Current review of Brugada syndrome: from epidemiology to treatment

Brugada sendromunun güncel incelemesi: Epidemiyolojiden tedaviye

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ABSTRACT

Brugada syndrome is a genetic cause of sudden cardiac arrest characterized by abnormal electrocardiographic (ECG) pattern in the right precordial leads either at rest or after provocation. In this condition, sudden death may occur due to polymorphic ventricular tachycardia or ventricular fibrillation. In approximately 30% of patients, sudden cardiac arrest is the initial clinical manifestation of Brugada syndrome. Treatment strategies for Brugada syndrome are evolving. Currently, the implanted cardioverter defibrillator (ICD) is the only proven treatment for Brugada syndrome. Candidates for ICD include patients include those with the type 1 ECG pattern or who have been successfully resuscitated from sudden death or have had unexplained syncope. *(Anadolu Kardiyol Derg 2009; 9: Suppl 2; 12-6)*

Key words: Brugada syndrome, implantable cardioverter defibrillator, sudden cardiac death

ÖZET

Brugada sendromu, istirahatta ve provokasyondan sonra sağ perikardiyal elektrotlarda anormal elektrokardiyogram (EKG) görünümleri ile karakterize, ani kalp durmasının genetik bir nedenidir. Bu durumda, polimorfik ventrikül taşikardisi ya da ventrikül fibrilasyonu sonucu olarak ani ölüm meydana gelir. Hastaların yaklaşık %30'unda ani kalp durması, Brugada sendromunun ilk klinik belirtisidir. Brugada sendromunun tedavi stratejisi gelişmektedir. Şu anda, takılabilir kardiyoverter defibrilatör (ICD) Brugada sendromu için kanıtlanmış tek tedavidir. Halen, tip 1 EKG örneği olanlar, ani ölümden sonra başarı ile resüssite edilenler ya da açıklanamayan senkoplu hastalar ICD adaylarıdır.
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Anahtar kelimeler: Brugada Sendromu, takılabilir kardiyoverter defibrilatör, ani kardiyak ölüm

Introduction

Brugada syndrome (BrS) is a genetic cause of sudden cardiac arrest (SCA). In this condition, SCA occurs due to the development of either polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).

In approximately 30% of patients, SCA is the initial clinical manifestation of BrS. When VT or VF occurs, it tends to be in the evening hours. This is thought to occur because of circadian rhythm.

Patients with BrS do not have structural heart disease on echocardiogram, stress testing, or cardiac catheterization. However, a standard electrocardiogram (ECG) usually shows the characteristic abnormality: right bundle branch block type morphology of the QRS complex with ST segment elevation in the right precordial leads (V_1 - V_3; Fig. 1). The differential diagnosis for the ECG pattern seen in BrS is extensive (Table 1) so not all patients with this sort of ECG abnormality actually have the BrS, and thus are not at risk for SCA. Even those with Brugada syndrome have variable risk for SCA. Brugada et al. (1) followed 422 asymptomatic patients with BrS for 24 months. In that study, patients with spontaneous type 1 Brugada pattern on ECG and inducible VT on electrophysiology testing had a 14 percent risk of SCA, while patients with a type 1 ECG pattern seen only after a pharmacological challenge and negative electrophysiology testing had a 0.5 percent risk of SCA (1). Because of this variability, it is important to identify and appropriately manage BrS patients at high risk according to best available evidence.

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Epidemiology

BrS typically presents during adulthood. Although most patients are in their 30's to 40's, BrS has been reported in patients as young as 2 years of age and as old as 84 years. Men are affected more commonly than women with a ratio of 8-9:1 (2). The reason for this male preponderance is possibly related to underlying differences in hormonal status. It is estimated that BrS is responsible for at least 4% of all sudden deaths and at least 20% of all sudden deaths occurring in patients without structural heart disease (3). The syndrome occurs more commonly in Southeast Asians, with the highest incidence occurring in the peoples of Northern Thailand (4).

Genetics and Pathophysiology

BrS is a genetic disorder. In the inherited form, the mutant genes are passed down from parents to offspring and the syndrome runs in families. Since BrS is an autosomal dominant disorder, offspring of people with the mutant gene have a 50% chance of inheriting it from their affected parent. A sporadic form is also seen due to spontaneous mutations in the parent's germ cells (ova or sperm) affecting the segments of DNA that code for the specific Brugada proteins.

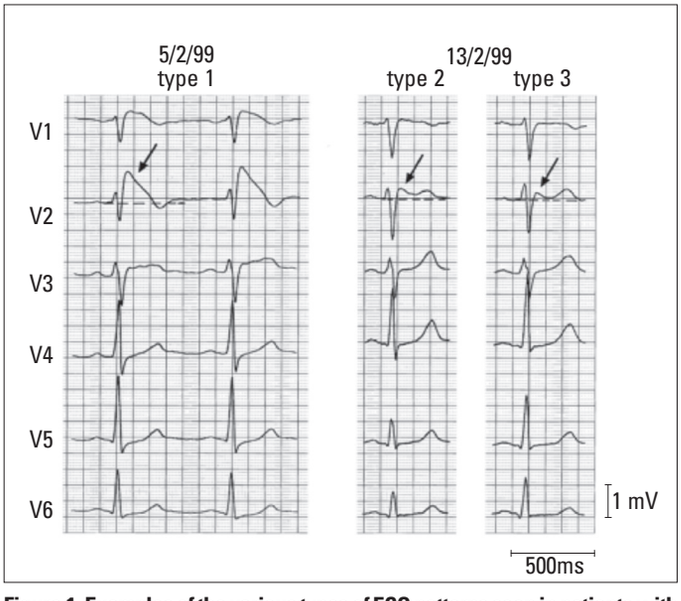

Figure 1. Examples of the various types of ECG patterns seen in patients with Brugada syndrome
ECG - electrocardiogram
(Reproduced with permission from Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002; 106: 2514-9. Copyright 2002, LWW)

The first gene linked with BrS was SCN5A which occurs on chromosome 3. It codes for the α subunit of the cardiac sodium channel (5). Only 15-30% of families with BrS have been found to have this mutant gene. Additional sodium and calcium channel mutations have been identified, SCN1B, CACNA1C, CACNB2, as well as GDP1L mutation of the glycerol-3-phosphate dehydrogenase-1 like protein (6). Genetic testing, now commercially available is recommended: 1) to support clinical diagnosis; 2) for early detection of relatives at potential risk; and 3) for research into genotype-phenotype relationship.

In patients with BrS, there is altered depolarization of the right ventricle making a person vulnerable to fatal ventricular arrhythmias. The gene mutations, mentioned above, lead to ion channel defects which cause either decreased sodium or calcium influx or increase potassium efflux from the myocyte. The most common mutation is SCN5A, in which, the mutant sodium channel leads to decrease in the sodium (I_{NA}) current due to either failure of expression of the sodium channel, accelerated inactivation, or prolonged recovery from inactivation (3). This causes a shortening of the action potential duration by blunting phase 0 depolarization. Furthermore, in the right ventricular (RV) epicardium, there is an increased number of transient outward potassium current channels, $I_{to.}$ This mismatch in potassium and sodium currents leads to decreased activation of the L-type calcium channels that maintain the depolarized state during phase 2 of the action potential. The net effect is loss of the action potential dome causing a short refractory period of the RV epicardium and heterogeneity of refractory periods between the RV endo-and epicardium (Fig. 2) (7). Since these mutant sodium channels fail to activate properly there is unidirectional block. The unidirectional block coupled with the short refractory period makes this substrate ideal for reentry; the reentrant circuit leads to continuous depolarization of the ventricular myocardium causing ventricular tachycardia and fibrillation. This form of reentry tends to occur in phase 2 of the action potential, thus is termed phase 2 reentry (7-10).

Table 1. Differential diagnosis of Brugada type electrocardiographic pattern

Atypical right bundle-branch block	Duchenne muscular dystrophy
Left ventricular hypertrophy	Thiamin deficiency
Early repolarization	Hyperkalemia
Acute pericarditis	Hypercalcemia
Acute myocardial ischemia or infarction	Arrhythmogenic right ventricular dysplasia/cardiomyopathy
Pulmonary embolism	Pectus excavatum
Prinzmetal angina	Hypothermia
Dissecting aortic aneurysm	Mechanical compression of the right ventricular outflow tract (RVOT)
Central and autonomic nervous system abnormalities	

Other Arrhythmias

Patients with BrS are also at increased risk for developing atrial fibrillation, an irregularly irregular rhythm originating from the upper chambers of the heart. Atrial fibrillation is observed clinically in up to 20% of these patients (11). Other arrhythmias include AV nodal reentrant tachycardia and Wolf-Parkinson-White syndrome (12). The increased incidence of these arrhythmias may reflect the diffuse nature of the sodium channel abnormality. These arrhythmias may lead to inappropriate firing from implanted cardioverter-defibrillator (ICD) highlighting the importance of appropriate device programming in the management of supraventricular arrhythmias in BrS (13).

Precipitating Factors

The ECG manifestations of Brugada syndrome are often concealed, but can be unmasked by various clinical conditions (fever), maneuvers, or administration of certain drugs (sodium channel blockers) (14-18). These precipitating factors and conditions lead to changes in ion currents that occur in the myocardial (heart) cells during depolarization, leading to the abnormal ECG pattern typical of BrS (Fig. 3).

Diagnosis

Three ECG patterns in the right precordial (chest) leads are recognized as being associated with BrS (Fig. 1) (19). Type 1 is diagnostic of Brugada pattern and is characterized by a coved ST-segment elevation ≥2 mm followed by a negative T wave. A definitive diagnosis of BrS can be made when a type 1 ST-segment elevation pattern is observed in >1 right precordial lead (V_1 to V_3) along with one of the following: 1) documented polymorphic VT or VF; 2) a family history of sudden cardiac death at <45 years of age; 3) similar type ECGs in family members; 4) inducibility of VT/VF during an electrophysiology study; 5) unexplained syncope, or 6) history of nocturnal agonal respiration (3).

The type 2 ST-segment elevation pattern has a saddleback appearance with a ST-segment elevation of ≥2 mm, a trough displaying ≥1 mm ST elevation, and then either a positive or biphasic T wave. The type 3 pattern has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. Unlike the type 1 pattern, type 2 and 3 pattern ECGs are not diagnostic of the Brugada pattern. In order for a diagnosis of BrS to be made in patients with either a type 2 or 3 pattern, conversion to a more diagnostic type 1 pattern must be observed, either spontaneously or after administration of a sodium channel blocker (e.g. procainamide, flecainide, or ajmaline), in conjunction with one or more of the clinical criteria described above (3). Placement of the right precordial leads in a superior position (up to the second intercostal space above normal) can increase the sensitivity of the ECG for detecting the BrS (20, 21).

Treatment

The pharmacological approach to therapy is based on rebalancing of currents during the action potential. Antiarrhythmic drugs, that affect the transient outward potassium current (I_{to}), have shown promise because they reestablish the action potential dome. Unfortunately medications

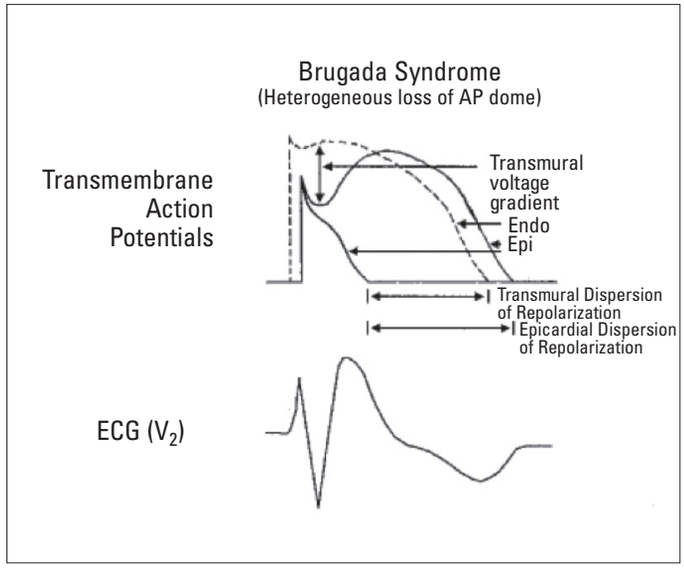

Figure 2. Differences in action potential between epicardial and endocardial myocytes in Brugada syndrome

AP - action potential, ECG - electrocardiogram

(Adapted, with modification from reference 7)

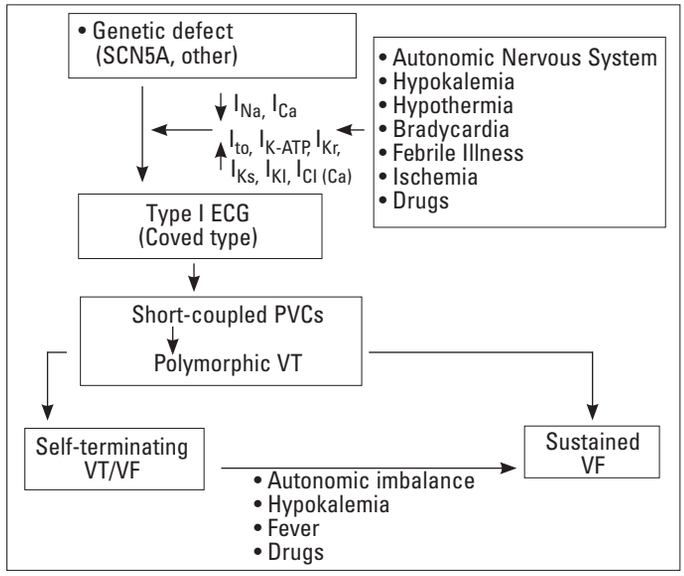

Figure 3. Precipitating factors for Brugada syndrome: ECG pattern and arrhythmias

ECG - electrocardiogram, PVC - premature ventricular contraction, VT - ventricular tachycardia, VF - ventricular fibrillation

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that specifically target I_{to} are not available. Instead, quinidine, which has some I_{to} blocking properties, is used most commonly. Quinidine has been used in some patients to reestablish a normal contour to the action potential and normalize the ECG pattern in patients with BrS (22). The recommended dosing of quinidine is 1200 to 1500 mg/day given in divided doses (23). However, clinical trials demonstrating the long-term efficacy of quinidine are limited; thus quinidine cannot be recommended as sole first-line therapy for patients with BrS (24-26).

Other agents that boost the L-type calcium current, such as isoproterenol, may be also useful in patients with BrS (27). The

phosphodiesterase III inhibitor, cilostazol, normalizes the ST segment by augmenting the calcium current (I_{Ca}), as well as by reducing I_{to} secondary to an increase in heart rate (28). Tedisamil, an experimental antiarrhythmic agent, with I_{to} blocking properties may be more potent than quinidine because it lacks the relatively strong inward Na current-blocking actions of quinidine (27). Nevertheless, appropriate clinical trials are needed to establish the effectiveness of all of the above pharmacological agents. These medications are reserved for controlling "electrical storms" (incessant episodes of VT/VF) in BrS (3).

Currently, ICDs are the only proven treatment for BrS (29-31). Furthermore, since SCA may be the initial manifestation of the disease, it is critically important to identify patients who many benefit from ICD implantation (Fig. 4). These patients include those with the type 1 ECG pattern (either spontaneous or induced by administration of a sodium channel blocker) who have been successfully resuscitated from SCA or have had unexplained syncope (loss of conciseness), seizures, or nocturnal agonal respirations (3, 32).

The indications for ICD become less clear in asymptomatic patients with the Brugada pattern on ECG, and unfortunately, there is no consensus among physicians. Indeed, implanting ICDs in young patients were the risk of SCA may accumulate over time must be balanced against the risk of the ICD complications which also increase with time (33). In Sacher's study (34), appropriate shocks occurred at an annual rate of 2.6 percent while inappropriate shocks occurred in 20% of the 220 patients with BrS and an implanted defibrillator at 38 month follow up. Similarly, Sarkozy et al. (35) demonstrated 14% of 47 patients with BrS and an ICD had appropriate therapy while 36% had inappropriate therapies delivered by their device at 48 month follow up. In addition to inappropriate therapies, mechanical stresses over time may result in device malfunction particularly lead fracture. Thus, it may become important to modify implantation techniques to minimize this risk (36).

Tools for risk stratifying asymptomatic BrS patients are lacking. One method for risk stratifying asymptomatic patients is with programmed electrical stimulation. Brugada et al. (1) performed programmed electrical stimulation in 408 patients with asymptomatic BrS. Of the 408 patients, 163 developed sustained arrhythmias. After a follow up of 24 months, 8% of theses patients suffered sudden death or documented ventricular fibrillation (1). Patients in whom a sustained ventricular arrhythmia (ventricular fibrillation, polymorphic ventricular tachycardia, or monomorphic ventricular tachycardia lasting >30 seconds) is inducible are felt to be at high risk and may warrant ICD implantation (3). However, the predictive value of this test in this patient population has been questioned (37, 38). Thus, the management of asymptomatic patients remains to be defined.

Conclusion

Much progress has been made in our understanding of BrS. However, more research is needed especially in the area of diagnosis and risk stratification. Frequently, patients with atypical right bundle branch morphologies are identified and subjected to non-standardized pharmacologic and electrophysiological testing with even greater variation in the interpretation of these results. This increases the financial burden placed on health care resources not to mention the psychological, emotional burden placed on patients and their families. The aim of this review was to formulate a comprehensive yet practical approach to the understanding and treatment of BrS. Only a Type 1 ECG pattern confirms the diagnosis of BrS. Patients with BrS, who have been resuscitated for SCA or have unexplained syncope should be treated with ICD therapy, while asymptomatic patients with low risk features need close observation with avoidance of precipitating factors. The role of programmed electrical stimulation in the risk stratification of BrS is debatable.

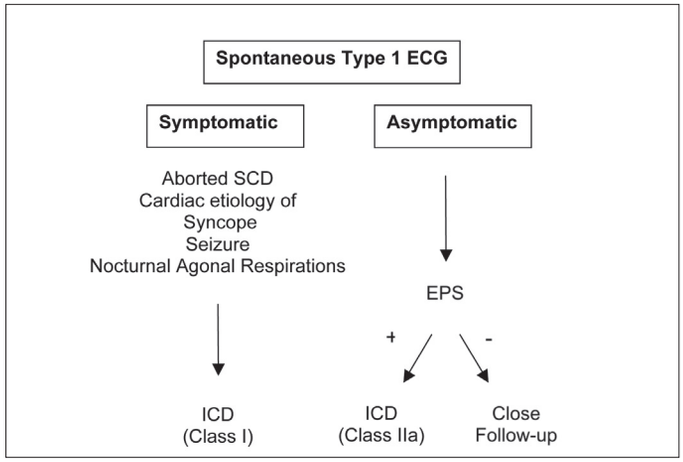

Figure 4. Indications for ICD Implantation in Brugada Syndrome
ECG - electrocardiogram, EPS - electrical programmed stimulation, ICD - implanted cardioverter defibrillator, SCD -sudden cardiac death
(Modified from reference 3)

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