

Detection of cardiac involvement in pulmonary sarcoidosis using high-resolution Holter electrocardiogram

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Abstract

Background: Early detection of cardiac involvement in patients with sarcoidosis is important but currently unresolved. The aim of this study was to elucidate the utility of frequency domain microvolt T-wave alternans (TWA), signal-averaged ECG (SAECG), and heart rate turbulence (HRT) using 24-hour Holter ECG for detecting cardiac involvement in patients with pulmonary sarcoidosis.

Methods: This study consisted of consecutive 40 pulmonary sarcoidosis patients (11 males, 62 ± 13 years) who underwent 24-hour Holter monitoring with and without cardiac involvement. All patients underwent frequency domain TWA, SAECG, and HRT using 24-hour Holter monitoring. Patients with atrial fibrillation pacing or wide QRS electrocardiogram were excluded.

Results: After 14 patients were excluded, a total of 26 patients (six males, 59 ± 14 years) were evaluated. Seven patients had cardiac involvement (cardiac sarcoidosis [CS] group). On the Holter SAECG, duration of low-amplitude signals $<40 \mu\text{V}$ in the terminal filtered QRS complex (LAS40) was significantly higher, and root mean square voltage of the terminal 40 ms of the filtered QRS complex (RMS40) was significantly lower in the CS group compared with the non-CS group (LAS40: 61.4 ± 35.9 vs 37.6 ± 9.2 ms; $P = .018$, RMS40: 11.4 ± 10.3 vs 23.6 ± 13.2 ms; $P = .023$). Prevalence of positive late potential (LP) was also significantly higher in the CS group than that in the non-CS group (85.7% vs 31.5%; $P = .026$). The sensitivity, specificity, positive, and negative predictive values of LP for identifying patients with cardiac involvement were 85.7%, 68.4%, 50.0%, and 92.8%, respectively.

Conclusion: Holter SAECG may be useful for detecting cardiac involvement in patients with pulmonary sarcoidosis.

KEYWORDS

Holter monitoring, risk assessment, sarcoidosis, signal-averaged electrocardiography

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1 | INTRODUCTION

Sarcoidosis is an idiopathic granulomatous disease involving multiple organs.¹ Although most patients have a relatively good prognosis, heart involvement often confers a poor prognosis after the development of atrioventricular block, lethal ventricular arrhythmias, and refractory heart failure. Therefore, early detection of cardiac involvement in sarcoidosis is important but is currently unresolved. We have previously reported a high prevalence of ventricular late potentials (LPs) on signal-averaged electrocardiography (SAECG) in patients with pulmonary sarcoidosis, and its association to cardiac events.^{2,3} However, the utility of other noninvasive tests, such as microvolt T-wave alternans (TWA) and heart rate turbulence (HRT), has not yet been explored. A high-resolution Holter ECG which can measure TWA, SAECG, and HRT simultaneously has recently been developed.⁴ The present study aimed to investigate the diagnostic value of TWA, SAECG, and HRT measured from 24-hour Holter ECG recordings for cardiac involvement in patients with pulmonary sarcoidosis.

2 | METHODS

We retrospectively studied consecutive 40 patients (11 males, 62 ± 13 years) with pulmonary sarcoidosis who underwent 24-hour ambulatory Holter monitoring that could analyze TWA, LPs, and HRT. All patients were referred to our hospital from April 1, 2014 to December 31, 2017. Seventeen patients had known cardiac involvement, and the remaining 23 patients were referred to the department of cardiovascular medicine for further examination of cardiac involvement. The diagnosis of pulmonary sarcoidosis was certified based on fiber-optic bronchoscopy finding of epithelioid, noncaseating granuloma without necrosis. The diagnosis of cardiac sarcoidosis (CS) was based on the Heart Rhythm Society (HRS) consensus criteria.⁵ Patients with atrial fibrillation, atrial or ventricular pacing,

wide QRS (≥ 120 msec) electrocardiogram including complete right bundle branch block (CRBBB), complete left bundle branch block (CLBBB), and nonspecific intraventricular conduction delay (NIVCD) were excluded from the present study. After applying the exclusion criteria, 14 patients were excluded because of pacing ($n = 4$) or wide QRS complex ($n = 10$) (Figure 1). A total of 26 patients (six males, 59 ± 14 years) were evaluated. Seven patients had cardiac involvement (CS group), in whom three patients had known cardiac involvement, and the remaining four patients were diagnosed with CS subsequently. From 12-lead ECG, Selvester QRS score was manually calculated by two expert cardiologists, as previously reported.⁶ Data from 24-hour continuous ambulatory digital Holter ECG (FM-180, Fukuda Denshi Co., Ltd.) recordings were measured for specific ECG markers including TWA, LP, and HRT, using a commercial system (SCM-8000; Fukuda Denshi Co., Ltd., Tokyo, Japan).

LPs were automatically analyzed every 30 minutes for 24 hours. The orthogonal Frank X, Y, and Z leads were recorded, and the signals were amplified, digitized, averaged, and filtered with a high-pass filter at 40 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 mV (LAS40) in the terminal f-QRS complex were measured at the smallest value of RMS40. LPs were considered to be positive when two of three criteria (fQRS > 135 ms, RMS40 < 15 μ V, and LAS40 > 39 ms in the system) were met.⁴

HRT was simultaneously measured, and turbulence onset (TO) and turbulence slope (TS) were determined. TO $\geq 0\%$ and TS ≤ 2.5 ms/R-R intervals are considered abnormal.⁷ HRT values are usually classified into three categories: 1) 0 indicates a normal TO and TS; 2) 1 indicates that either TO or TS is abnormal; and 3) 2 indicates that both TO and TS are abnormal. Patients were classified as HRT 0 if HRT could not be calculated because of none or too few suitable tachographs of premature ventricular contractions. In the present study, HRT 2 was defined as abnormal HRT, and HRT 0 and 1 were defined as normal HRT.⁴

Study Design and Patients Selection

Retrospective study

Between April 2014 and December 2017

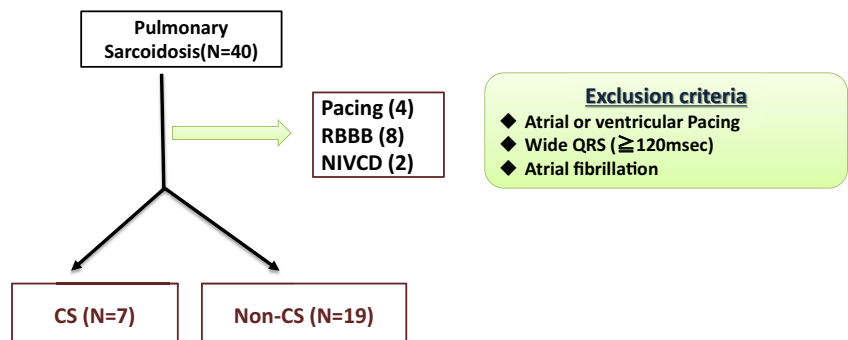
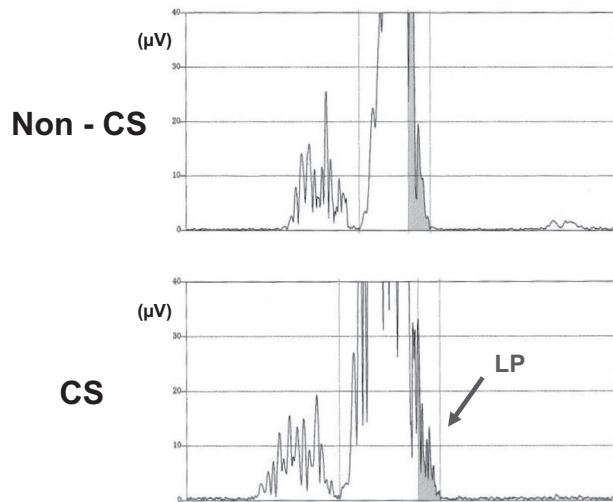


FIGURE 1 Flow diagram showing the selection of the study population. CS, cardiac sarcoidosis; NIVCD, nonspecific intraventricular conduction delay; RBBB, right bundle branch block



f-QRS 132ms
RMS₄₀ 31.4µV
LAS₄₀ 31ms

f-QRS 187ms
RMS₄₀ 11.0µV
LAS₄₀ 57ms

FIGURE 2 Representative cases of Holter SAECG in each group. Positive LP (arrow) was shown in a patient with CS (arrow). CS, cardiac sarcoidosis; f-QRS, filtered QRS duration, LAS₄₀, duration of low-amplitude signals < 40 mV; RMS₄₀, root mean square voltage of the terminal 40 ms

Frequency domain TWA was simultaneously measured, and the maximum TWA magnitude (max TWA) over 24 hours was determined using a previously described spectral method.⁸

We measured left ventricular ejection fraction (LVEF, measured by the Simpson's method) on echocardiography. Serum angiotensin-converting enzyme (ACE) levels and soluble IL-2 receptor (sIL-2R) levels, and plasma brain natriuretic peptide (BNP) concentrations were also assessed. Serum ACE levels were measured by a colorimetric method (colorimetric assay kit; Fujirebio, Tokyo, Japan). Plasma BNP concentrations were measured by a specific immunoassay (Shionoria Kit; Shionogi and Kyowa Medex, Tokyo). Serum sIL-2R was determined using chemiluminescent immunoassay.

We performed medical record review to identify patient characteristics including findings of cardiac magnetic resonance imaging (MRI), gallium scintigraphy, endomyocardial biopsy, positron emission tomography-computed tomography (PET-CT), conventional SAECG, and medications. Approval for this study was obtained from the Institutional Review Board of Nippon Medical School (Ref: 27-06-456) and written informed consent was obtained from all patients.

2.1 | Statistical analysis

Measurements are presented as mean value \pm SD. Comparisons of measurements between two groups were analyzed by Mann-Whitney U test. Fisher's exact test was used for discrete variables. A *P* value < .05 was considered as significant. Statistical calculations were performed with SPSS version 20 software (IBM Inc, Chicago, IL, USA).

3 | RESULTS

On the Holter SAECG, LAS₄₀ was significantly higher, and RMS₄₀ was significantly lower in the CS group than that of the non-CS group (LAS₄₀: 61.4 \pm 35.9 vs 37.6 \pm 9.2 ms; *P* = .018, RMS₄₀: 11.4 \pm 10.3

TABLE 1 Comparison of each parameter between patients with and without cardiac involvement

	Non - CS group (n = 19)	CS group (n = 7)	<i>P</i> value
Age (years)	60.4 \pm 14.2	54.1 \pm 13.7	.36
Male	4	2	1.0
LVEF (%)	70.8 \pm 6.5	53.4 \pm 19.1	.061
BNP (pg/mL)	20.3 \pm 14.0	59.7 \pm 61.7	.22
ACE (U/mL)	21.6 \pm 11.2	23.3 \pm 9.8	.52
s-IL2R (U/mL)	600.7 \pm 641.1	570.0 \pm 334.6	.73
f-QRS (ms)	145.1 \pm 11.9	181.4 \pm 36.0	.093
RMS ₄₀ (µV)	23.6 \pm 13.2	11.4 \pm 10.3	.018
LAS ₄₀ (ms)	37.6 \pm 9.2	61.4 \pm 35.9	.023
LPs	6	6	.026
max TWA (µV)	9.0 \pm 4.4	13.4 \pm 10.7	.67
HRT category 2	1 (5.3%)	1 (14.2%)	.47
nsVT	0	2	.065
PVC (beats)	7471 \pm 5903	2429 \pm 6092	.18
selvester score	0.2 \pm 0.5	0.6 \pm 1.1	.60
Steroid use	2	3	.10

Abbreviations: ACE, angiotensin converting enzyme; BNP, brain natriuretic peptide; CS, cardiac sarcoidosis; f-QRS, filtered; QRS duration; HRT, heart rate turbulence; LAS₄₀, duration of low amplitude signals < 40 mV; LVEF, left ventricular ejection fraction; LPs, late potentials; nsVT, non sustained ventricular tachycardia; PVC, premature ventricular contractions; s-IL2R, soluble IL-2 receptor; TWA, T wave alternans; RMS₄₀, root mean square voltage of the terminal 40 ms

vs 23.6 \pm 13.2 ms; *P* = .023). Prevalence of positive LPs was also significantly higher in the CS group than in the non-CS group (85.7% vs 31.5%; *P* = .026). Representative Holter SAECGs in CS and non-CS groups are shown in Figure 2. However, there were no significant differences in the Holter-based HRT and TWA parameter, LVEF, BNP, ACE, and sIL-2R levels between the two groups (Table 1). The sensitivity, specificity, positive, and negative predictive values of

LPs for identifying patients with cardiac involvement were 85.7%, 68.4%, 50.0%, and 92.8%, respectively.

Characteristics of the CS patients are shown in Table 2. None of the patients underwent endomyocardial biopsy. Gallium scintigraphy was performed in three patients, in whom one patient had positive Gallium uptake in the heart. One patient (No.4) was taking amiodarone for ventricular tachycardia (VT). Clinical manifestations of CS included sustained ventricular tachycardia (n = 2), nonsustained ventricular tachycardia (n = 2), atrial tachycardia (n = 1), and HF (n = 2). Conventional SAECG was performed in four patients, in whom two patients showed positive LPs.

4 | DISCUSSION

4.1 | High prevalence of LPs on Holter SAECG in cardiac sarcoidosis

The present study demonstrated that the prevalence of LPs was higher in the CS group than in the non-CS group. Cardiac involvement of sarcoidosis is often manifested as conduction abnormality, including atrioventricular block and bundle branch block. Therefore, SAECG, which can detect subtle conduction abnormality, would theoretically be useful for detecting cardiac involvement in sarcoidosis patients. Inflammation or fibrosis caused by sarcoid granulomas might produce delayed conduction which could be detectable by SAECG. Schuller et al demonstrated that the SAECG was abnormal in 14 of 27 sarcoidosis patients with cardiac involvement but only in 11 of 61 patients without cardiac involvement ($P < .01$).⁹

This is consistent with our results, which show the diagnostic utility of Holter SAECG for cardiac involvement. Another important finding is a relatively high prevalence of LPs (31.5%) in non-CS patients, which is consistent with our previous studies.^{2,3} Close follow-up should be considered in these patients.

4.2 | Potential role of Holter SAECG for early detection of cardiac involvement

The prognosis of patients with CS is poorer if they are not diagnosed in the early stage. Therefore, early diagnosis and initiation of steroid therapy are important to decrease mortality and improve outcomes.¹⁰ Steroid therapy has been reported to prevent LV remodeling in patients with LVEF \geq 30% but not in patients with LVEF $<$ 30%.¹¹ Furthermore, our previous study has demonstrated that steroid therapy is more effective for ventricular arrhythmias in patients with less advanced LV dysfunction than in patients with advanced LV dysfunction.¹² These findings suggest that early diagnosis and therapeutic intervention for cardiac involvement are crucial in patients with sarcoidosis.

LPs detected by SAECG may reflect delayed activation of ventricular tissue originating from areas of diseased myocardium. It has

TABLE 2 Characteristics of pulmonary sarcoidosis patients with cardiac involvement (CS group)

Patient	Age (years)	Gender	PVC (beats/day)	nsVT	ACE (IU/L)	s-IL2R (U/ml)	BNP (pg/ml)	LVEF (%)	f-QRS (ms)	RMS40 (μ V)	LAS40 (ms)	LPs	max TWA (μ V)	HRT category	other organ involvement	LGE on cardiac MRI	high T2 signal on cardiac MRI	cardiac FDG uptake on PET-CT	selvester score	dose of PSL (mg)	clinical manifestation
1	74	F	26	-	26.6	906	163.7	76	193	6.1	97	+	29.1	0	eye	NA	NA	+	0	5	AT
2	51	F	200	+	17.8	229	50.7	50	135	25	32.6	-	17.8	1	-	-	+	+	0	0	nsVT
3	58	F	883	-	31.9	521	30.8	42	246	4.6	137	+	9.1	1	skin	+	+	+	1	10	VT
4	38	M	6492	+	20.4	762	8.1	59	192	1.3	64	+	25.4	1	eye, skin	+	+	+	0	10	VT
5	40	M	6793	+	38.2	1034	34.4	80	166	6.3	45	+	3.4	1	eye, skin	-	+	+	0	0	nsVT
6	69	F	2508	-	19.4	328	127.4	32	187	11	57	+	3.1	0	Eye	+	+	+	3	0	HF
7	49	F	530	-	8.8	210	130	35	151	14.3	41	+	6.1	2	-	NA	NA	+	0	0	HF

Abbreviations: LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; PSL, prednisolone. Other abbreviations as in Table 1.

been reported to predict cardiac events in patients with ischemic heart disease and nonischemic cardiomyopathy.^{13,14}

We have previously demonstrated a high prevalence of LPs in pulmonary sarcoidosis, and found that LPs were associated with subsequent cardiac events.^{2,3} Therefore, Holter SAECG may also potentially be useful for early detection of cardiac involvement in patients with sarcoidosis. A disadvantage of conventional SAECG is the time needed for signal averaging. In contrast, Holter SAECG can save time and cost, as the measurement is obtained from routine Holter monitoring. Furthermore, LPs were positive in six of seven CS patients on Holter SAECG, whereas two of four CS patients on conventional SAECG in the present study. Although the small number of patients in this analysis may limit its power, Holter SAECG might be superior to conventional SAECG for detecting cardiac involvement.

A prospective study should be conducted to evaluate the utility of Holter SAECG.

4.3 | Holter TWA in sarcoidosis

TWA is a periodic beat-to-beat variation in the amplitude or morphology of the T wave on ECG. Beat-to-beat TWA may reflect increased dispersion of ventricular repolarization, and is known to often precede the development of lethal ventricular arrhythmias.¹⁵

Microvolt TWA is a noninvasive test which can detect subtle beat-to-beat fluctuations in T-wave morphology and amplitude using fast Fourier transformation.¹⁶ It has been widely reported to be a useful predictor for serious ventricular arrhythmias and sudden death in patients with structural heart disease including ischemic heart disease and nonischemic cardiomyopathy.¹⁷⁻²¹

Bicycle or treadmill exercise has been necessary for conventional TWA testing to increase heart rate. Time-domain modified moving average (MMA) method, which is a novel technique of measuring TWA using 24-hour Holter monitoring, has recently been developed. Previous studies have demonstrated its utility for predicting malignant ventricular arrhythmias, sudden cardiac death, and cardiovascular mortality.^{22,23} More recently, frequency domain TWA analysis, which is theoretically less affected by noise than time-domain TWA, has been developed.^{8,24}

In the present study, frequency domain TWA analysis showed no significant difference between sarcoidosis patients with and without cardiac involvement. There have been few reports on TWA in sarcoidosis. Although one study reported the utility of TWA for detecting cardiac involvement in patients with sarcoidosis, their sample size was similarly small.²⁵ A large-scale study is required to evaluate the utility of TWA in patients with sarcoidosis.

4.4 | HRT in sarcoidosis

HRT has been proposed as a novel marker of autonomic tone, and its prognostic value has been widely demonstrated especially in patients with myocardial infarction.²⁶⁻²⁸ Furthermore, a recent large

multicenter prospective study showed that abnormal HRT was significantly associated with all-cause mortality and fatal arrhythmic events in patients with structural heart disease including ischemic and nonischemic heart disease.⁴ However, no clinical studies have been conducted to evaluate the utility of HRT in patients with sarcoidosis. The present study demonstrated no significant difference in the prevalence of abnormal HRT between sarcoidosis patients with and without cardiac involvement, suggesting that HRT may not be closely associated with cardiac involvement in patients with sarcoidosis.

4.5 | Other parameters

The electrocardiography-based Selvester QRS score from 12-lead ECG has been reported to be useful for identifying myocardial scar in CS.²⁹ In the present study, three CS patients showed late gadolinium enhancement (LGE) on cardiac MRI, in whom one patient (No.6) had high Selvester score (3 points). Reduced LVEF is associated with cardiac involvement in sarcoidosis. However, there was no significant difference in LVEF between the CS group and non-CS group ($P = .061$). However, this may be an issue of selection bias as we excluded patients with wide QRS complex, atrial, or ventricular pacing including cardiac resynchronization therapy. Our study population had relatively preserved LVEF (mean 53.4%), suggesting that patients with reduced LVEF had been excluded.

BNP is a hormone produced mainly by ventricles in response to ventricular volume and pressure overload, and its levels have been shown to be elevated in patients with CS.^{30,31} However, there were no significant differences in BNP levels between the CS group and non-CS group and this may be affected by our small sample size and possible patient selection bias as aforementioned.

Although serum ACE and sIL-2R levels are elevated in patients with sarcoidosis, it is not specific for cardiac involvement.³² Accordingly, no significant differences were found in serum ACE and sIL-2R levels between CS group and non-CS group.

4.6 | Study limitations

There are limitations in this study. First, it was retrospective and the sample size was small, limiting the power of the study. A large-scale prospective study is warranted to validate our findings. Second, the present study did not include a control group. However, our previous study showed a high prevalence of LPs in pulmonary sarcoidosis patients compared to that in control subjects.² Third, no data were shown regarding arrhythmic events and cardiac death because of the retrospective nature of the study. The original purpose of SAECG is to predict cardiac events or death. Fourth, we did not evaluate daily variation of LPs. It has been reported that SAECG parameters fluctuate over 24 hours.³³ Finally, the present study excluded patients with CRBBB, CLBBB, and NIVCD, which have been reported to account for half of CS patients.³⁴

5 | CONCLUSIONS

Holter SAECG may be useful for detecting cardiac involvement in patients with pulmonary sarcoidosis.

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None.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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