**Non-Invasive Detection of Latent Cardiac Conduction Abnormalities in Patients With Pulmonary Sarcoidosis**
— Application of Signal Averaged Electrocardiogram —

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**Background**
Electrocardiographic conduction abnormalities including development of atrioventricular block, bundle branch block or ventricular arrhythmias are characteristic manifestations of cardiac sarcoidosis (CS). The present study seeks to show the minute conduction abnormality by detection of late potentials (LP) on signal averaged electrocardiogram (SAECG).

**Methods and Results**
Ten patients with CS, 52 patients with pulmonary sarcoidosis (PS) but no obvious cardiac manifestations and 52 normal controls were studied. All participants underwent SAECG to detect LP. In patients with CS (the CS group), LP were detected in 8 patients (80%). In 52 patients with PS, LP were detected in 25 patients (46.2%, PS-LP(+) group), comparing only 3 (5.8%) of normal controls (p<0.0001). The remaining 27 patients with PS with negative LP were classified in the PS-LP(–) group. In the CS group, premature ventricular contraction frequency on Holter’s monitoring and plasma B-type natriuretic peptide concentrations were significantly higher than those in the PS group. However, no significant difference in these parameters between PS-LP(+) and PS-LP(–) groups were found.

**Conclusions**
In the PS patients without obvious cardiac manifestations, LP were detected as high as 46.2%, suggesting latent minute conduction abnormality. The higher incidence of LP in PS might be considered as an expression of latent myocardial fibrosis. Close follow-up is needed in these patients. (Circ J 2007; 71: 540–545)

**Key Words:** Cardiac involvement; Late potentials; Sarcoidosis

**S**arcoidosis is a systemic granulomatous disease of unknown cause involving multiple organs. Overall the prognosis is not necessarily deleterious because organ involvement is usually asymptomatic except for ocular or cutaneous involvements and the disease is often self-limiting. However, once the heart is involved, the patient’s prognosis is poor because of the development of fatal arrhythmias, atrioventricular conduction disturbance or refractory congestive heart failure. In patients with definite biopsy-proven or clinically-proven cardiac sarcoidosis (CS), corticosteroid therapy should be recommended, even if myocardial biopsy results are negative. On the basis of this recommendation, a novel diagnostic approach has been challenged for earlier detection and assessment of cardiac involvement in sarcoidosis patients.

We recently reported that measurement of plasma A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) concentrations, and investigation of integrated backscatter cyclic variation with echocardiography combined with assessment of wall thickening are useful for identifying patients with high-risk CS. Although electrocardiographic conduction abnormalities, atrioventricular block (AVB) or bundle branch block (BBB) are well known as the characteristic manifestation of CS, these manifestations have been detected in less than 5% of patients with sarcoidosis. However, in autopsy studies, cardiac involvements have been found in 20% to 58% of the cases, indicating latent CS does exist in a larger part of the sarcoidosis patients, even if routine electrocardiogram (ECG) shows no abnormal findings.

Signal averaged ECG (SAECG) is a non-invasive method to detect conduction abnormalities in patients with structural heart disease and to predict the outcome (both sudden cardiac death and sustained ventricular tachycardia) in patients with coronary artery disease, idiopathic hypertrophic cardiomyopathy and non-ischemic dilated cardiomyopathy. Late potentials (LP) detected by SAECG correspond to fragmented activation of ventricular tissue and are thought to originate from areas of delayed and heterogeneous conduction within the myocardium.

We hypothesized that infiltration of lymphocytes or fibrosis of the ventricular myocardium caused by sarcoid granulomas would produce areas of delayed myocardial activation to be detectable by SAECG. To clarify the prevalence of latent myocardial involvement, SAECG was recorded in sarcoidosis patients with and without cardiovascular manifestations. Furthermore, we assessed the relationships between the latent myocardial involvement detected by SAECG and other parameters, such as numbers of premature ventricular contractions (PVC) on 24-h ambulatory Holter monitoring, serum angiotensin converting enzyme (ACE) concentrations, BNP concentrations and disease duration.

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Methods

Study Population

Ten CS patients (7 females and 3 males, 57.5±15.6 years old), 52 pulmonary sarcoidosis (PS) patients (38 females and 14 males, 54.3±14.3 years old) were analyzed. Informed consent was obtained from all participants enrolled and approval was made by the local ethical committee.

We applied the diagnostic criteria for CS developed by the Specific Diffuse Pulmonary Disease Research Group, Sarcoidosis Division of the Japanese Ministry of Health, Labor, and Welfare.\(^{14,17}\) The criteria include: (category 1) histologic confirmation of sarcoidosis in the heart, or (category 2) a histologic diagnosis of extra CS with: (a) the presence of electrocardiographic abnormalities as an essential item plus one or more of the following clinical findings; (b) left ventricular (LV) asynergy, local wall thinning, or hypertrophy on echocardiograms; (c) abnormal tracer uptake or perfusion defects on radionuclide examinations; (d) intracardiac pressure abnormalities during cardiac catheterization or wall motion abnormalities or decreased LV ejection fraction (LVEF) on left ventriculography; and (e) interstitial fibrosis or cell infiltration noted in endomyocardial biopsies, even if the findings are non-specific. The electrocardiographic abnormalities could include right BBB, left axis deviation, AVB, ventricular tachycardia, PVC (≥Lown grade 2), abnormal Q waves, or ST-T changes on standard 12-lead tracing or Holter monitoring. Category 1 findings were determined from patients with CS met these diagnostic criteria and 9 of them received steroid therapy.

All PS patients had been diagnosed by pulmonologists and were referred to the cardiology division for further examination of possible cardiac involvement, even if they had no cardiac symptoms. Nine patients were taking maintenance doses prednisolone (2.5 to 5 mg/day).

Patients with known other cardiac diseases were excluded from the present investigation. History, physical examination and standard 12-lead ECG were done in all patients. Each patient underwent an echocardiographic study to exclude individuals with structural heart disease, valvular alterations, pericardial effusion, etc. Patients with hypertension, cardiomyopathy, pericardial effusion, valvular involvement and heart failure were not eligible for the PS group. LV end-diastolic and end-systolic dimensions were determined from M-mode or B-mode echocardiograms and LVEF were measured by the Teichorlitz method.

Disease duration was calculated from the day of definitive diagnosis.

The presence of LP by SAECG was analyzed in all patients enrolled. SAECG records were obtained from the Frank X, Y, and Z-leads during sinus rhythm using a Signal Processor DP 1100 (NEC, Tokyo, Japan) in all 104 patients. A total of 200 cycles were averaged to obtain a noise level of <0.2\(\mu\)V. The signals were amplified, digitized, averaged and bi-directionally filtered with a band-pass filter at frequencies between 40 and 250 Hz. The filtered QRS (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\(\mu\)V (LAS40) in the terminal f-QRS complex were measured respectively. In the present study, positive LP was defined with the modified Gomes’ standard.\(^{15}\) LP were considered as ‘positive’ if 2 of the following criteria were met: (1) f-QRS ≥120 ms; (2) RMS\(40\) <20\(\mu\)V; (3) LAS40 >35 ms.

Laboratory Analysis

Serum ACE, Na\(^+\), K\(^+\), Ca\(^++\) and plasma BNP concentrations were measured in all sarcoidosis patients. Serum ACE levels were measured by a colorimetric method (colorimetric assay kit; Fujirebio, Tokyo, Japan) with p-hydroxyhippuryl-L-histidyl-L-leucine as the substrate\(^{16}\) and plasma BNP concentrations were determined with a specific immunoradiometric assay for human BNP with commercial kits (Shionoria kit; Shionogi and Kyowa Medex, Tokyo, Japan).

Ambulatory ECG

Twenty-four hour Holter monitoring was carried out in all sarcoidosis patients. The number of PVC and Lown’s grade were investigated.

Classification of Sarcoidosis Patients

Ten patients with CS were classified in the CS group. In 52 PS patients without obvious cardiac abnormality, patients with LP positive were classified as PS-LP(+) group and the remaining patients with LP negative were classified as PS-LP(−) group. Differences in SAECG parameters, numbers of PVC on 24-h Holter monitoring, serum ACE concentrations, plasma BNP concentrations and disease duration was also examined.

Statistical Analysis

Data are expressed as mean±standard deviation, and statistical analysis was performed by Student’s t-test, Mann-Whitney tests for unpaired variables, and the analysis of variance test for multiple comparisons, as appropriate. A p-value <0.05 was considered statistically significant.
Results

Comparison of Backgrounds Between Patients With PS and Normal Individuals

Serum electrolyte (Na⁺, K⁺) concentrations were within normal limits in all patients. The backgrounds of PS patients and normal controls are shown in Table 1. Average history of PS was 14.1 months. There was no significant difference between the 2 groups except for the SAECG parameters.

The SAECG records showed the presence of LP in 25 out of 52 sarcoidosis patients (46.2%) vs 3 out of 52 controls (5.8%). The difference between the 2 groups was statistically significant (p<0.001). The mean f-QRS recorded in the sarcoidosis patients tended to be larger but did not reach statistical significance (103.2±12.5 vs 99.0±9.1, p=0.054). The mean RMS40 and LAS40 in the sarcoidosis patients significantly differed from those in normal controls (RMS40: 16.1±8.9 vs 21.6±9.0, p<0.005; LAS40: 39.0±9.8 vs 32.7±5.2, p<0.001). The representative records of SAECG in PS patients with LP positive is shown in Fig 1. Majority (n=17, 68.0%) of LP positive sarcoidosis patients met criteria of LP in the combination of RMS40 and LAS40. Minority (n=8, 32%) of LP positive sarcoidosis patients met criteria of f-QRS ≥120 ms. The relationship between RMS40 and LAS40 are shown in Fig 2. LP positive patients were predominantly characterized by prolonged LAS40 rather than the small RMS40.

Comparison of the Parameters for the CS, LP Positive and Negative PS Patients

A comparative analysis was carried out in the CS patients (n=10, CS group), PS patients with LP (n=25, PS-LP(+) group) and without LP (n=27, PS-LP(–)). As shown in Table 2, the mean values of f-QRS, RMS40 and LAS40 statistically differed in the 3 groups (Fig 3). Age, sex, serum Ca²⁺ concentration, ACE concentration and disease duration were not significantly different for these 3 groups. In the CS group, the number of PVC on Holter monitoring and plasma BNP concentrations were significantly higher, otherwise LVEF were significantly lower than those in the other 2 groups. However, there were no significant differences in these parameters between PS-LP(+) group and PS-LP(–) group.

Discussion

Application of SAECG for Detection of Latent CS

As a diagnostic tool for the detection of latent CS, Kinney and Caldwell reported that myocardial imaging with thallium-201 showed segmental defects in some asymptomatic sarcoidosis patients, but the risk of cardiac dysfunction or sudden death in these patients was relatively low. Smedema et al showed that gadolinium-enhanced cardiovascular magnetic resonance is a useful diagnostic tool to determine cardiac involvement in patients with PS.

In the present study, we applied SAECG in sarcoidosis patients without clinical manifestation of cardiac involvement. SAECG showed significant differences in the prevalence of LP positivity between patients with sarcoidosis and controls, suggesting electrophysiological conduction abnor-
Late Potentials in Sarcoidosis

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mality would be present in these patients, even without obvious clinical manifestations of cardiac disease. The delayed conduction that manifests itself as LP can be caused mainly by 2 factors: slow conduction velocity and/or a long path length of conduction. The microanatomy of regions in which the fractionated electrograms are recorded is characterized by large amounts of fibrous tissue.19 Moreover, myocardial fibrosis has been associated with LP, even in the absence of myocardial infarction.20,21 In fact, myocardial activation might be delayed because the pathway of excitation is lengthened by islands of fibrosis. Thus, the higher incidence of LP in sarcoidosis shown in the current study would be considered as expression of myocardial fibrosis.

Infiltration of sarcoid granulomas might also induce delayed myocardial activation, but our study showed that there was no significant difference in serum ACE or BNP concentrations, which reflect disease activity and myocardial stress, between LP positive and negative sarcoidosis groups.

As one of the clinical indicators of cardiac involvement, we assessed the number of PVC on Holter monitoring and plasma BNP concentrations. Suzuki et al described that PVC of Lown's grade 4A or 4B were detected in 67% of patients with CS and Holter monitoring was a useful screening test for detecting cardiac involvement in sarcoidosis.22
However, regarding BNP, it has been shown that the measurement of plasma BNP concentrations is clinically useful not only for assessing the severity of heart failure but also as a screening for heart disease. Furthermore, we previously reported that ANP, BNP and assessment of integrated backscatter cyclic variation combined with wall thickening by echocardiography are useful markers identifying sarcoidosis patients with higher risk cardiac manifestations. BNP would be a mostly clinically useful indicator for cardiac involvement in sarcoidosis patients. However, in the present study, neither number of PVC on 24-h Holter monitoring, nor plasma BNP concentrations showed significant differences between LP positive and negative sarcoidosis group. As expected, definite CS patients presented significantly higher number of PVC on Holter monitoring and significantly higher plasma BNP concentrations than those in LP positive and negative sarcoidosis groups. These results suggest a hypothesis that LP might indicate ‘latent’ conduction abnormality in PS patients and this microvolt conduction abnormality does not necessarily relate to the development of ventricular arrhythmia or heart failure. However, this might become symptomatic over CS. Furthermore, our investigation showed that the majority of LP positive sarcoidosis patients met criteria of LP in combination of RMS and LAS and that prolonged LAS seemed to be more influential. This result indicated that the conduction abnormalities in sarcoidosis patients were so minute that it was not reflected in t-QRS duration. Further investigation is needed to support our hypothesis of latent minute conduction abnormality. Concerning the relationship between conduction abnormality and sarcoidosis, Aizer et al reported the usefulness of programmed ventricular stimulation in predicting future arrhythmic events in patients with CS. Furushima et al described that the mechanism of ventricular tachyarrhythmias associated with CS was re-entry because they were initiated by programmed stimulation. Regarding repolarization abnormalities, Uyarel et al reported that QT dispersion was prolonged in patients with CS. To the best of our knowledge, this is the first report applying LP in sarcoidosis. Furthermore, the present study has suggested that SAECG would be useful, economical and a non-invasive technique that can easily detect minute conduction abnormalities of cardiac tissue, and might be helpful particularly in those patients in whom no cardiac symptoms are yet evident.

Clinical Implication and Limitation of the Study

In this study, although LP were positive in more than 40% of patients with PS, so far there was no obvious manifestation of cardiac arrhythmia or heart failure. No reports have shown the process of cardiac involvement in sarcoidosis patients. Prospective observational follow-up study is needed to clarify the possibility of the relationship between the LP parameters and the risk for progression of cardiac involvement. The existence of LP may help identify a subset of patients who should be followed up carefully.

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References


