Prognostic significance of ventricular late potentials in patients with pulmonary sarcoidosis

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BACKGROUND Early detection of cardiac involvement in sarcoidosis is difficult but essential to achieve optimal treatment. Signal-averaged electrocardiography (SAECG) can detect subtle cardiac electrical abnormalities termed late potentials (LPs) and would be useful for the early diagnosis of cardiac involvement.

OBJECTIVE This study aims to investigate the prognostic significance of LP in patients with pulmonary sarcoidosis.

METHODS We prospectively studied 74 patients with pulmonary sarcoidosis without overt electrocardiographic abnormalities. All participants underwent SAECG, cardiac echocardiography, and 24-hour ambulatory Holter monitoring. Serum angiotensin-converting enzyme and B-type natriuretic peptide levels were also evaluated. We followed these patients for the evaluation of incidence of cardiac events including cardiac death, arrhythmias, and heart failure requiring hospital admission.

RESULTS Of the studied population, 29 patients (39.2%) had detectable LP. During a mean follow-up period of 9.8 years, 8 patients with LPs had cardiovascular events, including development of complete atrioventricular block (n = 4), ventricular tachycardia (n = 2), and heart failure (n = 2). Meanwhile, only 1 of 45 patients without LP developed cardiac event (heart failure). Multivariate analyses revealed that LPs were associated with an increased risk of developing cardiac events (hazard ratio 9.66; 95% confidence interval 1.20–78.01; P = .033) whereas age, sex, serum angiotensin-converting enzyme and B-type natriuretic peptide levels, number of premature ventricular contractions on 24-hour Holter monitoring, and echocardiographic parameters were not associated with subsequent cardiac events.

CONCLUSION SAECG might possibly be useful for the early detection of cardiac sarcoidosis and, if independently validated, could eventually be considered as a screening test for further risk stratification.

KEYWORDS Cardiac involvement; Electrocardiography; Prognosis; Sarcoidosis; Signal-averaged ECG

Introduction
Sarcoidosis is a multisystemic granulomatous disease of unknown etiology involving multiple organs.1 In general, sarcoidosis has a relatively good prognosis with many cases showing spontaneous remission. However, heart involvement often results in a poor prognosis because of the development of lethal ventricular arrhythmias, atrioventricular block, or refractory heart failure (HF). Therefore, early detection of cardiac involvement in sarcoidosis is critical. Unfortunately, this is hardly possible given the current recommendations for noninvasive testing. Signal-averaged electrocardiography (SAECG) can detect subtle cardiac electrical abnormalities termed ventricular late potentials (LPs). It may be useful for the early detection of cardiac involvement in patients with sarcoidosis. We previously reported a high prevalence of LPs in patients with pulmonary sarcoidosis even without any obvious cardiac abnormality.2 The present study seeks to investigate the prognostic value of LP in patients with pulmonary sarcoidosis.

Methods
We prospectively studied 74 patients with pulmonary sarcoidosis without overt electrocardiographic (ECG)
abnormalities who were referred to our hospital from April 1, 1996 to December 31, 2010. All patients were diagnosed by pulmonologists and referred to the cardiology division for further examination of possible cardiac involvement, even if they had no cardiac symptoms. The diagnosis of pulmonary sarcoidosis was certified on the basis of the fiber-optic bronchoscopy finding of epithelioid, noncaseating granuloma without necrosis. Patients with known cardiac diseases were excluded from the study. We also excluded patients who were taking corticosteroids. All participants underwent SAECG, cardiac echocardiography, and 24-hour ambulatory Holter monitoring. Serum angiotensin-converting enzyme (ACE) and B-type natriuretic peptide (BNP) levels were also evaluated. SAECG records were obtained from the Frank X, Y, and Z leads during sinus rhythm using a Signal Processor DP 1100 (NEC Corporation, Tokyo, Japan). A total of 200 cycles were averaged to obtain a noise level of <0.2 μV. The signals were amplified, digitized, averaged, and bidirectionally filtered with a band-pass filter at frequencies between 40 and 250 Hz. The filtered QRS duration (f-QRS), the root mean square voltage of the terminal 40 ms (RMS40) in the f-QRS complex, and the duration of low-amplitude signals <40 μV (LAS40) in the terminal f-QRS complex were measured. In the present study, LP were considered as “positive” if 2 of the following criteria were met: (1) f-QRS ≥ 120 ms, (2) RMS40 < 20 μV, and/or (3) LAS40 > 38 ms. Left ventricular ejection fraction (LVEF) was measured using the Simpson’s method, and early (E) and late (A) peak diastolic velocities were measured using pulsed-wave Doppler echocardiography to assess left ventricular (LV) diastolic function. We evaluated the total number of premature ventricular contractions (PVCs) on 24-hour ambulatory Holter monitoring. Serum ACE levels were measured using a colorimetric method (colorimetric assay kit, Fujirebio Inc., Tokyo, Japan) with p-hydroxyhippuryl-L-histidyl-L-leucine as substrate. Plasma BNP concentrations were determined using a specific immunoradiometric assay for human BNP with commercial kits (Shionoria kit, Shionogi & Co., Ltd. and Kyowa Medex Co., Ltd., Tokyo, Japan). We followed these patients for the evaluation of incidence of cardiac events including cardiac death, arrhythmias, and HF requiring hospital admission and investigated the association of LP with the subsequent development of cardiac events in patients with pulmonary sarcoidosis. Approval for this study was obtained from the institutional review board of Nippon Medical School, and written informed consent was obtained from all patients.

### Statistical analysis

Measurements are presented as mean ± SD or as number (percentage). Univariate and multivariate Cox proportional hazards regression analyses were performed to relate clinical parameters to the end point. The proportional hazard assumption was assessed graphically using log-log survival plots. Event-free rates in patients with and without LP were calculated using the Kaplan-Meier method, and the difference between them was compared using the log-rank test. A P value of <.05 was considered significant. Statistical calculations were performed using SPSS version 20 (IBM Inc., Chicago, IL).

### Results

Of the studied population, 29 patients (39.2%) had detectable LP (Table 1). Representative ECG and SAECG are shown in Figure 1. During a mean follow-up period of 9.8 years, 8 patients with LP had cardiovascular events including complete atrioventricular block (n = 4), sustained ventricular tachycardia (n = 2), and HF (n = 2). Meanwhile, only 1 of 45 patients without LP developed a cardiac event (HF) (Table 2). In all patients who had subsequent cardiac events, structural heart diseases rather than cardiac sarcoidosis as causes of cardiac events were excluded using echocardiography, cardiac magnetic resonance (CMR) imaging, 18F-fluorodeoxyglucose positron emission tomography/computed tomography, cardiac computed tomography scan, and coronary angiography. Univariate analysis revealed that male sex (P = .048) and LP presence (P = .022) were prognostic factors for cardiac events (Table 3). In multivariate analysis, presence of LP (P = .033) was the only independent prognostic factor for cardiac events (hazard ratio 9.66; 95% confidence interval 1.20–78.01; P = .033) whereas other variables were not associated with subsequent cardiac events. Kaplan-Meier analysis revealed that the event rate was significantly higher (log-rank, P = .004) in patients with LP than in patients without LP (Figure 2).

### Discussion

#### High prevalence of subclinical cardiac sarcoidosis

The present study demonstrated that up to 40% of pulmonary sarcoidosis without overt ECG abnormalities demonstrated...
LP, suggesting possible latent cardiac involvement. Inflammation or fibrosis caused by sarcoid granulomas might produce delayed conduction that could be detected by means of SAECG.

A prior autopsy study revealed myocardial involvement in 27% of patients with sarcoidosis, despite the fact that clinical evidence of myocardial involvement could be found in only 5% of cases. In addition, another study from Japan reported that cardiac involvement was detected by autopsy in 58% of patients with sarcoidosis. Furthermore, a recent study showed that late gadolinium enhancement (LGE) by CMR imaging was detected in 20% of patients with extracardiac sarcoidosis and LGE was a significant risk factor for death or ventricular tachycardia. These reports indicate a high prevalence of "subclinical cardiac involvement" in patients with sarcoidosis.

**Early detection of cardiac sarcoidosis**

The prognosis of patients with cardiac sarcoidosis worsens if they are not diagnosed in the early stages of the disease. Therefore, early diagnosis and prompt initiation of corticosteroid therapy is important to decrease mortality and improve outcomes. Steroid therapy was reported to prevent LV remodeling and improve LV function in patients with LVEF $\geq$ 30% but not in patients with LVEF $< 30\%$. Furthermore, our previous study has shown that steroid therapy is effective for ventricular arrhythmias in patients with LVEF $\geq 35\%$ but less effective in patients with LVEF $< 35\%$. These findings suggest that early diagnosis and therapeutic intervention for cardiac involvement is essential in patients with sarcoidosis. Recent investigations have demonstrated that ECG abnormalities are associated with subsequent cardiac events, but little has been reported on patients with sarcoidosis without ECG abnormalities. In the

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**Table 2** Characteristics of patients with pulmonary sarcoidosis who developed cardiac events

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>PVCs (beats/d)</th>
<th>ACE level (IU/L)</th>
<th>BNP level (pg/mL)</th>
<th>LVEF (%)</th>
<th>f-QRS (ms)</th>
<th>RMS$_{40}$ ($\mu$V)</th>
<th>LAS$_{40}$ (ms)</th>
<th>Other organ involvement</th>
<th>Time to cardiac events (y)</th>
<th>Primary cardiac symptoms</th>
<th>Cardiac event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>F</td>
<td>18</td>
<td>13.2</td>
<td>14</td>
<td>1.4</td>
<td>77</td>
<td>141</td>
<td>1.7</td>
<td>81</td>
<td>+ Skin</td>
<td>Dyspnea</td>
<td>HF</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>F</td>
<td>12</td>
<td>15.5</td>
<td>18</td>
<td>0.7</td>
<td>58</td>
<td>130</td>
<td>2.6</td>
<td>58</td>
<td>+ –</td>
<td>6</td>
<td>Dizziness</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>M</td>
<td>3</td>
<td>20.8</td>
<td>4.4</td>
<td>0.9</td>
<td>79</td>
<td>131</td>
<td>1.8</td>
<td>75</td>
<td>+ Eye</td>
<td>9</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>38</td>
<td>11.5</td>
<td>20</td>
<td>0.6</td>
<td>58</td>
<td>111</td>
<td>3.6</td>
<td>62</td>
<td>+ Skin</td>
<td>5.8</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>4</td>
<td>16.3</td>
<td>15.9</td>
<td>0.5</td>
<td>69</td>
<td>133</td>
<td>2.1</td>
<td>69</td>
<td>+ –</td>
<td>12</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>M</td>
<td>3</td>
<td>15.8</td>
<td>13.8</td>
<td>0.8</td>
<td>70</td>
<td>107</td>
<td>4.5</td>
<td>44</td>
<td>+ –</td>
<td>2.5</td>
<td>Syncope</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>M</td>
<td>77</td>
<td>31.1</td>
<td>8.1</td>
<td>1.8</td>
<td>74</td>
<td>104</td>
<td>4.2</td>
<td>43</td>
<td>+ Eye</td>
<td>3</td>
<td>Palpitation</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>2</td>
<td>30.5</td>
<td>17.5</td>
<td>1.4</td>
<td>65</td>
<td>126</td>
<td>1.1</td>
<td>70</td>
<td>+ Eye</td>
<td>6.3</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>F</td>
<td>26</td>
<td>24.8</td>
<td>25.4</td>
<td>1.2</td>
<td>62</td>
<td>97</td>
<td>13.7</td>
<td>34</td>
<td>– Eye</td>
<td>11.1</td>
<td>Dyspnea</td>
</tr>
</tbody>
</table>

CAVB = complete atrioventricular block; F = female; HF = heart failure; M = male; VT = ventricular tachycardia; + = positive; – = negative. Other abbreviations as in Table 1.
present study, we demonstrated that subsequent cardiac events can occur even in patients without ECG abnormalities.

**Application of SAECG for the early detection of cardiac sarcoidosis**

LP detected by SAECG reflect delayed activation of ventricular tissue, which is assumed to originate from areas of heterogeneous conduction in the diseased myocardium. It has been reported to predict lethal cardiac events in patients with various diseases such as ischemic heart disease, nonischemic dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. Schuller et al reported a high prevalence of LP in patients with sarcoidosis, which is consistent with findings from our study. However, there have been no studies on the prognostic significance of LP in patients with pulmonary sarcoidosis. In the present study, we found that LP were associated with subsequent cardiac events in patients with pulmonary sarcoidosis. To our knowledge, this is the first report demonstrating the prognostic significance of LP in patients with sarcoidosis.

**Other parameters**

Cardiac infiltration by sarcoid granulomas causes LV systolic or diastolic dysfunction, and conventional Doppler echocardiography is useful as a screening test for cardiac involvement in patients with sarcoidosis. Experts are of the consensus that the use of echocardiography is a class IIa recommendation for screening for cardiac involvement in patients with biopsy-proven extracardiac sarcoidosis. Fahy et al demonstrated that 7 of 50 patients with sarcoidosis had diastolic dysfunction (E/A < 1) on conventional Doppler echocardiography. However, our findings showed that both LVEF and E/A were not associated with subsequent cardiac events. This might be due to patient selection bias, as all our patients showed normal ECG findings, suggesting an absence of obvious cardiac abnormalities.

BNP is a hormone secreted predominantly by the ventricles in response to ventricular volume expansion and pressure overload. Its levels have been shown to be elevated in patients with HF. We previously reported that BNP levels were high in patients with cardiac sarcoidosis, and furthermore, Date et al showed that BNP levels are elevated in patients with cardiac sarcoidosis with a preserved ejection fraction. However, BNP levels were within the normal range in most of our patients and not associated with subsequent cardiac events. This could also be due to patient selection bias, as the present study population does not include patients with obvious cardiac manifestations.

Regarding Holter monitoring, 1 study found that 24-hour Holter monitoring detected cardiac sarcoidosis with a sensitivity of 67% and a specificity of 62% when PVCs numbered >100 per day. In the present study, none of the patients who developed cardiac events had frequent PVCs (100 beats/day) at the time of the initial evaluation, and the number of PVCs was not associated with subsequent cardiac events. This again could be due to selection bias previously mentioned.

Sarcoid granulomas produce ACE, and serum ACE levels are elevated in ~60%~70% of patients with sarcoidosis with a positive and negative predictive value of 84% and 74%, respectively. However, it is not specific for cardiac

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**Table 3** Univariate and multivariate Cox proportional hazards regression analyses for cardiac events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.99 (0.94–1.04)</td>
<td>.621</td>
</tr>
<tr>
<td>Sex: male</td>
<td>3.76 (1.01–14.02)</td>
<td>.048</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>2.25 (0.60–8.40)</td>
<td>.227</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>1.63 (0.34–7.89)</td>
<td>.542</td>
</tr>
<tr>
<td>PVCs (beats/d)</td>
<td>1.00 (0.99–1.01)</td>
<td>.983</td>
</tr>
<tr>
<td>ACE level (IU/L)</td>
<td>0.97 (0.90–1.06)</td>
<td>.538</td>
</tr>
<tr>
<td>BNP level (pg/mL)</td>
<td>1.09 (0.99–1.19)</td>
<td>.088</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.98 (0.87–1.10)</td>
<td>.685</td>
</tr>
<tr>
<td>E/A</td>
<td>0.46 (0.02–10.45)</td>
<td>.624</td>
</tr>
<tr>
<td>LP</td>
<td>8.61 (1.42–90.54)</td>
<td>.022</td>
</tr>
</tbody>
</table>

CI = confidence interval. Other abbreviations as in Table 1.

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**Figure 2** Kaplan-Meier survival curves of patients with pulmonary sarcoidosis with and without LP. The numbers at the bottom indicate the number of patients in each group at risk for cardiac events. The event rate was significantly higher in patients with LP than in patients without LP. LP = late potentials.
involvement and, as expected, the present study showed no association between ACE levels and cardiac events.

**Study limitations**

There are several limitations in this study. The first limitation is that our sample size was relatively small, limiting the power of the study. The second limitation is that advanced imaging modalities such as positron emission tomography and CMR imaging were not included in the baseline assessment. Some patients may already have had cardiac involvement, which can be detected by these advanced imaging modalities. However, such imaging modalities are expensive, time-consuming, and impractical in asymptomatic patients. SAECG is a simple, noninvasive, and economical technique that can be applied as a screening test in patients with pulmonary sarcoidosis. The third limitation is that all study patients were from Japan, leading to inevitable geographical differences that limit the broader applicability of findings. The last limitation is the low cardiac event rate in the study patients. However, SAECG may help identify patients who should be followed up closely.

**Conclusion**

SAECG might possibly be useful for the early detection of cardiac sarcoidosis and, if independently validated, could eventually be considered as a screening test for further risk stratification.

**Appendix**

**Supplementary data**

Supplementary data associated with this article can be found in the online version at [https://doi.org/10.1016/j.hrthm.2018.03.013](https://doi.org/10.1016/j.hrthm.2018.03.013).

**References**