Low Risk for Arrhythmic Events in Asymptomatic Patients With Drug-Induced Type 1 ECG
– Do Patients With Drug-Induced Brugada Type ECG Have Poor Prognosis? (Con) –
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The type 1 ST-segment elevation is diagnostic for Brugada syndrome (BS) and its presence may sometimes be associated with a high risk of arrhythmic events. The type 1 ECG is also known to be unmasked by administration of sodium-channel blockers in equivocal or suspected cases of BS, and the drug-challenge test is frequently used in the diagnostic approach. In large cohort studies the spontaneous appearance of the type 1 ECG with symptoms of aborted sudden death or unexplained syncope are indicative of a poor prognosis for patients with BS compared with not having clinical symptoms. Therefore, the spontaneous type 1 ECG appears to represent an important predictive sign for cardiac events. It is unknown, however, whether or not the drug-induced type 1 ECG is as useful as the spontaneous type 1 for predicting cardiac events in asymptomatic subjects showing non-type 1 ECG. Review of the literature for large cohort studies indicates that there is a low incidence of arrhythmic events in asymptomatic patients with either the spontaneous or drug-induced type 1 ECG compared with symptomatic subjects, and the drug-induced type 1 ECG in asymptomatic patients does not add to an increase in arrhythmic risk. Therefore, drug testing to unmask the type 1 ECG in asymptomatic patients with a non-type 1 BS ECG does not have an additional value for risk stratification of cardiac events, although it might be useful in symptomatic patients showing only the non-type 1 ECG. (Circ J 2010; 74: 2464–2473)

Key Words: Arrhythmia; Brugada syndrome; Implantable cardioverter defibrillator (ICD); Prognosis; Sodium-channel blockers

Patients with Brugada syndrome (BS) are recognized as having a high risk for sudden cardiac death (SCD) from ventricular fibrillation (VF) without major structural heart disease.1–8 The hallmark for diagnosing BS is ST-segment elevation in the right precordial leads, V1–3. Although the initial report indicated a persistent ST-segment elevation in the right precordial leads as the characteristic phenotype of this syndrome,1 typical ECG changes do not exhibit a stable expression but undergo spontaneous variations in time in both the level and morphology of the ST-segment elevation.3,4,6,7 In addition to spontaneous fluctuation, ST-segment elevation is influenced by various factors, including drugs,3,4 among which the sodium-channel blockers were shown to unmask or aggravate ST-segment elevation, and have been used as both a diagnostic tool and for risk stratification of arrhythmic events for BS patients; however, the use of these drugs might sometimes induce unwanted side effects.9,10 The consensus reports by the subgroup of the Heart Rhythm Society and European Heart Rhythm Association have proposed diagnostic ECG criteria for BS.11,12 According to these, there are 3 ECG patterns: types 1, 2 and 3. Type 1 is regarded as diagnostic for BS and a final diagnosis can be made when at least 1 of the following conditions are associated with the ECG changes: documented VF and/or polymorphic ventricular tachycardia (VT), a family history of SCD at <45 years old, type 1 ECG in family members, induction of VT/VF by programmed ventricular stimulation (PVS), and syncope or nocturnal agonal respiration. Type 1 ECG induced by sodium-channel blockers is also considered as diagnostic for BS.12 As to the predictive variables for development of arrhythmic events in BS patients, the Brugada group strongly insisted that induction of VT/VF by PVS is a good predictor for cardiac events,6,13 but other study groups, including those from Japan, do not support this conclusion.7,8,14–17 so the
The validity of VT/VF provocation by PVS as a predictor of arrhythmic events is still a matter of controversy. Spontaneous appearance of the type 1 ECG was proposed as having a high predictive value for arrhythmic events in patients with BS, but in Japan the spontaneous type 1 ECG was not confirmed as a single predictor for cardiac events in large cohort studies. The conflicting results about factors predicting cardiac events in patients with BS suggest a need for further evaluation of the prognostic variables and risk stratification, especially for asymptomatic patients, and various approaches have been undertaken without reaching a definite conclusion. In several large-scale, multicenter studies, the follow-up results for BS and related conditions have indicated a similar conclusion that symptomatic patients with documented VT/VF, aborted SCD and/or syncope, excluding non-cardiac causes, have a worse prognosis than asymptomatic patients. In particular, a spontaneous type 1 ECG in addition to the aforementioned symptoms is assumed to be a good predictor of arrhythmic events. It is not known, however, whether or not the drug-induced type 1 ECG in an asymptomatic patient is a clinical sign of a poor prognosis, with future development of arrhythmic events.

We review a question as to poor prognosis of patients with a drug-induced type 1 ECG from the point of view as a con.

Multiple Factors Influence ST-T Wave Changes in BS

Multiple factors have been shown to influence ST-segment elevation in both patients with BS and suspected cases (Figure 1), and include changes in heart rate, body temperature, autonomic imbalance, glucose-induced insulin, sodium-channel blockers etc. Among these factors, the sodium-channel blockers have the most critical influence on subjects with BS and related conditions because of their action in unmasking ST elevation, as well as inducing serious arrhythmic events as unexpected or side effects.

Not only the sodium-channel blockers but also other classes and types of drugs are also known to affects ST-segment elevation and arrhythmia development in manifest and latent subjects with BS. Recently, drugs to be avoided by BS patients have been recommended (www.brugadadrugs.org) because of the occasional and unexpected development of BS-type ST elevation and ventricular tachyarrhythmias. Drugs used in patients with BS and suspected cases are categorized into 4 groups: (1) drugs to be avoided; (2) drugs that are preferably avoided; (3) antiarrhythmic drugs and (4) diagnostic drugs. Sodium-channel blockers, such as procainamide, flecainide and pilsicainide, are recommended as diagnostic drugs for BS, and in Japan, pilsicainide, which exhibits the property of pure sodium-channel blocker, has been preferred for the diagnostic purpose of unmasking suspected cases. Quinidine, on the other hand, is classified as a sodium-channel blocker that will effectively suppress ST-segment elevation and prevent ventricular tachyarrhythmias. The preventive effects of quinidine are supposed to be exerted through its action on a specific K+ current, Ito. The morphology and degree of ST-segment elevation may also be influenced by different positions of the recording electrodes. Higher placement of the right precordial leads than the conventional position at V1-3 can also be used to unmask the BS-type ECG in subjects without typical ECG changes or unequivocal signs. Demonstrating and unmasking the type 1 ECG at the higher lead positions are also
regarded as of diagnostic value for BS, similar to its appearance at the conventional lead position of V1–3. In addition, similar ECG changes as those in BS are seen in various normal and abnormal conditions, including early repolarization in apparently healthy individuals and young athletes, and in cases of left ventricular hypertrophy, acute myocardial infarction, pericarditis, variant angina pectoris, arrhythmogenic right ventricular cardiomyopathy, pulmonary embolism, and hyperkalemia. Therefore, interpretation and diagnosis of the BS-type ECG are to be done with careful history taking, as well as physical and laboratory examinations.

**Clinical Diagnosis of BS and Risk Stratification of Arrhythmic Events**

The diagnosis of BS is generally based on the presence of typical ECG changes associated with symptoms of aborted SCD and/or documented VT/VF or syncope, but there are many borderline cases with patients showing atypical ECG with or without such clinical symptoms. The proposed diagnostic criteria in the consensus reports, including the presence of the type 1 ECG in association with at least 1 of 4 clinical conditions, appear to be widely supported (Figure 2). Therefore, the presence of the typical ECG pattern is critical for the diagnosis of BS and various approaches are directed to revealing or unmasking the type 1 ECG in equivocal or suspected cases. The drug challenge test by sodium-channel blocker is recommended by the consensus reports as having similar diagnostic usefulness as the spontaneous type 1 ECG. It should be pointed out, however, that there are several problems with the drug challenge test, including the different sodium-channel blockers used, lack of standardized doses or uniform application procedure and uncertain endpoints.
The demonstration of a type 1 ECG in recordings obtained with the higher lead positions is also regarded as a diagnostic sign, and the guideline of the Japanese Circulation Society proposes that findings at the higher lead placement (up to the 2nd intercostal space from the conventional lead position of V1–3) have the same diagnostic significance as a drug challenge test. Moreover, ECG recordings during exercise, glucose tolerance or full-stomach testing or during ingestion of meals are also considered as useful for inducing and unmasking the type 1 ECG in some cases.

As to risk stratification of arrhythmic events, the value of the induction of VT/VF by PVS is still a matter of controversy. The spontaneous type 1 ECG is regarded as a predictive factor for prognosis mainly in European studies, but is not supported in Japanese large cohort studies, especially in asymptomatic patients (details discussed later). In addition, multiple variables have been indicated as useful for predicting prognosis and risk stratification of patients with BS, but there is not a general consensus. These factors include prolongation of QRS duration, presence of a J wave, positive late potential, sex, family history of SCD, and the presence of the cardiac sodium channel gene (SCN5A).

**Recommendation for Implantable Cardioverter Defibrillators (ICD) Implantation in BS Patients**

The consensus report by the Heart Rhythm Society and European Heart Rhythm Association recommends ICD for BS patients. Symptomatic patients displaying the type 1 ECG both spontaneously and after provocation by sodium-channel blocker should undergo ICD implantation without further examinations or after exclusion of non-cardiac cause of the symptoms. On the other hand, asymptomatic patients exhibiting a type 1 ECG with or without drug challenge should undergo PVS if a family history of SCD is suspected to be caused by BS. PVS is justified in asymptomatic patients with a spontaneous type 1 ECG, even if the family history is negative for SCD. In patients with inducible VT/VF, ICD implantation should be recommended. However, asymptomatic patients without a family history of SCD, who display the type 1 ECG only after provocation by sodium-channel blocker, should be closely followed up without ICD implantation (Figure 3).

**Risk Stratification and Prognosis in Asymptomatic BS Patients**

The long-term prognosis of patients with the BS-type ECG and the therapeutic approach have recently been reported in multicenter studies, and according to their findings, risk stratification and prognosis in asymptomatic patients, espe-
Eckardt et al.\(^8\) report the long-term prognosis in a large population of individuals with a type 1 ECG. They demonstrated that only 1 of 123 asymptomatic patients (0.8\%) had a first arrhythmic event during a long follow-up period (mean, 32 months). The only asymptomatic individual who became symptomatic during the follow-up had a spontaneous type 1 ECG during a routine examination and none of those with a drug-induced type 1 ECG developed any arrhythmic events.

The Japan Idiopathic Ventricular Fibrillation Study (J-IVFS)\(^15\) followed a total of 166 BS patients with a type 1 ECG for a mean of 37±16 months. There were 84 symptomatic patients (syncope or documented VT/VF) and 82 asymptomatic cases. There was no significant difference in the presence or absence of symptoms between subjects with a spontaneous or drug-induced type 1 ECG. The symptomatic patients had a significantly higher incidence of arrhythmic events than the asymptomatic cases during approximately 3 years of follow-up. Induction of VT/VF by PVS was not shown to be a predictive factor for cardiac events. Although 36 of 84 symptomatic patients developed cardiac events (VT/VF and syncope), none of the 82 asymptomatic patients, including 64 with a spontaneous type 1 ECG. Multivariate analysis showed that an r-J interval in V\(_2\) ≥ 90 ms and QRS duration in V\(_6\) ≥90 ms had predictive values for cardiac events in symptomatic patients, but no predictive factors could be determined in asymptomatic patients, because of the low incidence of the events. In 2 cases among the 12 patients with a drug-induced type 1 ECG in the symptomatic group cardiac events occurred during the follow-up, but there were none in the 18 such cases in the asymptomatic group. That study’s results suggest that asymptomatic subjects displaying type 1 ST elevation, regardless of whether it is a spontaneous appearance or induced by a drug challenge test, appear to have a low risk for arrhythmic events.

The study by BS Investigators in Japan,\(^16\) which included patients with type 1 as well as non-type 1 ECG, also indicated that symptomatic patients had a worse prognosis than asymptomatic cases, and the annual incidence of arrhythmic events was similar to the 2 previous studies.\(^8,15\) A family history of SCD at age <45 years and presence of inferolateral early repolarization in the ECG were proven significant in indicators of poor outcome. However, neither VF inducibility nor spontaneous type 1 ST elevation correlated with the development of arrhythmic events during a mean follow-up period of 47 months. Among 207 asymptomatic individuals, only 3 who showed spontaneous type 1 ST elevation developed arrhythmic events, suggesting a low risk. Of particular interest in that study, it was noted that the long-term prognosis of probands with BS in the non-type 1 group was similar to that with BS in the type 1 group. As to the prognosis of the subjects with the drug-induced type 1 ECG, 3 of 26 patients (11\%) in the symptomatic group had cardiac events compared with 0 of 46 (0\%) in the asymptomatic group.

Recently, the largest cohort study of patients so far, the FINGER BS registry, has reported the prognosis and risk factors of arrhythmic events.\(^17\) A total of 1,029 consecutive cases were registered from 11 tertiary in 4 European countries. During a median follow-up of 31.9 months, cardiac event rate per year was 7.7\%, 1.9\% and 0.9\% in patients with aborted SCD, syncope and asymptomatic patients, respectively. Only 4 (1\%) of 386 asymptomatic patients with the drug-induced type 1 ECG had cardiac events during the follow-up, whereas 15 (8.5\%) of 175 symptomatic patients especially those exhibiting a drug-induced type 1 ST elevation, are still controversial.
**Figure 5.** ECG from a patient showing non-type 1 (saddleback type) ST elevation in the right precordial leads (Left). A transient spontaneous type 1 ECG was recorded on only 2 occasions 3 years ago (Right).

**Figure 6.** Ventricular fibrillation developed 3 years after ICD implantation in the same patient as shown in Figure 5. The patient had appropriate ICD shocks for VF at 0:17 and 0:27 am while sleeping, and VF was terminated spontaneously at 0:35 and 0:39 am. ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation.
had such events. The study concluded that symptoms and a spontaneous type 1 ECG were significant predictors of arrhythmic events during the long-term follow-up period, but a predictive value for inducibility of ventricular tachyarhythmias by PVS or the presence of a mutation in SCN5A was not found.

Prognosis of Asymptomatic Patients With Drug-Induced Type 1 ECG

The long-term prognoses of patients with the drug-induced type 1 ECG from the 4 multicenter studies are summarized in Table. Although cardiac events in symptomatic patients with the drug-induced type 1 ECG, including SCD, VT/VF and/or syncope, had an incidence of 3–17% during the follow-up period, asymptomatic patients with the drug-induced type 1 had a very low incidence of cardiac events (0–1%). Therefore, certain numbers of symptomatic patients with the drug-induced type 1 ECG carry a poor prognosis and a drug challenge test may be valuable to unmask the type 1 ECG and possible development of cardiac events in symptomatic cases with non-type 1 ECG at baseline. There is no clear evidence for a poor prognosis in asymptomatic patients with the drug-induced type 1 ECG.

In the studies discussed here, it should be noted that detection of the spontaneous type 1 ECG and the indication for a drug challenge test are not done under the same format. Namely, the frequency and number of ECG recordings to judge individuals as showing a type 1 or non-type 1 ECG at baseline are not defined among the different subjects, and the timing of the conduct of the drug-challenge test is not determined under the same format among different studies and cases. These factors are quite important to account for the spontaneous and drug-induced type 1 ECGs because of the fluctuating nature of ST-segment elevation in time at baseline and the difficulty in defining the type of ECG for each subject after either single or multiple examinations. Figures 5 and 6 show a representative case, highlighting the difficulty in determining the type of ECG on presentation and the indication for ICD implantation. This patient had shown a transient spontaneous type 1 ECG on only 2 occasions 3 years ago and the remaining several examinations during approximately 6 months of observation showed either type 2 or 3. Finally the patient underwent a drug challenge test with pilsicainide, resulting in the development of the type 1 ECG. VF was induced by PVS done on this occasion at baseline. Because of VF induction by PVS, together with the transient and spontaneous type 1 ECG at baseline, he underwent ICD implantation. He had been free of symptoms and VF episodes for 3 years after ICD implantation, with presentation of type 2 ECGs on several occasions, when he finally developed VF episodes, which were detected by ICD (Figure 6). In this case, we believe the presence of a transient spontaneous type 1 ECG rather than the drug-induced one was an important risk predictor for arrhythmia events.
In considering the infrequent appearance of the type 1 ECG in baseline recordings and its significance for detection of arrhythmic events, we evaluated the long-term prognosis of 35 asymptomatic patients who only showed the drug-induced type 1 ECG (unpublished data). None of them showed a spontaneous type 1 ST elevation with a mean of 12±8 ECG records. In 8 of the 35 patients there was a family history of SCD or BS; 25 of the 35 patients underwent PVS and VF was induced in 17. ICD implantation was performed in 10 of the 17 patients, who were followed for a mean of 45±42 months without developing any cardiac events. Therefore, drug testing in asymptomatic patients with non-type 1 ECG does not seem to be of additional value for risk stratification for cardiac events, but they should be followed to detect the transient appearance of a spontaneous type 1 ECG. It should be stressed that the level and morphology of ST elevation in patients with BS spontaneously fluctuate in time as shown in Figure 7.28 Another factor to be borne in mind is that hundreds of thousands of Japanese may exhibit a non-type 1 ECG, considering its prevalence in adults and children.24-46 The drug challenge test probably cannot be performed in such large numbers and might be associated with adverse reactions. Therefore, in asymptomatic individuals, multiple and repeated ECG recordings rather than drug testing is recommended for detecting the transient appearance of a spontaneous type 1 ECG, which may indicate future development of arrhythmic events.

**Adverse Effects of Drug Challenge With Sodium-Channel Blockers**

Although the presence of a type 1 ECG with or without sodium-channel blocker challenge is regarded as a diagnostic sign for BS, and sometimes can be used as the decision for therapy in symptomatic patients without a spontaneous type 1 ECG,11,12 the drug challenge test for asymptomatic patients is still controversial and may need careful consideration of its adverse effects.

Evain et al47 used flecainide or ajmaline for the sodium-channel blocker test in 158 patients displaying a type 2 or 3 ECG. Their results showed that the presence or absence of type 1 ST elevation during the test denoted a profound electrophysiological difference, but no serious complications were provoked in any of the 158 patients, suggesting the test might be safe. The efficacy of the sodium-channel blocker challenge test using pilosicainide in patients with a BS-type ECG or normal ECG has been explored in several studies.48-50 In these studies, adverse effects of pilosicainide administration, including VT/VF, frequent premature ventricular contractions, marked ST elevation or extensive QRS prolongation, occurred in approximately 13% of the study population who did not have a spontaneous type 1 ECG.49,50 Therefore, a pilosicainide challenge test should carefully be performed in asymptomatic individuals with a non-type 1 ECG, considering both the beneficial and adverse effects.

**Prevalence of Asymptomatic Patients With BS-Type ECG**

The BS-type ECG had an incidence of 0.14–0.7% in health screening examinations conducted in Japanese adult populations, in which diagnosis was mostly done macroscopically.41-44 The prevalence of a BS-type ECG in Japanese children was comparatively much lower (0.02–0.054%).45,46 In those reports, a large number of patients with a BS-type ECG obtained during health screening examinations were thought to be asymptomatic individuals displaying a non-type 1 (saddleback) ECG.

Recently, we proposed automatic criteria for computerized diagnosis of BS-type ECG.51 In that study, BS-type ST-segment elevation in V1–3 was classified into 3 types: 1, 2/3 and S. Type 1 was defined as the same as type 1 in the consensus reports.11,12 Type 2/3 was defined as a saddleback-type ST-segment elevation with a J-wave amplitude ≥0.2 mV and positive or biphasic T waves. Type S, as abbreviated terminology for “suggestive”, was defined as a coved-type ST-segment elevation with J-wave amplitude between 0.1 and <0.2 mV. The ECG data from the annual health examinations of 36,674 workers and 155,999 school children were used to explore the diagnostic accuracy of the proposed criteria. The automatic criteria had a comparable detection rate (0.6% in adults and 0.16% in children) of the 3 BS-type ECGs to macroscopic inspection. The numbers detected by the automatic criteria for types 1, 2/3 and S were 20 (0.05%), 161 (0.44%) and 40 cases (0.11%), respectively, of the total cases.51 Therefore, non-type 1 (types 2/3 and S) were detected in 0.55% of adults, most of whom were usually asymptomatic.

**Conclusions**

There is a low risk for arrhythmic events in asymptomatic patients with the type 1 ECG provoked only by sodium-channel blockers. A drug challenge test, therefore, appears to be a poorly significant tool for risk stratification of arrhythmic events in asymptomatic patients, considering their prevalence and the adverse effect of the test. On the other hand, because the demonstration of a drug-induced type 1 ECG is sometimes associated with development of arrhythmic events in symptomatic patients, the test may be applicable to symptomatic patients showing a non-type 1 ECG. Therefore, we believe that asymptomatic patients with a drug-induced type 1 ECG do not generally have a poor prognosis.

**References**


Authors’ Comments on the Pro-Side Authors

In the protagonist’s view, Dr. Shimizu mentions that patients with a drug-induced type 1 ECG carry a poor prognosis if they have a history of VF or aborted SCD. We agree with that opinion, because symptomatic patients have been shown to carry a worse prognosis than asymptomatic cases in various multicenter studies and the demonstration of a drug-induced type 1 ECG is sometimes associated with the development of arrhythmic events in symptomatic patients during the follow-up period. For this reason, it is conceivable that the drug challenge test may be applicable to symptomatic patients showing only a non-type 1 ECG at baseline. Second, Dr. Shimizu expresses a persuasive opinion that asymptomatic patients with a drug-induced type 1 ECG also have a poor prognosis on the basis of the possible presence of a VF substrate in many asymptomatic patients associated with a high inducibility of VF by EPS and estimated annual deaths of 360 among these patients in Japan, in which 40% of total cases with a type 1 ECG were arbitrarily taken as drug-induced type 1. As to the risk stratification of arrhythmic events, however, the utility of VT/VF provocation by EPS is still a matter of controversy in various multicenter studies, including those from Japan. Furthermore, the estimated number of annual deaths in asymptomatic patients was calculated from an annual event rate of 0.5% based on reference 16. However, the patients exhibiting arrhythmic events during follow-up in this paper represented spontaneous type 1 cases and none had a drug-induced type 1 ECG. Review of the literature for recent large cohort studies indicates a very low incidence of arrhythmic events in asymptomatic patients with a drug-induced type 1 ECG compared with symptomatic subjects. Therefore, we consider that the estimated annual event rate in asymptomatic patients with a drug-induced type 1 ECG can not be correctly determined because of the small numbers of such patients. On the contrary, as we discuss, asymptomatic patients only exhibiting a drug-induced type 1 ECG had a low incidence of arrhythmic events during a mean follow-up period of 31–47 months. Therefore, we believe that asymptomatic patients with a drug-induced type 1 ECG do not have a poor prognosis. Certainly, we need further study with increased numbers and longer follow-up of asymptomatic patients with exclusively a drug-induced type 1 ECG to achieve a firm conclusion.