Brugada Syndrome-An Update

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A diagnostic triad characterizes Brugada syndrome. It consists of a right bundle branch block, ST-segment elevation in leads V1-V3 and sudden cardiac death (SCD). Approximately 50% of patients with Brugada syndrome noted to have familial occurrence, this suggests a genetic component of the disease. Mutations in gene SCN5A, an encoder for human cardiac sodium channel on chromosome 3p21, causes Brugada syndrome. Before considering the diagnosis of Brugada syndrome, exclude precordial ST-segment elevation secondary to acute coronary syndrome, electrolyte imbalance, myocarditis, drug over dosage (cocaine, tricyclic antidepressants), and arrhythmogenic right ventricular cardiomyopathy/dysplasia. Intravenous administration of ajmaline, flecainide, and procainamide may exaggerate the ST-segment elevation, or unmask it when it is initially absent in patients with suspected Brugada syndrome. Programmed electrical stimulation (PES) may help in risk stratification, and in some cases, establish the diagnosis. However, the accuracy of PES in predicting outcome is debatable, especially in patients showing an asymptomatic Brugada ECG, and reporting no family history of SCD. Treatment with an implantable cardioverter-defibrillator (ICD) is the only established effective therapy for the disease. With ICD therapy, the mortality rate at a 10 year follow-up was 0%. Supporting data for long-term pharmacological therapy with quinidine, or isoproterenol for prevention of SCD, in these patients, is uncomplete. Future advances in understanding the molecular mechanisms of Brugada syndrome may provide answers to many of the controversial issues in the management of this disease. *(Chang Gung Med J 2005;28:69-76)*

Key words: sudden cardiac death, Brugada syndrome, implantable cardioverter-defibrillator, electrophysiological study, electrocardiogram.

In 1992 Pedro and Joseph Brugada described a new syndrome termed as the Brugada syndrome, it was characterized by a diagnostic triad consisting of 1) a right bundle branch block (RBBB) pattern in the electrocardiogram (ECG); 2) transient or persistent ST-segment elevation in leads V1-V3 and 3) sudden cardiac death (SCD). These individuals had a structurally normal heart with no evidence of atherosclerotic coronary artery disease.[1] Since its first formal description, cardiac electrophysiology literature shows a phenomenal rise in the related articles of this syndrome.

South East Asians have known this condition for many decades, and is refered to by various regional terms. The Philippines know Brugada syndrome as 'Bangungut' (scream followed by sudden death during sleep); Japan knows it as 'Pokkuri' (unexpected sudden death at night), and Thailand knows it as 'Lai Tai' (death during sleep).[2]

In 1989, Martin et al identified patients of aborted sudden death with a typical Brugada type ECG pattern.[3] However, Brugada & Brugada were the

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first to suggest this as a functional cardiac disorder.

Epidemiology

This entity is thought to be primarily a disease of South East Asian descent predominantly affecting young males, recent reports have noted the presence of this deadly syndrome in women and children and in non-Asian ethnic groups.[4,5] Brugada syndrome is suspected to be responsible for 40 to 60 % of what had previously been referred to as idiopathic ventricular fibrillation (VF).[6]

Genetics and Pathophysiology

A familial occurrence is noted to be present in approximately 50% of patients with Brugada syndrome, this suggests a genetic component of the disease.[7] Recent studies confirm a genetic association with mutations in gene SCN5A, an encoder for human cardiac sodium channel on chromosome 3p21, causes Brugada syndrome. This genetic basis proves that the disease is a channelopathy and primarily an electrical disease.[8] Insight from cellular electrophysiology suggests that the ST-segment elevation is caused by a shift in the ionic current balance and the creation of a voltage gradient with predominance of transient outward current (I_{to}) in the epicardium over the endocardium. A difference in the expression pattern of this current, in the right ventricle (RV) versus left ventricle (LV), accounts for the presence of the ECG pattern solely in the right precordial leads.[9] Research shows that the mutated channels get inactivated faster or rendered non-functional.[10] These non-functional channels, which act in phase 0 of the action potential, leave Ito currents unopposed in phase 1, creating a transmural voltage gradient and a substrate for reentrant arrhythmias. Electrophysiological research indicates worsening of channel function at higher temperatures in some mutations.[11] This may explain why some Brugada disease patients present with VF during febrile episodes. Weis et al located another locus to a ≈15-cM region on chromosome 3p22-25 in a multigenerational family with Brugada syndrome.[12]

Clinical Presentation

Syncope or sudden death is the predominant symptom in patients with Brugada syndrome. Polymorphic ventricular tachycardia (VT) is the underlying cause of these symptoms. Self-termination of VT episodes leads to syncope, whereas degeneration into VF leads to SCD, if untreated.[5] Priori et al in their study of families affected with Brugada syndrome noted that 80% of patients, with documented VF, had a history of (h/o) syncope.[13] SCD in these patients, occurs most commonly during sleep, particularly during early morning hours.[14] The mean age at which symptoms first appear in affected individuals is in the 3rd or 4th decade. However, reports describe the occurrences of symptoms at extremes of age.[15,1] Despite equal genetic transmission of the Brugada syndrome, the clinical phenotype is 8 to 10 times more prevalent in males than females. The basis for this sex related distinction is a more prominent Ito mediated action potential notch, in the RV epicardium of a male, than that of a female.[16,18] In addition, reported in these patients is atrial, atrioventricular reentrant tachycardia,[17] and rare monomorphic VT.

Diagnosis

ECG abnormality constitutes the hallmark of Brugada syndrome. It includes repolarization and depolarization abnormalities in the absence of identifiable structural cardiac abnormalities, or other conditions, or agents that are known to cause ST-segment elevation in the right precordial leads. Three types of repolarization patterns are recognized (Fig. 1). The details of the ECG pattern in all the three types are described in Table 1. These descriptions stem from the correct placement of the precordial leads. To obtain characteristic ECG features, consider the alternative placement of the right precordial leads in a superior intercostal space, or even right-sided chest leads in individuals with high clinical suspicion (aborted SCD, family history of Brugada syndrome). Consider this procedure when conventional ECG fails to disclose the presence of arrhythmic substrate. However the r' deflection in leads V3R-V4R should be interpreted with caution. ECG patterns recorded in the first few hours after the cardiac resuscitation or immediately after DC shock, cannot aid the diagnosis of Brugada syndrome. [19]

When considering the QT interval, it is often within normal limits (in the absence of antiarrhythmic drug therapy), but it may be prolonged. In the initial series described by Brugada & Brugada three out of six males had a QTc >440ms.[1] When considering the PR interval, it is usually increased

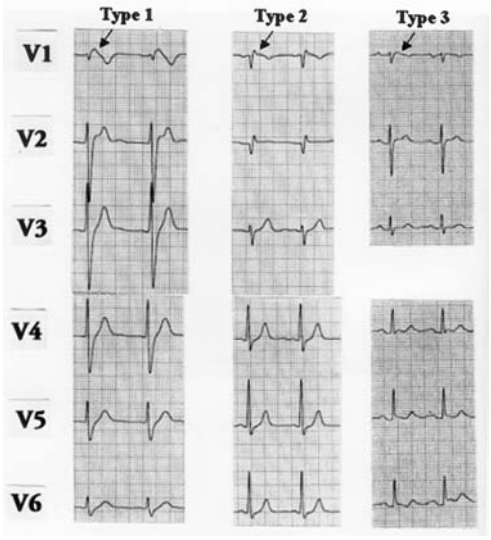

Fig. 1 Brugada syndrome ECG patterns- showing characteristic repolarization Changes in ST segment (arrow) and T wave.

(>200ms) and presumably reflects the presence of His-ventricular (HV) conduction delay. In a recent survey, HV prolongation was found to be present in 20/21 Brugada patients, it was in the range of 65 ms and in some as long as 110 ms.[6] However, Eckardt et al reported a mean HV interval of 49±12 ms in 35 patients and only 6 patients had HV interval over 60 ms.[17] RBBB was described as the diagnostic ECG abnormality in the initial description of Brugada & Brugada. However, some authors stated that many of the published cases do not have a true RBBB.[6,20] Mattu et al found, in their review of published cases, an incomplete RBBB pattern with ST- elevation confined to lead V1-V2.[21]

A signal average electrocardiogram demonstrates late potentials in patients with Brugada syndrome, especially in the anterior wall of the RV outflow tract.[22] Although late potentials are commonly regarded as representative of delayed activation of the myocardium, they are often due to structural defects. Recent studies suggest that in the case of Brugada syndrome, the late and delayed potentials may represent the delayed second upstroke of the epicardial action potential or local phase 2 reentry.[23]

Drug Challenge

Intravenous administration of class I antiarrhythmic drugs may modify the ECG pattern. Ajmaline (1mg/kg body weight, 10 mg/min), flecainide (2mg/kg, maximum 150 mg in 10 min), and procainamide (10mg/kg, maximum 150mg in 10 min) may exaggerate the ST-segment elevation or unmask it when it is initially absent. Sensitivity and specificity (with genetic data as the gold standard) for IV drug challenge are disputed.[24,25] It has been shown that ajmaline is the most potent, followed by flecainide, with procainamide the least likely to uncover the ECG abnormality.[26] Reproducibility of the test has not been established, and a recent study suggests that it's accuracy may be less than 100%.[13] A drug challenge should be done with close monitoring of the patient's 12 lead ECG and blood pressure. A defibrillator and other resuscitative equipment should be at hand. Drug testing is considered positive in the case of a negative base line ECG, a J point elevation of ST-segment amplitude >2 mm in lead V1, and/ or V2, and /or V3, with or without RBBB. Stop drug administration when the test is positive, or when ventricular arrhythmias including ventricular premature contractions appear, or when QRS widening (>30%) is observed. Serious ventricular arrhythmias including VF may occur during the test. Isoproterenol infusion (1-3 ug/ min) might be needed to treat the ventricular arrhythmias.[15] Strict monitoring of the patient should be done until the ECG is normalised in a patient with a positive drug challenge test (plasma half-life of flecainide is 20 hrs, of procainamide is 3-4 hrs, and ajmaline is inactivated

Table 1. Brugada Syndrome-Electrocardiogram Types

Leads V1-V3	Type 1	Type 2	Type 3
ST-T pattern	Coved	Saddleback	Saddleback
Terminal ST- segment	Gradual down slope	Elevated (≥ 1mm)	Elevated (≥ 1mm)
J point*	≥ 2mm	≥ 2mm	≥ 2mm
T wave	Negative	Positive or biphasic	Positive

*J point-Junction point between the end of QRS complex and beginning of the ST-segment. P-Q segment is the baseline reference for J point elevation consideration.

within few minutes).

In patients with type I Brugada ECG, drug testing has no additional diagnostic value. Consider the conversion of a type II or type III ECG to a type I ECG as a positive result. Conversion of type III ECG to type II is considered inconclusive.[19]

Programmed Electrical Stimulation (PES)

PES helps risk stratification and in some cases establishes the diagnosis. In VF survivors, PES may not be of much diagnostic value. Yet, in approximately 50% of cases, ventricular arrhythmias are inducible from the RV outflow tract, so, a protocol using 2 stimulation sites (RV apex and outflow tract) with 3 basic cycle lengths, up to 3 extra stimuli and a minimum coupling interval of 200 ms is recommended. The diagnostic value of repeating PES after a drug challenge with sodium channel blockers is inconclusive.[19] Similarly, the value of RV mapping with monophasic action potentials[27] and epicardial stimulation too, is inconclusive.[28] Still scrutinized is the accuracy of PES in predicting outcome in asymptomatic patients with Brugada ECG, without a positive family h/o SCD. The PES positive predictive value varies from 37% to 50% and negative value varies from 46% to 97%.[13,29]

Differential Diagnosis

Exclude precordial ST-elevation secondary to acute coronary syndrome, electrolyte imbalance, myocarditis, drug over dosage (cocaine, tricyclic antidepressants), before considering the diagnosis of Brugada syndrome.[19]

Exclude Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) , as it may mimic Brugada syndrome.[30] Corrado et al described a subpopulation of ARVC/D patients showing features of Brugada syndrome. They suggested that a subgroup of ARVC/D patients could display a Brugada like phenotype during the relatively early stage of the disease.[31] Presence of morphological changes in the RV/LV with fibrofatty replacement of the myocardium, and a drug challenge with sodium channel blockers may help in the differentiation of ARVC/D from Brugada syndrome. A genetic interpretation also differentiates the two conditions. The Brugada syndrome has been linked only to mutations in SCN5A on chromosome 3, where as, ARVC/D has been linked to seven different chromosomal sites and three putative genes.[32] Early repolarization syndrome with the elevated J wave in both right and left precordial leads helps in distinguishing it from Brugada syndrome, which has J wave elevation only in right precordial leads.[33] Drug challenge helps in the differentiation of male patients with a normal degree of right precordial ST elevation, and those with Brugada syndrome.[19]

Treatment

In spite of significant progress over the last decade in the diagnosis and characterization of the Brugada syndrome, the progress of an effective therapy for Brugada syndrome is minimal. Treatment with an implantable cardioverter-defibrillator (ICD) is the only established, effective treatment for this disease.[34] With ICD therapy, mortality at a 10 year follow-up is 0%.[2]

The pharmacological approach to this condition focuses on rebalancing the currents active in the early phase of the RV epicardial action potential, in order to effectively reduce the magnitude of the action potential notch and restore the action potential dome.[35] Research suggests the use of agents that block the Ito, such as quinidine, tedisamil, or drugs that enhance the calcium channel current (I_{ca}), such as isoproterenol.[9,36] Cilostozol an oral phosphodiasterase III inhibitor, was found to normalize the ST-segment, in this condition, by reducing Ito secondary, increasing in the heart rate, and furthermore by augumenting Ica.[37] The use of beta-adrenergic blocking agents, or amiodarone, or a combination of both, did not present any benefit in patients with Brugada syndrome.[6]

Both quinidine and isoproterenol show effectiveness in normalizing the ST-segment elevation in Brugada syndrome, and in the control of electrical storms, particularly in children.[38,39] Belhassen et al. found quinidine to be useful as a long-term therapy for prevention of SCD in patients with Brugada syndrome.[40] At present, supporting data is inconclusive for advocating long term pharmacological therapy for prevention of SCD in these patients.

Patients with Brugada syndrome, resuscitated from SCD, are at high risk for another episode and should receive an ICD. Family members of patients with Brugada syndrome, should undergo a medical investigation, specifically, screening for signs of Brugada syndrome in an ECG. The recommendation

of ICD therapy to patients with a typical Brugada ECG, and unexplained syncope, or a family history of SCD unrelated to acute coronary syndrome, is a plausible step in the treatment of Brugada syndrome.[41] The development of asymptomatic individuals with a Brugada ECG, no family history of SCD unrelated to acute coronary syndrome, remains a topic of discussion.[6,7,20] A study by Brugada et al found an 8% occurrence of arrhythmic cardiac events, initially, in asymptomatic patients. Asymptomatic patients at higher risk displayed a typical Brugada ECG spontaneously. Furthermore, patients in whom ST-segment elevation appeared after provocation with sodium channel blockers appeared to be at minimal or no risk for arrhythmic events.[42] The Brugada brothers in their most recent publication of Brugada syndrome patients without prior cardiac arrest, noted that the combination of a spontaneous abnormal ECG, a history of syncope and inducible ventricular arrhythmias during PES, constituted higher risk for SCD, with an event rate of 27.2% over two years. Patients considered as low risk (0.5% event rate) have an absence of syncopal episodes, a diagnostic ECG exclusively after a drug challenge, and non-inducibility of ventricular arrhythmias during PES. They advocated ICD therapy for patients with syncope and asymptomatic patients with inducible ventricular arrhythmias during PES.[43]

Studies by Priori et al,[41] Kanda et al,[44] Eckardt et al,[45] failed to find an relationship between inducibility of ventricular arrhythmias during PES and recurrence of VT/VF among patients with Brugada syndrome. The same authors view PES as not beneficial in identifying individuals with Brugada syndrome at high risk of major arrhythmic events. As 60-70% of Brugada patients test positive for inducible ventricular arrhythmias during PES, the advocation of ICD therapy to all such patients results in large number of asymptomatic individuals being administered the device. Before conclusive statements are made on the value of PES in Brugada syndrome, data on a larger number of patients, studied with the same protocol, with a longer follow-up period, is needed.[41]

Haissaguerre et al. reported radiofrequency ablation of the focus of the monomorphic ventricular premature contractions, which were triggers of VF in three patients with Brugada syndrome. At a six to seven month follow-up there was no recurrence of VF.[46] Although this study shows new insight in the treatment of this disease, there is still a need for a more comprehensive study, with longer follow-up period, in order to support this mode of therapy in patients with Brugada syndrome.

A genetic defect on the SCN5A gene not associated with a higher risk of events, suggests that genetic analysis is an important and useful diagnostic parameter yet, not benefitial for risk stratification.[41]

ICD therapy for Brugada disease patients is often not feasible in developing countries, in view of the economic constraints, and not a definite solution for infants and young children with the disease.[35]

The role of pacemaker therapy in Brugada syndrome is largely unexplored. Arrhythmia and SCD generally occur during sleep or at rest, and are commonly associated with bradycardia states, suggesting a potential therapeutic role for pacing. The development of a cardio-selective and I_{to} specific blocker would be a welcome addition to the limited therapeutic treatments currently available to combat this disease.[47]

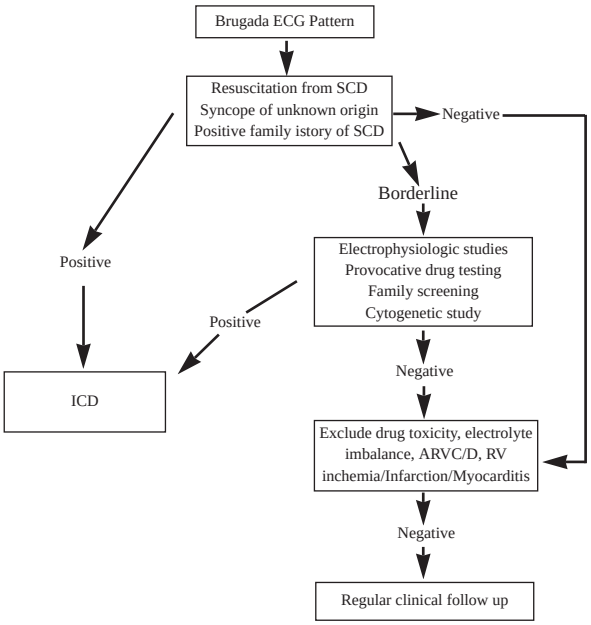

Fig. 2 Management algorithm suggested for the patients with Brugada ECG pattern. ICD: implantable cardioverter-defibrillator; SCD: sudden cardiac death; ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia; RV: right ventricle.

Based on available data, shown in Figure 2 is the management algorithm for patients with Brugada syndrome.

Conclusion

The Brugada syndrome's simple description in early 90s has become the subject of intense investigation to clinicians, molecular biologists, and electrophysiologists. Little doubt exists that advances in the further unraveling of the molecular mechanisms in this syndrome will occur in the near future. As a result, the advances, will contribute to invaluable solutions to many controversial issues that arise in the management of patients, especially, asymptomatic patients with a positive Brugada ECG.

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Brugada Syndrome：最新整理及回顧

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Brugada syndrome 的診斷有三個特殊的要件，首先爲心電圖有右側束枝傳導障礙，其次爲V1-V3導程有ST節段上升的現象，第三則爲心因性猝死。Brugada syndrome 的病人大約有50％有家族病史，顯示基因的問題在這個疾病的成因中佔有一定角色。已知人類染色體3p21位址上負責心肌細胞鈉離子通道的 SCN5A 基因若是產生突變會造成 Brugada syndrome。在診斷 Brugada syndrome 之前，其他會引起心電圖胸前導程ST節段上升的狀況，例如：急性冠心症、電解質失衡、心肌炎、藥物過量（古柯鹼、三環抗鬱劑）、心律不整性右心室心肌病變等，必須先加以評估並排除。靜脈注射 ajmaline、flecainide 以及 procainamide 會加強ST節段的上升，對於臨床上懷疑是 Brugada syndrome，但是一開始心電圖沒有明顯ST節段上升的病患，有診斷上的價值。電生理學檢查對於風險分級有幫助，在某些病例上亦有助於建立診斷。但是，電生理學檢查對於沒有家族心因性猝死病史，但是心電圖呈現 Brugada syndrome 變化，無臨床症狀的病人，作爲預測後果的工具，其準確性仍有爭議。裝置體內自動去顫器是目前已知唯一有效防止心因性猝死的治療方式，可將十年的死亡率降到0％。現階段，並無足夠資料證實利用 quinidine 或 isoproterenol 等藥物治療方式可以有效預防心因性猝死的發生。希望在不久的將來，隨著對 Brugada syndrome 致病機轉的進一步瞭解，對於此疾病處理上一些仍有爭議的議題，能得到完全的解答。(長庚醫誌 2005;28:69-76)

關鍵字：心因性猝死，Brugada syndrome，體內自動去顫器，電生理學檢查，心電圖。

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