Prognostic value of phase analysis on gated single photon emission computed tomography in patients with cardiac sarcoidosis

Kazuhiro Koyanagawa, MD[1], Masanao Naya, MD, PhD[1*], Tadao Aikawa, MD, PhD[1], Osamu Manabe, MD, PhD[2], Masato Kuzume, MD[1], Hiroshi Ohira, MD, PhD[3], Ichizo Tsujino, MD, PhD[3], Nagara Tamaki, MD, PhD[4], and Toshihisa Anzai, MD, PhD[1]

1 Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan

2 Department of Nuclear Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan

3 First Department of Medicine, Hokkaido University Hospital, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan

4 Department of Radiology, Kyoto Prefectural University of Medicine, Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

*Correspondence Masanao Naya

Tel.: +81-11-706-6973

Fax: +81-11-706-7874

E-mail: naya@med.hokudai.ac.jp

Running title: Phase analysis and outcomes in cardiac sarcoidosis

Financial support: None

Word count: 4314

Abstract

Background

We aimed to determine the correlation between phase analysis, reflecting the heterogeneity of perfusion defects, and the dyssynchrony of the left ventricle wall motion, and adverse cardiac events in cardiac sarcoidosis (CS) patients.

Methods

Fifty-seven consecutive patients with diagnosed CS (64 [IQR 55–71] years old, 14 males), who underwent ^{18}F-FDG PET/CT and ECG-gated SPECT, were studied. FDG PET was analysed to measure cardiac metabolic volume (CMV), and total lesion glycolysis (TLG). The SPECT findings, such as LVEF, summed rest score (SRS), bandwidth (BW) were evaluated.

Results

The median of BW was 56° (IQR, 40–95). BW showed a strong inverse correlation with LVEF (r = -0.60, p < 0.0001), and positive correlation with SRS (r = 0.82, p < 0.0001). However, there were no significant correlations between BW and CMV or TLG. The Kaplan-Meier curves revealed a significantly higher rate of MACE in the high BW group (BW > 56°) than the low BW group (BW ≤ 56°) (15.1%/y vs. 4.4%/y, p = 0.025). In multivariable analysis, BW was a significant independent predictor of MACE (p = 0.015).

Conclusion

Phase analysis on gated SPECT was a significant and independent predictor of MACE in patients with CS.

Abbreviations list

CS = cardiac sarcoidosis,

SPECT = single photon emission computed tomography

FDG = ^{18}F-fluorodeoxyglucose

PET = positron emission tomography

CT = computed tomography

SRS = summed rest score

BW = bandwidth

MACEs = major adverse cardiac events

MPI = myocardial perfusion imaging

Keywords

Cardiac sarcoidosis • Electrocardiography-gated single-photon emission computed tomography • ^{18}F-fluorideoxyglucose positron emission tomography-computed tomography • Phase analysis • Major adverse cardiac events

Introduction

Cardiac lesions in patients with cardiac sarcoidosis (CS) are characterised by the formation of non-caseating granulomas and scar in focal and multiple segments in the heart (1, 2) and are very diverse for each patient. Although low left ventricular ejection fraction (LVEF), and ^{18}F-fluorideoxyglucose (FDG) uptake/perfusion mismatch can predict adverse outcomes, the heterogeneity of the disease activity could also be an important prognostic factor (3-6). Such data is particularly needed since autopsy studies have suggested that only a small subset of patients with CS are at increased risk of sudden death (1).

Phase analysis by using electrocardiography (ECG)-gated single-photon emission computed tomography (SPECT) perfusion imaging reflects the heterogeneity of perfusion defects in terms of its magnitude and area, as well as the dyssynchrony of LV wall motion (7, 8). However, the relationship between phase analysis findings and clinical outcome in patients with CS has not been well-explored. Therefore, this study aimed was to test how phase analysis relates to adverse cardiac events in patients with CS.

Materials and methods

Study population

This study was a retrospective evaluation of the clinical records of patients with known or suspected

CS. In total, 133 consecutive patients, who underwent gated myocardial perfusion imaging (MPI) and FDG positron emission tomography (PET) / computed tomography (CT) at our institute from January 2010 to December 2017, were screened. Out of them, 66 patients were diagnosed with CS. Patients who underwent ^{99m}Tc-tetrofosmin (n = 6) and no ECG-gated MPI (n = 3) were excluded. Thus, a total of 57 patients were included in this analysis (Figure 1). Cardiac involvement was defined based on the 2016 Japanese Circulation Society (JCS) guidelines for criteria of CS (Supplement table 1). We assessed their blood examination at baseline. The study protocol was approved by the Ethics Committee of Hokkaido University Hospital (IRB No. 017-0446). The investigation conformed with the principles outlined in the Declaration of Helsinki.

Transthoracic echocardiography

Echocardiography was performed using either an Aplio Artida ® SSH-88-CV or Aplio® SSA-770A (Toshiba Medical Systems, Tochigi, Japan). The LV end-diastolic and end-systolic dimensions were analysed using M-mode or B-mode echocardiography. E/A ratio, deceleration time, E/e′ ratio were included for the assessment of LV diastolic function. LVEF was obtained using the modified biplane Simpson's method. Findings, such as abnormal wall motion, regional wall thinning or thickening, and dilatation of the LV were considered as abnormal for transthoracic echocardiography (TTE) based on JCS guidelines (9).

ECG data analysis

The QRS intervals were automatically analysed by electrocardiography. Findings, such as right bundle branch block (RBBB), atrioventricular (AV) block, left-axis deviation, ventricular tachycardia (VT), premature ventricular contraction (PVC) (grade > 2 in Lown's classification), and abnormal Q were defined as abnormal based on the JCS guidelines (9).

PET imaging procedure and analysis

All patients fasted for at least 18 h before FDG PET/CT studies to reduce physiological myocardial FDG uptake (10). Thirty patients were injected with unfractionated heparin (UFH; 50 IU/kg, Mochida, Tokyo) alone, five patients were given a low-carbohydrate diet (LCD) alone. The remaining 22 patients were given both UFH and LCD. PET imaging was performed using a Gemini TF PET/CT scanner (Philips Healthcare, Cleveland, OH) or a Biograph 64 TruePoint with TrueV® PET/CT scanner (Siemens Japan, Tokyo).

The software system METAVOL® (Department of Nuclear Medicine, Hokkaido University, Sapporo, Japan) was used to obtain maximal standard uptake value (SUVmax), cardiac metabolic volume (CMV), and total lesion glycolysis (TLG) (11). CMV was a volume-based parameter such as inflammatory activity in patients with CS, defined as the volume within the boundary determined by the FDG uptake threshold (SUV mean of blood pool × 1.5) (12). TLG was calculated by

multiplying CMV by mean SUV.

MPI imaging procedure and analysis

ECG-gated SPECT was performed 60 min after injection of 600 MBq of ^{99m}Tc-sestamibi (FUJI RI Pharma, Tokyo, Japan).

For the assessment of LV dyssynchrony and baseline cardiac parameters, we used a dedicated phase analysis software (cardioREPO®: collaboration between EXINI Diagnostics AB and Fujifilm RI Pharma Co., Ltd., Tokyo, Japan) (8). Fourier curve fitting was performed to obtain a phase distribution and represent the regional onset of the LV mechanical contraction. Phase analysis generated a phase distribution (0°-360°) spanning the R-R interval, and the following quantitative indexes were obtained: 1. phase standard deviation (SD), which is the SD of the phase distribution; 2. bandwidth (BW), which includes 95% of the elements of the phase distribution; and 3. entropy, which is an index of ‘‘disorder’’ calculated (7). The LVEF, the LV end-diastolic volume (EDV), and the LV end-systolic volume (ESV) were calculated automatically. The summed rest score (SRS) which is an index of myocardial injury was also automatically analysed.

Ascertainment of outcomes

Outcomes were ascertained by electrical medical records, and scripted phone interviews. The primary endpoint of the study was composite of major adverse cardiac events (MACE), such as all cause death,

sustained VT (SVT), ventricular fibrillation (VF), AV block, and hospitalization due to worsening of heart failure. In patients with implantable cardiac defibrillators (ICDs), device interrogation records were used to identify any ventricular arrhythmias requiring cardioversion or antitachycardia pacing.

Statistical analysis

Patient demographics and baseline characteristics were summarized as medians and interquartile ranges or means and standard deviation for continuous variables, as appropriate based on normality, and frequencies for dichotomous and ordinal variables. Statistical significance was assessed using the Student t tests or the Wilcoxon tests for normal and non-normal continuous data and with the Fischer's exact test or the Chi-square tests for dichotomous and ordinal variables. Correlation between continuous BW and continuous LVEF, SRS, CMV, and TLG were assessed using linear regression analysis. Differences in event-free time were analysed by the Kaplan-Meier method. The log-rank test was used to compare the survival curves. The univariate and multivariate Cox proportional hazard regression models were used to identify independent predictors of cardiac events. The multivariate Cox proportional hazards models were used to assess the impact of BW, phase SD, and entropy on MACE after adjustment for age, sex, LVEF. Two-sided p values <0.05 were considered significant. All analyses were performed with JMP Pro® 13.0 (SAS Institute, Cary, NC, USA).

Results

Characteristics data

Patient characteristics are shown in Table 1. Patients were classified into two groups: the high BW group (BW > 56°) (n = 27) and the low BW group (BW ≤ 56°) (n = 30) at the median of BW. The high BW group had significantly higher New York Heart Association (NYHA) classifications and higher levels of (brain natriuretic peptide (BNP) than the low BW group.

There were no significant differences in pacing, complete left bundle branch block (CLBBB), and complete right BBB (CRBBB) between the two groups. History of sustained VT or ventricular fibrillation (VF), LV end-diastolic diameter (LVDd), LV end-systolic diameter (LVDs), LV mass index (LVMI), EDV, ESV, SRS, CMV, and TLG in the high BW group were significantly higher than those in the low BW group (Tables 1 and 2). LVEF in the high BW group was significantly lower than that in the low BW group. There was no significant difference in LV diastolic function between the two groups.

Medication and device data

The conditions of drug and device between the baseline and after the 2-months follow-up were compared in Supplement table 2. At baseline, only three patients (5%) were treated with steroid, which reflected that this cohort mainly consisted of newly diagnosed CS. At follow-up, β-blockers, angiotensin-converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARB), amiodarone,

and steroids were titrated well in the high BW group compared with the low BW group. Likewise, ICDs and cardiac resynchronization therapy defibrillator (CRT-D) were more frequently implanted in the high BW group.

Relationship between BW and LVEF, SRS, CMV, or TLG

BW showed a strong inverse correlation with LVEF, and strong correlation with SRS. However, there were no significant positive correlations between BW and CMV or TLG (Figure 2).

Predictors of MACE

During the median of 2.78 years (IQR 1.43-4.42 years IQR) of follow-up, 15 MACEs occurred among 57 patients (Table 3). Among these, ventricular arrhythmia in the high BW group was significantly higher than that in the low BW group. The Kaplan-Meier curves revealed a significantly higher rate of MACE in the high BW group than the low BW group (15.1%/y vs. 4.4%/y, $p = 0.025$) (Figure 3).

The univariate analysis showed that age, BW, phase SD, and entropy were significantly associated with MACE, while LVEF, SRS, and CMV were not (Table 4). In prespecified subgroups of preserved EF (LVEF ≥ 50%, n = 51) and mild myocardial injury (SRS ≤ 10, n = 38), BW, phase SD, and entropy were significant predictors of MACE. A subgroup of high CMV of ≤ 20 showed no significant difference due to the small number (n = 28) of cases.

A series of multivariable models were constructed to assess the impact of BW, phase SD, and entropy on MACE after adjustment for age, sex, and LVEF (Table 5). These models demonstrated that BW, phase SD, and entropy were independent predictors of MACE.

Discussion

This study demonstrated that BW was correlated with LVEF and SRS, but not with CMV or TLG, and BW, phase SD, and entropy estimated by phase analysis on ECG-gated SPECT were significant and independent predictors of MACE in patients with guideline-proven CS.

The parameters of phase analysis were significant in prespecified subgroups with preserved LVEF and high SRS. Previous studies showed that RV involvement, mismatch of LV perfusion/metabolism, low LVEF, and no steroid use are significant predictors of poor outcomes in patients with CS (3, 5, 6, 13). However, RV uptake and LV mismatch patterns on FDG metabolism/perfusion were less likely to be useful in patients who were well treated by steroid therapy. In this respect, phase analysis on perfusion SPECT may contribute to the prognosis.

Hess et al. demonstrated the usefulness of dyssynchrony for prognosis in patients with coronary artery disease. They showed that the BW measured by ECG-gated SPECT had a stronger relationship with outcomes than electrical dyssynchrony measured by QRS duration (14). Mori et al. reported that increased BW and phase SD might be prognostic predictors in chronic kidney disease patients, even

with normal perfusion (15). In our results, dyssynchrony parameters estimated by ECG-gated SPECT were independent predictors of MACE in patients with CS. Therefore, dyssynchrony parameters could provide the additional information on the prognosis in the patients with CS.

Involvement of epithelioid granuloma in the LV wall is diverse for each patient with CS. Especially, focal and patchy involvement, the magnitude in depth of LV wall, the patterns of scar and inflammation, and the timing of LV systole differ for each patient (16). Mismatch patterns and global LVEF fail to detect these characteristics of CS, while phase analysis can account for these phenomena (17). Accordingly, phase analysis can successfully predict MACE in patients with CS. Interestingly, phase SD and BW were scattered in patients with preserved EF. In fact, phase SD and BW were useful to predict MACE over LVEF. The mechanism of sustained VT in CS patients is presumed to be re-entry related to the myocardial scar burden(18). Parameters derived from phase analysis were increased due to the extent of the myocardial damage, which affected MACE, especially ventricular arrhythmia. Also, this result raises the question that CRT(-D) therapy might improve the prognosis even in patients with preserved LVEF and high phase SD or BW (8). This might warrant further studies in the future.

In cardiac FDG PET/CT, the suppression of physiological uptake reveals the presence of metabolically active inflammatory cells, such as lymphocytes and macrophages (17, 19). In contrast,

SPECT identified areas of fibrotic changes replacing the normal myocardium . In the current study, the association between BW and CMV was not significant, which suggests that cardiac involvement of sarcoidosis consists of various stages of disease activity, such as initiation of inflammation, active inflammation with reduced myocardial perfusion, and end-stage of scar with reduced inflammation.

Although three parameters（bandwidth, phase SD, and entropy）were obtained from phase analysis, each parameter on its own was a powerful predictor of outcomes in the current study. Accordingly, we can use these parameters equally.

Limitations

This study has some limitations. This was a single-centre, retrospective study with a small sample size and cardiac events. In addition, we did not compare the findings of the phase analysis with the pathological findings. In the current study, the effects of steroid, β-blockers, ACE inhibitors, and ARBs on indices of the phase analysis have not been investigated, which is warranted to be studied in the future.

New Knowledge Gained

Phase analysis on ECG-gated SPECT reflects the extent of myocardial damage and the timing of contraction and can detect CS patients at risk independently from the inflammatory activity.

Conclusions

BW was correlated with LVEF and SRS, but not with CMV or TLG. Phase analysis on ECG-gated SPECT was a significant and independent predictor of MACE in patients with CS. These findings offer clinical impact of phase analysis in addition to LVEF and metabolic activity on FDG PET/CT in terms of prognosis.

Acknowledgements

Not applicable.

Disclosure

All authors have no conflicts of interest to disclose.

References

(1) Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. The New England journal of medicine 2007;357:2153-65.

(2) Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation 1978;58:1204-11.

(3) Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol 2014;63:329-36.

(4) Sperry BW, Tamarappoo BK, Oldan JD, Javed O, Culver DA, Brunken R et al. Prognostic Impact of Extent, Severity, and Heterogeneity of Abnormalities on (18)F-FDG PET Scans for Suspected Cardiac Sarcoidosis. JACC Cardiovasc Imaging 2017.

(5) Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol 2001;88:1006-10.

(6) Chiu CZ, Nakatani S, Zhang G, Tachibana T, Ohmori F, Yamagishi M et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. Am J Cardiol 2005;95:143-6.

(7) Nakajima K, Okuda K, Matsuo S, Kiso K, Kinuya S, Garcia EV. Comparison of phase dyssynchrony analysis using gated myocardial perfusion imaging with four software programs: Based on the Japanese Society of Nuclear Medicine working group normal database. Journal of nuclear cardiology 2017;24:611-21.

(8) Naya M, Manabe O, Koyanagawa K, Tamaki N. The role of nuclear medicine in assessments of cardiac dyssynchrony. Journal of nuclear cardiology 2017 in press.

(9) Terasaki F, Yoshinaga K. New guidelines for diagnosis of cardiac sarcoidosis in Japan. Annals of Nuclear Cardiology 2017;3:42-5.

(10) Manabe O, Yoshinaga K, Ohira H, Masuda A, Sato T, Tsujino I et al. The effects of 18-h fasting with low-carbohydrate diet preparation on suppressed physiological myocardial (18)F-fluorodeoxyglucose (FDG)

uptake and possible minimal effects of unfractionated heparin use in patients with suspected cardiac involvement sarcoidosis. Journal of nuclear cardiology 2016;23:244-52.

(11) Hirata K, Kobayashi K, Wong KP, Manabe O, Surmak A, Tamaki N et al. A semi-automated technique determining the liver standardized uptake value reference for tumor delineation in FDG PET-CT. PLoS One 2014;9:e105682.

(12) Manabe O, Kroenke M, Aikawa T, Murayama A, Naya M, Masuda A et al. Volume-based glucose metabolic analysis of FDG PET/CT: The optimum threshold and conditions to suppress physiological myocardial uptake. Journal of nuclear cardiology 2017 in press.

(13) Manabe O, Yoshinaga K, Ohira H, Sato T, Tsujino I, Yamada A et al. Right ventricular (18)F-FDG uptake is an important indicator for cardiac involvement in patients with suspected cardiac sarcoidosis. Ann Nucl Med 2014;28:656-63.

(14) Hess PL, Shaw LK, Fudim M, Iskandrian AE, Borges-Neto S. The prognostic value of mechanical left ventricular dyssynchrony defined by phase analysis from gated single-photon emission computed tomography myocardial perfusion imaging among patients with coronary heart disease. Journal of nuclear cardiology 2017;24:482-90.

(15) Mori H, Isobe S, Suzuki S, Unno K, Morimoto R, Kano N et al. Prognostic value of left ventricular dyssynchrony evaluated by gated myocardial perfusion imaging in patients with chronic kidney disease and normal perfusion defect scores. Journal of nuclear cardiology 2017 in press.

(16) Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H et al. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. JACC Cardiovasc Imaging 2010;3:1219-28.

(17) Kadkhodayan A, Chareonthaitawee P, Raman SV, Cooper LT. Imaging of Inflammation in Unexplained Cardiomyopathy. JACC Cardiovasc Imaging 2016;9:603-17.

(18) Winters SL, Cohen M, Greenberg S, Stein B, Curwin J, Pe E et al. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable

antitachycardia device. J Am Coll Cardiol 1991;18:937-43.

(19) Ohira H, Birnie DH, Pena E, Bernick J, Mc Ardle B, Leung E et al. Comparison of (18)F-fluorodeoxyglucose positron emission tomography (FDG PET) and cardiac magnetic resonance (CMR) in corticosteroid-naive patients with conduction system disease due to cardiac sarcoidosis. Eur J Nucl Med Mol Imaging 2016;43:259-69.

Figure legends

Fig. 1 Study population. A total of 133 patients with suspected or diagnosed CS, who underwent ^{18}F-FDG PET/CT and ECG-gated SPECT, were retrospectively enrolled. After excluding patients with non-cardiac sarcoidosis, ^{99m}Tc-tetrofosmin and no ECG-gated MPI, the remaining 57 patients were studied

Fig. 2 Relationship between bandwidth and each parameters. Relationship between bandwidth (BW) and left ventricular ejection fraction (LVEF) (a), summed rest score (SRS) (b), cardiac metabolic volume (CMV) (c), and total lesion glycolysis (TLG) (d)

Fig. 3 Phase analysis predicts major adverse cardiac events (MACEs). Event-free rate of MACE is stratified into the high bandwidth (BW) group (> 56°) and the low BW group (≤ 56°) at the median of BW.

Table 1. Characteristics data

	All (n = 57)	**BW > 56 (n = 27)**	**BW ≤ 56 (n = 30)**	***P* value**
Age (y)	64 (55-71)	61 (54-68)	67 (59-73)	0.05
Male	14 (25)	5 (19)	9 (30)	0.37
NYHA(Ⅰ/Ⅱ/Ⅲ/Ⅳ)	(26/12/16/3)	(7/6/11/3)	(19/6/5/0)	0.001
HT	17 (30)	8 (30)	9 (30)	1.0
DLp	21 (37)	11 (41)	10 (33)	0.59
DM	6 (11)	3 (11)	3 (10)	1.0
CAD	5 (9)	4 (15)	1 (3)	0.18
Blood data				
BNP (pg/ml) (n = 56)	65 (17-270)	169 (76-463)	29 (14-65)	0.0003
ACE (U/L)	14.2 ± 6.4	14.1 ± 7.2	14.3 ± 5.6	0.91
TnT (ng/ml) (n = 17)	0.015 (0.011-0.024)	0.014 (0.008-0.022)	0.021 (0.015-0.031)	0.26
sIL2R (U/ml) (n = 43)	503 (334-716)	400 (259-641)	567 (426-719)	0.12
ECG data				
QRS (msec)	137 (101-164)	152 (108-167)	107(94-160)	0.05
Pacing	12 (21)	7 (26)	5 (17)	0.52
CLBBB	2 (4)	1 (4)	1 (3)	1.0
CRBBB	19 (33)	11 (41)	8 (27)	0.27
NSVT	9 (16)	5 (19)	4 (13)	0.72
SVT / VF	7 (12)	6 (22)	1 (3)	0.04
TTE data				
LVEF (%) (n = 54)	57 (40-69)	40 (35-55)	65 (57-74)	<0.0001
LVDd (mm)	50 ± 9	56 ± 8	45 ± 6	<0.0001
LVDs (mm)	31 (27-45)	45 (33-53)	28 (25-31)	<0.0001
LVMI (g/m^2) (n = 29)	112 ± 33	124 ± 35	95 ± 20	0.017
DT (ms) (n =	209 ± 53	206 ± 62	212 ± 47	0.67

48)				
e/a (n = 49)	0.82 (0.65-1.2)	0.81 (0.61-1.28)	0.83 (0.68-1.0)	0.86
e/e' (n = 48)	10.0 (7.5-12.0)	11.0 (7.0-12.9)	9.0 (7.6-11.6)	0.18

Values are median (IQR) or n (%) or mean ± standard deviation

NYHA, New York Heart Association; HT, hypertension; DLp, dyslipidaemia; DM, diabetes mellitus; CAD, coronary artery disease; BNP, brain natriuretic peptide; ACE, angiotensin converting enzyme; TnT, troponin t; sIL2R, soluble interleukin-2 receptor; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; NSVT, non-sustained ventricular tachycardia; SVT; sustained ventricular tachycardia; VF, ventricular fibrillation; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVMI, left ventricular mass index; Dt, deceleration tine

Table 2. MPI and FDG PET data

	All (n = 57)	**BW > 56 (n = 27)**	**BW ≤ 56 (n = 30)**	***P* value**
MPI data				
LVEDV (ml)	90 (74-115)	102 (89-158)	77 (67-94)	0.0005
LVESV (ml)	27 (21-46)	42 (29-63)	22 (19-27)	<0.0001
LVEF (%)	67 (58-74)	59 (50-68)	69 (66-77)	0.0003
SRS	7 (2-17)	15 (8-29)	3 (1-7)	<0.0001
Phase SD (°)	14 (10-25)	26 (18-38)	10 (9-12)	<0.0001
Entropy (%)	52 (45-60)	60 (57-76)	46 (41-49)	<0.0001
FDG PET data				
Heparin	52 (91)	25 (93)	27 (90)	1.0
BS (mg/dl) (n = 55)	90 ± 11	92 ± 11	88 ± 11	0.21
Hypocarbohydrate diet	27 (47)	8 (30)	19 (63)	0.02
Fasting time (h)	20 (18-21)	20 (18-21)	20 (19-22)	0.15
FDG dose (MBq)	245 (222-280)	250 (226-291)	238 (220-256)	0.14
SUV max	6.6 ± 4.1	6.7 ± 3.2	6.4 ± 4.8	0.78
CMV (ml)	21 (4-85)	75 (8-123)	12 (3-25)	0.007
TLG (ml)	72 (12-331)	278 (28-412)	42 (10-112)	0.009

Values are median (IQR) or mean ± standard deviation or n (%)

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; SRS, summed rest score; phase SD, phase standard deviation; BS, blood sugar; FDG dose, ^{18}F- fluorodeoxyglucose dose; SUV max, standard uptake value max; CMV, cardiac metabolic volume; TLG, total lesion glycolysis

Table 3. MACE data

	All (n = 57)	**BW >56 (n = 27)**	**BW ≤56 (n = 30)**	***P* value**
All events	15 (26)	11 (41)	4 (13)	0.03
All cause death	3 (5.3)	2 (7.4)	1 (3)	0.6
SVT/VF	8 (14)	7 (26)	1 (3)	0.02
AV block	2 (3.5)	2 (7.4)	0 (0)	0.22
Hospitalization	4 (7)	2 (7.4)	2 (6.6)	1.0

Values are n (%)

SVT, sustained ventricular tachycardia; VF, ventricular fibrillation; AV block, atrioventricular block

Table 4. Predictor of MACE at univariate analysis

		All (n = 57)		**Subgroups**			
				LVEF ≥ 50 (n = 51)		**SRS ≤ 10 (n = 38)**	
Variables	Category	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)	≧ 65	3.02 (1.05-9.89)	0.04	3.14 (1.04-10.79)	0.04	2.66 (0.69-12.86)	0.16
Sex	male	1.41 (0.44-3.98)	0.54	1.51 (0.46-4.37)	0.47	1.53 (0.32-5.79)	0.56
LVEF (%)	＜ 50	0.62 (0.03-3.12)	0.63	NA	NA	NA	NA
SRS	＞ 6	1.82 (0.65-5.85)	0.26	2.04 (0.70-6.66)	0.19	NA	NA
CMV (ml)	＞ 20	1.93 (0.69-6.21)	0.22	1.96 (0.68-6.40)	0.22	1.64 (0.43-6.63)	0.46
BW (°)	＞ 56	3.43 (1.17-12.41)	0.02	4.10 (1.37-15.00)	0.01	6.89 (1.67-33.87)	0.0083
Phase SD (°)	> 14	5.15 (1.63-22.65)	0.004	6.30 (1.96-27.93)	0.0015	15.28 (3.46-105.31)	0.0003
Entropy (%)	> 53	4.23 (1.44-15.29)	0.014	5.28 (1.76-19.31)	0.0027	33.54 (7.24-238.09)	<0.0001

CI, confidence interval; LVEF, left ventricular ejection fraction; SRS. summed rest score; CMV, cardiac metabolic volume, BW, bandwidth; phase SD, phase standard deviation

Table 5. Predictor of MACE at multivariate analysis

	Model 1 ($\chi^2 = 5.96$, $p = 0.073$)		Model 2 ($\chi^2 = 7.08$, $p = 0.046$)		Model 3 ($\chi^2 = 7.67$, $p = 0.036$)	
Variables	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)	1.04 (0.99-1.10)	0.08	1.04 (0.99-1.09)	0.12	1.04 (0.99-1.09)	0.12
Male gender	1.90 (0.28-5.67)	0.28	1.90 (0.56-5.47)	0.30	1.67 (0.50-4.93)	0.38
LVEF (%)	1.01 (0.97-1.06)	0.64	1.01 (0.97-1.07)	0.50	1.02 (0.97-1.08)	0.42
BW (＞ 56°)	4.88 (1.36-20.16)	0.015	---	---	---	---
Phase SD (> 14°)	---	---	5.67 (1.57-23.84)	0.008	---	---
Entropy (> 53%)	---	---	---	---	6.21 (1.69-26.96)	0.006

CI, confidence interval; LVEF, left ventricular ejection fraction; BW, bandwidth; phase SD, phase standard deviation

Figure 1.

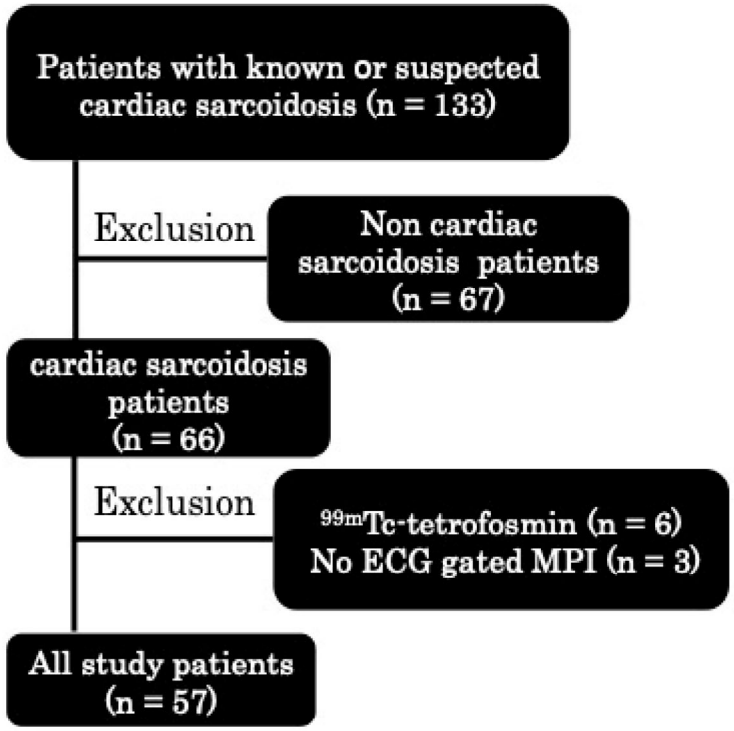

Patients with known or suspected cardiac sarcoidosis (n = 133)
Exclusion
Non cardiac sarcoidosis patients (n = 67)
cardiac sarcoidosis patients (n = 66)
Exclusion
99mTc-tetrofosmin (n = 6)
No ECG gated MPI (n = 3)
All study patients (n = 57)

Figure 2-a.

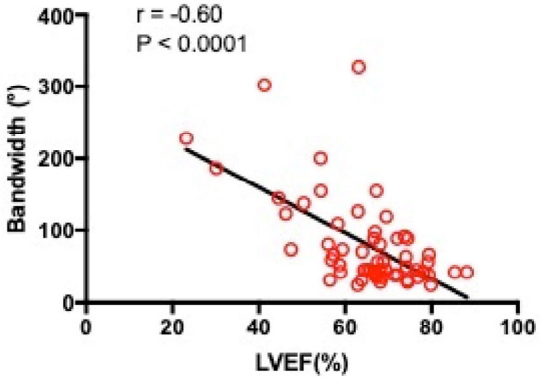


Figure 2-b.

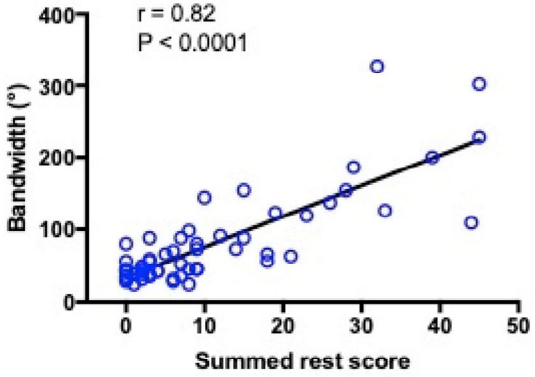


Figure 2-c.

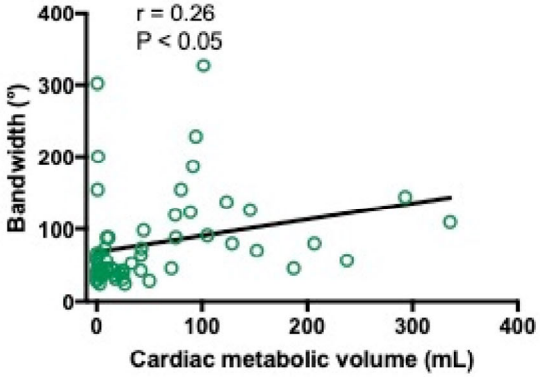


Figure 2-d.

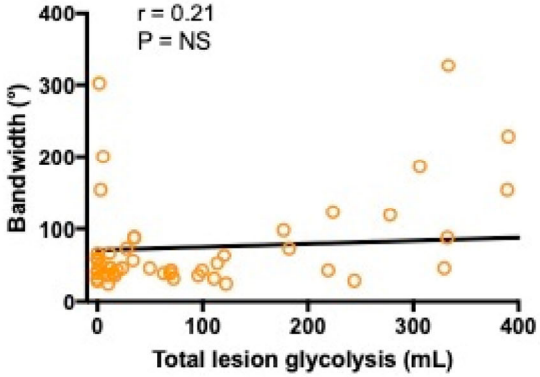
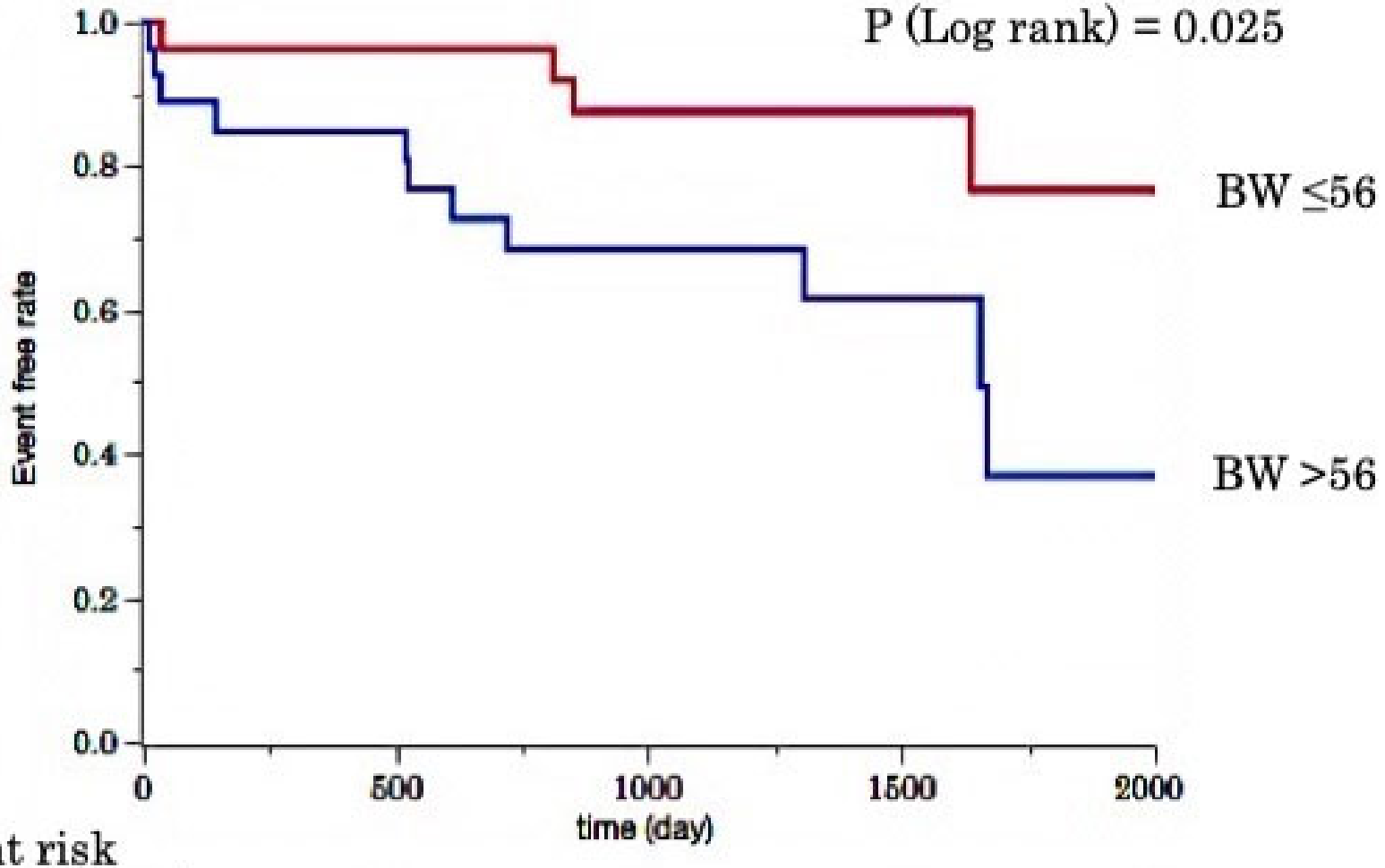


Figure 3.



Patients at risk				
BW ≤56 (n = 30)	21	11	8	2
BW >56 (n = 27)	23	18	9	3