# Importance of extracardiac FDG uptake to diagnose cardiac sarcoidosis

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Sarcoidosis is a multisystem disorder of unknown etiology, characterized by the formation of non-caseating granulomas in many organs including eye, skin, bone, muscle, nerve system, lymph node, lung, liver, and heart. Although sarcoidosis is generally recognized as having a low mortality rate,[1] cardiac involvement could present a life-threatening situation such as conduction disturbance, ventricular tachyarrhythmia, and congestive heart failure.[2] In 1992, the Japanese Ministry of Health and Welfare established preceding guidelines for the diagnosis of cardiac sarcoidosis (CS).[3] Typical granulomatous myocarditis based on endomyocardial biopsy was determined as histopathologically diagnosed CS. However, endomyocardial biopsy shows the limited sensitivity no better than 30% by sampling errors due to patchy distribution of cardiac granulomas.[2,4,5] Sarcoidosis often has been determined by extracardiac biopsy specimens from skin, muscle, and lymph node. While cardiac involvement is clinically apparent in < 5% of all patients with sarcoidosis, over 20% of the patients have been found cardiac granulomas at autopsy.[6,7] Therefore, the diagnosis of CS was often a challenging issue for physicians.

In 2006, the joint committee of the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Japanese College of Cardiology modified the guidelines (Table 1).[8] Briefly, the modified guidelines required that a histopathological or clinical diagnosis of sarcoidosis in any organs except the heart is prerequisite for evidence of sarcoidosis. If endomyocardial biopsy is negative, presence of cardiac abnormalities compatible with CS was defined as clinically diagnosed CS (Table 1). Serial electrocardiogram, 24 h Holter monitoring of electrocardiogram, echocardiography, myocardial perfusion scintigraphy, and $^{67}$Gallium scintigraphy can be helpful tools for clinically diagnosed CS. Especially, the revised guidelines included a positive $^{67}$Gallium uptake in the heart as a major criterion. However, these conventional tools are far from satisfactory for the detection of cardiac involvement.

With advances in imaging technologies, the molecular targeting approach using $^{18}$Fluorine-fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to visualize inflamed tissues and help to identify occult lesions.[9–11] The shortcomings of the conventional tools stimulated the use of FDG-PET to identify and quantify granulomatous inflammation. The diagnostic approach and assessment of treatment effect in a CS patient using FDG-PET was first reported in 2002.[12] Thereafter, FDG-PET has been employed for the assessment of granuloma localization and inflammatory activity in the heart with varying degrees of success to develop a treatment strategy in CS patients.[8,13–15] It has been demonstrated that the focally increased FDG uptake in the heart indicates inflammatory activity within granulomas.[13–15] Also, an index of heterogeneity of myocardial FDG uptake can determine the diagnosis of CS and the effect of corticosteroid therapy.[8] Further, FDG-PET can identify individuals having a higher risk of future adverse events.[16,17] However, some patients may exhibit physiological myocardial FDG uptake on PET imaging under 6-12 h of fasting conditions. Recent studies have revealed that preparation including more than 18 h of long fasting and a low-carbohydrate diet

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**Table 1.** Guidelines for diagnosis of cardiac sarcoidosis (2006)

Histologic diagnosis group
Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid cell granuloma with histological or clinical diagnosis of extracardiac sarcoidosis
Clinical diagnosis group
Although endomyocardial biopsy specimens do not demonstrate non-caseating epithelioid cell granuloma, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one in 6 basic diagnostic criteria
(1) Two or more of 4 the major criteria are satisfied
(2) One in 4 the major criteria and 2 or more of the 5 minor criteria are satisfied
Major criteria
(a) Advanced atrioventricular block
(b) Basal thinning of the inter-ventricular septum
(c) Positive $^{67}$Gallium uptake in the heart
(d) Depressed ejection fraction of the left ventricle (< 50%).
Minor criteria
(a) Abnormal ECG findings: ventricular arrhythmias (ventricular tachycardia, multifocal or frequent PVCs), CRBBB, axis deviation or abnormal Q-wave
(b) Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening)
(c) Nuclear medicine: perfusion defect detected by $^{201}$Tl or $^{99m}$Tc myocardial scintigraphy
(d) Gadolinium-enhanced cardiac MRI: delayed enhancement of myocardium
(e) Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade

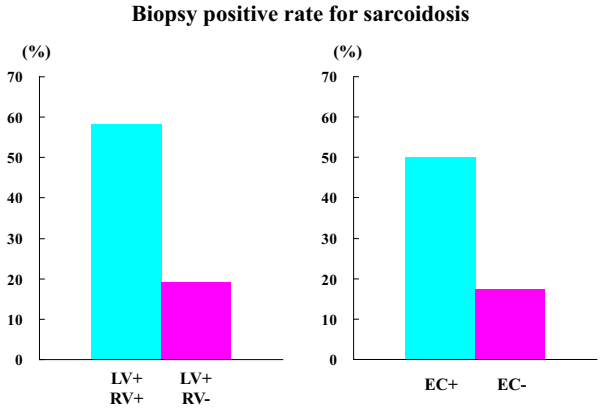


**Figure 1.** Biopsy positive rate for sarcoidosis. *LV*, left ventricle; *RV*, right ventricle; *EC*, extracardiac; +, pathological FDG uptake; -, no pathological FDG uptake.

modification prior to FDG-PET scan can reduce myocardial physiological FDG uptake and visualize accurate granulomatous inflammatory activity of CS.[18–20] In these days, FDG-PET has been widely utilized for the initial diagnosis, assessment of disease activity, and monitoring of treatment response in CS.[21]

In this issue of the journal, Tuominen et al. report data from a single-center retrospective study that assessed the imaging features of FDG uptake on PET in 137 consecutive patients with suspected CS.[22] In the study, 33 (24.1%) patients had pathological cardiac FDG uptake, and 12 (36.4%) of these patients showed FDG uptake in both left and right ventricles (LV and RV). Of the 12 patients, 7 (58.3%) indicated biopsy positive for sarcoidosis such as endomyocardial biopsy or extracardiac biopsy. A positive biopsy finding for sarcoidosis was more seen in patients with pathological uptake in both ventricles than those with only pathological LV uptake (19.0%) (Figure 1: left). Also, 16 (48.5%) of 33 patients with pathological cardiac FDG uptake had abnormal extracardiac FDG uptake. Among them, 8 (50.0%) patients showed biopsy positive for sarcoidosis. A positive biopsy finding for sarcoidosis was more recognized in patients with abnormal extracardiac FDG uptake than those without it (Figure 1: right). In regard to extracardiac uptake sites, FDG uptake in mediastinal and hilar lymph nodes was more often seen in patients with pathological uptake in both ventricles than those with only pathological LV uptake. Pathological uptake in both ventricles may be associated with abnormal uptake in mediastinal and hilar lymph nodes, but not with uptake at other extracardiac sites. Especially, pathological cardiac uptake was stronger in patients having abnormal extracardiac uptake than those without

**Table 2.** Guidelines for diagnosis of cardiac sarcoidosis (2017)

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| Histologic diagnosis group (those with positive myocardial biopsy findings) |
| Cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas |
| Clinical diagnosis group (those with negative myocardial biopsy findings or those not undergoing myocardial biopsy) |
| The patient is clinically diagnosed as having sarcoidosis (1) when epithelioid granulomas are found in organs other than the heart, and clinical findings strongly suggestive of the cardiac involvement criteria (Table 3) are present; or (2) when the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least two of the five characteristic laboratory findings of sarcoidosis as below; and clinical findings strongly suggest the cardiac involvement criteria (Table 3) |
| Characteristic laboratory findings of sarcoidosis |
| (1) Bilateral hilar lymphadenopathy |
| (2) High serum angiotensin-converting enzyme (ACE) activity or elevated serum lysozyme levels |
| (3) High serum soluble interleukin-2 receptor (sIL-2R) levels |
| (4) Significant tracer accumulation in $^{67}$Ga citrate scintigraphy or $^{18}$F-FDG PET |
| (5) A high percentage of lymphocytes with a CD4/CD8 ratio of $> 3.5$ in bronchoalveolar lavage fluid |
| Clinical diagnosis of sarcoidosis is supported when at least two of the above five characteristic findings are observed |
| (*Source* Japan Society of Sarcoidosis and other Granulomatous Disorders 2015) |

**Table 3.** Criteria for cardiac involvement of sarcoidosis (2017)

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| Major criteria |
| (a) High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e.g., sustained ventricular tachycardia and ventricular fibrillation) |
| (b) Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening) |
| (c) Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50%) |
| (d) $^{67}$Ga citrate scintigraphy or $^{18}$F-FDG PET reveals abnormally high tracer accumulation in the heart |
| (e) Gadolinium-enhanced MRI reveals delayed contrast enhancement of the myocardium |
| Minor criteria |
| (a) Abnormal ECG findings: ventricular arrhythmias (nonsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves |
| (b) Perfusion defects on myocardial perfusion scintigraphy (SPECT) |
| (c) Endomyocardial biopsy: Monocyte infiltration and moderate or severe myocardial interstitial fibrosis |
| Cardiac findings should be assessed based on the major criteria and the minor criteria. Clinical findings that satisfy the following (1) or (2) strongly suggest the presence of cardiac involvement |
| (1) Two or more of the five major criteria (a) to (e) are satisfied |
| (2) One of the five major criteria (a) to (e) and two or more of the three minor criteria (a) to (c) are satisfied |

it. The key finding of the study was that pathological uptake in both ventricles and abnormal extracardiac uptake were associated factors that could predict a positive biopsy finding for sarcoidosis. This is noteworthy because it is better to get a histologic proof of granulomatous inflammation for accurately diagnosing CS, which has important prognostic and therapeutic implications to the individual involved. In a previous study by Kandolin et al, FDG uptake in mediastinal lymph nodes was seen in 71.4% of CS patients.[23] Another study by Simonen et al showed FDG-avid mediastinal lymph nodes in 66.7% of CS patients.[24]

Compared to these reports, there were relatively small number of patients with abnormal extracardiac uptake in this study. It may be due to a low proportion of sarcoidosis, which could lead to a selection bias. In any case, metabolically active mediastinal lymph nodes evaluated by FDG-PET can be a candidate for extracardiac biopsy to confirm the histology of sarcoidosis, if no positive endomyocardial biopsy.

The Heart and Rhythm Society (HRS) has indicated a consensus of the role of FDG-PET for the detection of CS.[25] In 2017, the Japanese Circulation Society and its collaborative organizations updated the guidelines for the diagnosis and treatment of CS (Chair: Fumio Terasaki) (Tables 2, 3).[26] The updated guidelines have shown that CS patients having positive endomyocardial biopsy findings was diagnosed as the histological diagnosis group and those with negative endomyocardial biopsy findings or not undergoing myocardial biopsy as the clinical diagnosis group. (Tables 2, 3). Of particular note is that strongly suggestive pulmonary or ophthalmic sarcoidosis and meet criteria for cardiac involvement based on the major criteria and the minor criteria (Table 3) are needed for the clinically diagnosed CS in the updated guidelines. Notably, a positive FDG uptake in the heart is included in the major criteria of the updated guidelines. Against the expert consensus statement from the Heart Rhythm Society,[25] diagnosing CS without any histologic proof has been possible.[26] Cautious interpretation is necessary as not to misdiagnosis.

## Disclosures

*Nobuhiro Tahara, Munehisa Bekki, Yoichi Sugiyama, Atsuko Tahara, and Yoshihiro Fukumoto have nothing to disclose.*

## References

1. Reich JM. Mortality of intrathoracic sarcoidosis in referral vs population-based settings: influence of stage, ethnicity, and corticosteroid therapy. Chest 2002;121:32–9.
2. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. Am Heart J 1999;138:299–302.
3. Hiraga HHM, Iwai K. Guidelines for diagnosis of cardiac sarcoidosis: study report on diffuse pulmonary disease (in Japanese). Tokyo: The Japanese Ministry of Health and Welfare; 1993. p. 2.
4. Ardehali H, Howard DL, Hariri A, Qasim A, Hare JM, Baughman KL, Kasper EK. A positive endomyocardial biopsy result for sarcoid is associated with poor prognosis in patients with initially unexplained cardiomyopathy. Am Heart J 2005;150:459–63.
5. Kandolin R, Lehtonen J, Graner M, Schildt J, Salmenkivi K, Kivistö SM, Kupari M. Diagnosing isolated cardiac sarcoidosis. J Intern Med 2011;270:461–8.
6. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al Case Control Etiologic Study of Sarcoidosis (ACCESS) research group. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001;164:1885–9.
7. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357:2153–65.
8. 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(12):1219–28.
9. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972–80.
10. Kubota R, Kubota K, Yamada S, Tada M, Ido T, Tamahashi N. Microautoradiographic study for the differentiation of intratumoral macrophages, granulation tissues and cancer cells by the dynamics of fluorine-18-fluorodeoxyglucose uptake. J Nucl Med 1994;35:104–12.
11. Mochizuki T, Tsukamoto E, Kuge Y, Kanegae K, Zhao S, Hikosaka K, et al FDG uptake and glucose transporter subtype expressions in experimental tumor and inflammation models. J Nucl Med 2001;42:1551–5.
12. Takeda N, Yokoyama I, Hiroi Y, Sakata M, Harada T, Nakamura F, et al Positron emission tomography predicted recovery of complete A-V nodal dysfunction in a patient with cardiac sarcoidosis. Circulation 2002;105:1144–5.
13. Yamagishi H, Shirai N, Takagi M, Yoshiyama M, Akioka K, Takeuchi K, Yoshikawa J. Identification of cardiac sarcoidosis with $^{(13)}$N-NH$_{(3)}$/$^{(18)}$F-FDG PET. J Nucl Med 2003;44:1030–6.
14. Okumura W, Iwasaki T, Toyama T, Iso T, Arai M, Oriuchi N, et al Usefulness of fasting $^{18}$F-FDG PET in identification of cardiac sarcoidosis. J Nucl Med 2004;45:1989–98.
15. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakaue S, Kamigaki M, et al Focal uptake on $^{18}$F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. Eur Heart J 2005;26:1538–43.
16. 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.
17. 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 2018;11:336–45.
18. Langah R, Spicer K, Gebregziabher M, Gordon L. Effectiveness of prolonged fasting 18f-FDG PET-CT in the detection of cardiac sarcoidosis. J Nucl Cardiol 2009;16:801–10.
19. 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. J Nucl Cardiol 2016;23:244–52.
20. Lu Y, Grant C, Xie K, Sweiss NJ. Suppression of myocardial $^{18}$F-FDG uptake through prolonged high-fat, high-protein, and very-low-carbohydrate diet before FDG-PET/CT for evaluation of patients with suspected cardiac sarcoidosis. Clin Nucl Med 2017;42:88–94.
21. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, Gulenchyn KY, Dekemp RA, et al The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. J Nucl Med 2012;53:241–8.
22. Tuominen H, Haarala A, Tikkakoski A, Kähönen M, Nikus K, Sipilä K. 18-FDG-PET in a patient cohort suspected for cardiac

sarcoidosis: Right ventricular uptake is associated with pathological uptake in mediastinal lymph nodes. J Nucl Cardiol 2018. https://doi.org/10.1007/s12350-018-1291-y.

23. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, et al Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. Circulation 2015;131:624–32.
24. Simonen P, Lehtonen J, Kandolin R, Schildt J, Marjasuo S, Miettinen H, et al F-18-fluorodeoxyglucose positron emission tomography-guided sampling of mediastinal lymph nodes in the diagnosis of cardiac sarcoidosis. Am J Cardiol 2015;116:1581–5.
25. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014;11:1305–23.
26. Terasaki F, Yoshinaga K. New Guidelines for Diagnosis of Cardiac Sarcoidosis in Japan. Ann Nucl Cardiol 2017;3:42–5.