Brugada Syndrome

Review Article

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Summary

This article discusses the importance of diagnosis and the management of Brugada Syndrome. Epidemiological and pathophysiological aspects of the syndrome and modern approaches to therapy and genetic analysis will be introduced.

Keywords: Brugada syndrome; Epidemiology; Pathophysiology; Recommendations

Background

Brugada syndrome (BS) is defined by ST-segment elevation in right precordial leads (V1 to V3) that as it was reported in early 1953 is unrelated to ischemia, electrolyte disturbances, or obvious structural heart disease. BS was first described as a distinct clinical entity associated with a high risk of sudden cardiac death in 1992 by the Brugada brothers [1,2]. In 1992 it has originally been described as an autosomal-dominant inherited arrhythmic disorder defined by ST elevation with successive negative T wave without structural cardiac abnormalities in the right precordial leads [3]. In 1996, in the description of the cellular basis for the J-wave of the ECG by Yan and Antzelevitch, focal point was the importance of ST-segment elevation (accentuated J-wave) and apparent right bundle branch block (RBBB) syndrome, specified by Brugada and Brugada, and named it the "Brugada syndrome" Kobayashi et al. and Miyazaki et al. followed suit that same year [4].

Epidemiology

As in parts of Asia (eg, the Philippines, Thailand, Japan) it seems to be the most common cause of natural death among men younger than 50 years, Brugada syndrome is known as Lai Tai (Thailand), Bangungot (Philippines), and Pokkuri (Japan). In Northeast Thailand, the mortality rate from Lai Tai is approximately 30 cases per 100,000 inhabitants per year [5,6]. Since Brugada syndrome has been identified recently, the predominance of it isn't enacted well. In a large university hospital on the West Coast of the United States, the prevalence of a Brugada ECG pattern among unselected, mainly white and Hispanic adults was 2 of 1348 patients (0.14%); in both cases, the ECG patterns were type 2. Brugada syndrome is 8-10 times more predominant in men than in women. The penetrance of the mutation appears to be much higher in men than in women, even though that the probability of having a mutated gene does not differ by sex. Brugada syndrome most commonly affects healthy men aged 30-50 years, but affected patients aged 0-84 years have been reported. Meanwhile the mean age of patients who die suddenly is 41 years [7].

Pathophisiology

Brugada syndrome is a Na channelopathy, which is caused by a variation in the transmembrane ion currents that in conjunction form the cardiac action potential. In 10-30% of cases mutations are discovered in the SCN5A gene (encodes cardiac voltage-gated sodium channel) that reduce the sodium current (INa) available during the phases 0 and 1 of the cardiac action potential. This decrease in INa is believed to affect the right ventricular endocardium differently from the epicardium. It underlies both the Brugada ECG pattern and the clinical manifestations of the Brugada syndrome. The exact mechanisms of the ECG alterations and arrhythmogenesis in Brugada syndrome are contentious since the repolarization-defect theory underlies on the fact that right ventricular epicardial cells display a more conspicuous notch in the action potential than endocardial cells. This is believed to be because of an increased contribution of the transient outward current (Ito) to the action potential waveform in that tissue [8]. One of the studies that used ajmaline provocation to elicit a type 1 Brugada ECG pattern in 91 patients, found that the repolarization abnormalities were consistent with the depolarization abnormalities and turned out to be secondary to the depolarization changes [9].

ECG

One true diagnostic Brugada pattern, two others may suggest the disease. Type 1: It is characterised by a prominent coved ST-segment elevation displaying J-point amplitude or ST-segment elevation ≥2 mm, followed by a negative T wave. Type 2: It has ≥2 mm J-point elevation, ≥1 mm ST-segment elevation and a saddleback appearance, followed by a positive or biphasic T-wave. Type 3: It has either a saddleback or coved appearance, but with an ST-segment elevation <1 mm (Figure 1).

Genetic

Thus far, mutations in 11 genes have been associated with the Brugada syndrome. Most of these mutations reduce the cardiac sodium current (INa), the other ones decrease the L-type calcium current (ICaL). The first ones are located in SCN5A, the gene encoding the cardiac sodium channel, its β-subunits SCN1B

and SCN3B or in GPD1L and MOG1 which are thought to impair trafficking of the cardiac sodium channel to the cell membrane, mutations decreasing the ICaL are located in CACNA1C, CACNB2b and CACNA2D1 which encode the α1-, β2b-, and α2δ-subunit of the L-type calcium channel. Finally, with the Brugada syndrome were associated both the mutations in KCNE3 which encode MiRP2, a β-subunit of several potassium channels and in KCNJ8 encoding the ATP-sensitive potassium channel. Earlier, during the action potential some currents were activated, for increasing the repolarization of those, these mutations have been suggested [10,11].

ESC recommendations

In 2015 ECS has published new guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death, in which Brugada Syndrome is mentioned too. Brugada syndrome is diagnosed in patients with ST-segment elevation with type 1 morphology ≥2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after provocative drug test with intravenous administration of sodium channel blockers (such as ajmaline, flecainide, procainamide or pilsicainide). ESC recommendations suggest the ICD as the only treatment able to reduce the risk of SCD in Brugada syndrome, thus the appliance can be applyed in patients both with documented VT or VF and in patients presenting with a spontaneous type 1 ECG and a history of syncope [12] (Table 1).

AHA recommendations

There is no significant difference between the recommendations of ESC and AHA for the BS therapeutic interventions. The only difference that has to be mentioned is that AHA recommentations don't indicate ICD implantation in asymptomatic BS in patients with a drug-induced Type I ECG and based on family history of SCD (Table 2).

On the AHA recommendations In asymptomatic patients, the following findings are considered supportive for the diagnosis of BrS:

i. Attenuation of ST-segment elevation at peak of exercise stress test followed by its appearance during recovery phase. It should be noted, however, that in selected BrS patients, usually SCN5A mutation-positive patients, it has been observed that ST-segment elevation might become more evident during exercise.

ii. Presence of first-degree atrioventricular (AV) block and left-axis deviation of the QRS.

iii. Presence of atrial fibrillation.

iv. Signal-averaged ECG; late potentials.

v. Fragmented QRS.

vi. ST-T alternans, spontaneous left bundle branch block. (LBBB) ventricular premature beats (VPB) during prolonged ECG recording.

vii. Ventricular effective refractory period (ERP) o200 ms recorded during electrophysiological study (EPS) and HV interval 460 ms

viii. Absence of structural heart disease including myocardial ischemia [13].

Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of Brugada syndrome: (a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org) (b) Avoidance of excessive alcohol intake and large meals (c) Prompt treatment of any fever with antipyretic drugs.	I	C	This panel of experts
ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who (a) Are survivors of an aborted cardiac arrest and/or (b) Have documented spontaneous sustained VT.	I	C	451
ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope.	IIa	C	451
Quinidine or isoproterenol should be considered in patients with Brugada syndrome to treat electrical storms.	IIa	C	453
Quinidine should be considered in patients who qualify for an ICD but present a contraindication or refuse it and in patients who require treatment for supraventricular arrhythmias.	IIa	C	454
ICD implantation may be considered in patients with a diagnosis of Brugada syndrome who develop VF during PVS with two or three extrastimuli at two sites.	IIb	C	120
Catheter ablation may be considered in patients with a history of electrical storms or repeated appropriate ICD shocks.	IIb	C	201, 455

ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; PVS = programmed ventricular stimulation; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Table 1: Risk stratification and management in Brugada Syndrome by ESC.

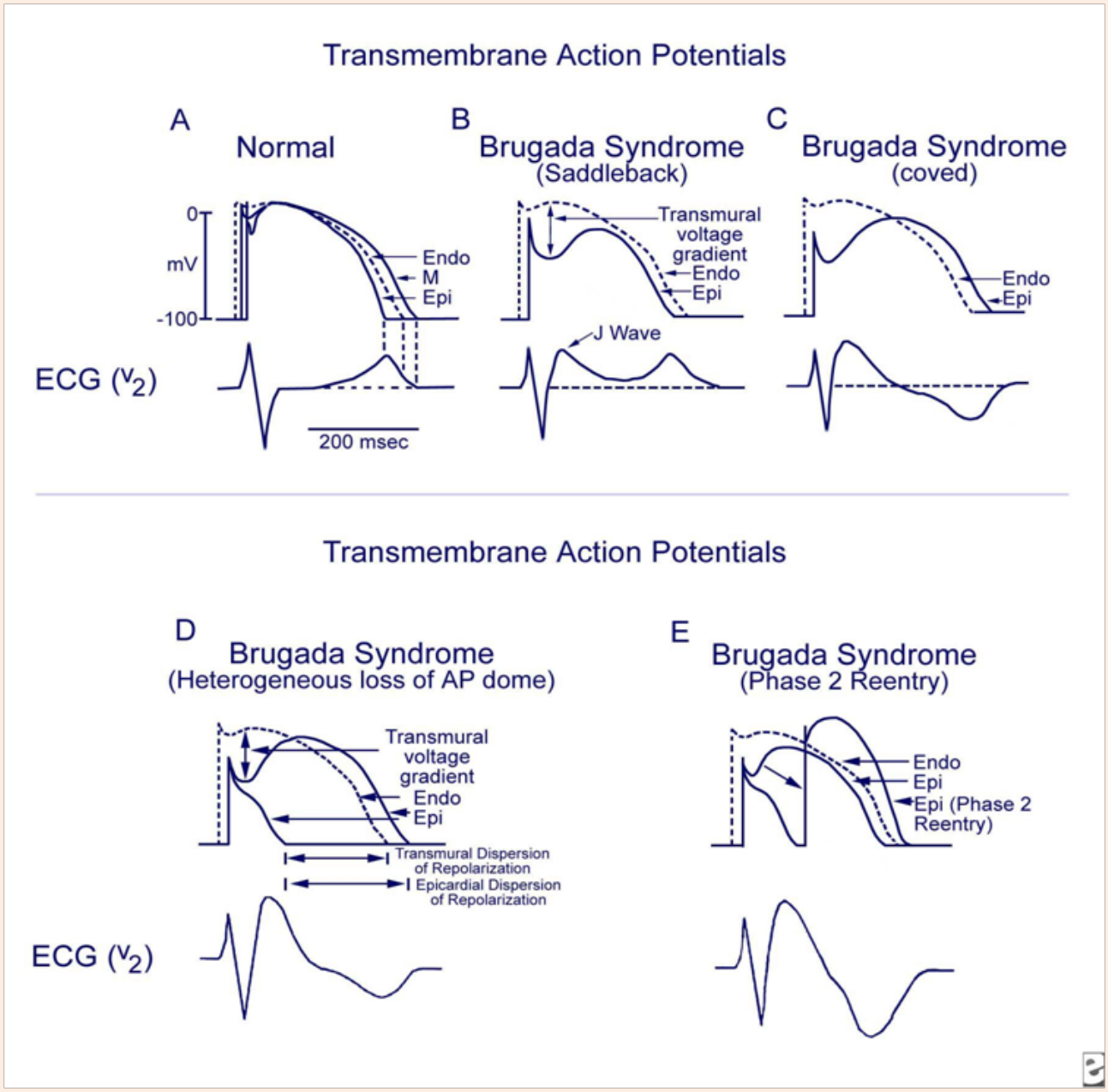

Figure 1: Transmembrane action potentials in patients with Brugada syndrome.

Quinidine therapy

Quinidine was the most commonly used medication for the prevention of ventricular and atrial arrhythmias as recently as 2 decades ago. Nowadays the use of quinidine is limited because of its side effects and the presence of more safe and effective modern antiarrhythmic drugs. Thus far, in the Brugada syndrome genetic mutations reducing sodium inflow currents are detected in defective myocardial sodium channels which resulted in shorter-than-normal action potentials. Since prominent Ito (transient outward) current in the right ventricular epicardium further shortens the action potentials, Antzelevitch propose that quinidine may exert its favorable effects in Brugada syndrome by inhibiting Ito, and as a result restores electrical homogeneity. Quinidine has effectively been used by Belhassen et al. [14] as the sole therapy (without ICD back-up) for patients with symptomatic Brugada syndrome, including patients who had spontaneous VF before the initiation of therapy. Recent study shows that none of the 50 patients with symptomatic or asymptomatic Brugada syndrome developed symptomatic ventricular arrhythmias at

the same time on quinidine therapy during a follow-up period within from 3 months to more than 10 years. 600-1500mg/d dosage of quinidine is recommended (In special cases dose can vary from 475 to 2000mg/d). (The effective level of quinidine in serum blood ranges from 1.29 to 5.2 mg/L). The effective quinidine serum blood levels ranges from 1.29 to 5.2 mg/L. The effectiveness of low dose quinidine (200mg/d) is not proven but Belhassen et al. used it for patients with side effects of quinidine after the administration of standard dosage. Most of the quinidine side effects are dose related [14,15].

Expert Consensus Recommendations on Brugada Syndrome Therapeutic Interventions	
Class I	1. The following lifestyle changes ***are recommended*** in all patients with diagnosis of BrS: a) Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads (for example, visit Brugadadrugs.org), b) Avoidance of excessive alcohol intake. c) Immediate treatment of fever with antipyretic drugs. 2. ICD implantation ***is recommended*** in patients with a diagnosis of BrS who: a) Are survivors of a cardiac arrest and/or b) Have documented spontaneous sustained VT with or without syncope.
Class IIa	3. ICD implantation ***can be useful*** in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias. 4. Quinidine ***can be useful*** in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours. 5. Quinidine ***can be useful*** in patients with a diagnosis of BrS: a) Who qualify for an ICD but present a contraindication to the ICD or refuse it *and/or* b) Have a history of documented supraventricular arrhythmias that require treatment. 6. Isoproterenol infusion **can be useful** in suppressing arrhythmic storms in BrS patients.
Class IIb	7. ICD implantation ***may be considered*** in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients). 8. Quinidine ***may be considered*** in asymptomatic patients with a diagnosis of BrS with a spontaneous **type I** ECG. 9. Catheter ablation ***may be considered*** in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.
Class III	10. ICD implantation **is not indicated** in asymptomatic BrS patients with a drug-induced **type I** ECG and on the basis of a family history of SCD alone.

Table 2: Expert Consesus Recommendations on Brugada Syndrome Therapeutic Interventions by AHA.

The implied risk of a tragic and preventable event - sudden death - in young and, otherwise, healthy individuals because of Brugada Syndrome determines the huge importance of right diagnosis and management of BS by healthcare professionals all over the world.

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