THE FIRST VIRTUAL SYMPOSIUM ABOUT THE BRUGADA SYNDROME

The Suggested Topic: #7 and #20

Noninvasive Markers to Identify Patients at Risk in the Brugada Syndrome: Insight into Risk Stratification

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In patients with the Brugada-type electrocardiography (ECG), particularly asymptomatic individuals, identification of high-risk patients is important for preventing fatal ventricular arrhythmias and sudden death. At present, several indices have been proposed and suspected for the risk stratification of patients with Brugada syndrome (**Table**), but most of them have not yet been fully established and some of them are still controversial.

Table. Proposal risk stratification of arrhythmic events or sudden cardiac death with noninvasive markers in individuals with the Brugada-type ECG

Proposal indices
Age, 30-50 yr
Gender, male
Family history of sudden death
Symptomatic episodes
Coved-type ST-segment elevation
Magnitude of ST-segment elevation
Transient normalization of ST-segment elevation
Spontaneous ST-segment elevation
Higher intercostal space lead ECG
ECG manifestation by antiarrhythmic drugs
Increased vagal activity
Abnormal sympathetic nervous system
Late potentials by signal-averaged ECG
T-wave alternans
QT-interval dispersion
Electron-beam computed tomography
Sodium channel gene (*SCN5A*)

Gender and Age

In data on 63 patients with Brugada syndrome by Brugada et al.,[1] there was no relationship between gender/age and recurrent arrhythmic events. In contrast, in an evaluation of 60 patients diagnosed with the syndrome from 52 families by Priori et al.,[2] the ECG diagnosis was predominant among males (75%), and 82% of the cardiac arrests occurred in males at a mean age of 37 years. A number of previous and subsequent reports agree with the observation by Priori et al.[2] Thus, being male may be a risk factor for sudden death. The age of 30-50 may be also a risk factor of the syndrome because most of events occur in these ages. As a novel observation, Priori et al.[3] reported that pediatric cases of Brugada syndrome that was suspected based on a genetic analysis of five children from the same family who had died after unexplained cardiac arrest. Suzuki et al.[4] have also experienced an infant case with a malignant form of Brugada syndrome. Corrado et al.[5] have recently indicated that in an assessment on RBBB, right precordial ST-segment elevation and sudden death in young people (≤35 years), ST-segment elevation compatible with the Brugada-type ECG was found in 14% of young sudden death victims, whereas it mostly reflected underlying arrhythmogenic right ventricular cardiomyopathy. To confirm the prognostic value of gender and age, a larger population study with Brugada patients without any structural heart problems may be necessary.

Family History

Since Brugada syndrome is considered to be a genetically transmitted arrhythmogenic disease that is inherited as an autosomal dominant trait,[6] a family history of unexpected sudden death may be a risk factor for sudden cardiac death. Numerous clinical reports have mentioned that the patients with sudden cardiac death or life-threatening events often have a family history of this. However, the incidence of positive family history was not as high among patients with Brugada syndrome[7] and interestingly, no study has provided any evidence that a family history of unexpected sudden death is a predictor of future arrhythmic events.

Symptomatic Episodes

Brugada et al.[1] initially described that asymptomatic patients with the ECG anomaly have the same risk of arrhythmic events as patients who have had an episode of aborted sudden death. Recently, in two larger cohorts of individuals with a Brugada-type ECG,[8,9] they reported an alternative result regarding the incidence of arrhythmic events among symptomatic and asymptomatic patients. In first cohort (n=252) with an alternative result,[8] 45 of the 116 symptomatic patients (39%) developed a recurrent or first arrhythmic event during a mean follow-up of 34±40 months, and the highest incidence of arrhythmic events occurred in patients previously resuscitated from near sudden cardiac death (32 of 54 patients [59%]). In contrast, only 7 of 136 asymptomatic individuals (5%) developed a first arrhythmic event during the follow-up. In the second cohort (n=334),[9] 44 of the 71 patients (62%) identified after a resuscitated cardiac arrest had a new arrhythmic event during 54±54 months of follow-up and 14 of the 73 patients (19%) identified after a syncopal event had a new event during 26±36 months of follow-up, whereas in asymptomatic individuals, only 16 of 190 individuals (8%) had a first arrhythmic event during a mean follow-up of 27±29 months. As a similar result, Atarashi et al.,[10] reported that only one patient (1.5%) had an arrhythmic event (VF) among 67 asymptomatic individuals during a 3-year follow-up. In the study (n=30) by Priori et al.[2] and the small sample (n=11) by Takenaka et al.,[11] none of the asymptomatic individuals had defined arrhythmic events or sudden death during a mean follow-up of 33±38 months and 43±22 months, respectively. Miyasaka et al.[12] have reported one death among 98 subjects with the Brugada-type ECG (1.0%) and 139 deaths among 13,831 subjects without the Brugada-type ECG (1.0%) during 2.6±0.3 years of follow-up in a community-based population. They stated that the total mortality of subjects with the Brugada-type ECG did not differ from the mortality of those without the Brugada-type ECG; it is unknown whether the subjects with the Brugada-type ECG had symptoms or not.

It appears that asymptomatic individuals with the Brugada-type ECG have a rare cause of sudden cardiac death and a benign clinical course that does not differ from individuals without the Brugada-type ECG. In contrast, the

symptomatic patients who had a history of VF or syncope develop cardiac events more frequently, as shown in the studies by Brugada et al.[8] (45/116 patients [39%] during the follow-up of an average of 34 months), Brugada et al.[9] (58/144 patients [40%] during the follow-up of 26-54 months), Priori et al.[2] (5/30 patients [16%] during the follow-up of an average of 33 months), and Atarashi et al.[10] (26% of the 38 patients during a 3-year follow-up). Thus, symptomatic episodes could be a useful index for identifying high-risk patients in the syndrome.

Resting Surface ECG Parameters

As shown in many clinical reports, a coved-type ST-segment elevation has been observed more frequently than the saddle-back type in patients diagnosed with Brugada syndrome, especially in patients at risk. This evidence may indicate that a coved pattern of ST-segment elevation may be one of the risk stratifiers in the syndrome. In the study by Atarashi et al.,[10] the coved type was present in 17 of 20 patients (85%) with ventricular fibrillation and 11 of 18 patients (61%) with syncope, and the remaining lower incidence of patients had the saddle-back type. However, these types may be changed during the follow-up, as shown in the study by Matuso et al.[13] This issue was not discussed in the study by Atarashi et al.[10]

There are no reports that the magnitude of ST-segment elevation on the resting surface ECG can serve as an independent index for identifying patients at risk in the Brugada syndrome. The relationship between life-threatening events and the magnitude of J-point elevation at rest have been evaluated in patients with the syndrome.[14] No relationship was found to exist among their values. Matsuo et al.[13] have also compared the magnitude of ST-segment elevation in leads V_1/V_2, QRS width and the corrected QT interval measured during the follow-up between the unexpected death group and the other group. These ECG parameters were not associated with unexpected death. In addition, Brugada et al.[15] have showed that patients with transient normalization of the ECG were at risk of ventricular arrhythmias, as well as patients in whom it was persistent. The magnitude of ST-segment elevation on the resting surface ECG would not be a risk factor. Rather the transient normalization of the ECG may represent an important diagnostic challenge.[15,16] However, a dynamic

elevation of the ST segment in lead V_1 to V_3 may be a signal for the sudden onset of ventricular arrhythmia because much clinical evidence has revealed that the ECG was dynamically enhanced before the occurrence of ventricular arrhythmias.[17,18] In a recent study by Brugada et al.,[9] it has been shown that patients with a spontaneously abnormal ECG have the poorer prognosis. As a similar result, Priori et al.[19] have reported the combined presence of a spontaneous ST-segment elevation in leads V_1-V_3 and the history of syncope identifies patients at risk in the syndrome.

Recently, Sangwatanaroj et al.[20] presented that the higher intercostal space V_1 to V_3 lead ECG, with or without antiarrhythmic drugs is superior to the conventional 12-lead ECG in the detection of the Brugada-type ECG in both sudden unexplained death syndrome survivors and their relatives. This observation may suggest only that more individuals with ST-segment elevation are identified when leads are moved one intercostals space above standard positions because it remains to be proven if those patients showing the ECG abnormalities only with the leads in the modified positions are true positive or false positive individuals for the syndrome. No study on genotyped individuals has demonstrated the value of this novel position in unmasking carriers of the genetic defect that are silent with conventional position of the leads and positive when leads are moved upward. Therefore, it is unknown if this alternative technique on the resting surface ECG serve as an independent index for identifying patients at risk in the syndrome.

Pharmacological Manifestation

The ECG feature of Brugada syndrome is dynamic and sometimes concealed, but it is well known that the administration of sodium channel blockers such as flecainide, pilsicainide, ajmaline, procainamide and disopyramide can unmask its concealed forms.[15,21-26] Although intravenous administration of these drugs is most effective in unmasking the Brugada-type ECG,[15,21,22,25,26] oral administration of class IC antiarrhythmic drugs such as flecainide, pilsicainide and encainide has been shown to be effective as well.[23,24] It has also been shown that these drugs are useful in evaluating the inducibility of VT/VF during electrophysiologic study.[8] Priori et al.[2] have shown that a pharmacological challenge with

sodium channel blockers was unable to unmask most silent gene carriers of the Brugada syndrome. With respect to the prognostic significance and risk stratification of the pharmacological effect, it remains assessed fully. No study has revealed a difference in the occurrence of arrhythmic events between patients with and without the manifestation of Brugada-type ECG by antiarrhythmic drugs. Only some case reports[27,28] that documented the spontaneous induction of ventricular tachycardia by intravenous administration of class IA antiarrhythmic drugs support this hypothesis.

Vagal Activity

First, Miyazaki et al.[21] provided the modulator effects of the autonomic nervous system on the ST segment by intravenous administration of autonomic receptor agonists and blockades in patients with Brugada syndrome. Kasanuki et al.[22] have proposed that vagal activity represented by heart rate variability patterns during 24-hour Holter monitoring influences a possible new mechanism of VF in patients associated with Brugada syndrome. Heart rate spectral analysis just before VF episodes in Holter monitoring showed a sudden rise in the HF (i.e., vagal activity) and a decrease in the LF/HF ratio (sympathetic activity) in the two patients studied. Matsuo et al.[29] also reported that increased nocturnal vagal activity and withdrawal sympathetic activity play an important role in the arrhythmogenesis of Brugada syndrome. Samniah et al.[30] have demonstrated the occurrence of a vasovagal syncope during the recovery period after an exercise stress test in a patient with ECG and pharmacological findings suggestive of Brugada syndrome. Itoh et al.[31] suggested that malignant ventricular arrhythmias were associated with pronounced ST-segment elevation that occurred at night or early in the morning. Although an association between vagal activity and arrhythmogenesis of the syndrome is an interesting point, no study has revealed the prognostic significance of vagal activity in the triggering of VF.

An Abnormal Sympathetic Nervous System

Recently, Wichter et al.[32] investigated the sympathetic nervous system in 17 patients with Brugada syndrome with

the use of [^{123}I]m-iodobenzylguanidine (^{123}I-MIBG), single-photon emission CT (SPECT), and quantitative 33-segment bull's-eye analysis. As a result, this study demonstrated an abnormal ^{123}I-MIBG uptake in the inferior and septal left ventricular wall in patients with Brugada syndrome, indicating presynaptic sympathetic dysfunction of the heart. These findings may have the impact on the pathophysiology in patients with Brugada syndrome. However, it remains unknown if an abnormal sympathetic nervous system is associated with arrhythmogenesis of the syndrome.

Late Potentials by Signal-Averaged ECG

Several clinical studies[14,22,33,34] in patients with Brugada syndrome have demonstrated that late potentials by signal-averaged ECG were observed in most patients with documented VF. In a small patient population compatible with this syndrome by Kasanuki et al.,[22] all 5 patients with a history of VF had LP when the characteristic ECG findings were present. Kasanuki et al.[22] have also shown a conduction delay in the area between the anterior wall and the septal region of the right ventricular outflow tract using body-surface mapping. In reports from Nademanee et al.[33] and Kobayashi et al.,[34] late potentials were shown in 11 of 13 Brugada patients and in all 4 Brugada patients studied, respectively. The value of this noninvasive marker has been assessed to identify high-risk patients in a larger population (n=33).[14] The results were used to test the hypothesis that arrhythmogenesis in this syndrome is associated with conduction disturbance in the right ventricle. There were a total of 33 patients (45±14 years, 31 men) who had an ECG with an RBBB pattern (i.e., mimic RBBB) and ST-segment elevation $\geq$0.1 mV (either a coved or saddle-back type) in leads V_1 to V_3, and structurally normal hearts. In this study, late potentials were defined as positive when two criteria (abnormal RMS_{40} and LAS_{40}) excluding prolonged f-QRS were met because the QRS width influences the outcome of late potentials. Late potentials were present in 24 Brugada patients (73%). The incidence of late potentials in Brugada patients was significantly higher than in the controls. Of 19 patients with life-threatening events, 17 patients (89%) documented late potentials. The presence of LP had significant correlation with the occurrence of life-threatening events (positive predictive value 71% and negative predictive value 78%).

However, it is still not really known whether late potentials can serve as an independent risk stratifier for cardiac events because this study assessed the prognostic value retrospectively.[35] An analysis of the follow-up data would resolve this question.

Noninvasive Markers of Repolarization Inhomogeneity

Antzelevitch et al.[36,37] have shown that the pathogenesis of the ECG manifestations of this syndrome are due to heterogeneous loss of the action potential dome, causing a marked epicardial and transmural dispersion of repolarization, which may result in the production of ST-segment elevation, thus giving rise to phase 2 reentry. These observations support the hypothesis that the mechanism of malignant ventricular arrhythmias in this syndrome is caused by repolarization abnormality. T-wave alternans (i.e., a temporal repolarization abnormality) and QT-interval dispersion (i.e., a spatial repolarization abnormality) have been provided as noninvasive tools in identifying patients at risk; although, there are two case reports[38,39] showing the occurrence of visible T-wave alternans without subsequent ventricular arrhythmias after intravenous administration of class I antiarrhythmic drugs in a patient with Brugada syndrome. No study has shown the prognostic value of T-wave alternans as well as QT-interval dispersion in patients with Brugada syndrome. The prognostic value of microvolt T-wave alternans and QT-interval dispersion were assessed as noninvasive risk stratification markers in patients with Brugada syndrome.[14] The incidence of microvolt T-wave alternans and QT-interval dispersion was not significantly different from that of the controls and both markers were not correlated with the occurrence of life-threatening events.

Electron-Beam Computed Tomography

Takagi et al.[40] have shown that the sites of morphological abnormalities detected by electron-beam computed tomography and not detected by echocardiography and right ventriculography in patients with Brugada syndrome were

related to the origins of premature ventricular contractions recorded only in the acute phase, which may trigger VF, and have proposed that these morphological abnormalities may be related to arrhythmogenic substrates in the syndrome. The abnormalities were detected not only in the right ventricular outflow tract but also in the right ventricular apex in some patients. Their observations may prompt discussion regarding the relationship between these morphological abnormalities and arrhythmogenic right ventricular cardiomyopathy.[41]

Genetic Marker (*SCN5A*)

A molecular defect in the cardiac sodium channel gene, *SCN5A*,[42] which is the same gene implicated in the LQT3 form of patients with long-QT syndrome, has been reported as the genetic basis of the syndrome.[6] Therefore, the syndrome is considered as a genetically transmitted arrhythmogenic disease that is associated with an increased risk of sudden cardiac death. Many genetic reports for Brugada syndrome have revealed the importance of mutations that enhance sodium channel inactivation.[2,43-50] At present, the only gene linked to the syndrome is the cardiac sodium channel gene (*SCN5A*). Priori et al.[2] have revealed that mutations of the *SCN5A* gene were identified in 8 of 52 families (15%); 3 were symptomatic and 5 were asymptomatic. This observation may demonstrate that other genes are involved in the syndrome. Priori et al.[2] have also reported that the administration of flecainide or ajmaline failed to unmask the disease in all carriers of the genetic defect with a normal ECG. In contrast, Brugada et al.[15] have reported that the administration of ajmaline, procainamide, or flecainide revealed the disease in all patients with transient normalization of the ECG and *SCN5A* mutation. Thus, the pharmacological effect with sodium channel blockers in gene carriers is at variance. In addition, no study has shown the impact of genetic analysis in risk stratification of the syndrome. Assessing an *SCN5A* mutation as the index to detect patients at high risk in the syndrome will be a task of interest for electrophysiologists in this field.

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