Comparison of Late Potentials for 24 Hours Between Brugada Syndrome and Arrhythmogenic Right Ventricular Cardiomyopathy Using a Novel Signal-Averaging System Based on Holter ECG

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Background—Late potentials (LP) detected with signal-averaged ECGs are known to be useful in identifying patients at risk of Brugada syndrome (BS) and arrhythmogenic right ventricular cardiomyopathy (ARVC). Because the pathophysiology is clearly different between these disorders, we clarified the LP characteristics of these disorders.

Methods and Results—This study included 15 BS and 12 ARVC patients and 20 healthy controls. All BS patients had characteristic ECG changes and symptomatic episodes. All ARVC patients had findings that were consistent with recent criteria. Three LP parameters (filtered QRS duration, root mean square voltage of the terminal 40 ms of the filtered QRS complex, and duration of low-amplitude signals [<40 µV] in the terminal, filtered QRS complex) were continuously measured for 24 hours using a novel Holter-based signal-averaged ECG system. The incidences of LP determination in BS (80%) and ARVC (91%) patients were higher than in healthy controls (5%; P<0.0001 in both) but did not differ between BS and ARVC patients. In BS patients, the dynamic changes of all LP parameters were observed, and they were pronounced at nighttime. On the contrary, these findings were not observed in ARVC patients. When the SD values of the 3 LP parameters (filtered QRS duration, root mean square voltage of the terminal 40 ms of the filtered QRS complex, and duration of low-amplitude signals [<40 µV] in the terminal, filtered QRS complex) over 24 hours were compared for the 2 patient groups, those values in BS patients were significantly greater than those in ARVC patients (P<0.0001 in all).

Conclusions—LP characteristics detected by the Holter-based signal-averaged ECG system over 24 hours differ between BS and ARVC patients. Dynamic daily variations of LPs were seen only in BS patients. This may imply that mechanisms of lethal ventricular arrhythmia in BS may be more correlated with autonomic abnormality than that of ARVC.

Key Words: Brugada syndrome ■ arrhythmogenic right ventricular cardiomyopathy ■ late potentials ■ signal-averaged electrocardiogram ■ Holter monitoring

The Brugada syndrome (BS), which is characterized by a pattern of right bundle branch blocks and ST-segment elevations in leads V1 and V2 on an ECG, is considered to be a primary electric disease of the heart caused by a defect in the ion channel gene, resulting in abnormal electrophysiological activity in the right ventricle and a propensity to malignant ventricular arrhythmias. On the other hand, arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary myocardial disease, often familial, that is characterized histologically by structural abnormalities of the right ventricle because of replacement by fibrous and fatty tissue. The clinical manifestation of this disease is lethal ventricular arrhythmias, which occasionally cause sudden cardiac death because of a degenerated myocardium. With both disorders, although their pathophysiology is clearly distinct, it has been reported that a conduction delay in the right ventricle plays an important role in arrhythmogenesis. Several studies have reported an overlap between the characteristics of BS and ARVC, such as ECGs similar to those with BS for ARVC patients with a sodium channel blocker and fibrofatty replacement similar to that for ARVC found in right ventricular biopsies in BS patients.

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Late potentials (LPs) detected by signal-averaged ECGs (SAECGs), which reflect a conduction delay, have been widely used to detect high-risk individuals among patients with cardiac disorders, such as myocardial infarctions, BS, and ARVC. At present, it is possible to monitor LPs continuously for 24 hours using a newly developed SAECG system that is applied to Holter ECG recordings.

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In the present study, we assessed the value of monitoring LPs continuously for 24 hours using the developed signal-averaging system to compare daily varying LP characteristics and to investigate the clinical differentiation of arrhythmogenesis for BS and ARVC.

Methods

Patient Enrollment

BS Patients

Fifteen patients (13 men and 2 women; mean age, 42±12 years) who were referred to our medical centers between 2005 and 2011 were enrolled. All the patients showed typical Brugada-type ECGs (ie, a coved pattern of ST-segment elevations in the V1 and V2 leads), including transiently spontaneous changes during the sinus rhythm on 12-lead ECGs. In other words, patients who only had the saddle-back pattern were excluded from the study. In addition, all BS patients had a history of syncope or life-threatening arrhythmic events. Before diagnosing BS, we excluded patients who had evidence of organic heart disease, including ARVC, myocardial ischemia of the right ventricle, and other infiltrative cardiomyopathies. These diagnoses were based on the Report of the Second Consensus Conference in 2005 using echocardiography, coronary angiography with acetylcholine, other diagnostic techniques, such as scintigraphy, helical computed tomography scanning, and magnetic resonance imaging, and endomyocardial biopsies in some cases. As a result, all BS patients studied were believed to have structurally normal hearts.

ARVC Patients

During the same period, we enrolled 12 patients (9 men and 3 women; mean age, 33±12 years), who had right ventricular dilation determined using imaging modalities and diagnosed with ARVC as their clinical findings fulfilled the Task Force Criteria of 2010. All patients underwent 12-lead ECGs, echocardiography, other diagnostic techniques, such as scintigraphy, helical computed tomography scanning, and magnetic resonance imaging, and endomyocardial biopsies in some cases. As a result, all BS patients studied were believed to have structurally normal hearts.

Controls

Twenty healthy controls (16 men and 4 women; mean age, 40±11 years), who had routine healthcare examinations at the healthcare department of our institutes between 2006 and 2008, were included in the study. They are matched for age and sex to BS patients. All controls underwent a 24-hour Holter ECG to measure LPs for 24 hours similar to the 2 patient populations.

Measurements

Detection of Continuous LPs by the Signal-Averaging System

In this study, LPs were analyzed for 24 hours using a newly developed signal-averaging system (SCM-6600; Fukuda Densi Co, Ltd, Tokyo, Japan), which is capable of analyzing LPs automatically every 30 minutes using data from a digital Holter ECG recorder (FM-180; Fukuda Densi Co Ltd). This system was developed using the same algorithm as is applied in FDX-6500 from Fukuda Densi Co, Ltd, and is now commercially available in Japan.

This analysis is based on the quantitative time-domain measurements of the filtered vector magnitude of the orthogonal 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 using a computer algorithm: the filtered QRS duration (fQRS), the root mean square voltage of the terminal 40 ms of the filtered QRS complex (RMS_{40}), and the duration of low-amplitude signals (<40 μV) in the terminal, filtered QRS complex (LAS_{40}). These 3 parameters were assessed using a computer algorithm, every 30 minutes for 24 hours, and the values for the parameters were presented on a trend graph covering the 24 hours.

Results

Characteristics of BS and ARVC Patients

The characteristics of 15 BS and 12 ARVC patients are summarized in Table 1. With regard to the features of 12-lead ECGs, a coved pattern of ST-segment elevations was demonstrated in all BS patients. An epsilon wave was documented in 4 ARVC patients.

All patients in both groups had a history of at least 1 event, which was defined as either a ventricular arrhythmia (8 in BS patients and in all ARVC patients) or a syncopal episode (11 in BS patients and 10 in ARVC patients). In 8 BS patients with ventricular arrhythmias, ventricular fibrillation or polymorphic ventricular tachycardia (VT) was documented, but sustained monomorphic VT was not. On the contrary, in 10 of 12 ARVC patients with ventricular arrhythmias, sustained monomorphic VT was documented by ambulatory monitoring ECGs or 12-lead ECGs, and the remaining 2 patients had either ventricular fibrillation or polymorphic VT.
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Table 1. Characteristics of BS and ARVC Patients Enrolled in This Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>BS Patients (n=15)</th>
<th>ARVC Patients (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), yr</td>
<td>42±12</td>
<td>33±12</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>13 (87)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Family history of SCD (%)</td>
<td>3 (20)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>ECG features (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covered pattern ST elevation</td>
<td>15 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Epsilon wave</td>
<td>...</td>
<td>4 (33)</td>
</tr>
<tr>
<td>History of events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>11 (74)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Aborted sudden death</td>
<td>4 (27)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Document of ventricular arrhythmias</td>
<td>8 (53)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>VF and polymorphic VT</td>
<td>8 (53)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>0 (0)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Time of events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>4 (27)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>11 (73)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

BS indicates Brugada syndrome; ARVC, arrhythmogenic right ventricular cardiomyopathy; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

In consideration of the time of events, 11 (73%) BS patients had events at night or in the early morning (22:00 to 08:00 hours). No life-threatening events occurred during exercise in the BS patients. Conversely, all 12 ARVC patients had events during the day (08:00 to 22:00 hours). The events occurred during physical exercise in 6 (50%) ARVC patients.

Comparisons of LP Parameters

The test results of LP parameters in 15 BS and 12 ARVC patients and controls are shown in Table 2. For BS patients, LPs were determined in 12 (80%) patients. For ARVC patients, LPs were identified in 11 (91%) patients. In healthy controls, LPs were identified in only 1 (5%) subject. The incidences of LP determination were significantly different among the 3 groups. Subsequently, pair-wise comparisons between BS and ARVC patients and controls were performed. The numerical values of fQRS, RMS<sub>40</sub>, and LAS<sub>40</sub> for LP determination were significantly different among the 3 groups. Subsequently, pair-wise comparisons between BS and ARVC patients and controls were performed. The numerical value of fQRS in BS patients was significantly lower than that in ARVC patients (P=0.0004), but the values of RMS<sub>40</sub> and LAS<sub>40</sub> did not differ between both patients. When compared between BS patients and controls, the values of fQRS, RMS<sub>40</sub>, and LAS<sub>40</sub> in BS patients were significantly greater than those in healthy controls (P<0.0001 in all).

Table 2. Comparisons of LP Parameters for BS and ARVC Patients and Controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>BS Patients (n=15)</th>
<th>ARVC Patients (n=12)</th>
<th>Controls (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determinate LP (%)</td>
<td>12/15 (80)*</td>
<td>11/12 (91)*</td>
<td>1/20 (5)</td>
<td>0.003</td>
</tr>
<tr>
<td>fQRS, ms</td>
<td>147 (139–150)†‡</td>
<td>160 (156–163)†</td>
<td>122 (118–125)  &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>RMS&lt;sub&gt;40&lt;/sub&gt;, µV</td>
<td>10.8 (8.2–16.8)†</td>
<td>11.5 (10.4–12.9)†</td>
<td>26.5 (18.2–32.2) &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LAS&lt;sub&gt;40&lt;/sub&gt;, ms</td>
<td>47.0 (42.5–50.5)†</td>
<td>47.3 (44.0–54.0)†</td>
<td>35.3 (30.0–36.8) &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SD over 24 hours of fQRS, ms</td>
<td>4.52 (3.41–5.72)§</td>
<td>1.26 (0.89–1.68)§</td>
<td>1.73 (1.50–2.44) &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SD over 24 hours of RMS&lt;sub&gt;40&lt;/sub&gt;, µV</td>
<td>2.81 (2.44–4.05)§</td>
<td>0.89 (0.83–1.02)§</td>
<td>1.22 (0.98–1.41) &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SD over 24 hours of LAS&lt;sub&gt;40&lt;/sub&gt;, ms</td>
<td>4.50 (4.14–4.96)§</td>
<td>1.37 (1.37–1.97)§</td>
<td>1.39 (1.20–1.59) &lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

LP indicates late potentials; BS, Brugada syndrome; ARVC, arrhythmogenic right ventricular cardiomyopathy; fQRS, filtered QRS duration; RMS<sub>40</sub>, root mean square voltage of the terminal 40 ms of the filtered QRS complex; LAS<sub>40</sub>, duration of low-amplitude signals (<40 µV) in the terminal, filtered QRS complex.

LP parameters are shown as medians with 25%–75% values. P values are attained by a single test that compares 3 groups simultaneously. These were done using an extension of a Fisher exact test for a 3×2 table for categorical data and a Kruskal-Wallis test for continuous data.

*P<0.0001 by a Fisher exact test comparing controls.
†P=0.0001 by the Bonferroni procedure as pair-wise comparisons comparing controls.
‡P=0.0004 and §P<0.0001 by the Bonferroni procedure as pair-wise comparisons comparing ARVC patients.

Daily Variation of LP Parameters

In all BS patients, dynamic daily variations of LP parameters were observed. Figure 1 shows a representative example of the trend graphs of each LP parameter (fQRS, RMS<sub>40</sub>, LAS<sub>40</sub>) in a BS patient. All parameters fluctuated over 24 hours, and measured values of LP parameters increased at night and decreased during the day. In this patient, the maximum LP values were recorded from 03:00 to 05:00 hours (middle of the night) and the minimum values from 12:00 to 14:00 hours (afternoon). In 11 (73%) of the 15 BS patients, similar trend graphs were recorded. LPs were identified, and events occurred at night in these 11 patients. In contrast, the dynamic daily changes of LP parameters were not observed in any ARVC patient (Figure 2), whereas LPs were identified in most (91%) of the ARVC patients.

Because LP parameters showed dynamic change in BS patients, we calculated the SD of the continuous values of QRS, RMS<sub>40</sub>, and LAS<sub>40</sub> from each patient over 24 hours (ie, daily variation of the parameters) and compared these values for the 3 groups (Table 2). The SD of a patient’s observations over 24 hours of each LP parameter was significantly different among the 3 groups. We did pair-wise comparisons between BS and ARVC patients and controls. All SD values of BS patients were significantly higher than those of ARVC patients (P<0.0001 in all). We also compared each value between BS and ARVC patients and controls were performed. The incidences of LP determination in BS and ARVC patients were higher than that in healthy controls (P<0.0001 in both) but did not differ significantly for both BS and ARVC patients.

The numerical values of fQRS, RMS<sub>40</sub>, and LAS<sub>40</sub> for LP determination were significantly different among the 3 groups. Subsequently, pair-wise comparisons between BS and ARVC patients and controls were performed. The numerical value of fQRS in BS patients was significantly lower than that in ARVC patients (P=0.0004), but the values of RMS<sub>40</sub> and LAS<sub>40</sub> did not differ between both patients. When compared between BS patients and controls, the values of fQRS, RMS<sub>40</sub>, and LAS<sub>40</sub> in BS patients were significantly greater than those in healthy controls (P<0.0001 in all).
patients and controls. Similarly, all SD values of BS patients are significantly higher than controls ($P<0.0001$ in all).

**Discussion**

The major finding of the present study was to document the different dynamics of LPs detected by SAECG over 24 hours, for both BS and ARVC. Although the incidences of LPs that reflect depolarization abnormalities or conduction delays were high for both disorders, BS patients had daily variations of LPs with nighttime ascendency, but ARVC patients did not. This finding may reveal that the pathophysiology of lethal ventricular arrhythmias differs for both BS and ARVC. The pathophysiological mechanism of LPs in BS patients with a structurally normal heart may be closely associated with both depolarization abnormality and autonomic modulation.

The characteristic 12-lead ECG features of BS are dynamic and often concealed. Modulation abnormalities of the autonomic system may directly affect the ECG properties and increase vulnerability to fatal arrhythmias. Several reports showed, for BS patients, that ST-segment elevations on 12-lead ECGs have diurnal and daily variations; therefore, it is considered that the occurrence of events may also have circadian and daily variations. Matsuo et al analyzed the circadian pattern of 30 ventricular fibrillation episodes in 12 BS patients who underwent an implantable cardioverter-defibrillator treatment and reported that ventricular fibrillation occurred more frequently at night (93%) than during the day (7%). In this study, 73% of episodes of BS patients occurred at night or in the early morning. The remaining 27% of episodes occurred during the daytime. Of note, no patients had life-threatening events during exercise. The circadian pattern of the events in our population was similar to those of previous studies.

In contrast, islands of fibrofatty tissues generate the arrhythmogenic substrate and form an electric reentrant circuit for malignant ventricular arrhythmias responsible for serial events in ARVC patients. These arrhythmias are typically induced by adrenergic stimulation, such as a catecholamine infusion or physical exercise. It has been shown that physical exercise is a precipitating factor for lethal ventricular arrhythmias in patients with ARVC. Corrado et al reported that sudden cardiac death occurred among young ARVC patients, and Leclercq et al documented VT on a 24-hour Holter ECG after an autonomic imbalance of increasing sympathetic tone in ARVC patients. Furthermore, it has been reported that adrenergic stimulation, an isoproterenol infusion mimicking the catecholamine effect, induced VT with ARVC. Succinctly, VT with ARVC is the result of sympathetic stimulation but not vagal tone. In this study, the events during the day, when physical activity is high, occurred in all ARVC patients. Conversely, none of the patients had an event...
at night. The events occurred during physical exercise in 50% of the ARVC patients.

The presence of LPs is an established marker that is useful for risk stratification in patients with structurally abnormal hearts, for example, patients having had a myocardial infarction. However, with ARVC, the clinical values are still controversial as to whether they are markers of the pathophysiological substrate, namely fibrofatty substrate, or the index of vulnerability to ventricular arrhythmias. The relationship between the features of ECGs (epsilon wave and inverted T wave in leads V, and V) and LPs is still unknown.

By assessing LPs by SAECGs over 24 hours for BS patients who have been identified as having a high risk for lethal ventricular arrhythmias, a dynamic manner of changes for LP parameters were found during this study. These dynamic changes were accentuated at night, and all the LP parameters at night were greater than during the day. In contrast, all the values of LP parameters for ARVC over 24 hours did not fluctuate as largely as they did in BS patients. The SD values of the LP parameters over 24 hours for the ARVC patients were significantly less than those for BS patients. ARVC patients who were identified as being at high risk for ventricular arrhythmias were considered as being less likely to be influenced by autonomic balance in comparison with BS patients, because no clear peak for either night or day was observed. Therefore, the role of LPs in ARVC may be as a pathophysiological substrate rather than electric instability. The analysis of LPs over 24 hours may play an important role as a noninvasive technique for diagnosing both disorders in their early stages.

**Clinical Implications**

In identifying patients with BS and ARVC at high risk for serious arrhythmic events, noninvasive methods are more desirable than invasive or genetic methods. Our study shows that, for asymptomatic BS patients, the detection of LPs using the SAECG system with a 24-hour Holter ECG could be a useful technique for identifying the subgroup at high risk for arrhythmic events. If such patients have dynamic changes of LPs over 24 hours, with night ascendancy, they could be considered candidates for an implantable defibrillator.

One application of the information from this study would be to consider doing SAECG using commercial non-Holter-based SAECG 2x (one in the middle of the night and the other in the afternoon). These are the times reported at maximum daily changes of LPs in this study. However, the Holter-based SAECG would be necessary when we assess daily variations of LPs in BS patients because BS patients are awake (not
sleeping) to undergo the standard SAECG and have the same situation as daytime.

**Study Limitations**
In this study, we only analyzed LPs as a tool to determine electrophysiological abnormalities and did not realize the value of other markers, such as electrophysiological testing, drug infusion tests, and genetic analysis, which were assessed in previous studies.

Because we have not investigated daily variations of LPs in terms of arrhythmic event, an additional or follow-up study will be necessary to determine the prognostic significance of LP variability for stratifying patients at risk of BS.

**Conclusions**
The LP characteristics detected using SAECG over 24 hours differ between BS and ARVC patients. LPs in BS patients dynamically change during the day, whereas this is not the case for ARVC patients. It may imply that the mechanisms of lethal ventricular arrhythmias in BS patients are more correlated to autonomic abnormalities than ARVC patients.

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**Disclosures**
None.

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