_2 (≥ 120 msec) measured from standard 12-lead ECG has been associated with symptoms and could serve as a simple non-invasive risk marker of vulnerability to life-threatening ventricular arrhythmias in BS. An S wave width ≥ 0.08 s in V_1 and ST-segment elevation ≥ 0.18 mV in V_2 are highly specific indicators of VF and were proposed as new criteria for high risk patients with BS. Finally, the aVR sign, defined as R wave ≥ 0.3 mV or R/q ≥ 0.75 in lead aVR, has been associated with an increased risk of arrhythmic events in subjects with BS. The presence of late potentials is of prognostic significance for life-threatening events. The predictive value of inducibility of

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sustained ventricular arrhythmias during electrophysiological study (EPS) still remains a matter of debate. However, two meta-analyses and two large prospective studies (FINGER and PRELUDE) failed to show any benefit from VT/VF inducibility in risk stratification of patients with BS. More specifically, the PRELUDE study showed that VT/VF inducibility is unable to identify high-risk patients, whereas the presence of a spontaneous type 1 ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic implantable cardioverter defibrillator (ICD). In a recent meta-analysis of 30 prospective studies including 1,545 patients with BS ECG pattern, a history of syncope or SCD, the presence of a spontaneous type 1 Brugada ECG, and male gender predicted a more malignant natural history. These findings are now supported by the FINGER and PRELUDE registries. Asymptomatic individuals are at very low risk for arrhythmic events.

The only effective management of patients with definite BS is implantation of an ICD. However, given the wide variation in the incidence of events, the appropriate indication for

ICD implantation remains uncertain. Patients with a spontaneous or drug-induced Type 1 Brugada ECG and a history of syncope or SCD should undergo ICD implantation. Based on the Second Consensus Conference on BS published in 2005, asymptomatic patients with a spontaneous Type 1 Brugada ECG or asymptomatic patients with a drug-induced Type 1 Brugada ECG and a family history of SCD should undergo electrophysiological study (EPS) to guide the selection of patients for ICD implantation. However, according to the results of FINGER and PRELUDE studies, VT/VF inducibility at EPS does not provide any information in risk stratification, and therefore, the Consensus Conference on BS should be revisited. At present, there is no specific pharmacologic treatment to prevent SCD in patients with BS. Quinidine has been shown to be effective in reducing arrhythmic events, and a large prospective study is now running in order to test this efficacy. Finally, in a recent report, catheter ablation over right ventricular outflow tract epicardium led to normalization of the Brugada ECG pattern and prevented VT/VF.