Brugada Syndrome in Japan

Masayasu Hiraoka, MD

The incidence of Brugada syndrome (BS) is relatively high in Japan compared with the rest of the world, ranging between 0.1% and 0.2% in the general population. BS in Japan, as in other countries, is most prevalent in middle-aged men, and has characteristics ECG changes, a high recurrence rate in symptomatic patients, and relatively low incidence of SCN5A mutations. In contrast, both the incidence of a family history of BS and/or sudden cardiac death and the rate of developing cardiac events in asymptomatic patients are less in Japan than in other countries. Increased vagal tone and/or decreased sympathetic activity are suggested as provoking cardiac events. Several factors should be evaluated in risk stratification for recurrence of life-threatening arrhythmias, because there appears to be no single determinant for risk stratification: spontaneous ST elevation of coved-type (Type 1), family history of sudden cardiac death, inducible ventricular tachycardia/ventricular fibrillation and positive late potentials. An implantable cardioverter defibrillator is recommended for patients with aborted sudden cardiac death. (Circ J 2007; Suppl A: A-61–A-68)

Key Words: Brugada syndrome; Japan; Mutations; Risk stratification

Since the first description of the Brugada syndrome (BS) by Brugada and Brugada, there have been many studies from Japan characterizing the syndrome, partly because of the high prevalence of BS in Asian countries. In the review by Alings and Wilde in 1999 58% of 163 patients who met the criteria for BS were of Asian origin. Another reason for BS to attract so much clinical and research interest is the fact that apparently healthy individuals are victims of sudden cardiac death (SCD). Furthermore, one of the most important diagnostic parameters of BS is easily detected by routine ECG examination, so that not only cardiologists but also other physicians can recognize suspected individuals. Among the various reports dealing with BS and related conditions, the disease characteristics share a certain similarity and dissimilarity among Japanese patients and those from elsewhere. This review will focus on the significant contribution of studies done in Japan to our understanding of the clinical and mechanistic features of BS by the year of 2006.

History of BS in Japan

Although the first report of BS came from Europe in a the survey of a multicenter study, its clinical characteristics and unique ECG signs have attracted strong interest and attention in Japan. In 1988, 4 years before the first report, Aihara et al reported 4 cases of idiopathic ventricular fibrillation (VF), in which 3 of them showed ECG patterns compatible with BS. It was widely recognized by cardiologists and medico-legal authorities in Japan that there was a type of SCD, called “Pokkuri disease”, in which the victim, an apparently healthy young or middle-aged man, dies suddenly at night, usually with a groan or moan, and at autopsy most victims are proven to have no structural heart disease. Because of sudden and unexpected nature of the death, ECG recordings of the victim before the cardiac event were usually not available, but in 1 case the ECG record of the subject, who had been admitted to the hospital for an extra-cardiac problem and had suffered SCD, demonstrated right-bundle branch block (RBBB) and left axis deviation with ST-segment elevation in V_{1-3}, which shared a certain analogy with the ECG findings of BS. Sudden and unexpected death of young and middle-aged men during sleep, similar to BS and to “Pokkuri disease”, had also been recognized in Southeast Asian countries. In the Philippines, the condition is known as “Bangungut” (“to rise and moan in sleep”) and in Thailand, it is called “Lai Tai” (“death during sleep”). These disorders are known comprehensively as sudden unexplained nocturnal death syndrome (SUNDS). SUNDS and BS appear to share similar phenotype, genetic background and biophysical abnormalities.

Incidence and Prevalence of BS

The actual incidence of BS in the general population is difficult to estimate because the typical ECG signs (ST-segment elevation in V_{1-3}) are prone to fluctuate in appearance with time, and there are significant numbers of individuals demonstrating unequivocal ECG changes without clinical symptoms of syncope and/or aborted SCD, or a family history of SCD. According to previous studies, the incidence of BS in the general population of Japan ranges from 0.04% to 1.22%. Miyasaki et al examined the incidence of ECG signs of the BS-type in a community-based general population (Moriguchi, Osaka) and found that the incidence of subjects showing RBBB with ST elevation ≥0.1 mV was 0.70% of the total adult population and 2.14% among men. A typical BS-type ECG (coved-type ST elevation) accounted for 0.12% of 13,929 subjects, with apparent male predominance. Matsuo et al studied the ECG records from biennial health examinations conducted between 1958 and 1999 as follow-up studies of atomic bomb victims in Nagasaki and Hiroshima cities. Among 4,788 subjects, there were 0.15% of cases showing ST

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elevation ≥0.1 mV of either the coved- or saddleback-type. Of a total of 32 BS-type ECG cases, the prevalence was 146.2 in 100,000 persons and the incidence was 14.2 persons/100,000 person-year. The incidence was 9-fold higher in men than in women. Sakabe et al13 followed up the ECGs of 3,339 healthy subjects who underwent periodic medical examinations from 1992 to 2002. None of the subjects had a family history of SCD. Their results gave the annual mean proportion of 1.22% for ST elevation (J-point elevation) ≥0.2 mV, including the coved- and saddleback-type. The majority of them (97%) were men and the male incidence of coved-type ST elevation was 0.28%. Other studies of annual health check-ups in working populations gave a similar incidence of the coved-type (Type 1) ST elevation14–16. Most of those reports dealt with adult populations and disclosed that the incidence of a typical BS-type ECG (coved-type ST-segment elevation) was in a range of 0.12–0.28% of subjects. The incidence of BS-type ECGs in the Japanese adult population appears to be generally higher than in Europe and the USA.2–6,17–19

In school-aged children, the incidence of BS is very low, compared with adults. Yamakawa et al20 studied the incidence of children with RBBB and ST-segment elevation ≥0.1 mV (coved- and saddleback-type). Of the children aged between 6 and 15 years old 0.054% had these ECG signs and 91% were boys. Coved-type ST elevation in these children was 0.005%. The researchers also noticed the incidence of positive ECG signs increased with age.

As to prognosis, Miyasaka et al did not notice any increase in risk of SCD in the subjects with BS-type ECG signs11 although Matsuo et al, in contrast, claimed there was an increased risk of unexpected death among individuals with BS-type ECG signs compared with those without the signs.12 Their different results might relate to the longer follow-up period in the latter study. These and other studies dealing with general populations seem to represent asymptomatic BS and the overall rate of SCD or arrhythmic events was approximately 0.5%.13–16

Pathophysiological Mechanism of BS

The mechanism of ST-segment elevation in V1–3 is explained by the voltage difference between the epicardial and endocardial cells of the right ventricular outflow tract (RVOT) region, where the former has a well-developed transmural voltage gradient. The MAP from the epicardium showed a deep notch during the early repolarization at the RVOT, whereas the MAP from the endocardium had a minimal notch, indicating the presence of voltage gradient between the 2 regions during the repolarization phase. These observations were concordant with findings in animal preparations.25 Nagase et al26 recorded the local epicardial electrogram of the RVOT in 5 Brugada patients, using an electrode introduced into the conus branch of the right coronary artery, and found that the delayed potential (DP) after termination of the QRS complex occurred only in the epicardium, not in the endocardium. The epicardial DP was significantly prolonged after the administration of class Ic agents. They suggested that these findings were caused by a myocardial abnormality of BS, although the true nature of the DP was not defined. As to the genesis of the ventricular arrhythmias, Aiba et al27 used high-resolution optical mapping method to examine the depolarization and repolarization abnormalities in the development of both phase 2 reentry and VT/VF in an animal model of BS. Their study results suggested that phase 2 reentry, which can degenerate into VT/VF, is caused by a steep repolarization gradient in the epicardium, but not in the endocardium.

In addition to a repolarization abnormality, altered depolarization is thought to be involved in the ST-segment elevation and development of VT/VF in BS. DPs detected by body surface mapping and by signal-averaged electrocardiography (SAECG) are positive in many cases, especially in subjects showing the coved-type ST elevation25,30,32 and could be used as a marker for a high risk of cardiac events.33 Nagase et al observed that this might not simply indicate a repolarization abnormality, but represent a local delay of secondary depolarization (dome) of the plateau phase.30 The spatial distributions of the depolarization and repolarization abnormalities, using 87-lead body surface potential mapping, disclose that the depolarization abnormalities are distributed homogeneously, whereas the repolarization abnormalities are localized in the RVOT.31

The identification of mutations of SCN5A encoding the cardiac sodium channel in patients with BS was a strong indication that decreased INa was the possible underlying electrophysiological mechanism for the ECG changes. Shimizu et al28 examined the efficacy of different sodium-channel blockers on the induction or unmasking of ST-segment elevation. Among these drugs, class Ic agents could most effectively amplify or unmask ST-segment elevation because of their strong INa blocking action, whereas class Ia and Ib agents had moderate or minimal effects on ST-segment elevation, respectively, because of their relatively weak INa blocking action. These provocations effects of sodium-channel blockers were then applied in their use as a diagnostic tool or a marker for risk stratification.10,27,28

Another mechanistic explanation of the ECG changes in BS is a repolarization abnormality in the epicardium of the RVOT region. Kurita et al29 studied the monophasic action potential (MAP) recordings from the epicardium and endocardium of a patient with BS during ICD implantation. The MAP from the epicardium showed a deep notch during the early plateau, whereas the MAP from the endocardium had a minimal notch, indicating the presence of voltage gradient between the 2 regions during the repolarization phase. These observations were concordant with findings in animal preparations.25 Nagase et al26 recorded the local epicardial electrogram of the RVOT in 5 Brugada patients, using an electrode introduced into the conus branch of the right coronary artery, and found that the delayed potential (DP) after termination of the QRS complex occurred only in the epicardium, not in the endocardium. The epicardial DP was significantly prolonged after the administration of class Ic agents. They suggested that these findings were caused by a myocardial abnormality of BS, although the true nature of the DP was not defined. As to the genesis of the ventricular arrhythmias, Aiba et al27 used a high-resolution optical mapping method to examine the repolarization and depolarization abnormalities in the development of both phase 2 reentry and VT/VF in an animal model of BS. Their study results suggested that phase 2 reentry, which can degenerate into VT/VF, is caused by a steep repolarization gradient in the epicardium, but not in the endocardium.

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The identification of mutations of SCN5A encoding the cardiac sodium channel in patients with BS was a strong indication that decreased INa was the main contributing factor to the ST-segment elevation and the genesis of this syndrome.

Genetic Background of BS

Mutations of SCN5A, which encodes the β-subunit of the
cardiac sodium channel have been identified as the genetic abnormalities responsible for BS. Another locus on chromosome 3 close to that of SCN5A has also been linked to the syndrome, but no causative gene has been identified. Over 60 mutations have been reported worldwide, but functional studies have been carried out in less than half of them. Functional assays of these mutated genes revealed decreased voltage shifts and kinetic changes in activation, inactivation, and reactivation, or accelerated access to a slow inactivation. Familial cases of BS show autosomal dominant inheritance, but sporadic cases account for 60–70% of all patients in Europe. In Japan, familial cases are quite rare and most affected individuals are sporadic cases.

The incidence of mutations of SCN5A in BS is reportedly approximately 20% or less in Europe. My survey in countries. Functional assays of these mutated genes showed a marked reduction of the In,, with a fast inactivation, a shift in voltage dependence during inactivation and activation, and a slow recovery from inactivation. Since then, the literature describing mutations of SCN5A in Japanese Brugada patients has been accumulating. The mutations are scattered throughout the subunit of the channel and no hot spots have been identified. To date, mutations found in Japanese subjects have been mainly scattered in Repeat I (D I) and Repeat IV (D IV) of the subunit (Table 1), and most have been novel, but there is a certain overlap with those found in patients from other countries. Functional assays of these mutated genes show loss-of-function with different mechanisms (Table 1). Makita et al reported that the subunit was responsible for aggravating channel dysfunction in BS and mutations of the sodium channel would cause not only BS, but also the conditions of decreased conduction and excitability. Takehara et al reported a case of BS complicated with atrial standstill and genetic analysis revealed a missence mutation (R367H) in SCN5A. Makiyama et al examined the genotype–phenotype relationship in 38 Japanese patients. Four heterozygous mutations (T187I, D356N, K1578fs/s2, and R1623X) were identified in 4 of the 38 patients, who had bradyarrhythmic complications (3 sick sinus syndrome and 1 paroxysmal atrioventricular block) and all the mutations encoded non-functional sodium channels. Bradyarrhythmias were complicated in only 2 of 34 patients with non-SCN5A-linked BS. They concluded that loss-of-function SCN5A mutations resulting in BS are distinguished by profound bradyarrhythmias. In contrast, Yokoi et al described a case of asymptomatic BS with double SCN5A mutations (K1527R and A1569P). Functional assay of these mutated genes revealed decreased In because of a negative shift in steady-state inactivation and enhanced slow inactivation. From the discrepant results for phenotype and genetic abnormalities, they suggested that there are unknown factors or modifier genes influencing arrhythmogenesis.

Not only mutations of SCN5A but also polymorphisms may be involved in the genesis of BS. Bezzina et al demonstrated that an SCN5A promoter polymorphism common in Asians (variant haplotype) was associated with variable conduction abnormalities in subjects, including Japanese BS which may explain, at least in part, why there is a high prevalence of this syndrome in Japanese.

### Table 1 SCN5A Mutations in Japanese Brugada Patients in the Literature

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Type</th>
<th>Sites</th>
<th>In</th>
<th>Biophysical mechanisms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>#T187I</td>
<td>Missense</td>
<td>D I, S2-S3</td>
<td>(–)</td>
<td>(+) shift in Act, single cond.</td>
<td>45</td>
</tr>
<tr>
<td>#R282H</td>
<td>Missense</td>
<td>D I, S5 pore</td>
<td>□</td>
<td>(+) shift in Act, single cond.</td>
<td>43</td>
</tr>
<tr>
<td>#G292S</td>
<td>Missense</td>
<td>D I, S5-S6</td>
<td>ND</td>
<td>Traffic detection</td>
<td>41</td>
</tr>
<tr>
<td>#D356N</td>
<td>Missense</td>
<td>D I, S5-S6</td>
<td>(–)</td>
<td>(+) shift in Act, enhanced slow Inact.</td>
<td>45</td>
</tr>
<tr>
<td>#R367H</td>
<td>Missense</td>
<td>D I, S5-S6</td>
<td>(–)</td>
<td>(+) shift in Act, enhanced slow Inact.</td>
<td>40</td>
</tr>
<tr>
<td>#N406S</td>
<td>Missense</td>
<td>D I, S6</td>
<td>□</td>
<td>(+) shift in Act, enhanced slow Inact.</td>
<td>44</td>
</tr>
<tr>
<td>#S835L</td>
<td>Missense</td>
<td>D II, S4-S5</td>
<td>ND</td>
<td>No tonic block by pilsicainide Enhanced use-dependent block by quinidine</td>
<td>41</td>
</tr>
<tr>
<td>#1527R</td>
<td>Missense</td>
<td>D IV, S1</td>
<td>□</td>
<td>(–) shift in Inact, enhanced slow Inact.</td>
<td>42</td>
</tr>
<tr>
<td>+ (double mutations)</td>
<td>A1569P</td>
<td>Missense</td>
<td>D IV, S2</td>
<td>□</td>
<td>(+) shift in Act, enhanced slow Inact.</td>
</tr>
<tr>
<td>#K1578fs2</td>
<td>Frameshift</td>
<td>D IV, S2</td>
<td>(–)</td>
<td>(+) shift in Act, enhanced slow Inact.</td>
<td>45</td>
</tr>
<tr>
<td>#R1623X</td>
<td>Missense</td>
<td>D IV, S4</td>
<td>(–)</td>
<td>(+) shift in Act, enhanced slow Inact.</td>
<td>45</td>
</tr>
<tr>
<td>#1710L</td>
<td>Missense</td>
<td>D IV, S5-S6</td>
<td>□</td>
<td>(+) shift in Inact &amp; (+) shift in Act.</td>
<td>39*</td>
</tr>
</tbody>
</table>

D I-D IV, repeat I-repeat IV; (–), no current; (+)shift, positive shift in voltage; ND, not done; (–)shift, negative shift in voltage; Inact., inactivation; Act., activation Single cond. single channel conductance.

*Case of idiopathic VF without typical ECG sign of BS.

### Clinical Characteristics

#### General Characteristics

The Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) is a multicenter study that started in 2002, with the aim of exploring the clinical characteristics, risk stratification, and prospective survival of patients with idiopathic VF, including BS. From February 2002 to November 2005, 216 cases of BS were enrolled. The diagnostic ECG criteria for BS were J-point amplitude >0.2 mV with either coved- or saddleback-type ST-segment elevation (>0.1 mV) in V1–3. Preliminary results are shown in Table 2 (Takagi et al...
Factors Influencing ST-Segment Elevation

Multiple factors have been shown to influence ST-segment elevation in BS. The effects of class Ia and Ic agents (sodium-channel blockers) have been described repeatedly in terms of their diagnostic usefulness. Many cardiac and noncardiac drugs acting on the inward and outward currents during the action potential have been shown to affect or unmask ST-segment elevation in symptomatic and asymptomatic patients. Vagal stimulation and vagotonic agents aggravated and/or induced ST-segment elevation in the early report by Kasanuki et al. Because the cardiac events in BS frequently occur during rest and/or sleep, vagotonic conditions might facilitate VT/VF. The previous studies on this issue have disclosed that not only increased vagal tone, but also bradycardia itself, is associated with the abnormal repolarization responses in symptomatic patients. Increased vagal tone and decreased sympathetic activity, assessed by heart rate variability, have been suggested as prominent signs in symptomatic patients with BS. Abnormal MIBG-uptake, indicating presynaptic sympathetic dysfunction, was dominant in cases with the coved-type ST elevation. These observations suggest that a combination of increased vagal tone, decreased sympathetic activity and bradycardia may contribute to the development of cardiac events and symptoms in BS. Effects of insulin on induction and aggravation of ST-segment elevation have also been reported, although the mechanism was not exactly known, but the action of insulin on different ionic channels and/or autonomic functions as a result of food intake might be involved. In conjunction with these studies, Ikeda et al suggested that the “full stomach test” could be a useful provocative procedure for stimulating vagal activity and identifying Type 1 ECG changes in patients at risk of BS. In addition, various cardiac and noncardiac drugs, autonomic changes, electrolyte imbalances, body temperature, tumor and extracardiac mass have been shown to mimic or unmask BS and the BS-type ECG, as acquired forms of BS.

Similarity between the ST elevation seen in BS and that seen in coronary vasospasm suggests that the 2 conditions share a common mechanistic background. The incidence of vasospastic angina is relatively high in Japan, as is BS. In fact, Chinushi et al first reported the coexistence of BS and vasospastic angina in 2 cases. They found that 5 of 38 Brugada patients (13.1%) had associated coronary vasospasm and 4 had clinical angina. Two of the 4 patients with vasospastic angina experienced syncope with their ischemic attacks. Noda et al evaluated the frequency of coronary vasospasm, augmentation of ST-segment elevation in V1–3 and induction of VF by intracoronary injection of acetylcholine or ergonovine maleate in 27 symptomatic Brugada patients and 30 control subjects. With right coronary injection of either agent, 3 cases (11%) developed coronary vasospasm, 11 (33%) had aggravation of ST elevation and 3 (9%) showed inducible VF in BS. Neither ST elevation nor VF was observed in any of the control subjects. The researchers suggest that mild ischemia and increased vagal tone may act additively or synergistically with the substrate responsible for BS in favor of ST-segment elevation and the occurrence of VF.

Risk Stratification of BS

Risk stratification of patients for SCD is an important issue in the management of actual and suspected cases of
BS. Brugada et al found that patients with aborted SCD had the highest risk for recurrence (69%) and those with syncope had a recurrence rate of 19%, whereas asymptomatic patients showed an 8% rate of recurrence.63,64 Spontaneous appearance of Type I ST-segment elevation was also suggested as a marker of high risk, whereas ST elevation that developed only after a provocation test with sodium-channel blockers may indicate minimal risk.64 Male BS patients with inducible VT/VF, a family history of SCD and spontaneous ST-segment elevation are suggested to be at higher risk.63,64 Whether this schema for risk stratification is applicable to Japanese patients or not is an important and unsettled issue. In a follow-up study of Brugada patients by Kamakura et al for a mean of 46 months, there were 32 cases of cardiac events. The annual rate of cardiac events was 10.7% in the VF group and 0.4% in the asymptomatic group. In J-IVFS, we followed for a mean of 36 months 182 patients who had survived more than 1 year after enrollment and found cardiac events in 15 of 94 symptomatic cases (VF and syncope groups) (16%) but none in the 88 asymptomatic cases (unpubl data). The Japanese results confirm that symptomatic patients (VF and syncope groups) have higher rates of recurrence than asymptomatic patients, but overall rates of cardiac events are much less than in patient populations in foreign studies.63,64 In particular, cardiac events in the asymptomatic group had a much lower incidence in Japanese patients than in their European counterparts, which may reflect the different patient populations, because the European studies mainly deal with probands and their family members, whereas the Japanese studies include mostly probands without a family history.

In addition to the coved-type (Type I) ST-segment elevation, various ECG parameters have been suggested as markers of high risk for the development of cardiac events. Atarashi et al examined Japanese Brugada patients and found that a prolonged r’ in V1–3 or S in V5 and V6 were signs of high risk for cardiac events.65 Our preliminary results from J-IVFS also indicate a higher incidence of prolonged QRS in V1–3, especially the r–J interval (the interval from the beginning of r or R wave to the J-point) (Fig 1), in symptomatic patients compared with asymptomatic groups (unpubl data). Ikeda et al reported that positive LPs in SAECG could be a good predictor of life-threatening arrhythmias in BS.63 Other groups have also indicated that positive LPs and abnormal values on SAECG in symptomatic patients have a high risk for recurrence in cardiac events compared with negative or less abnormal values.66–68 However, there are significant numbers of asymptomatic patients who present with positive LPs and abnormal SAECG. Therefore, the high predictive value of LPs seems applicable to symptomatic patients, because most of the studies indicating its usefulness have been done at institutions dealing with many symptomatic patients. The value of positive LPs for predicting cardiac events in our large-scale study of patients including many asymptomatic cases, however, appears not so specific, because J-IVFS did not show any difference in the positive rates of LPs between symptomatic and asymptomatic groups (unpubl data). It should be noted that the finding of positive LPs also fluctuates on a daily basis, as does ST elevation.66,69 Therefore, the presence of positive LPs is not the single parameter for prediction of cardiac events.

Inducible VT/VF by programmed ventricular stimulation (PVS) has been suggested as a good indicator for predicting high risk in patients with BS.69,70 But is still controversial because results from other groups in Europe do not agree with its high predictive value.64,71 The protocol of PVS and the endpoints of the study were highly variable among the different institutions, which makes it difficult to interpret the results. Various studies have explored the predictive efficacy of inducible VT/VF as a marker for recurrence of cardiac events in Japanese Brugada patients, but most of them did not reveal a high predictive value for cardiac events. In patients with inducible VT/VF compared with non-inducible cases, there was a high incidence of abnormal electrophysiological parameters, including conduction and refractoriness, but inducibility itself could not predict the recurrence of cardiac events.72,73 Inducible VT/VF after the administration of sodium-channel blockers was also assessed for its usefulness as a marker of cardiac events, but no strong evidence was achieved and no large-scale trials to confirm its usefulness in Japanese patients have been conducted so far.

**Therapeutic Aspects of BS**

The only and the best therapeutic means of preventing SCD of BS patients is ICD implantation. Therefore, the patients with aborted SCD or documented VF should be treated by ICD. Because these patients are prone to recurrence of cardiac events, Syncope of unknown etiology is also considered an indication for ICD implantation, if patients show spontaneous ST elevation associated with a family history of SCD, or inducible VT/VF.9,10 In asymptomatic patients, ICD implantation is generally not recommended, because of the good prognosis, but the indication should be individualized according to the presence or absence of the multiple factors (ie, male, spontaneous ST elevation...
elevation, family history of SCD, inducible VT/VF, results of drug provocation test and positive LPs).

Drug treatments for BS are not feasible at the present time, because no single drug has been shown to successfully prevent cardiac events. Drug treatments are, therefore, indicated only as an adjunct under certain conditions, such as the acute phase of repeated VF episodes, electrical storms after ICD implantation, or patients who refuse implantation. Isoproterenol infusion has been effective for repeated VF episodes in the acute phase and for VF storms after ICD implantation.4 Experiences from Japanese institutions indicate cilostazol75 and low-dose quinidine treatment76 as ad- junctive therapy. Isoproterenol is supposed to increase the L-type Ca2+ current and cilostazol is an inhibitor of phosphodiestrase, which increases intracellular cyclic AMP and thus increases the L-type Ca2+ current. Quinidine has multiple actions on ionic currents and a potent inhibitory action on Ito. The actions of these agents are supposed to the decrease voltage gradient in the early phase of the plateau and repolarization at the RVOT. Other agents that exhibit similar actions to isoproterenol, cilostazol or quinidine are expected to exert positive effects, but so far none have been proven effective in many patients with BS.

Conclusion

BS has a relatively high incidence in Japan and is a major cause of SCD in apparently healthy individuals. Patients with aborted SCD with spontaneous ST-segment elevation are at high risk for recurrence of cardiac events. However, there is no single parameter for predicting that risk or the recurrence of cardiac events, but risk stratification can be considered by reviewing multiple factors, including spontaneous ST elevation, prolonged r-J interval in V1–3, family history of SCD, inducible VT/VF, positive provocation test with class Ic agents and positive LPs. The prognosis of asymptomatic patients is generally seen good, with certain exceptional cases. The identification of these asymptomatic patients at risk awaits further results of large-scale, long-term studies.

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