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Review

Clinical features of Brugada syndrome

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ABSTRACT

Brugada syndrome is a clinical entity characterized by type-1 (coved) ST-segment elevation in the right precordial electrocardiographic leads (V1–V3) and an aborted sudden cardiac death due to ventricular fibrillation (VF) in the absence of structural heart disease. Since 1992, when Brugada and Brugada reported the first case, numerous studies across the world have characterized the clinical, electrocardiographic, electrophysiologic, and prognostic features of Brugada syndrome. Several multicenter studies also suggested the natural history and proposed the risk stratification for subsequent cardiac events. In this review article, the clinical features of Brugada syndrome will be updated.

Contents

1. Introduction

Brugada syndrome is characterized by specific ST-segment changes in the right precordial electrocardiographic leads, known as the type-1 or coved-type Brugada electrocardiogram (ECG). In addition, Brugada syndrome is associated with a high risk of sudden cardiac death due to ventricular fibrillation (VF) without structural heart diseases. Since Brugada and Brugada first described 8 patients with a history of aborted sudden cardiac death due to VF and type-1 ECG in 1992, Brugada syndrome has become a distinct clinical entity [1–8].

2. Epidemiology

The worldwide prevalence of Brugada syndrome [8] is estimated to be 1 in 10,000, but it is much higher in Asian and

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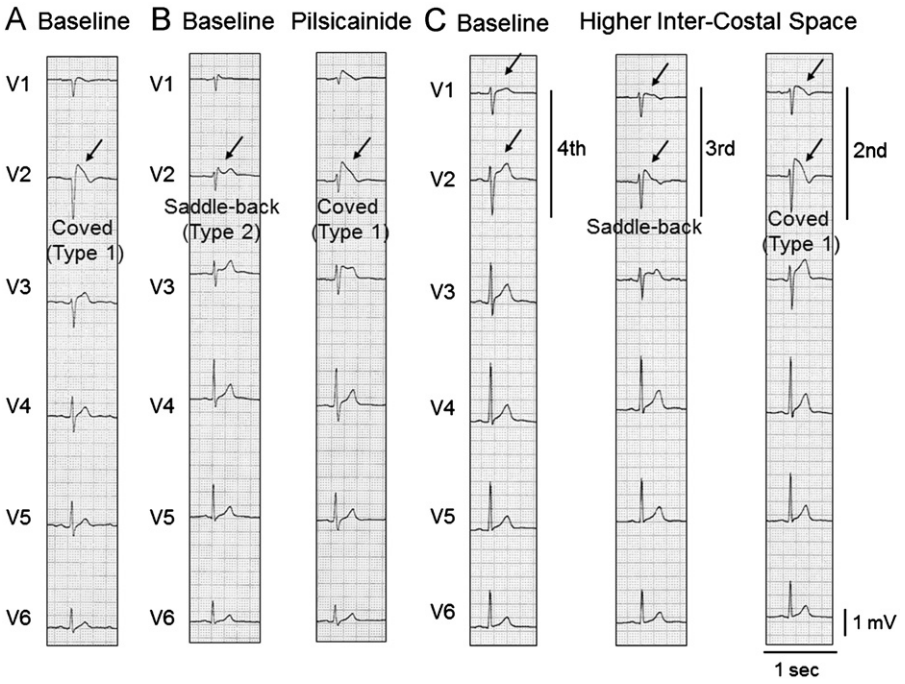

Fig. 1. (A) Spontaneous type-1 (coved) ST-segment elevation (arrow). (B) Unmasking of ST-segment elevation by a class IC sodium channel blocker, pilsicainide. Under baseline condition, type-2 (saddle-back) ST-segment elevation is recorded in lead V2 (left, arrow). Pilsicainide injection (30 mg) unmasks type-1 electrocardiogram (ECG) in lead V2 (right, arrow). (C) Unmasking of type-1 ECG by recordings of right precordial (V1–V2) leads at third and second intercostal spaces. No significant ST-segment elevation is observed in leads V1 and V2 of the standard 12-lead ECG (fourth intercostal space) (left, arrow), while type-2 (middle, arrow) and type-1 (right, arrow) ST-segment elevation are unmasked in leads V1 and V2 recorded from the third and second intercostal spaces, respectively.

Southeast Asian countries, especially Japan, the Philippines, and Thailand, reaching 5–10 in 10,000, while it is much lower in some Eastern European countries like Denmark, with an estimated prevalence of 1.1 in 100,000. Brugada syndrome, also known as pokkuri (Japan), bangungot (the Philippines), and lai tai (Thailand), seems to be the most common cause of natural death in Asian men younger than 50 years. The reason for this higher prevalence in Asia may be in part related to an Asian-specific sequence in the promoter region of *SCN5A* [9].

Brugada syndrome usually manifests during adulthood, with a mean age of sudden death of 41 ± 15 years; however, cases in children are rare [8]. A family history of unexplained sudden death is present in 20–40% of cases in Western countries and 15–20% of cases in Japan [5,8,10,11].

Male predominance in patients with Brugada syndrome is also well known. Since all of the mutations identified in patients with Brugada syndrome display an autosomal dominant mode of transmission, men and women are genetically expected to equally inherit the defective gene. However, the clinical phenotype is 8–10 times more prevalent in men than in women [8]. Experimental studies in dogs have suggested that the presence of a more prominent transient outward current (I_{to}) in males may contribute to the male predominance of the syndrome [12]. Some clinical studies have suggested that higher testosterone levels in men than in women may also have a significant role in the male predominance [13].

Episodes of VF occur more frequently at night or during sleep (2000–0800) than during the daytime as a form of sudden unexplained nocturnal death, syncope, or agonal respiration in approximately 70–80% of patients with Brugada syndrome [8,14,15]. Some authors speculate that this circadian pattern is related to increased vagal tone [16]. Our data detected by implantable cardioverter defibrillator (ICD) have shown that about half of the VF episodes are preceded by ventricular premature complex (VPC) with a similar morphology to initiating VPC of VF [15]. Atrial fibrillation is associated with 10–20% of Brugada cases in Western countries and 20–30% of Brugada cases in Japan [17]. The association of atrioventricular nodal reentrant tachycardia or Wolff-Parkinson-White (WPW) syndrome has also been reported.[18]

3. Electrocardiographic characteristics

The fist Brugada Consensus Report in 2002 suggested 3 types of ST-segment elevation patterns in the right precordial leads of the ECG (Fig. 1) [6]. Type-1 or coved-type ST-segment elevation is characterized by a J-point elevation of ≥ 2 mm (0.2 mV) followed by a negative or isoelectric T-wave (Fig. 1A). Type-2 ST-segment elevation shows a saddleback appearance with a J-point elevation of ≥ 2 mm followed by a trough displaying a ≥ 1-mm ST elevation with either a positive or biphasic T-wave (Fig. 1B). Type-3 ST-segment elevation has a saddleback appearance with a J-point elevation of < 1 mm. The morphology and level of the ST-segment elevation are often accentuated; however, the type-1 or coved-type Brugada ECG is more frequently recognized just before and after episodes of VF [19,20] and is linked to a higher incidence of VF and sudden cardiac death [21]. Although the original report by Brugada and Brugada described the presence of right bundle branch block (RBBB), the RBBB was revealed to be nonessential for the diagnosis of Brugada syndrome [6]. Mild depolarization abnormalities, such as widening of the P wave and QRS duration, and prolongation of the PQ interval are observed in patients with Brugada syndrome, more often in those with *SCN5A* mutations than in those without *SCN5A* mutations [22].

4. Diagnostic criteria

Brugada syndrome is definitively diagnosed when a type-1 ST-segment elevation is observed in at least 1 right precordial lead

(V1 and V2) [23], placed in a standard or a superior position (up to the second intercostal space) (Fig. 1C) [24,25], in the presence or absence of a sodium channel blocking agent (ajmaline, flecainide, pilsicainide, or procainamide) (Fig. 1B). Although the diagnostic criteria from the Second Consensus Report in 2005 require a type-1 ECG in at least 2 right precordial leads (V1–V3) for the definitive diagnosis, several clinical studies thereafter have indicated that a type-1 ECG recorded in at least 1 right precordial lead (V1 and V2) was enough for definitively diagnosing Brugada syndrome [26].

5. Differential diagnosis

Diseases and conditions that can lead to Brugada-like ECG abnormality should be differentially diagnosed. These diseases and conditions include atypical RBBB, left ventricular hypertrophy, early repolarization, acute pericarditis, acute myocardial ischemia or infarction, pulmonary embolism, Prinzmetal angina, dissecting aortic aneurysm, various central and autonomic nervous system abnormalities, Duchenne muscular dystrophy, thiamin deficiency, arrhythmogenic right ventricular cardiomyopathy (ARVC), pectus excavatum, and mechanical compression of the right ventricular outflow tract as occurs in mediastinal tumor or hemopericardium [8,23,27].

6. Acquired form of Brugada syndrome

The ST segment in the right precordial leads is well known to be modulated by several drugs (mainly antiarrhythmic drugs) and autonomic agents [20]. Class IC antiarrhythmic drugs amplify or unmask the ST-segment elevation most effectively as a result of their strong effect of blocking fast sodium current (I_{Na}) [28,29] and are used as a diagnostic tool in latent Brugada syndrome. Many drugs and conditions that increase outward currents (e.g., I_{to}, adenosine triphosphate sensitive potassium current [$I_{K\text{-}ATP}$]) or decrease inward currents (e.g., L-type calcium current [$I_{Ca\text{-}L}$], fast I_{Na}) at the end of phase 1 of the action potential can accentuate or unmask ST-segment elevation, similar to that found in Brugada syndrome (Table 1). This is described as an "acquired" form of Brugada syndrome similar to the "acquired" form of long QT syndrome. Several drugs and conditions other than class IC antiarrhythmic drugs have been reported to produce an acquired form of Brugada syndrome. These drugs and conditions include antianginal drugs; psychotropic drugs; histaminic H1 receptor antagonists; anti-inflammatory drugs; psychoactive recreational drugs; antipsychotic drugs; local anesthetics; short-acting hypnotic agents; hypertestosteronemia; hyperthermia (febrile state); hypothermia; and electrolyte abnormalities, such as hyperkalemia, hypokalemia, hypercalcemia, or hyponatremia [27,30,31]. These drugs and conditions unmask Brugada phenotype mainly by depressing fast I_{Na} and $I_{Ca\text{-}L}$. (See also www.brugadadrugs.org.)

Table 1
Acquired form of Brugada Syndrome.

1. Antiarrhythmic drugs
- **(1) Sodium channel blockers**
  - **Class IC drugs (Flecainide, Pilsicainide, Propafenone)**
  - **Class IA drugs (Ajmaline, Procainamide, Disopyramide, Cibenzoline)**
- **(2) Calcium channel blockers**
  - **Verapamil**
- **(3) β blockers**
  - **Propranolol, etc.**

2. Antianginal drugs
- **(1) Calcium channel blockers**
  - **Nifedipine, Diltiazem, etc.**
- **(2) Nitrate**
  - **Isosorbide dinitrate, Nitroglycerine, etc.**
- **(3) Potassium channel openers**
  - **Nicorandil, etc.**

3. Psychotropic drugs
- **(1) Tricyclic antidepressants**
  - **Amitriptyline, Nortriptyline, Desipramine, Clomipramine, dosulepin, etc.**
- **(2) Tetracyclic antidepressants**
  - **Maprotiline, etc.**
- **(3) Phenothiazine**
  - **Perphenazine, Cyamemazine, etc.**
- **(4) Benzodiazepine**
  - **Clonazepam, Alprazolam, Lorazepam, etc.**
- **(5) Selective serotonin reuptake inhibitors**
  - **Fluoxetine, Paroxetine, etc.**
- **(6) Other antidepressants**
  - **Trazodone, Risperidone, etc.**

4. Other drugs
- **(1) Histaminic H1 receptor antagonists**
  - **Dimenhydrinate, etc.**
- **(2) Anti-inflammatory drugs**
  - **Mesalazine, etc.**
- **(3) Psychoactive recreational drugs**
  - **Cocaine, Cannabis**
- **(4) Antipsychotic drugs**
  - **Lithium, Thioridazine**
- **(5) Local anesthetics**
  - **Bupivacaine**
- **(6) Short-acting hypnotic agents**
  - **Propofol**

5. Hypertestosteronemia

6. Low visceral fat

7. Myocardial ischemia
- **(1) Right ventricular infarction/ischemia**
- **(2) Vasospastic angina**

8. Myocarditis, Pericarditis
- **(1) Acute myocarditis**
- **(2) Chronic myocarditis**
- **(3) Acute Pericarditis**

9. Temperature
- **(1) Hyperthermia (Febrile state)**
- **(2) Hypothermia**

10. Electrolyte abnormalities
- **(1) Hyperkalemia**
- **(2) Hypokalemia**
- **(3) Hypercalcemia**
- **(4) Hyponatremia**

11. Meal, Increased insulin level

12. Polymorphisms in *SCN5A*

7. Clinical features and natural history

Several symptoms related to Brugada syndrome include (1) VF or aborted sudden cardiac death (more frequent at night than during the day), (2) syncope, (3) nocturnal agonal respiration, (4) palpitations, and (5) chest discomfort. These symptoms are documented frequently at rest, during sleep, or under other vagotonic conditions, but rarely during exercise.

Identification of patients at high risk for sudden cardiac death due to VF is important for managing patients with Brugada syndrome [5,7,10,11,32,33]. Brugada et al. reported that patients with type-1 Brugada ECG initially presenting with aborted sudden cardiac death or VF are at the highest risk for a recurrence (69% at 54 ± 54 months of follow up) [7]. Patients presenting with syncope and a type-1 ECG are also reported to have a high recurrence rate (19% at 26 ± 36 months of follow-up). Even in asymptomatic Brugada patients, a relatively high cardiac-event rate (8%) was reported in their registry. In contrast to the Brugada registry, a recent European registry found a lower incidence of subsequent arrhythmic events. The FINGER study by Probst et al. reported that the annual rates of subsequent or new arrhythmic events in patients with prior aborted sudden cardiac death, patients with prior syncope, and asymptomatic patients are

7.7%, 1.9%, and 0.5%, respectively [32]. Our Japanese registry endorsed by the Japanese Ministry of Health, Labour and Welfare also demonstrated a lower rate of arrhythmic events than those of the Brugada registry. The annual rate of arrhythmic events in probands with type-1 Brugada ECG was 10.2% in the VF group, 0.6% in the syncope group, and 0.5% in the asymptomatic group [33]. The discrepancy in clinical outcomes of patients between the Brugada registry and the other 2 registries is most likely due to inclusion of particular families with a very severe form of the disease in the Brugada registry.

It is generally agreed that a previous history of aborted cardiac arrest, syncope, presence of a spontaneous type-1 ECG, and male gender are significant predictors of further arrhythmic events [5,7,10,11,32,33].

8. Risk stratification

Considering the natural history of Brugada patients, there is little controversy on the indication of ICD in Brugada patients with a history of aborted cardiac arrest or those with a history of syncope likely caused by VF as class I or class IIa ICD indication. The more important goal is to stratify risk in asymptomatic patients with Brugada syndrome displaying a typical type-1 ECG. Several clinical examinations have been useful in supporting the diagnosis of Brugada syndrome and stratifying high-risk patients.

9. Exercise testing

Some clinical studies have reported the augmentation of ST-segment elevation and/or unmasking of type-1 ECG in the right precordial leads at early recovery periods after exercise in some patients with Brugada syndrome (Fig. 2) [34,35]. We recently investigated the prevalence and the clinical significance of the augmentation of ST-segment elevation at the early recovery phase for risk stratification in Brugada patients [35]. Treadmill exercise testing was conducted in 93 patients with Brugada syndrome (22 documented VF, 35 syncope alone, and 36 asymptomatic) and 102 healthy control subjects. Augmentation of ST-segment elevation ≥ 0.05 mV in leads V1 through V3 compared with baseline was observed at early recovery (1–4 min at recovery) in 34 Brugada patients (37%) (Fig. 2A and B) but not in the remaining 59 Brugada patients (63%) (Fig. 2C) or 102 control subjects. The ST-segment elevation was usually ameliorated at peak exercise (Fig. 2A), but it was augmented even at peak exercise in some patients (Fig. 2B). The Brugada patients associated with the ST-segment augmentation at the early recovery phase had a greater risk of subsequent VF than those without (15/34 [44%] vs. 10/59 [17%], $P=0.004$) during 76 ± 38 months of follow up. Multivariate Cox regression analysis showed that augmentation of ST-segment elevation at the early recovery phase was a significant and independent predictor for cardiac events ($P=0.007$), especially in patients with a history of syncope alone (6/12 [50%] vs. 3/23 [13%]) and in asymptomatic patients (3/15 [20%] vs. 0/21 [0%]). Thus, augmentation of ST-segment elevation at the early recovery phase during exercise testing was specific in patients with Brugada syndrome and can be a predictor of poor prognosis, especially in patients with syncope alone and in asymptomatic patients.

10. Signal-averaged ECG

Frequency of late potentials (LP) in the signal-averaged ECG has been reported to be higher in patients with Brugada syndrome than in control subjects. In a single-center study, Ikeda et al. reported a sensitivity of 89%, specificity of 50%, positive

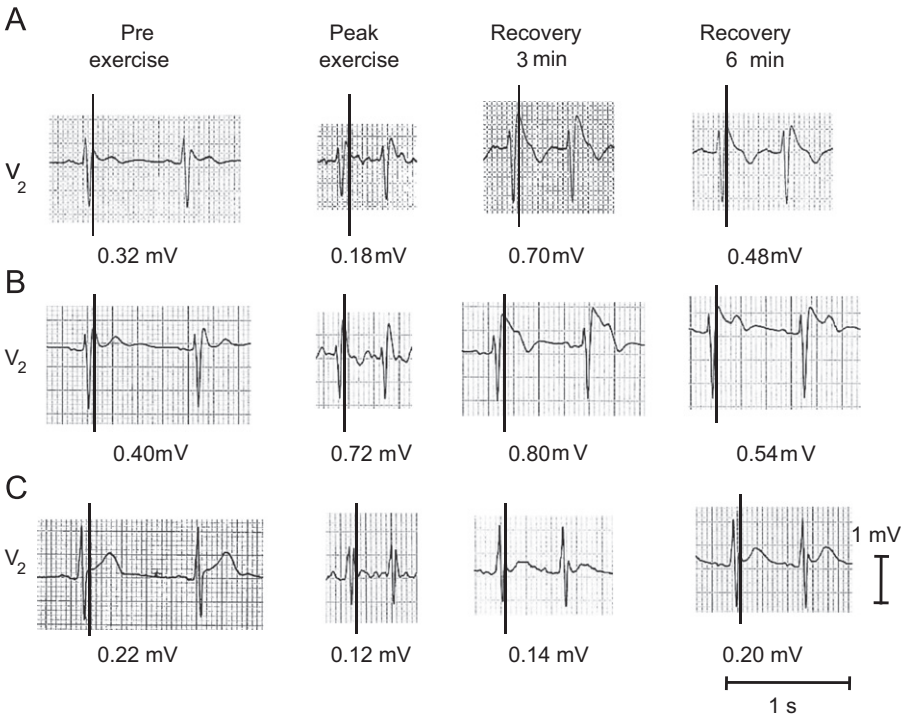

Fig. 2. Responses of ST-segment elevation in lead V2 during exercise testing in 3 patients with Brugada syndrome. (A). The ST-segment elevation was decreased at peak exercise but re-ascended at the early recovery phase (3 min) resulting in typical type-1 ST-segment elevation. (B). In some cases, the ST-segment elevation was augmented at peak exercise and remained augmented at the early recovery phase. (C). The ST-segment elevation was decreased at peak exercise and gradually recovered to the baseline at recovery phase. ST-segment amplitudes are shown as numeric values.

predictive value of 70%, and negative predictive value of 77% for LP for risk stratification of life-threatening events [36].

11. Fragmented QRS

Morita and colleagues reported that fragmented QRS recorded in the standard 12-lead ECGs (with 0- to 150-Hz filters) was more often observed in Brugada patients with VF episodes than in those with syncope or in asymptomatic patients [37]. They also reported that patients who had fragmented QRS frequently experienced recurrence of syncope due to VF within 4 years of the first episode of syncope or VF. More recently, in the PRELUDE study, Priori et al. reported that fragmented QRS was an independent predictor for arrhythmic events in Brugada patients without a history of VF [38].

12. Atrial fibrillation

Spontaneous atrial fibrillation (AF) has been reported to appear in 10–53% of patients with Brugada syndrome and to be associated with a higher incidence of syncopal episodes (60.0% vs. 22.2%, $P < 0.03$) and documented VF (40.0% vs. 14.3%, $P < 0.05$) [39,40].

13. Programmed electrical stimulation

The usefulness of programmed electrical stimulation (PES) to stratify risk of subsequent arrhythmic events has long been controversial between the Brugada registry and other registries [5,7,10,11,32,33]. To fill this gap, Priori organized a multicenter prospective registry (PRELUDE study) with a uniform protocol in patients with Brugada syndrome without a history of VF [38]. They suggested that arrhythmia inducibility during PES was not a predictor of subsequent events during follow-up but that a ventricular effective refractory period < 200 ms was an independent predictor for arrhythmic events. Makimoto et al. recently reported a significance of the number of extrastimuli at PES as a predictor of arrhythmic events in patients with type-1 Brugada ECG [41]. Multivariate Cox regression demonstrated that the induction of VF with up to double extrastimuli was an independent predictor. Therefore, they suggested that up to double extrastimuli were adequate at PES to stratify risk in patients with Brugada syndrome.

14. Cardiac imaging

Several cardiac imaging techniques, such as exercise radionuclide imaging (RI), computed tomography (CT), magnetic resonance imaging (MRI), or echography, are required to prove the absence of structural heart disease, including myocardial ischemia and ARVC.

15. Head-up tilt testing

Head-up tilt (HUT) testing is recommended to judge an episode of syncope to be likely caused by VF by excluding neurally mediated syncope (NMS). However, NMS may coexist with Brugada syndrome [42]. We conducted HUT testing in 46 patients with type-1 Brugada ECG, 20 healthy control subjects, and 15 patients with suspected NMS [43]. HUT testing was positive in 35% of Brugada patients (16/46), 10% of control subjects (2/20), and 67% of suspected NMS patients (10/15). The HUT-positive rate was significantly higher in Brugada patients with VF (7/14; 50%) than that in control subjects (10%) ($P < 0.05$). Augmentation of ST-segment amplitude (≥ 0.05 mV) in leads V1 through V3 was observed in 69% of the HUT-positive Brugada patients (11/16) during vasovagal responses and was associated with augmentation of parasympathetic tone following sympathetic withdrawal, which was evaluated by the heart rate variability. These data suggested that some Brugada patients have an impaired balance of the autonomic nervous system, which may relate to their syncopal episodes.

Conflict of interest

The author have no conflicts of interest to disclose.

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