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

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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)

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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 (RMS_{40}) in the f-QRS complex, and the duration of low-amplitude signals <40 μV (LAS_{40}) 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 $\geq$ 120 ms, (2) $RMS_{40} < 20$ μV, and/or (3) $LAS_{40} > 38$ 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.[3] 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).

Table 1 Baseline characteristics of the study patients (N = 74)

Characteristic	Value
Age (y)	55.4 ± 14.5
Sex: male	20 (27.0%)
Other organ involvement	
Eye	20 (27.0%)
Skin	11 (14.9%)
Others	4 (5.4%)
ACE level (IU/L)	19.7 ± 8.3
BNP level (pg/mL)	13.7 ± 6.4
PVCs (beats/d)	21.2 ± 53.7
E/A	1.1 ± 0.2
LVEF (%)	68.2 ± 5.7
LP	29 (39.2%)
f-QRS (ms)	106.7 ± 13.3
RMS_{40} (μV)	16.6 ± 9.5
LAS_{40} (ms)	39.6 ± 12.5

Values are presented as mean ± SD or as n (%).

ACE = angiotensin-converting enzyme; BNP = B-type natriuretic peptide; E/A = ratio of mitral inflow peak early velocity to mitral inflow peak late velocity; f-QRS = filtered QRS duration; LAS_{40} = duration of low-amplitude signals <40 μV; LP = late potentials; LVEF = left ventricular ejection fraction; PVC = premature ventricular contraction; RMS_{40} = root mean square voltage of the terminal 40 ms.

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, ^{18}F-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-lank, $P = .004$) 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