

# BRUGADA SYNDROME WITHOUT MUTATION OF THE CARDIAC SODIUM CHANNEL GENE IN A TAIWANESE PATIENT

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**Abstract:** We describe a 45-year-old Taiwanese man with specific features of Brugada syndrome but no clinical features of structural heart disease. He was successfully treated with an implantable cardioverter-defibrillator. His electrocardiogram (ECG) patterns changed intermittently. Alpha-adrenoceptor stimulation and beta-adrenoceptor blockade augmented the characteristic ST-segment elevation, whereas alpha-adrenoceptor blockade and beta-adrenoceptor stimulation mitigated the ST-segment elevation. Intravenous procainamide administration did not aggravate ST-segment elevation when ECG had shown coved ST elevation in the right precordial leads. Molecular study did not reveal the same mutations in the cardiac sodium channel gene (*SCN5A*) as previously reported in Brugada syndrome. This case demonstrates the genetic heterogeneity of *SCN5A* in Brugada syndrome.

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**Key words:**  
sudden cardiac death  
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In 1992, Brugada and Brugada described eight cases of aborted sudden cardiac death without demonstrated structural heart disease but with a peculiar electrocardiogram (ECG) pattern consisting of right bundle branch block and ST-segment elevation in leads V1 to V3 [1]. The autonomic nervous system may play a role in the induction of ventricular fibrillation (VF) in Brugada syndrome. Recently, molecular genetic study has revealed that missense or frameshift mutations in the cardiac sodium channel gene (*SCN5A*) contribute to the risk of developing VF [2]. This syndrome occurs mainly in males of Asian origin. Herein, we report a case of Brugada syndrome in a Taiwanese patient who showed the unusual characteristics of selective stimulation and blockade by alpha- and beta-adrenergic receptors. Studies of *SCN5A* did not show the same mutation as previously reported.

## Case Report

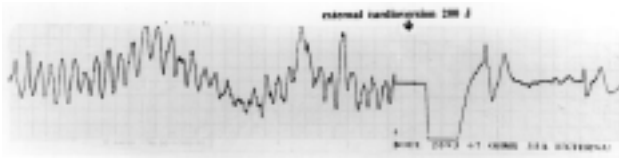
This 45-year-old man had been asymptomatic before suffering from syncope episodes in the early morning (3 AM) of 10

June 1997. He was brought to the emergency room, where ECG showed VF. Direct current defibrillation was given a total of eight times to convert the VF to sinus rhythm (Fig. 1). There was no family history of sudden cardiac death or ventricular tachyarrhythmias. No abnormalities were identified on physical examination, blood chemistry analyses, chest autoradiography, or echocardiogram. The ECG showed sinus rhythm, normal P wave and PR interval, and complete right bundle branch block with ST-segment elevation in leads V1 to V3 (Fig. 2A). The QRS interval, QT interval, and corrected QT interval (QTc) were 0.12, 0.44, and 0.43 seconds, respectively.

The right bundle branch block pattern and the peculiar ST-segment elevation in the anteroseptal leads changed during the 10 days of hospitalization and the following 1.5 years (Fig. 2B). Coronary angiography revealed normal coronary arteries. A sustained polymorphic VT (ventricular tachycardia)/VF was reproducibly initiated with triple ventricular extra-stimuli (V4) from the outflow tract of the right ventricle and was terminated with 200 J direct current shocks.

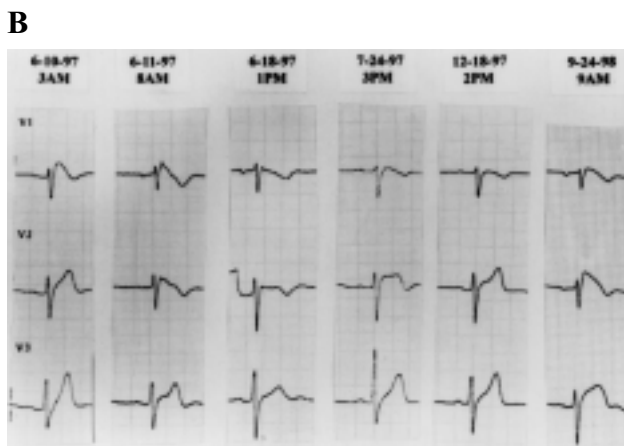
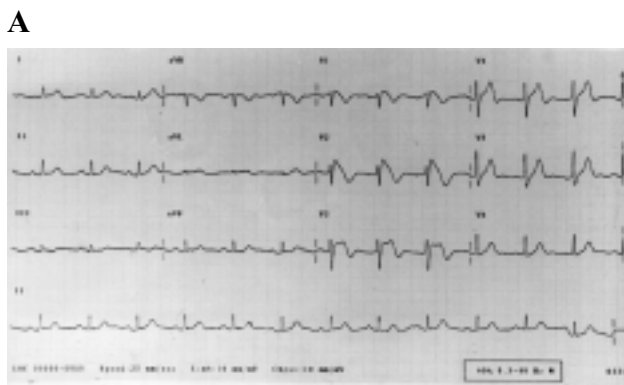
An autonomic test was performed at the bedside to determine the effects of autonomic receptor stimulation and blockade on the ST segment. Twelve-lead ECG showed that intravenous procainamide (450 mg) had no obvious effect on the ST segment during sinus rhythm (Fig. 3A). Beta-

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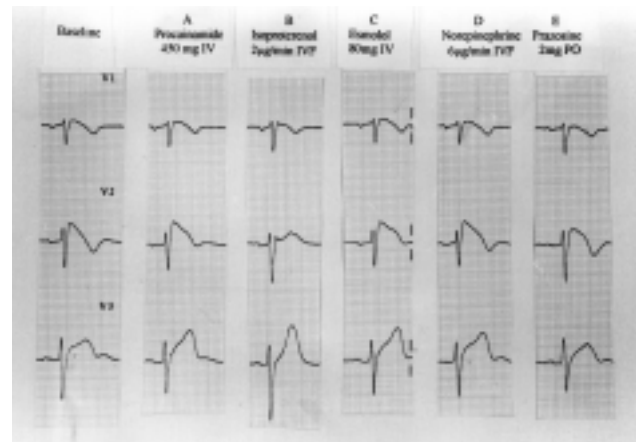


**Fig. 1.** Electrocardiogram on admission to the emergency room. The patient was unconscious and the electrocardiogram showed ventricular fibrillation. External cardioversion at 200 J converted this to a sinus rhythm.

adrenoceptor stimulation by intravenous isoproterenol at a dose of 2 µg/min consistently decreased ST-segment elevation by at least 0.1 mV at 80 ms after the J point (Fig. 3B). Beta-receptor blockade with intravenous esmolol at a dose of 1 mg/kg body weight (80 mg) for 30 seconds increased ST-segment elevation (Fig. 3C). In contrast, selective alpha-adrenoceptor stimulation with intravenous norepinephrine at an infusion rate of 6 µg/min increased ST-segment elevation (Fig. 3D). Alpha blockade with oral prazosin (2 mg) decreased ST-segment elevation (Fig. 3E).



**Fig. 2.** A) On admission, the electrocardiogram showed complete right bundle branch block and coved AT-segment elevation in V1-2. The QT and QTc intervals were 0.44 and 0.43 seconds, respectively. B) The right bundle branch block pattern and peculiar ST-segment elevation in the anteroseptal leads changed occasionally.



**Fig. 3.** Procainamide and autonomic test.

An implantable cardioverter-defibrillator (ICD) was implanted on 18 June 1997. The patient was discharged without receiving any medication. On 29 July 1998, he experienced two recurrent episodes of sustained VF at night (1:30 AM and 4:30 AM, respectively), which were appropriately detected and converted to sinus rhythm by the ICD.

Molecular studies of *SCN5A* using the polymerase chain reaction (PCR) and direct DNA sequencing were performed according to the methods described by Chen et al [2]. We focused on the mutations in exons 21, 23, and 28. The sequencing results did not reveal any of the missense or frameshift mutations in *SCN5A* reported by Chen et al.

## Discussion

There have been only a few reports of Brugada syndrome in the Chinese population. Most patients with Brugada syndrome are males of Asian origin and the peak age of onset is the late 40s [3]. Matsuo et al reviewed the dynamic changes of 12-lead ECGs in a patient with Brugada syndrome [4]. They found a progressive elevation of both the ST segments and J points just preceding and following the VF. Miyazaki et al evaluated the autonomic and antiarrhythmic drug modulation of ST-segment elevation in patients with Brugada syndrome [5]. They found that ST-segment elevation in Brugada syndrome was augmented by selective stimulation of alpha-adrenoceptors or muscarinic receptors or by class IA drugs, but was mitigated by beta-adrenoceptor stimulation or alpha-adrenoceptor blockade. We evaluated our patient with selective stimulation and blockade of alpha- and beta-adrenoceptors, which further confirmed the findings of previous reports. Intravenous procainamide administration did

not aggravate ST-segment elevation when the patient's ECG had shown coved ST elevation in the right precordial leads at baseline [6]. These autonomic nervous system responses might be explained by postulating the presence of an area of early repolarization or a local depolarized area in the ventricle causing ST-segment elevation in this syndrome.

Arrhythmogenic right ventricular dysplasia (ARVD) is a predominant disorder of the right ventricle (RV) characterized by progressive replacement of the myocardium by fibroadipose tissue and arrhythmic manifestation. ARVD can present as Brugada syndrome [7]. In our patient, although echocardiography and RV angiography showed no abnormalities of the RV, ARVD cannot be completely ruled out since magnetic resonance imaging and ultrafast computed tomography scan and RV biopsy were not performed.

DNA sequence analysis has revealed two C-to-A base substitutions, one in exon 21 and the other in exon 28, which lead to the substitution of arginine by tryptophan at codon 1232 (R1232W) and of threonine by methionine at codon 1620 (T1620M) [2]. These mutations lead to more rapid recovery of sodium channel current after inactivation than with the unmutated gene, as demonstrated by heterologous expression in *Xenopus* oocytes. Another mutation at codon 1397 (exon 23), a single nucleotide (A) deletion, results in a frameshift mutation that causes the sodium channel to be non-functional [2]. We could not demonstrate these mutations in our patient by PCR DNA sequencing.

Brugada syndrome is a treatable disease and can be diagnosed on the basis of clinical and ECG manifestations. The autonomic nervous system and genetic factors (cardiac ionic-channel genes, *SCN5A* mutation)

have been suggested to play a role in this syndrome [2]. An ICD is the treatment of choice at present. Although the incidence of Brugada syndrome in the Chinese population remains unclear, the results of molecular analysis in the present case demonstrate the genetic heterogeneity of *SCN5A* in Brugada syndrome in Taiwanese.

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