BMIPP SPECT in cardiac sarcoidosis: A marker of risk?

Roxana Campisi, MD,[a,b] María Fernanda Merani, MD,[a,b] and Marina I. Rodríguez , MD[a]

[a] Departments of Nuclear Medicine and Cardiovascular Imaging, Diagnóstico Maipú, Buenos Aires, Argentina
[b] Department of Nuclear Medicine, Instituto Argentino de Diagnóstico y Tratamiento S.A, Buenos Aires, Argentina

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Sarcoidosis is a multisystem inflammatory disorder of unknown etiology characterized by the formation of non-caseating granulomas that can affect different organs.[1] The rate of cardiac involvement by sarcoidosis is variable and ranges from 20% to 75%.[2,3] Granulomas in cardiac sarcoidosis (CS) can be found in any part of the heart, but the left ventricle, interventricular septum, and the papillary muscle are the most frequently involved.[3,4] The prevalence of clinically evident cardiac involvement is ~ 5% and is one of the major causes of disease-related death.[4] Patients with CS might start with asymptomatic myocardial injury followed by congestive heart failure, ventricular tachyarrhythmia, conduction disturbances, or sudden cardiac death.[5] Early diagnosis of CS is a key factor for implementing specific strategies to improve the prognosis.[4] In fact, treatment with corticosteroids may slow the progression of heart failure, whereas implantable cardiac defibrillators can be lifesaving.[6]

Current diagnostic criteria are based on the modified Japanese Ministry of Health and Welfare (JMHW) guidelines published in 2006 and revised in 2017 and on the Heart Rhythm Society (HRS) expert consensus statement published in 2014.[7-9] Both involve histological demonstration of CS on endomyocardial biopsy (EMB) or integration of relevant clinical and imaging features. However, accurate diagnosis of CS remains challenging because of the limitations of existing clinical criteria and the low diagnostic yield of EMB related to the patchy and mid-myocardial involvement.[1,3,5] Since sarcoidosis can affect the myocardium causing inflammation, edema, scarring, and remodeling, contemporary non-invasive imaging techniques can be of clinical help for detecting the whole spectrum of the disease.[1,6]

RADIONUCLIDE IMAGING IN CARDIAC SARCOIDOSIS: WHERE ARE WE NOW?

Cardiac radionuclide imaging with ^{67}gallium (^{67}Ga) and ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) is part of the diagnostic algorithm for CS in the JMHW guidelines and HRS expert consensus criteria.[7-9] ^{67}Ga is taken up by activated macrophages in inflamed tissue and correlates with both clinical and histological evidence of CS. Because of the higher patient radiation exposure and the lower sensitivity in comparison with FDG-PET, ^{67}Ga scintigraphy is used in areas with limited access to PET.[3] FDG-PET has emerged as a powerful tool for assessment of myocardial inflammation in patients with known or suspected CS.[10] Inflammatory cells like macrophages and lymphocytes utilize glucose as their primary energy source. Accumulation of FDG (a glucose analog) in these activated cells is the underlying mechanism for detection of active granulomatous sarcoid lesions.[1-3] FDG crosses the membrane via glucose transporter (GLUT 1 and 3) and is trapped by the myocardium after being phosphorylated by hexokinase.[3,4] The sensitivity and specificity

Reprint requests: Roxana Campisi, MD, Departments of Nuclear Medicine and Cardiovascular Imaging, Diagnóstico Maipú, Diagnóstico Maipú, Av. Maipú 1668, Vicente López (B1602ABQ), Buenos Aires, Argentina; *roxanacampisi@yahoo.com*
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of FDG-PET as an initial diagnostic tool for CS are 89% and 78%, respectively, using the JMHW criteria as the gold standard.[1,5] In order to improve specificity in identifying abnormal FDG uptake, physiological myocardial glucose metabolism must be suppressed.[3] Therefore, optimal patient preparation is critical when using FDG-PET to evaluate for CS. The Joint Society of Nuclear Medicine and Molecular Imaging (SNMMI)-American Society of Nuclear Cardiology (ASNC) Expert Consensus Document recommends a high-fat and low-carbohydrate diet, prolonged fasting, and/or unfractionated heparin administration prior to the FDG-PET study.[11] Nevertheless, even after following these recommendations, approximately 30% of potential CS patients have a non-interpretable PET scan due to incomplete FDG suppression.[2,10]

Current protocol for assessment of CS includes myocardial perfusion imaging (MPI) at rest in conjunction with FDG-PET.[1,10,11] Adding resting MPI to FDG-PET has been shown to increase diagnostic accuracy and specificity in the detection and characterization of this disease.[10] MPI can be performed with PET using ^{13}N-Ammonia or ^{82}Rubidium, or with single photon emission computed tomography (SPECT) using ^{99m}Technetium-labeled tracers or ^{201}Thallium, preferably with attenuation correction.[11] Gated perfusion images are recommended, because the presence of left ventricular dysfunction has important diagnostic and prognostic implications.[11] Perfusion defects in patients with CS can represent areas of scar or microvascular compression by inflammation, while abnormal FDG myocardial uptake represents inflammation (Table 1).[1,3,10] The presence of focal or multifocal increased FDG uptake associated with perfusion defects (perfusion-metabolic mismatch) is highly diagnostic for active inflammatory CS.[10] Importantly, this pattern can also be present in patients with myocardial hibernation; therefore, alternative diagnoses like coronary artery disease must be rule out.[1,3] Recent studies have highlighted the clinical importance of identifying myocardial perfusion defects and abnormal FDG myocardial uptake, because these patients are at the highest risk for death or ventricular arrhythmias as compared to those with a normal scan.[2,6] Specifically, patients who exhibit mismatch pattern as well as right ventricle FDG uptake have the worse prognosis.[2,3,5]

To ameliorate the potential adverse outcome of clinically manifest CS, contemporary treatment is often multifactorial and comprises anti-inflammatory therapy, pharmacotherapy for cardiac arrhythmias and/or congestive heart failure and cardiac devices.[4] Due to the high side effects of immunosuppressive drugs, image-guided initiation and tailoring of therapy are of clinical relevance.[1] PET is the preferred imaging modality for monitoring anti-inflammatory therapy response because of its capability to quantify inflammation.[1,4,10,11] To do that, the Joint SMMMI/ASNC Consensus Expert Document recommends using standardized uptake value (SUV)-based quantitative metrics for serial FDG-PET imaging interpretation.[11] Observational studies have shown through quantitative metrics that a reduction in the intensity (i.e., SUVmax) and extent of inflammation (i.e., volume of inflammation above a pre-specified SUV threshold) in serial FDG-PET scans were associated with an increase in left ventricular ejection fraction[12] as well as a decrease in major cardiac events in CS

Table 1. Myocardial perfusion and ^{18}F-FDG-PET imaging patterns for cardiac sarcoidosis

Myocardial perfusion	Normal	Normal	Abnormal	Abnormal
^{18}F-FDG uptake	No uptake Diffuse/lateral wall uptake (non-specific pattern)	Focal increase	Focal increase (different areas)	No uptake
Scan interpretation	Normal	Inflammation and no scar (early disease)	Scar and inflammation (mismatch pattern)	Scar with absence of active inflammation

Adapted from Wiefels et al.[3] and Blankstein et al.[6]
^{18}F-FDG, ^{18}F-Fluorodeoxyglucose, *PET*, positron emission tomography

patients.[13] Serial FDG-PET imaging can also be of help in management decisions like duration, the intensity of immunosuppressive treatment, or when changes in pharmacotherapy are being considered.[3,6,10] Albeit the optimal timing for repeating PET studies is not well established, current recommendations suggest performing a PET study 3 to 6 months after the initiation of anti-inflammatory treatment.[3,4] It is important to acknowledge that data showing advantages of FDG-PET-guided therapy in CS are limited, and no clinical randomized trials are available.[11] Hence, the decision to use cardiac FDG-PET to guide treatment relies on physician judgment and expertise of the center for performing the test.[3,4]

BMIPP SPECT IMAGING: AN ADDED VALUE IN THE MANAGEMENT OF CARDIAC SARCOIDOSIS PATIENTS?

^{123}I-betamethyl-p-iodophenylpentadecanoic acid (BMIPP) allows evaluation of fatty acid metabolism. BMIPP is a tracer widely used in Japan to detect myocardial ischemia without stress testing in unstable or vasospastic angina.[14] Its accumulation is related to intracellular adenosine triphosphate concentration, mitochondrial function, intracellular triglyceride concentration, and serum levels of metabolic substrates.[15] Under ischemic condition, β-oxidation of fatty acid in the mitochondria is reduced, and then back diffusion and early washout of non-metabolized BMIPP occur.[14] This abnormal metabolic pathway is considered to be responsible for the reduction in myocardial uptake of BMIPP. The impairment of fatty acid metabolism in the mitochondria may persist in the post-ischemic myocardium, a phenomenon called ''ischemic memory.''[14,15] Previous studies have shown that BMIPP can detect earlier CS disease than MPI, which suggests that myocardial injury can be identified more sensitively using BMIPP than myocardial perfusion tracers.[15,16] Thus, BMIPP emerges as a novel tracer for identifying CS patients at the early stages of the disease.[17]

In this edition of the Journal, Yamamoto et al.[18] investigated the relationship between recurrence and myocardial damage obtained from BMIPP SPECT and explored the potential of BMIPP and FDG-PET as prognostic factors in CS patients undergoing steroid therapy. This was a single-center, retrospective study of 73 consecutive patients (mean age, 61 years; male, 38%) newly diagnosed with CS between January 2010 and May 2018. All patients underwent invasive coronary artery angiography and had no obstructive coronary artery disease (< 50% stenosis). For all patients, both BMIPP SPECT and FDG-PET were performed within 2 months. One set of BMIPP SPECT and FDG-PET was performed at least 3 times throughout the follow-up period. All patients underwent a high-fat and low-carbohydrate diet for 24 hours prior to FDG-PET scan and fasted at least 18 hours. The authors adopted SUV $\geq$ 4.0 as a low cutoff threshold for inflammatory activity. They defined recurrence of CS based on prednisolone treatment-induced SUV variability from serial FDG-PET studies. Patients who continuously had SUVmax $<$ 4 after the introduction of prednisolone for more than 2 years were classified as recurrence-free and those with SUVmax $>$ 4 at least once under prednisolone over the follow-up period as recurrence. The volume of the left ventricular wall with SUV $\geq$ 4.0 and the total lesion glycolysis were also calculated. Patients were injected with BMIPP (111 MBq) to assess myocardial injury and left ventricular function by gated-SPECT. Images were interpreted using a 17-segment model, and a semiquantitative analysis for BMIPP SPECT defect score (BDS) calculation was performed. Patients were divided by the first BDS into mild (0-7), moderate (8-15), and severe ($\geq$ 16) groups. The predictability of the initial BDS and SUVmax for major adverse cardiac events (MACE) was analyzed. Prednisolone was introduced to patients with active inflammation immediately after the diagnosis of CS. Two hundred and fifty BMIPP SPECT and FDG-PET sets were analyzed retrospectively (mean follow-up, 3.5 years). BDS in the mild, moderate, and severe groups did not change significantly during the follow-up period. Recurrence was observed in 29% of the study population. The median follow-up periods were similar in the recurrence-free and recurrence groups. Left ventricular ejection fraction was comparable between the two groups (43 ± 11% vs. 40 ± 11%, P = NS). BDS in the recurrence group was greater than that in the recurrence-free group (20 ± 13 vs. 14 ± 12, P = 0.041). Over a median follow-up of 1264 ± 996 days, 20 MACEs were recorded. BDS among patients with MACE was greater than that in patients without MACE (24 ± 14 vs. 13 ± 10, P = 0.0005). The receiving operating characteristics curves of BDS for MACE showed that the threshold, area under the curve (AUC), sensitivity, and specificity were 14%, 0.73%, 80%, and 62%, respectively, and those of SUVmax were 4.33%, 0.50%, 50%, and 51%, respectively. BDS had a higher AUC for MACEs than SUVmax. Patients with BDS $\geq$ 16 had a significantly higher rate of MACE; on the contrary, the prognosis of patients with SUV $\geq$ 4 was comparable to that with SUV $<$ 4. No significant difference in SUVmax, metabolic volume, total lesion glycolysis, and the frequency of right ventricular involvement was observed between patients with MACE and without MACE. The similar incidence of MACE in the recurrence and recurrence-free groups can be attributed to the increase in the steroid doses and the

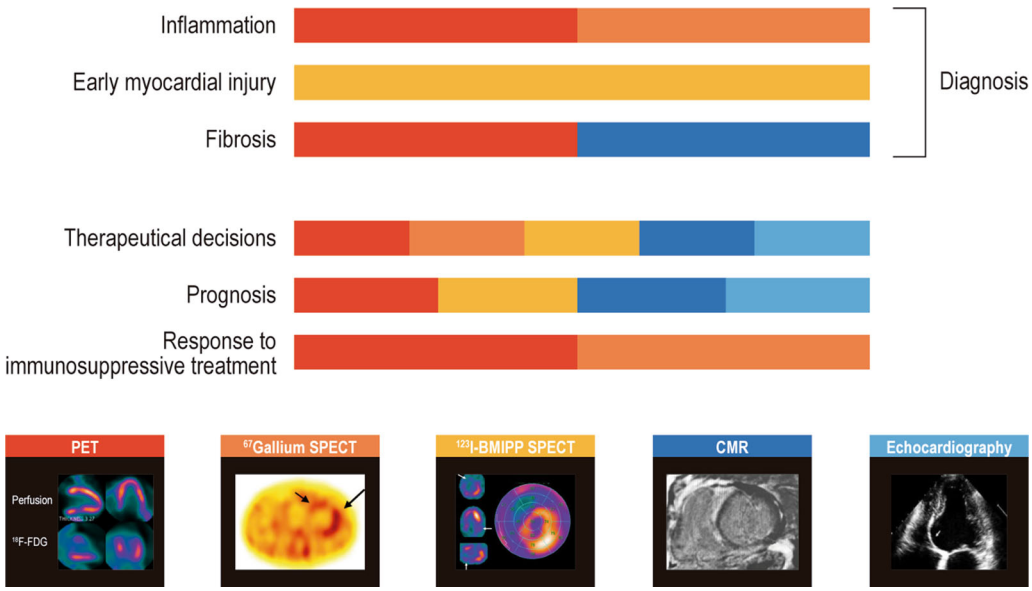

Figure 1. Role of non-invasive imaging techniques in cardiac sarcoidosis. FDG-PET allows the assessment of the extension and the magnitude of myocardial inflammation. Myocardial perfusion defects are expression of scar or alterations in the microcirculation. Quantitative FDG-PET along myocardial perfusion imaging may be complementary for diagnosing and monitoring progression of scar and inflammation and assess response to immunosuppressive therapies. ^{67}Ga is recommended when PET is not available. BMIPP SPECT can detect early myocardial injury and emerges as a potential imaging modality to predict recurrence and cardiac events when combined with FDG-PET. CMR provides an integral assessment of myocardial scar (through late gadolinium enhancement), edema, perfusion defects, and abnormalities in biventricular function. The addition of T2 mapping to CMR might prove valuable in identifying areas of edema/inflammation in CS patients. Echocardiography in CS has a primary role to assess and follow biventricular function, LV remodeling, and evaluation for new wall motion abnormalities. The assessment of global longitudinal strain has been suggested to be useful for prognosis in patients with suspected CS. The aforementioned concepts stem from references.[1,3,5,6,11,16,18-20] Abbreviations: *PET*, positron emission tomography; *^{18}F-FDG*, ^{18}F-Fluorodeoxyglucose; *^{123}I-BMIPP*, ^{123}I-beta-methyl-p-iodophenylpentadecanoic; *SPECT*, single photon emission computed tomography; *CMR*, cardiac magnetic resonance.

addition of methotrexate during the follow-up period, which was more frequent in the former group than in the latter. Yamamoto et al.[18] describe for the first time that BDS (i.e., BMIPP defect score of the entire left ventricle) is a predictor of recurrence and MACE in patients with CS. Moreover, the authors propose a new definition for evaluating recurrence of CS defined by prednisolone treatment-induced SUV variability from serial FDG-PET studies. Adding classification of myocardial damage by BMIPP SPECT at the time of CS diagnosis could be of relevance in developing a therapeutic strategy. In the study, the majority of cases initially classified as severe by BDS remained severe after prednisolone therapy. This finding suggests that myocardial damage was irreversible at this stage. Of note, patients in this group presented the highest risk for MACE during follow-up. Therefore, a multidisciplinary therapy approach including additional immunosuppressive agents and cardiac devices should be considered for patients with severe myocardial damage. In contrast, in patients categorized as mild by BDS at the initial evaluation, recurrence and MACE were infrequent.

Despite these important findings, some study limitations should be acknowledged: (a) This was a retrospective study of a single-center cohort, (b) In 38% of the study population, the first BMIPP SPECT and FDG-PET scans were performed after starting prednisolone therapy. The authors stated that the first scans, however, were acquired within 5 days of the initial steroid treatment, and (c) cardiac magnetic resonance (CMR) was performed in 56% of the study population due to contraindications for implant of cardiac devices or renal dysfunction. In these patients, the extent score of late gadolinium enhancement (LGE), as an expression of damage of myocardial tissue or a

scar, showed a significant positive correlation with the initial BDS but a lack of correlation with the initial SUVmax. Whether BMIPP SPECT could be an alternative when CMR-LGE is contraindicated needs to be investigated.

FUTURE PERSPECTIVES FOR NUCLEAR CARDIOLOGY IN CARDIAC SARCOIDOSIS

Early and accurate detection of CS is of highest importance for therapeutic and prognostic purposes.[2] Combining imaging modalities can improve the identification of the whole spectrum of myocardial involvement in CS patients (from early myocardial damage, inflammation to tissue fibrosis), Fig. 1. Yamamoto et al.[18] described that the addition of BMIPP SPECT to FDG-PET has a potential clinical role since BMIPP can detect early myocardial injury. Early diagnosis is a key factor because the anti-inflammatory treatment has the goal to slow fibrosis progression in the myocardial tissue.[18,19] BMIPP is also a predictor of recurrence and MACE in CS patients.[18] The combination of quantification of BMIPP defects with SUV-derived quantitative measurements can be of help for therapeutical decisions. Further investigations are needed in large-scale clinical trials to prove these novel concepts.

There is growing evidence of clinical relevance of combining CMR and FDG-PET for diagnosis, monitoring treatment response, and progression of CS.[5,6,20] CMR and FDG-PET provide different and complementary information on the different stages of CS, making it useful to patient´s management.[5,6] The combination of both imaging modalities in a single acquisition is now possible with hybrid PET/MR cameras which improve spatial relationship between the findings of scar and inflammation.[1,2,5]

The development of more specific targets for imaging inflammation is an area of interest for the nuclear cardiology field to overcome limitations of current FDG-PET imaging. In this regard, PET tracers like ^{68}Ga-DOTATOC/TATE/NOC, ^{18}F-FLT (fluorothymidine), and ^{8}F-FMISO, among others, are promising.[5,19] The possible advantages of these agents over FDG imaging in CS are under investigation. [5,19]

Despite all the available diagnostic armamentarium, CS remains a challenging disease in daily practice. Integrating clinical and surrogate cardiac imaging findings will likely enhance diagnostic and therapeutical strategies in CS patients.

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Disclosure

The authors have no conflicts of interest to declare.

References

1. Slart RHJA, Glaudemans AWJM, Lancellotti P, Hyafil F, Blankstein R, Schwartz RG, et al. A joint procedural position statement on imaging in cardiac sarcoidosis: From the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging, and the American Society of Nuclear Cardiology. J Nucl Cardiol 2018;25:298-319.
2. Bois JP, Muser D, Chareonthaitawee P. PET/CT evaluation of cardiac sarcoidosis. PET Clin 2019;14:223-32.
3. Wiefels C, Lamai O, Kandolin R, Birnie D, Leung E, Tinoco Mesquita C, et al. The role of 18F-FDG-PET/CT in cardiac sarcoidosis. Int J Cardiovasc Sci 2020;33:389-400.
4. Trivieri MG, Spagnolo P, Birnie D, Liu P, Drake W, Kovacic JC, et al. Challenges in cardiac and pulmonary sarcoidosis. J Am Coll Cardiol 2020;76:1878-901.
5. Bravo PE, Singh A, Di Carli MF, Blankstein R. Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis. J Nucl Cardiol 2019;26:188-99.
6. Blankstein R, Waller AH. Evaluation of known or suspected cardiac sarcoidosis. Circ Cardiovasc Imaging 2016;9:e000867.
7. Hiraga H, Yuwai K, Hiroe M. Diagnostic standard and guidelines for sarcoidosis [in Japanese]. Jpn J Sarcoidosis Other Granulomatous Disord 2007;27:89-102.
8. Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, et al. JCS 2016 Guidelines for the diagnosis and treatment of cardiac sarcoidosis—digest version. Circ J 2019;83:2329-88.
9. 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.
10. Schindler TH, Bateman TM, Berman DS, Chareonthaitawee P, De Blanche LE, Dilsizian V, et al. Appropriate use criteria for PET myocardial perfusion imaging. J Nucl Med 2020;61:1221-65. https://doi.org/10.2967/jnumed.120.246280.
11. Chareonthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, et al. Joint SNMMI-ASNC expert consensus document on the role of 18F-FDG-PET/CT in cardiac sarcoid detection and therapy monitoring writing group. J Nucl Med 2017;58:1341-53.
12. Osborne MT, Hulten EA, Singh A, Waller AH, Bittencourt MS, Stewart GC, et al. Reduction in 18F-fluorodeoxyglucose uptake on serial cardiac positron emission tomography is associated with improved left ventricular ejection fraction in patients with cardiac sarcoidosis. J Nucl Cardiol 2014;21:166-74.
13. Muser D, Santangeli P, Castro SA, Liang JJ, Enriquez A, Werner TJ, et al. Prognostic value of serial quantitative evaluation of (18)F-fluoro-deoxyglucose uptake by PET/CT in patients with cardiac sarcoidosis presenting with ventricular tachycardia. Eur J Nucl Med Mol Imaging 2018;45:1394-404.
14. Chikamori T, Fujita H, Nanasato M, Toba M, Nishimura T. Prognostic value of I-123 15-(p-iodophenyl)-3-(R, S)

methylpentadecanoic acid myocardial imaging in patients with known or suspected coronary artery disease. J Nucl Cardiol 2005;12:172-8.
15. Kaminaga T, Takeshita T, Yamauchi T, Kawamura H, Yasuda M. The role of Iodine-123-labeled 15-(p-iodophenyl)-3R, S-methylpentadecanoic acid scintigraphy in the detection of focal myocardial involvement of sarcoidosis. Int J Cardiol 2004;94:99-103.
16. Momose M, Fukushima K, Kondo C, Serizawa N, Suzuki A, Abe K, et al. Diagnosis and detection of myocardial injury in active cardiac sarcoidosis—significance of myocardial fatty acid metabolism and myocardial perfusion mismatch. Circ J 2015;79:2669-76.
17. Yoshinaga K. Role of metabolic imaging in detecting cardiac involvement in sarcoidosis. Circ J 2015;79:2551-2.
18. Yamamoto A, Nagao M, Watanabe E, Inamura Y, Suzuki A, Fukushima K, et al. Prognosis and recurrence in cardiac sarcoidosis: Serial assessment of BMIP SPECT and FDG-PET. J Nucl Cardiol 2021. https://doi.org/10.1007/s12350-021-02567-0.
19. Genovesi D, Bauckneht M, Altini C, Popescu CE, Ferro P, Monaco L, et al. The role of positron emission tomography in the assessment of cardiac sarcoidosis. Br J Radiol 2019;92:20190247.
20. Bokhari S, Lin JC, Julien HM. FDG-PET is a superior tool in the diagnosis and management of cardiac sarcoidosis. J Am Coll Cardiol April 10, 2017. Expert analysis.