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Ngai-Shing Mok

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# Brugada Syndrome: A Newly Recognized Sudden Death Syndrome in Hong Kong

NGAI-SHING MOK

From Cardiology Team, Department of Medicine & Geriatrics, Princess Margaret Hospital, Hong Kong

**MOK: Brugada Syndrome: A Newly Recognized Sudden Death Syndrome in Hong Kong.** Since Brugada syndrome was first described in 1991, it has been recognized world-wide as an important cause of sudden cardiac death. The past decade witnessed a large body of medical literature that has shed light on the epidemiology and pathophysiology of this peculiar syndrome. In Hong Kong this syndrome was first reported in April 1999. Since then it has been increasingly identified among local Chinese patients as a cause of sudden arrhythmic death and unexplained syncope or seizure. Local study on the clinical and genetic aspects of Brugada syndrome is underway. This article reviews our current understanding of the Brugada syndrome and the clinical profile of local Chinese patients suffering from this syndrome. (*J HK Coll Cardiol* 2001;9:144-148)

*Brugada syndrome, idiopathic ventricular fibrillation, ST-segment elevation, sudden death*

## 摘要

自1991年Brugada綜合徵最先被提出後，它被認為是世界性的導致猝死的重要原因。在過去的十年裏，大量醫學文獻從流行病學和病理生理學角度闡明了這種奇特的綜合徵。在香港，這種綜合徵首先被報道是在1999年4月。此後越來越多的發現在本港的中國患者中，它是導致猝死和不能解釋的暈厥或癲癇的原因。本地關於Brugada綜合徵臨床和基因方面的研究正在進行中。該篇文章討論了目前我們對Brugada綜合徵的理解和患有該綜合徵的中國患者的臨床情況。

關鍵詞：Brugada綜合徵 特發性室性心律失常 ST段擡高 猝死

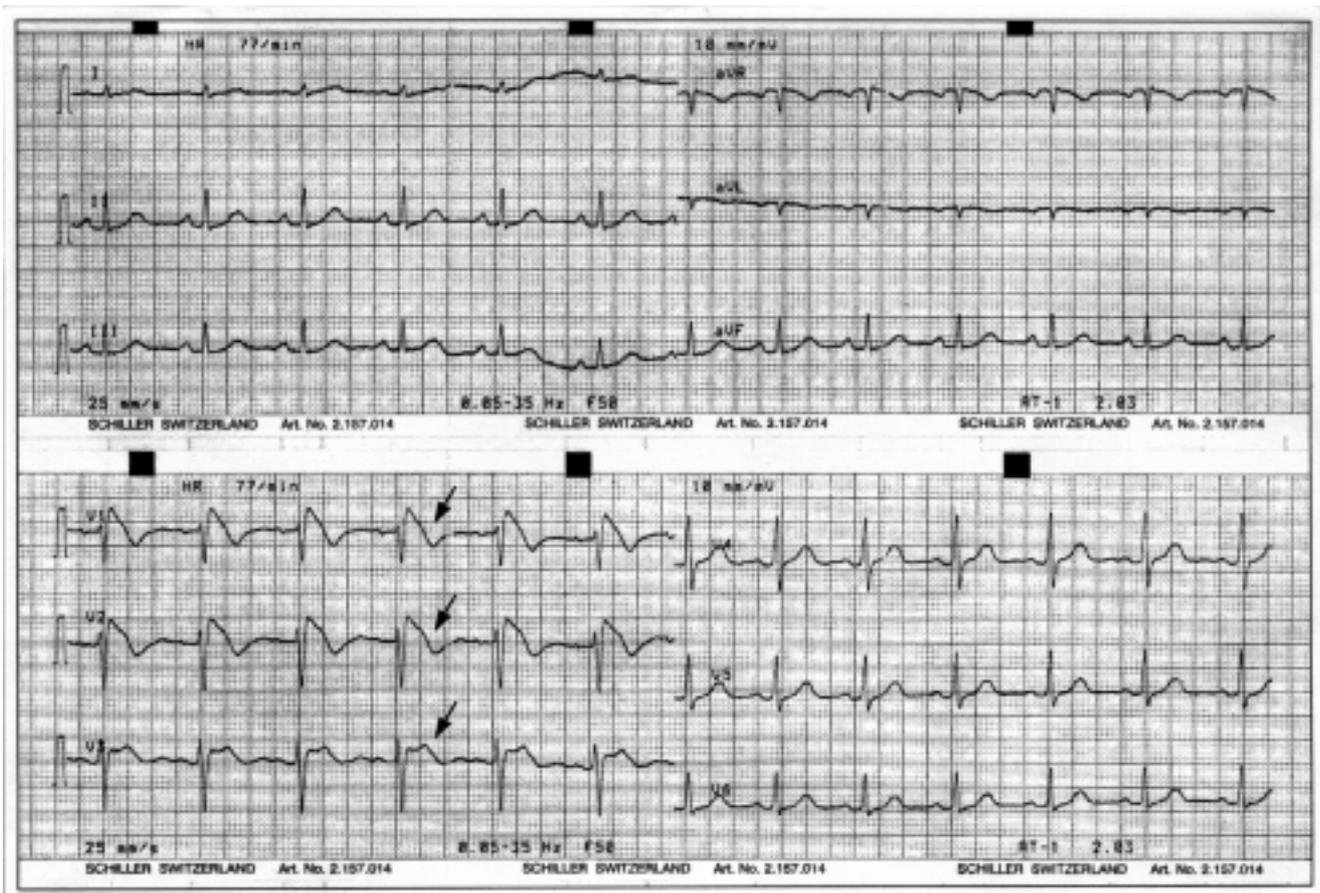
Idiopathic ventricular fibrillation (VF) has been reported to account for 3-9% of all sudden arrhythmic deaths.<sup>1</sup> In 1991, Pedro and Josep Brugada first described a specific form of idiopathic VF which is now known as the Brugada syndrome.<sup>2</sup> It is a primary electrical disease characterized by a marked ST segment elevation in leads V<sub>1</sub>-V<sub>3</sub> on electrocardiogram (ECG) during sinus rhythm with or without right bundle branch block (Figure 1) and a propensity for life-threatening ventricular tachyarrhythmias in the absence of any structural heart disease. Recognizing the Brugada ECG pattern is easy when the characteristic coved type or less commonly

saddle-back type ST segment elevation is present. However, dynamic changes or transient normalization of the ST segment may obscure the correct diagnosis. Shimizu et al.<sup>3</sup> recently demonstrated that recognition of the Brugada ECG pattern may be facilitated by placing electrodes for leads V<sub>1</sub>-V<sub>2</sub> in the 2nd and 3rd intercostal spaces (ICS) in addition to the conventional 4th ICS. Sodium channel blockers including flecainide, procainamide and ajmaline were shown to be effective in unmasking the syndrome in affected subjects who had normal baseline ECG.<sup>4</sup> Whenever a typical Brugada ECG pattern is identified, any underlying structural heart disease should be ruled out by imaging techniques, cardiac catheterization and/or endomyocardial biopsy before the diagnosis of Brugada syndrome can be established. Patients with Brugada syndrome may present with syncope, convulsion or sudden cardiac death. However, they may be totally asymptomatic with their Brugada ECG pattern only discovered incidentally

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Address for reprints: Dr. Ngai-Shing Mok  
Department of Medicine & Geriatrics, Princess Margaret Hospital,  
2-10 Princess Margaret Hospital Road, Kowloon, Hong Kong  
Tel: (852) 2990 1111, Fax: (852) 2990 3329

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**Figure 1.** 12-lead surface electrocardiogram in a patient with Brugada syndrome demonstrating the typical RBBB pattern and down-sloping coved type ST-segment elevation in leads  $V_1$ - $V_3$  (arrows) followed by inverted T waves.

or found during family screening for Brugada syndrome. Although Brugada syndrome is mainly found in adults with a male predominance, children are not immune.<sup>5</sup> In fact this syndrome may account for the death of some victims of the sudden infant death syndrome.

In the past decade, results of numerous clinical and basic scientific research studies on this peculiar syndrome have gradually unraveled its mystery. It is now known that this syndrome is genetically determined with an autosomal dominant pattern of transmission. Genetic data has linked this syndrome to mutations in cardiac sodium channel gene *SCN5A* in chromosome 3.<sup>6</sup> The ionic basis and arrhythmia mechanisms in Brugada syndrome have been elegantly described by Antzelevitch.<sup>7</sup> It is the loss of action potential dome in right ventricular epicardium but not endocardium which underlies the ST segment elevation in this syndrome. Sodium channel blockers by enhancing the loss of action

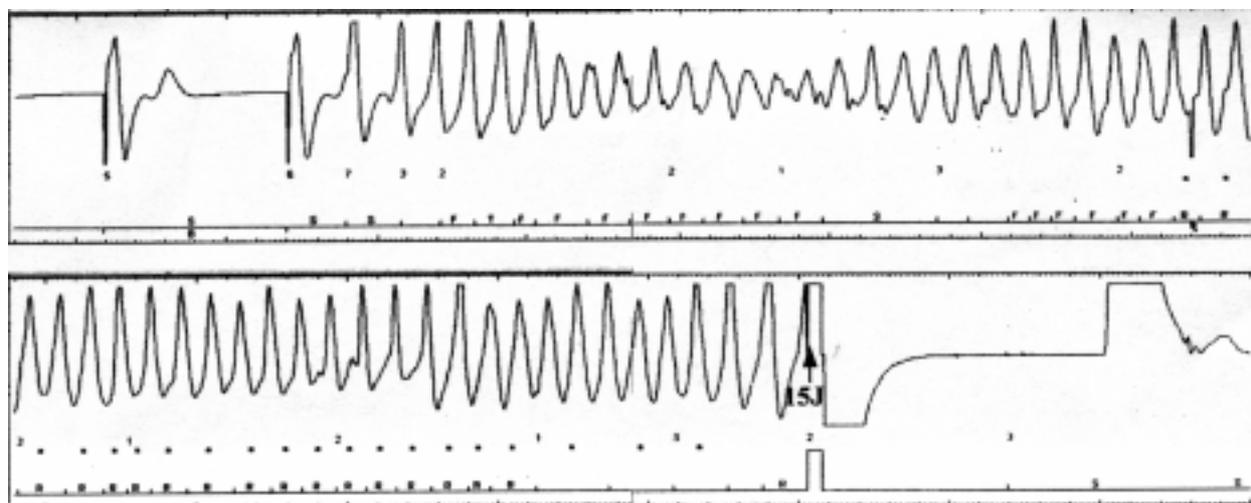
potential dome can augment or unmask the ST segment elevation in affected subjects. The electrical heterogeneity across the wall of the right ventricular outflow tract provides a substrate for phase 2 reentry between endocardial and epicardial layers that leads to polymorphic ventricular tachycardia (VT) or VF and sudden cardiac death.

Prognosis is poor for symptomatic patients with this syndrome. Brugada et al.<sup>8</sup> reported a 60% recurrence of arrhythmic events among symptomatic patients over a 4-year follow-up. However, the prognosis for asymptomatic subjects is uncertain. Latest data from Brugada et al.<sup>8</sup> showed an 8% event rate in asymptomatic patients in the 3 years after recognition of the abnormal ECG. On the contrary, other groups from Italy and Japan reported no clinical events among their asymptomatic patients over a mean follow-up period of 15-42.5 months.<sup>9-11</sup> To date, implantable cardioverter-defibrillator

(ICD) is the only effective intervention for preventing sudden death in symptomatic patients with Brugada syndrome while anti-arrhythmic drugs including amiodarone and beta-blockers were found not useful.<sup>12</sup> Use of quinidine at a dose that can render previously inducible polymorphic VT or VF non-inducible in electrophysiology study was shown to be useful in a retrospective study by Belhassen et al.<sup>13</sup> to prevent VF recurrence in patients with idiopathic VF or Brugada syndrome. However, as data from prospective randomized trials are lacking, routine use of quinidine in the treatment of Brugada syndrome is therefore not recommended. As for the optimal management of those patients who are asymptomatic, there is as yet no consensus. While Brugada et al.<sup>14</sup> advocated the prophylactic implantation of an ICD in asymptomatic patients who have a history of familial sudden death or are inducible into polymorphic VT or VF by means of programmed ventricular stimulation, Priori et al.<sup>10</sup> favoured a more conservative use of ICDs and a more accurate monitoring of asymptomatic individuals using insertable loop recorders in light of their own findings that these patients are at a much lower risk for sudden death than previously described.

Brugada syndrome appeared to be ubiquitous but it was only rarely reported in Chinese patients. The first three cases of Brugada syndrome in Chinese were reported by Teo et al. in 1998.<sup>15</sup> Although Brugada syndrome was first described in 1991, it was not until

April 1999 when the first two local Chinese patients with Brugada syndrome were reported in medical literature.<sup>16,17</sup> The first patient was a 52-year-old male who presented with recurrent nocturnal seizures. Holter monitoring recorded a self-terminating VF which lasted 2.5 minutes and was accompanied by seizure and loss of consciousness. The second patient was a 29-year-old male who survived a sudden cardiac death due to VF. Both patients received ICD implants and experienced appropriate shocks for polymorphic VT or VF during the follow-up period (Figure 2). Naturally one would ask why it took 8 years before Brugada syndrome could be identified for the first time in Hong Kong. Is it because Brugada syndrome is rare among Hong Kong Chinese or was it just underdiagnosed in the past? To answer this question, we initiated a local multicentre prospective study on Brugada syndrome in September 1999 on behalf of the Hong Kong Interhospital Network of Pacing and Cardiac Electrophysiology (HK-IN-PACE). Patients with Brugada ECG pattern were enrolled and their clinical characteristics studied. Genetic study in collaboration with Professor SG Priori in Italy was also performed in our patients to look for any mutation in the cardiac sodium channel gene SCN5A in chromosome 3. An interim report of the study was presented in the Hong Kong College of Cardiology 9th Annual Scientific Congress.<sup>18</sup> As of January 2001, a total of 40 patients were enrolled into the study from 5 regional hospitals. Seventeen patients were symptomatic and 23

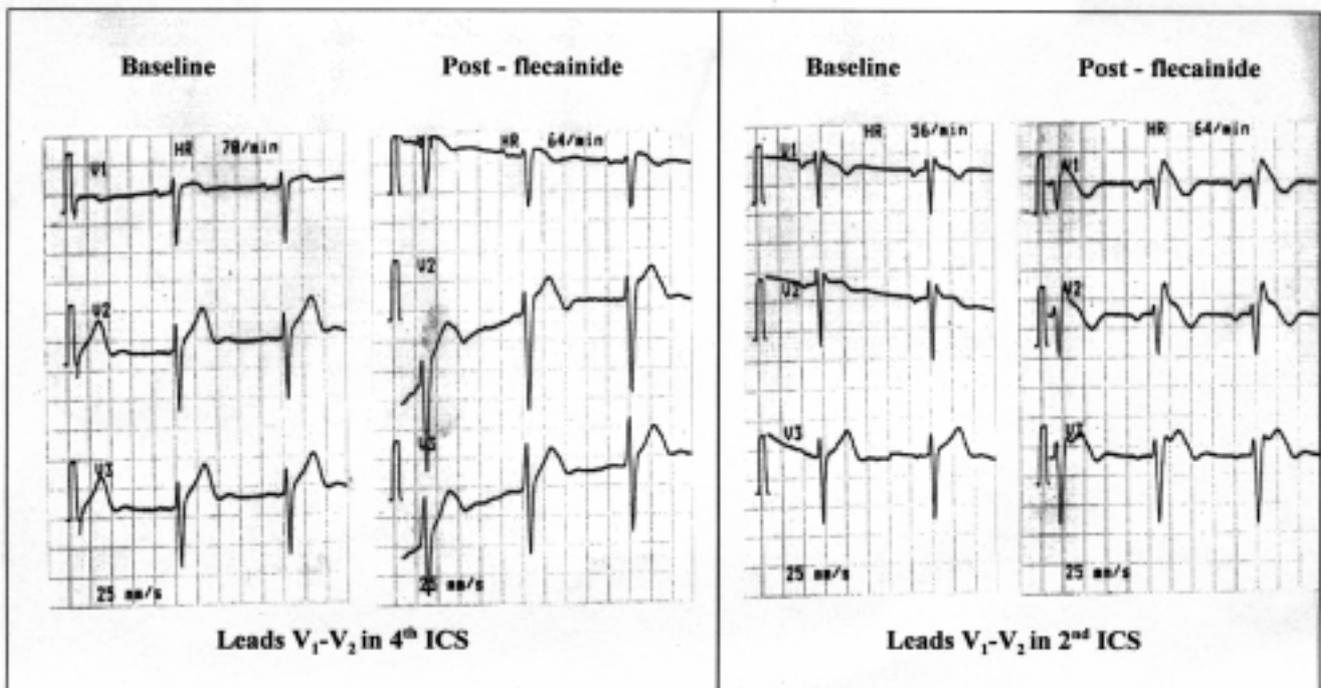


**Figure 2.** Stored electrocardiogram in ICD (continuous strip) implanted in a symptomatic patient with Brugada syndrome showing an episode of polymorphic VT correctly detected and successfully cardioverted by an electric shock of 15 Joules (arrow) delivered by the ICD.

asymptomatic prior to their enrollment. All symptomatic patients had a history of syncope and 5 of them had survived sudden cardiac death. Of the 23 patients who were genotyped, 5 (22%) of them were found to have mutation in their SCN5A gene (unpublished data). Seven symptomatic patients received ICD implants while 5 were put on antiarrhythmic agents. On the contrary only 1 asymptomatic patient received treatment with ICD. Notably, 1 symptomatic patient presented in 1989 at the age of 44 with sudden VF arrest but was misdiagnosed as acute myocardial infarction. His ECG during sinus rhythm showed ST segment elevation in leads  $V_1$ - $V_3$  which could be augmented after flecainide provocation. Subsequent work-up ruled out structurally heart disease and symptomatic Brugada syndrome presenting with VF was diagnosed in retrospect in that patient. Thus Brugada syndrome could be found in Hong Kong in as early as 1989, even before this syndrome was first described in literature.

In one quarter of our enrolled patients, the Brugada ECG pattern was not visible on routine 12-lead ECG but could be uncovered by flecainide provocation test (FPT). Recently we reported our experience in

Princess Margaret Hospital in using FPT to unmask Brugada syndrome in Chinese patients with a concealed form of the syndrome.<sup>19</sup> During FPT, flecainide at a dosage of 2 mg/kg not exceeding 150 mg was given intravenously over 10 minutes under continuous cardiac monitoring. A positive test was defined as occurrence of terminal R wave and  $>1$  mm ST segment elevation in leads  $V_1$ - $V_3$  after flecainide infusion. From February 1999 to December 2000, a total of 26 subjects with normal baseline ECG have undergone FPT. None had structural heart disease. Thirteen of these 26 subjects had a positive FPT (M:F 11:2, mean age  $45 \pm 16$  years). Among these 13 subjects, 5 were family members of patients with known Brugada syndrome and 3 were previously labeled as suffering from syncope of unknown origin. In 4 subjects, the FPT was positive only when leads  $V_1$ - $V_2$  were recorded in 2nd and 3rd ICS at the level of right ventricular outflow tract instead of the conventional 4th ICS. (Figure 3). Among those with positive FPT, the maximum rise in ST segment was seen in lead  $V_2$  ( $1.7 \pm 0.9$  mm in  $V_1$ ,  $2.5 \pm 1.1$  mm in  $V_2$  &  $1.5 \pm 0.8$  mm in  $V_3$ ). During FPT, only 3 subjects experienced transient nausea and dizziness that did not



**Figure 3.** Results of flecainide provocation test in a patient with unexplained syncope. No significant rise in ST-segment during flecainide infusion when leads  $V_1$ - $V_2$  was recorded in the 4th ICS (left panel). Typical Brugada ECG pattern was unmasked by flecainide when leads  $V_1$ - $V_2$  was recorded in 2nd ICS (right panel).

require treatment and transient unifocal ventricular ectopic beats were found in 3 subjects who had a positive FPT. No VF or significant bradyarrhythmia was documented in any of the subjects during the test.

In conclusion, Brugada syndrome is newly recognized in Hong Kong as a cause of sudden cardiac death. Local data suggested that this syndrome is not rare but grossly underdiagnosed in the past in Hong Kong. A history of unexplained syncope, seizure or cardiac arrest in young healthy adults should raise the suspicion of this peculiar syndrome, particularly when patients have a family history of sudden death. Recognition of the typical ECG pattern and judicious use of FPT in clinically suspicious patients should help in improving the diagnostic yield in our local patients. Appropriate management of these patients will improve their prognosis. Local experience in using FPT to unmask the Brugada ECG pattern in patients with concealed form of the syndrome was consistent with the overseas experience that this test, when used appropriately, is both useful and safe. Electrodes for recording leads  $V_1$ - $V_2$  should be positioned in 2nd and 3rd ICS in addition to 4th ICS during FPT to improve its sensitivity in identifying patients with Brugada syndrome.

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