Assessment of Noninvasive Markers in Identifying Patients at Risk in the Brugada Syndrome: Insight Into Risk Stratification

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OBJECTIVES
The aim of this study was to compare the use of various noninvasive markers for detecting risk of life-threatening arrhythmic events in patients with Brugada syndrome.

BACKGROUND
The role of conduction disturbance in arrhythmogenesis of the syndrome is controversial, whereas it is well established that repolarization abnormalities are responsible for arrhythmias. The value of noninvasive markers reflecting conduction or repolarization abnormalities in identifying patients at risk for significant arrhythmias has not been shown.

METHODS
We assessed late potentials (LP) using signal-averaged electrocardiography (ECG), microvolt T-wave alternans (TWA), and corrected QT-interval dispersion (QTD) in 44 consecutive patients who had ECGs showing a pattern of right bundle branch block and ST-segment elevation in leads V1 to V3 but structurally normal hearts. The patients were compared with 30 normal individuals.

RESULTS
Eleven patients were excluded from data analysis because of an absence of ECG manifestations of Brugada syndrome at the time of the tests. A history of life-threatening events defined as syncope and aborted sudden death was present in 19 of 33 patients (58%); in 15 of the 19 patients, stimulation induced ventricular fibrillation or polymorphic ventricular tachycardia. The LP were present in 24 of 33 patients (73%); TWA were present in 5 of 31 patients (16%); and a QTD > 50 ms was present in 9 of 33 patients (27%). The incidence of LP in Brugada patients was significantly (p < 0.0001) higher than in the controls, whereas incidences of TWA and QTD were not significantly different. Multivariate logistic regression analysis revealed that the presence of LP had the most significant correlation to the occurrence of life-threatening events (p = 0.006).

CONCLUSIONS
Late potentials are a noninvasive risk stratifier in patients with Brugada syndrome. These results may support the idea that conduction disturbance per se is arrhythmogenic. (J Am Coll Cardiol 2001;37:1628–34) © 2001 by the American College of Cardiology
fying patients at risk for life-threatening ventricular arrhythmias has not been studied in Brugada syndrome. The aim of the present study was to compare usefulness of LP, TWA, and QTD for identifying patients with Brugada syndrome susceptible to life-threatening events associated with ventricular fibrillation (VF) or polymorphic ventricular tachycardia (VT). Our results were used to test the hypothesis that a conduction abnormality marker is better than repolarization abnormality markers in predicting patients at high risk in the syndrome and that arrhythmogenesis in this syndrome is associated with the conduction disturbance in the right ventricle.

METHODS

Patient population. A total of 44 consecutive patients who had an ECG with either persistent or transient RBBB pattern and ST-segment elevation ≥0.1 mV (either of a coved or saddle-back type) in leads V_1 to V_2 or V_3 during sinus rhythm were entered into this study (Fig. 1). In all patients studied, a typical widened S-wave and a wide QRS complex (≥120 ms) in the left lateral leads were absent, suggesting patients did not have a true RBBB (i.e., mimic RBBB). These patients were treated at Toho University Ohashi Hospital and Tokyo Metropolitan Hiroo General Hospital between December 1996 and May 2000. Although all patients underwent all three noninvasive tests, 11 patients were excluded from data analysis because of an absence of characteristic ECG manifestations (an RBBB pattern and ST-segment elevation in the right chest leads) for Brugada syndrome at the time of the tests. A total of 33 patients (45 ± 14 years, 31 men) were assessed in this study.

Before diagnosing Brugada syndrome, we excluded patients who had evidence of organic heart disease, including arrhythmogenic right ventricular cardiomyopathy, myocardial ischemia of the right ventricle, and other infiltrative cardiomyopathies. These diagnoses were based on echocardiography (all 33 patients), coronary angiography with acetylcholine (25 patients), left or right ventriculography (23 patients), scintigraphy (16 patients), helical CT scan (15 patients), magnetic resonance imaging (14 patients), and endomyocardial biopsy (9 patients). Therefore, all patients studied were believed to have structurally normal hearts. No patient had used antiarrhythmic drugs or had electrolyte disturbances when the characteristic ECG findings were identified. The values of LP, TWA, and QTD in patients with the syndrome were sequentially assessed and compared. These values were also compared to those of normal individuals who were matched for age and gender.

Measurements of noninvasive risk markers. LATE POTENTIALS BY SIGNAL-AVERAGED ECG. The LP were analyzed using one of two signal-averaged ECG Systems (Arrhythmia Research Technology 1200EPX or Corazonix Predictor Unit). The analysis is based on the quantitative time domain measurements of the filtered vector magnitude of the orthogonal Frank X, Y, and Z leads. The QRS complexes (≥200 beats) were amplified, digitized, averaged, and filtered with a high pass filter (40 Hz). Three parameters were assessed via a computer algorithm: 1) the filtered QRS duration (f-QRS); 2) the root mean square voltage of the terminal 40 ms in the filtered QRS complex (RMS_{40}); and 3) the duration of low-amplitude signals <40 μV in the terminal filtered QRS complex (LAS_{40}). In the present study, LP were considered as positive when two criteria (RMS_{40} <20 μV and LAS_{40} >38 ms) were met in both systems.

MICROVOLT T-WAVE ALTERNANS. After LP acquisition, the patient was kept in the same supine position as during the signal-averaged ECG recordings, and the orthogonal Frank X, Y, and Z leads and associated vector magnitude

Figure 1. Twelve-lead electrocardiogram from a patient with a pattern of right bundle branch block and ST-segment elevation in leads V_1 through V_6. The configuration of the ST-segment in leads V_1 to V_3 is a coved type. Absence of a widened S-wave and a wide QRS complex in the left lateral leads suggests that this is not a true right bundle branch block. The QT interval and the corrected QT interval are normal (408 ms and 414 ms, respectively).
at a heart rate
alternans (i.e., alternans with a duration
beats/min. The TWA was defined as positive if sustained
development of alternans between 80 beats/min and 110
patients have a patient-specific heart rate threshold for the
increase the heart rate to 110 beats/min, because most
TWA analysis, a graded bicycle ergometer was used to
increase the heart rate to 110 beats/min, because most
TWA was considered increased when the dispersion was
for the development of alternans between 80 beats/min and 110
beats/min. The TWA was defined as positive if sustained
alternans (i.e., alternans with a duration ≥1 min) occurred
at a heart rate ≥110 beats/min, an alternans voltage ≥1.9
μV during exercise, and an alternans ratio ≥3.0 in single
orthogonal leads or two adjacent precordial leads. The
TWA was defined as negative if these criteria were not met
at a heart rate ≥105 beats/min.
CORRECTED QT-INTERVAL DISPERSION. Just prior to LP
and TWA measurements, the 12-lead ECG was recorded
using a computerized ECG machine (FDX-6521, Fukuda
Denshi, Tokyo, Japan) with newly developed software
(QTD-1, Fukuda Denshi) for QT-interval analysis. The
QT intervals and corrected QT intervals (QTc) for each
lead and QTc dispersion (QTD) were automatically calcu-
lated. In brief, the QT intervals are measured by averaging
beats from similar cycles. A global QRS onset and T-wave
offset are determined in all 12 leads, and then an individual
QT interval is measured for each lead. When the T-waves
were too flat or U-waves were present, these leads were
manually excluded from analysis of the QT interval. The
QT intervals were automatically corrected for heart rate
with Bazett’s formula. The QTc was defined as a mean
value of QTc from 12 leads. The QTD was defined as the
difference between the minimal and maximal QTc
(QTcmax – QTcmin) in any of the 12 ECG leads in which it
could be reliably determined. In the present study, QTD
was considered increased when the dispersion was >50 ms
(18).
Electrophysiologic studies. Programmed ventricular stimu-
lation was performed in all patients with syncopal episodes
or aborted sudden death, and in five patients with no
symptomatic episodes. At the time, the H-V interval was
also measured. The stimulation was performed using up to
triple extrastimuli at cycle lengths of 600 or 500 and 400 ms
and twice the diastolic current threshold delivered from the
right ventricular apex and outflow tract. When VF or
polymorphic VT was not inducible, antiarrhythmic drugs,
including flecainide, pilsicainide, cibenzoline, or procain-
amide, were used. Ventricular fibrillation was defined as a
polymorphic ventricular tachyarrhythmia with an R–R in-
terval ≤200 ms (≥300 beats/min) and hemodynamic de-
compensation requiring cardioversion for termination.
Polyomorphic VT was defined as ≥6 polymorphic consecu-
tive ectopic beats that terminated spontaneously.

Statistical analysis. Data are expressed as the mean ± SD.
Differences in incidence of the LP, TWA, and increased QTD
between the patient group and the control group were exam-
ined by contingency chi-squared tests, calculating the odds
ratios. Differences in RMS40 (μV), LAS40 (ms), an alternans
voltage (μV), mean QTc (ms), and QTcmax – QTcmin (ms)
between the two groups were examined by unpaired t tests.
Differences in the H–V interval (ms) and the magnitude (mV)
of ST-segment (J-point) elevation between the presence and
the absence of LP were also examined by unpaired t tests. The
magnitude of J-point elevation was measured on enlarged
ECG leads V1 through V3. Univariate analyses using chi-
squared tests evaluated the independent predictive values of the
three noninvasive indices associating susceptibility to life-
threatening events in the patient group. Multivariate logistic
regression analysis was performed using LP as a response
variable and two indices (TWA and QTD) as explanatory
variables. Sensitivity, specificity, positive and negative predic-
tive values, and predictive accuracy of life-threatening events
were also evaluated by standard methods. A value of p < 0.05
was considered statistically significant.

RESULTS
Life-threatening events and induced ventricular arrhyth-
mias. The characteristics of the 33 Brugada patients are
summarized in Table 1. Nineteen patients (58%) had a
history of life-threatening events defined as syncopal epi-
isodes (12 patients) and aborted sudden death (7 patients).
In nine of these patients, VF was documented before the
study. Eleven patients had a history of one or more family
members with sudden death of unknown etiology. In 15 of
19 patients with life-threatening events, malignant ventricu-
lar arrhythmias were inducible by ventricular electrical
stimulation under with (five patients) or without (10 pa-
tients) the use of antiarrhythmic drugs (Fig. 2). Of these 15
patients, VF was inducible in 11 patients, and rapid,
nonsustained polymorphic VT in four patients. Eleven
patients with inducible VF or polymorphic VT received
subsequent implantation of a cardiac defibrillator. Of the
remaining four patients, two patients were treated with
either beta-blocker or amiodarone, and two patients had no
therapy. Although ventricular electrical stimulation was
performed in five patients with no symptomatic episodes,
none of these patients had inducible VF or polymorphic
VT.
Noninvasive determination test results. Individual test
results of the three noninvasive indices in the 33 patients are
shown in Table 1. In all patients, an RBBB pattern and
ST-segment elevation were present in the right chest leads
at the time of the tests, whereas they were absent in the left
lateral leads.
All of the study patients had interpretable test results for
LP. A representative example of a positive LP is shown in
Figure 3. Of the 33 patients, LP were present in 24 patients
(73%). Of 19 patients with life-threatening events, 17
patients (89%) had documented LP. The mean RMS40 and LAS40 were 15.4 ± 10.4 μV and 46 ± 11 ms, respectively. An indeterminate TWA result was obtained in two of 33 patients due to extrasystoles during exercise testing. These two patients were excluded from analysis for TWA, but they were included in the assessment of LP and QTD. Of the 31 patients, the TWA was present in five patients (16%). The mean alternans voltage in the VM lead was 1.18 ± 1.67 μV.

The mean QTc and the mean QTc max

\[2\] QTcmin were 417 ± 16 ms and 45 ± 14 ms, respectively. The QTc was

<table>
<thead>
<tr>
<th>Table 1. Comparison of Brugada Patient and Control Groups</th>
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<tbody>
<tr>
<td>Patient Group (n = 33)</td>
</tr>
<tr>
<td>Control Group (n = 30)</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
</tr>
<tr>
<td><strong>Odds Ratio</strong></td>
</tr>
<tr>
<td>Age (mean ± SD) (yrs) 45 ± 14</td>
</tr>
<tr>
<td>Gender, male 31</td>
</tr>
<tr>
<td>Defined life-threatening events 19 (58%)</td>
</tr>
<tr>
<td>Syncope 12</td>
</tr>
<tr>
<td>Aborted sudden death 7</td>
</tr>
<tr>
<td>Documented VF 9 (27%)</td>
</tr>
<tr>
<td>Family history of sudden death 11 (33%)</td>
</tr>
<tr>
<td>Induction of ventricular arrhythmia in patients with defined events 15/19 (79%)</td>
</tr>
<tr>
<td>VF 11</td>
</tr>
<tr>
<td>Polymorphic VT 4</td>
</tr>
<tr>
<td>Determinate LP 24 (73%)</td>
</tr>
<tr>
<td>RMS40 (μV) 15.4 ± 10.4</td>
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<tr>
<td>LAS40 (ms) 46 ± 11</td>
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<tr>
<td>Determinate TWA 5/31 (16%)</td>
</tr>
<tr>
<td>Alternans voltage in VM lead (μV) 1.18 ± 1.67</td>
</tr>
<tr>
<td>Increased QTD 9 (27%)</td>
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<tr>
<td>Mean QTc (ms) 417 ± 16</td>
</tr>
<tr>
<td>QTcmax–QTcmin (ms) 45 ± 14</td>
</tr>
</tbody>
</table>

| LAS40 | the duration of low-amplitude signals <40 μV in the terminal filtered QRS; LP = late potentials; QTc = corrected QT interval; QTcmax = maximal QTc; QTcmin = minimal QTc; QTD = QTc dispersion; RMS40 = the root mean square voltage of the terminal 40 ms in the filtered QRS; TWA = T-wave alternans; VF = ventricular fibrillation; VM = vector magnitude; VT = ventricular tachycardia. |

Figure 2. Polymorphic ventricular tachycardia generating into ventricular fibrillation induced by programmed electrical stimulation without the use of antiarrhythmic drugs in a patient with Brugada syndrome and several syncopal episodes. This patient required cardioversion for termination of this rhythm. HBE = His bundle electrogram; HRA = high right atrium; RVA = right ventricular apex.
normal (<460 ms) (18) for all but one patient (462 ms). An increased QTD (>50 ms) (17) was present in nine of 33 patients (27%). Differences in the three noninvasive indices between the patient group and control group are shown in Table 1. The incidence of LP-positive patients was significantly (p < 0.0001) higher in the patient group than in the controls, showing a significant difference in the RMS40 and LAS40. The odds ratio of the patient group compared with the control group was 77.3. Incidences of TWA and increased QTD were not significantly different between the patient and the controls. Although the mean QTc of the patient group was significantly (p = 0.006) higher in the patient group than in the controls, showing a significant difference in the RMS40 and LAS40. The mean maximal magnitude of ST-segment (J-point) elevation in leads V1 through V3 was evaluated. The mean H-V interval was 52 ± 10 ms. The mean maximal magnitude of ST-segment (J-point) elevation in leads V1 through V3 was 0.3 ± 0.1 mV. The mean H-V interval was not significantly different between the presence and the absence of LP (53 ± 11 ms vs. 51 ± 9 ms, respectively). The mean maximal magnitude of J-point elevation was also not significantly different between the presence and the absence of LP (0.32 ± 0.1 mV vs. 0.3 ± 0.09 mV, respectively). We also evaluated the relationship between life-threatening events/inducibility and the H-V interval/magnitude of J-point elevation. No relationship existed between their values.

### DISCUSSION

Brugada syndrome has been recognized as a distinct clinical entity characterized by an RBBB pattern and ST-segment elevation in the right chest leads, a structurally normal heart, and sudden cardiac death due to arrhythmic events. At present, the role of conduction disturbance in the right ventricle in arrhythmogenesis of the syndrome is a matter of some controversy, whereas repolarization abnormalities have been linked to malignant ventricular tachyarrhythmias (3,4,6). Although the high incidence of LP detected by signal-averaged ECG in Brugada syndrome is well known, no studies have shown whether or not LP could serve as an independent noninvasive technique to identify patients at risk for life-threatening events in this syndrome.

### Table 3. Predictive Values of Three Noninvasive Indices Associated With Life-Threatening Events

<table>
<thead>
<tr>
<th>Indices</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determinate LP</td>
<td>89%</td>
<td>50%</td>
<td>71%</td>
<td>78%</td>
<td>73%</td>
</tr>
<tr>
<td>Determinate TWA</td>
<td>22%</td>
<td>92%</td>
<td>80%</td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td>Increased QTD</td>
<td>32%</td>
<td>79%</td>
<td>67%</td>
<td>46%</td>
<td>52%</td>
</tr>
</tbody>
</table>

LP = late potentials; NPV = negative predictive value; PA = predictive accuracy; PPV = positive predictive value; QTD = corrected QT-interval dispersion; TWA = T-wave alternans.

This analysis was performed to test the statistical significance of LP in predicting life-threatening events. Of the three markers, the LP had the most significant relation to the occurrence of life-threatening events (p = 0.006). The predictive values of LP, TWA, and QTD for occurrence of life-threatening events are shown in Table 3. The LP achieved the highest predictive accuracy (73%), and they showed the highest sensitivity (89%) and negative predictive value (78%). Although TWA and QTD had a higher specificity (92% and 79%, respectively) than LP, the sensitivity of TWA and QTD was quite low (22% and 32%, respectively).

**No relationship between LP and His-Purkinje conduction/ST-segment elevation.** The relationship between the presence of LP/the H-V interval at the time of electrophysologic investigation and between the presence of LP/the maximal magnitude of J-point elevation in leads V1 through V3 was evaluated. The mean H-V interval was 52 ± 10 ms. The mean maximal magnitude of ST-segment (J-point) elevation in leads V1 through V3 was 0.3 ± 0.1 mV. The mean H-V interval was not significantly different between the presence and the absence of LP (53 ± 11 ms vs. 51 ± 9 ms, respectively). The mean maximal magnitude of J-point elevation was also not significantly different between the presence and the absence of LP (0.32 ± 0.1 mV vs. 0.3 ± 0.09 mV, respectively). We also evaluated the relationship between life-threatening events/inducibility and the H-V interval/magnitude of J-point elevation. No relationship existed between their values.
Conduction disturbance and life-threatening events. Several clinical studies (7–10) in a small patient population with Brugada syndrome have demonstrated that LP were observed in most patients with documented VF. Kasanuki et al. (8) studied five patients with idiopathic VF and structurally normal hearts, compatible with this syndrome, using signal-averaged ECG. All five patients had LP when the characteristic ECG findings were present. The investigators 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. (7) and Kobayashi et al. (9), LP were shown in 11 of 13 Brugada patients and in all 4 Brugada patients studied, respectively. In the present study, we assessed the presence of LP in a larger population (n = 33) with an RBBB pattern and ST-segment elevation in leads V1 through V3 at time of the tests. Seventy-three percent of the patients demonstrated the presence of LP. Of the 19 patients with a history of life-threatening events, 89% of patients demonstrated LP. Univariate and multivariate analyses revealed that the presence of LP is an independent predictor of life-threatening events and had the most significant relation to the occurrence of such events of the three markers tested. Therefore, the presence of LP is a noninvasive risk stratifier in patients with Brugada syndrome. To clarify the value of LP, a longer follow-up study of these patients will be necessary.

Late potentials are abnormal low-amplitude signals in the terminal portion of the QRS complex that reflect delayed conduction of the ventricle. The value of LP in predicting ventricular arrhythmias or sudden death has been demonstrated in numerous previous studies of patients with structurally abnormal hearts, especially in studies of patients after myocardial infarction. In the postinfarct setting, the incidence of LP ranges from 12% to 38% (11–13). Although the hearts of patients with Brugada syndrome are structurally normal, LP were observed with a high incidence (73%) in our study. It is known that bundle branch block causes delay and fragmentation of the electrical signal (i.e., LP) by a different mechanism that is encountered with areas of conduction block, while an impulse is transmitting through the His bundle to the ventricles. Although our Brugada patients had an RBBB pattern in the right chest leads for the syndrome, no patients had a true RBBB (i.e., mimic RBBB) because of an absence of a typical widened S-wave and a wide QRS complex in the left lateral leads. In addition, no association existed between the presence of LP and the H–V interval. Therefore, the presence of LP is not looking at an abnormally prolonged His-Purkinje conduction (RBBB) in our Brugada patients. In this study, all patients had a significant ST-segment elevation for the syndrome at the time of tests; however, 27% of patients had an absence of LP, and no association existed between the presence of LP and the magnitude of J-point elevation. Also, the presence of LP may not be the mechanism responsible for the observed ST-segment elevation in these patients.

Repolarization abnormalities and life-threatening events. Theoretical considerations and recent experiments have suggested one possible mechanism for ST-segment elevation in the early precordial leads and arrhythmogenesis in the syndrome (i.e., repolarization abnormalities hypothesis). Antzelevitch et al. (3,4,6) have proposed that epicardial-endocardial heterogeneity of repolarization is responsible for the ST-segment elevation observed in patients with the Brugada syndrome. Several studies (19–21) with sodium channel blockers support their observations.

Recently, the presence of TWA or QTD (noninvasive markers), which reflect repolarization abnormalities, has been reported to be associated with an increased risk of ventricular arrhythmias in several clinical settings (13–17). No studies have demonstrated the clinical values of these markers with respect to life-threatening events or malignant ventricular arrhythmias in the setting of Brugada syndrome. A case report (22) has demonstrated that a visual TWA was observed during ST-segment elevation augmented by intravenous administration of a sodium channel blocker (cibenzoline) in a patient with Brugada syndrome. In the present study, we assessed the value of two markers (TWA and QTD) for identifying Brugada patients who are at risk for life-threatening events by testing for inducible VF or polymorphic VT. Our results suggest that TWA and QTD are not independent predictors of life-threatening events, despite the presence of ST-segment elevation at the time of the tests. In addition, the values of both markers in the patients were not different from those of normal individuals matched for age and gender. Therefore, TWA and QTD, both repolarization abnormality markers, are not useful for identifying high-risk patients in the syndrome.

Study limitations. In the present study, we assessed only LP, TWA, and QTD as noninvasive markers. For other noninvasive markers such as heart rate variability (8,23), an association with this syndrome is unknown. Our selected noninvasive markers may be used to determine the full scope of arrhythmogenic mechanisms underlying Brugada syndrome. Therefore, additional studies with different technologies will be necessary to confirm the conduction abnormality hypothesis in arrhythmogenesis of Brugada syndrome. Brugada et al. (24) have reported that asymptomatic patients with the classic ECG abnormalities have the same risk of arrhythmic events as do patients who have had an episode of syncope or aborted sudden death. Unfortunately, the present study did not include follow-up data in the asymptomatic patients. Nademanee et al. (7) have demonstrated that, during exercise, the ECG abnormalities associated with this syndrome can disappear. For TWA measurements, we used exercise testing. In our study population, all patients had persistent ECG abnormalities even during exercise testing because it was a low grade of exercise.
Clinical implications. In identifying patients at high risk for sudden cardiac death due to VF and who may be candidates for an implantable cardiac defibrillator, noninvasive measurements are more desirable than invasive electrophysiologic studies. As shown in our present study and several previous studies (19,24–26), VF or polymorphic VT can be occasionally induced by programmed ventricular stimulation in these patients. Our study shows that detection of LP by signal-averaged ECG is a useful noninvasive technique for identifying such patients because it significantly predicts life-threatening events. Regarding the mechanism of arrhythmogenesis in this syndrome, our clinical results may support the conduction abnormality hypothesis.

REFERENCES


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