

# Quinidine for Brugada syndrome: Panacea or poison?

Jo-Jo Hai, MBBS,\* Chun-Ka Wong, MBBS,\* Pak-Hei Chan, MBBS,\* Hung-Fat Tse, MD, PhD,\* Tak-Cheung Yung, MBBS,<sup>†</sup> Chung-Wah Siu, MD<sup>†</sup>

From the \*Division of Cardiology, Department of Medicine, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Hong Kong, and <sup>†</sup>Department of Pediatric and Adolescent Medicine, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Hong Kong.

## Introduction

Brugada syndrome is associated with sudden cardiac death in young patients. Currently guidelines recommend the use of implantable cardioverter-defibrillator (ICD) in high-risk patients to prevent sudden cardiac death and adjunctive therapy with quinidine in those who have recurrent ventricular tachyarrhythmias to prevent electrical storm.<sup>1,2</sup> Nevertheless, not all patients respond to quinidine, and management of those who do not respond to the therapy is frequently challenging. In this report, we presented the management of a difficult case of Brugada syndrome with recurrent ventricular tachyarrhythmias that did not respond to quinidine therapy.

## Case report

A 41-year-old man with a diagnosis of Brugada syndrome and an ICD was admitted for frequent appropriate shocks. He had first been admitted 9 years ago with unprovoked syncope. At that time, standard 12-lead electrocardiogram (ECG) showed sinus rhythm, partial right bundle branch block with coved-type ST-segment elevation, and negative T-wave deflections in leads V<sub>1</sub> and V<sub>2</sub>, compatible with type I Brugada pattern (Figure 1A). Echocardiography, coronary angiogram, and magnetic resonance imaging of the brain were unremarkable. There was no family history of unexplained sudden death. In view of a spontaneous type I Brugada ECG and unprovoked syncope, an ICD was implanted. Two weeks after discharge, the patient received 2 appropriate ICD shocks (Figure 1B). Quinidine bisulfate 500 mg twice daily was therefore initiated. Despite medical therapy, he subsequently had 2–3 appropriate ICD shocks per year. Two months ago, quinidine was stopped owing to abnormal liver function test. This was complicated by an

increase in ICD shocks to more than 3 times per week, leading to the current admission.

On admission, he was found to have frequent premature ventricular complexes (PVCs) of right ventricular outflow tract origin (Figure 1C). Frequent runs of torsades de pointes initiated by a long–short sequence secondary to ventricular bigeminy were also documented (Figure 1D). He was treated with intravenous isoproterenol infusion and high-rate atrial pacing that suppressed the arrhythmia. Careful review of his initial 12-lead ECG 9 years ago revealed that in addition to the type I Brugada pattern, there was a prolonged corrected QT (QTc) interval of 493 msec with late peaking of T wave (Figure 1A), suggestive of a mixed Brugada and long QT phenotype. Subsequent genetic analysis revealed 2 previously reported missense mutations in the SCN5A, the gene encoding Na<sub>v</sub>1.5, the  $\alpha$ -subunit of the cardiac sodium channel (Figure 2A–C). The first mutation was identified in exon 20, which was a substitution of arginine by glutamine at codon 1192 (R1192Q) previously reported in patients with Brugada syndrome (Figure 2A) and long QT syndrome (LQTS).<sup>3,4</sup> The second mutation was identified in exon 28, which was a substitution of glutamic acid by lysine at codon 1784 (E1784K)<sup>5</sup> previously reported to be associated with the Brugada and long QT overlap syndrome (Figure 2B). Genetic analysis of the SCN5A gene of the patient's son and daughter showed that one carried the R1192Q mutation and the other carried the E1784K mutation. Both of them were found to have prolonged QTc but no Brugada phenotype on resting ECG.

Although the resting ECG exhibited features of both Brugada and LQTS, the clinical ventricular tachyarrhythmia was typical of LQTS with torsades de pointes initiated by a long–short sequence. Based on his genetic testing result and clinical manifestation, a therapeutic trial of mexiletine, a class Ib antiarrhythmic drug that blocks the late sodium current, was attempted.<sup>1</sup> The effects of mexiletine on the QTc interval were assessed at an identical atrial paced rate of 70 beats per minute and confirmed a shortening of QTc from 480 msec to 438 msec (Figure 3A). After the patient started mexiletine, torsades de pointes were completely abolished and the patient was discharged from the hospital.

**KEYWORDS** Brugada syndrome; Long QT syndrome; Genetic analysis; Quinidine; Mexiletine

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Drs Hai and Wong contributed equally to this work. **Address reprint requests and correspondence:** Dr Chung Wah Siu, Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China. E-mail address: cwdsiu@hku.hk.

**KEY TEACHING POINTS**

- Brugada and long QT overlap syndrome is a special entity with clinical and electrophysiological features of both conditions.
- Prolonged corrected QT is difficult to be appreciated in patients with type I Brugada electrocardiogram.
- Genetic analysis in patients with inherited arrhythmias helps confirm the diagnosis and guide medical decision.

During subsequent follow-up at 1 month, our patient had no further ICD shocks but persistent frequent PVCs. To prevent recurrence of ventricular tachyarrhythmias in the future, we elected to ablate the triggering PVC. After ablation of the clinical PVC at the anterior right ventricular outflow tract, a second PVC emerged and was ablated at the subpulmonary valvular region. This was followed by the emergence of a third PVC that originated from the anterior right ventricular Purkinje network. After ablation of the third PVC, no more new PVCs were seen (Figure 3B). The patient was discharged with mexiletine 150 mg twice daily and remained free from ICD shocks for 2 years.

**Discussion**

We present a challenging case of Brugada and long QT overlap syndrome that resulted from a compound heterozygosity of R1192Q and E1784K mutations. Despite implantation of an ICD to prevent sudden cardiac death, the frequent ICD shocks significantly impaired the quality of life of our patient, necessitating adjunctive therapy to reduce the burden of ventricular tachyarrhythmias.

To date, more than 100 mutations within the *SCN5A* gene have been identified to be responsible for Brugada syndrome. Based on the results of a canine wedge preparation experiment, Yan and Antzelevitch<sup>6</sup> proposed that the ventricular tachyarrhythmia in Brugada syndrome was the result of a phase 2 reentry secondary to reduced inward sodium current ( $I_{Na}$ ), due to loss-of-function *SCN5A* mutations, and subsequent unopposed transient outward current ( $I_{to}$ ), particularly at the right ventricular outflow tract. Later, electrophysiological evidence supported a conduction abnormality as the culprit of the disease pathogenesis. Despite ongoing debate about the pathogenetic mechanism of Brugada syndrome,<sup>7</sup> quinidine, a class Ia antiarrhythmic drug with prominent  $I_{to}$  blocking property, has been demonstrated in an

observational cohort to reduce inducibility of ventricular fibrillation and suppress spontaneous ventricular tachyarrhythmias in affected patients.<sup>8</sup> Indeed, quinidine has been recommended as a class IIa therapy in the latest guideline for patients with Brugada syndrome who refuse ICD, who are contraindicated for ICD, or who have electrical storms.<sup>1,2</sup> Nonetheless, this drug appeared to be suboptimal in preventing ventricular tachyarrhythmias in our patient. In our case, although the age of diagnosis and the resting ECG features were suggestive of Brugada syndrome, the hallmark long-short initiating sequence leading to torsades de pointes was typical of that of LQTS. Genetic analysis found 2 interesting mutations in our patient. The first mutation, R1192Q, has been shown to destabilize inactivation of the sodium current but have no effects on steady-state activation.<sup>3,4</sup> The second mutation, E1784K, has been reported to cause concomitant reduction in the peak sodium current (loss-of-function) and persistent (late) inward sodium current (gain-of-function).<sup>5</sup> Genetic testing of his children confirmed that he was a compound heterozygote in Trans. In patients with such mutations, the  $I_K$ -blocking property of quinidine may prolong their QTc interval and precipitate ventricular tachyarrhythmias. In a stark contrast, mexiletine, which blocks the late sodium current, has been shown to effectively shorten the QTc interval and reduce life-threatening ventricular tachyarrhythmias in patients with gain-of-function mutations in the *SCN5A*. In our case, the use of mexiletine, as guided by his typical manifestation of LQTS and genetic testing result, effectively shortened his QTc interval and completely abolished torsades de pointes.<sup>9</sup>

Despite temporary suppression of recurrent ICD shocks, the persistent frequent PVCs may serve as a trigger for recurrent ventricular tachyarrhythmias at times of inadvertent QTc prolongation in the future. As a result, we elected to perform radiofrequency ablation for our patient. During the procedure, consecutive PVCs originating from the right ventricular outflow tract continued to emerge until ablation was performed at the anterior right ventricular Purkinje network. This is consistent with the findings of the original paper on ventricular fibrillation ablation by Haissaguerre et al,<sup>10</sup> who showed that PVCs originating from the right ventricular outflow tract and right ventricular Purkinje network trigger ventricular fibrillation in some patients with Brugada syndrome. It is possible that frequent PVCs associated with Brugada syndrome serve as a trigger of torsades de pointes in the setting of prolonged QTc. The combined therapy of mexiletine and radiofrequency ablation successfully prevented recurrent ventricular tachyarrhythmias in our patient.

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