Hybrid positron emission tomography and magnetic resonance imaging in cardiac sarcoidosis diagnosis: a pilot experience

Imágenes híbridas de tomografía por emisión de positrones y resonancia magnética en el diagnóstico de la sarcoidosis cardíaca: experiencia piloto

MARINA ILEANA RODRÍGUEZ1,*, MARÍA FERNANDA MERANI1,*, JUAN CRUZ GALLO1, MARÍA NIEVES LÓPEZ DE MUNAÍN1, ROXANA CAMPISI1

ABSTRACT

Background: Recent studies suggest combining the findings of cardiac magnetic resonance (CMR) and positron emission tomography (PET) to increase sensitivity in the diagnosis of cardiac sarcoidosis (CS).

Objective: To evaluate the complementary value of CMR and PET in the diagnosis of CS.

Methods: From December 2018 to July 2020, 6 patients (4 male and 2 female) with suspected CS were referred to our facility for evaluation of myocardial inflammation. A resting 13N Ammonia myocardial perfusion test and a 18F Fluorodeoxyglucose (FDG) PET were performed to evaluate myocardial inflammation and/or fibrosis. All patients had a previous gadolinium-enhanced CMR.

Results: The average age was 60 ± 9 years. Fifty percent of the patients had a history of systemic sarcoidosis and the remaining 50% had suspected isolated CS. None of the patients had active myocardial inflammation based on the PET findings. With the combination of PET patterns and enhanced CMR, the patients were reclassified as follows: 50% had less than 10% chance of having CS and the other 50% was classified as possible cases of CS. None of the patients received immunosuppressants.

Conclusion: In our patient population with suspected CS and inflammation, we conducted a PET study following a CMR to assess the potential for CS. In the absence of a gold standard, it is suggested that the diagnosis of CS should be based on probabilities according to specific imaging patterns and clinical features.

Keywords: Cardiac Sarcoidosis – Magnetic Resonance Imaging – Positron Emission Tomography – Fibrosis – Myocardial Inflammation

RESUMEN

Introducción: Estudios recientes sugieren combinar los hallazgos de la resonancia magnética cardíaca (RMC) y los de la tomografía por emisión de positrones (PET) para incrementar la sensibilidad del diagnóstico de la sarcoidosis cardíaca (SC).

Objetivo: Evaluar el valor complementario de la RMC y la PET en el diagnóstico de la SC.

Material y métodos: Entre diciembre 2018 y julio 2020, 6 pacientes (4 hombres y 2 mujeres) fueron referidos a nuestro servicio con sospecha de SC para evaluación de inflamación del miocardio. Se efectuó un estudio de perfusión miocárdica en reposo (N-13 Amonio) y de F-18-Fluordesoxiglucosa (FDG)-PET para evaluar inflamación y/o fibrosis. A todos los pacientes se les realizó previamente una RMC con gadolinio.

Resultados: La edad media fue de 60 ± 9 años. El 50% de los pacientes presentaban antecedentes de sarcoidosis sistémica y el otro 50% sospecha de SC aislada. Ninguno de los pacientes presentó inflamación activa del miocardio por PET. Con la combinación de los patrones-PET y el realce por RMC se reclasificó a los pacientes: 50% tuvo menos del 10% de probabilidad de padecer SC y el otro 50% se clasificó como posible. Ninguno de los pacientes recibió tratamiento inmunosupresor.

Conclusión: En nuestra población de pacientes con sospecha de SC e inflamación, realizamos un estudio PET luego de la RMC para calcular probabilidades de padecer SC. En ausencia de un patrón oro, se sugiere que el diagnóstico de SC se base en probabilidades de acuerdo con patrones de imágenes y cuadro clínico específicos.

Palabras clave: Sarcoidosis cardíaca - Resonancia magnética - Tomografía por emisión de positrones – Fibrosis – Inflamación miocárdica
INTRODUCTION
Sarcoidosis is a multisystemic inflammatory disorder of unknown etiology characterized by formation of non-caseating granulomas that may affect different organs. (1,2) The rate of cardiac involvement as a result of sarcoidosis varies, ranging from 20% to 75%. In cardiac sarcoidosis (CS), granulomas can be found in any part of the heart; however, the left ventricle, the interventricular septum and the papillary muscle are the more commonly affected. (2) Prevalence of clinically evident cardiac involvement is ~5% and one of the main causes of sarcoidosis-related death. Patients with CS may first show an asymptomatic myocardial injury followed by congestive heart failure, ventricular tachyarrhythmia, conduction disorders, or sudden cardiac death. Early CS diagnosis is essential to improve prognosis using specific strategies. Current diagnostic criteria are based on modified Japan Ministry of Health and Welfare (JMHW) guidelines, published in 2016 and revised in 2017, and on the Heart Rhythm Society (HRS) expert consensus statement, published in 2014. (3, 4) Both of them involve histological evidence or integration of clinical features and relevant imaging. However, precise CS diagnosis continues to be a challenge due to the restraints of existing clinical criteria and the low diagnostic performance of endomyocardial biopsy caused by patched areas of affected cardiac muscle. As sarcoidosis may affect the myocardium and cause inflammation, oedema, fibrosis, and remodeling, non-invasive imaging may be of clinical benefit to identify the full spectrum of this disease. (5)

In inflammatory cells, glucose metabolism is increased and may be detected by an increased $^{18}$F Fluorodeoxyglucose (FDG) uptake on the positron emission tomography–computed tomography (PET-CT). (6-8) This technique is used to document the presence or absence of active myocardial inflammation; therefore, there is growing interest in using the PET-CT for diagnosis and potential treatment guidance in patients with suspected CS. (7-9) The current protocol recommended by the American Society of Nuclear Cardiology (ASNC) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) (8,10) is to perform a cardiac PET-CT both of FDG metabolism and of myocardial perfusion at rest in order to evaluate the two CS components: inflammatory and fibrotic.

Recent studies recommend combining the findings of PET-CT and late enhancement patterns in cardiovascular magnetic resonance imaging (CMR) to increase sensitivity in the diagnosis of this condition (11-14).

The objective of the present study was to evaluate the supporting value of CMR and PET-CT in order to determine the potential for CS and active myocardial inflammation in patients with suspected CS.

METHODS
Six consecutive patients (4 male and 2 female) referred to our PET facility from December 2018 to July 2020 with suspected CS were retrospectively evaluated for myocardial inflammation. All the patients had a high-fat low-carbohydrate diet 36 h before the PET and fasted for 12 h. A gated $^{13}$N Ammonia (0.17 mCi/kg) myocardial perfusion test was performed at rest, and then FDG 0.11 mCi/kg were injected, with heart and whole-body imaging acquisition at the time of administration. All PET images were aligned with a low-dose CT and subject to attenuation correction. Perfusion images at rest were interpreted based on a summed perfusion score of 0 to 4 (0: Normal, and 4: No uptake). To evaluate FDG uptake, a visual 0 to 4 score was used (0: No uptake, 1: Diffuse, 2: Focal diffuse, 3: Focal, and 4: Multifocal), for each of the 17 sections. In addition, a semiquantitative imaging test was performed by estimating the maximum FDG uptake value in the abnormal area (SUVmax). Based on the combined findings from myocardial perfusion and FDG up-
take, the following PET patterns were described (8): 1. Normal: Normal perfusion with no FDG uptake; 2. Unspecific: Normal perfusion with diffuse FDG uptake; 3. Inflammation: Abnormal perfusion with focal FDG uptake (mismatch PET pattern); 4. Fibrosis: Abnormal perfusion with no FDG uptake.

All patients had a clinically indicated gadolinium-enhanced CMR prior to the PET. Late enhancement presence and pattern were rated as subendocardial, intramyocardial, subepicardial, and patched. Probability of CS via CMR was: none (<10%), possible (10-50%), probable (50-90%), or highly probable (>90%). Each patient was definitively diagnosed based on a combination of CMR-PET, clinical data review, and other supporting diagnostic tests (12,14,15).

All patients signed an informed consent before the PET and the CMR.

Statistical analysis
Continuous variables are shown as the mean ± SD, while categorical variables are shown as percentages.

RESULTS
The characteristics of the population are displayed on Table 1. The mean age was 60 ± 9 years. Fifty percent of patients were hospitalized when the CMR and PET were requested. None of the patients had a history of acute myocardial infarction. The mean left ventricular ejection fraction by gated PET was 42 ± 15%. Three out of 6 patients had non-significant epicardial artery obstructions according to the coronary angiography; two had moderate obstructions, and one patient had a history of angioplasty of the left anterior descending artery. All patients had adequate physiological suppression of glucose after strict adherence to the diet. FDG PET images could be interpreted in 100% of patients.

Half of patients referred to the PET study had a history of systemic sarcoidosis (Group: With SS): one case was confirmed by extracardiac biopsy, and the other two by clinical diagnosis. CS was suspected in 2 patients due to non-sustained ventricular tachycardia documented by Holter ECG, and in one patient because of left ventricular dysfunction and myopericarditis. Sixty-seven per cent of this group had late gadolinium enhancement on the CMR. One patient had baseline inferolateral intramyocardial enhancement, and the other had patchy enhancement (categories: possible/probable, respectively). Cardiac dedicated PET images showed the following patterns: 2 patients with a normal pattern, and 1 patient with fibrosis. For the whole-body image, one patient showed adenopathies with mild to moderate metabolic activity (SUVmax: 4.1) on both hila and the mediastinum, and the other 2 patients had supra and infradiaphragmatic lymph node involvement, with a diffuse increase of 18F FDG uptake in the bone marrow in one case (SU Vmax: 3.6).

The other half had suspected isolated CS (Group: No SS). Two patients had decompensated heart failure in addition to non-sustained ventricular tachycardia, and one patient had highly responsive atrial fibrillation as part of left ventricular dysfunction. The CMR for all the patients in this group showed extensive and patchy late enhancement of intramyocardial prevalence, with myocarditis as a differential diagnosis (Categories: probable for CS). PET images showed the following patterns: 1 patient had a normal pattern; 2 patients had an unspecific pattern (SUVmax: 1.27± 2.02) (Figure 2). Whole-body images showed no pathological FDG uptake. Only one patient showed diffuse FDG uptake increase in the thyroid gland (SUVmax: 5.3) as an incidental finding.

Patients were reclassified after combining the patterns of FDG PET and CMR enhancement: 50% of patients had less than 10% chance of having CS, and the remaining 50% was classified as possible cases of CS (Figure 3). None of the 6 patients received immunosuppressants.

Three out of six patients in our study had an endomyocardial biopsy (EMB). The EMB was unspecific in 2 patients and positive in 1 patient. The 3 patients showed late enhancement on the CMR, while the PET showed a normal and unspecific pattern in patients with unspecific EMB. The PET pattern for the patient with a positive EMB was fibrosis (no active myocardial inflammation, but myocardial perfusion defects).

<table>
<thead>
<tr>
<th>Table 1. Population characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Clinical history</td>
</tr>
<tr>
<td>Systemic sarcoidosis</td>
</tr>
<tr>
<td>Previous AMI</td>
</tr>
<tr>
<td>Non-significant coronary artery disease</td>
</tr>
<tr>
<td>Moderate injuries</td>
</tr>
<tr>
<td>Angioplasty of the LAD artery</td>
</tr>
<tr>
<td>Previous CMR</td>
</tr>
<tr>
<td>Late enhancement</td>
</tr>
<tr>
<td>Baseline LVEF by gated PET (%)</td>
</tr>
<tr>
<td>Extracardiac/endomyocardial biopsy</td>
</tr>
</tbody>
</table>

Abbreviations: AMI: Acute myocardial infarction; LAD: Left anterior descending; CMR: Cardiac magnetic resonance, LVEF: Left ventricular ejection fraction, PET: Positron emission tomography.
DISCUSSION
The main finding of the present study is that combining the CMR and the PET in our group of patients made it possible to reclassify the potential for CS. When adding the findings from CMR-PET imaging patterns to the clinical condition, to other imaging studies available and to histopathological information, none of the patients received immunosuppressants.

Diagnostic criteria for CS are based on the Japan Society and Heart Rhythm Society guidelines, which involve histological evidence of CS via an EMB, and integration of clinical data and specific patterns in supporting imaging studies. (3,4) Advanced techniques, such as the CMR and FDG PET, both recently included in the guidelines, have emerged as new ways to improve precise diagnosis of this disease. (3,4) In general, the FDG PET is more sensitive, and the CMR
is more specific in terms of CS diagnosis. (7,11,13) When both are combined for CS diagnosis, there is a 94% sensitivity. (12) Importantly, few studies have been published comparing the sensitivity and specificity of the combination of both techniques to evaluate suspected CS. This is likely because this condition lacks a gold standard to compare findings from imaging studies. (12,13)

Vita et al. (14) have recently published the supporting value of this multimodal approach, which they used to categorize CS diagnostic possibilities for 107 patients with suspected CS. These authors reported that 85% had late gadolinium enhancement on the CMR, and 76% had FDG pathological uptake. Among patients with late enhancement, 66% had abnormal FDG uptake, supporting the hypothesis that the mere presence of late enhancement cannot be used as an anti-inflammatory therapeutic guideline. In our population, 83% of patients had late enhancement on the CMR, and 67% showed no FDG uptake in the PET study, which means absence of active myocardial inflammation. Our findings reinforce the supporting role of both techniques when evaluating suspected CS.

Although various CMR late enhancement patterns can be observed in patients with CS, the most common findings are multifocal and patched. Typical findings in CS patients include subepicardial and intramyocardial enhancement next to the basal septum, usually extended to right ventricular insertion and the inferolateral wall. While there is no specific CMR pattern to diagnose CS, late enhancement extension is a major prognostic marker. (11, 14,16)

Based on ASNC and SNMMI guidelines, PET studies on this disease need to include both a myocardial perfusion study at rest and a FDG study in order to characterize different patterns of the disease. (8) We used FDG to obtain images of sarcoidosis inflammation, as FDG uptake is increased in myocardial areas with a large number of macrophage cells. The reason for the increased FDG uptake is that macrophage cells have high GLUT proteins and hexokinase levels. (5,17,18) When combining the myocardial perfusion study with the FDG study, the PET can be used to evaluate the full CS spectrum (from a normal myocardium to active myocardial inflammation, to non-inflammatory fibrosis). (5, 8) Importantly, a combined evaluation of perfusion and inflammation has prognostic value. (8, 9, 12, 14, 19) Recent studies have shown that the prognostic value of an abnormal FDG uptake seems to be higher when associated with myocardial perfusion defects. (8, 12, 14) We need to highlight the clinical importance of identifying perfusion defects and an abnormal FDG myocardial uptake, as these patients have a very high risk of death and ventricular arrhythmias as compared to patients with a normal PET image. (19, 20) Especially, patients with the mismatch PET pattern and FDG uptake on the right ventricle have the worst prognosis. (20) This means that, in a certain way, the diagnostic precision of a FDG image will depend on an adequate physiological suppression of glucose by a normal myocardium, achieved through an appropriate high-fat low-carbohydrate diet. (20-23) In our study, patients had a suppression diet prior to the PET, and thus, we obtained high-quality images for all participants. Therefore, our study findings cannot be assigned to technical factors as a result of inadequate patient preparation. Following the guidelines recommendations, all patients were tested according to combined patterns of 13 N Ammonia myocardial perfusion and FDG, and treatment was determined based on the patients’ clinical conditions and other supporting studies. (8,14)

Study limitations
Our study had several limitations: 1) As described above, the CMR and FDG PET evaluate different pathological processes: fibrosis via enhancement in the former, and inflammation via FDG uptake by macrophages in the latter. (24) It is important to note that none of these two techniques is specifically used to diagnose fibrosis or inflammation caused by CS. (20,22, 24-28) Myocarditis, necrosis, and myocardial hibernation, among other conditions, may show patterns similar to those described for suspected CS by both tests. (14,20) Consequently, the information gathered both through a CMR and a PET always needs to be interpreted as part of the patient’s clinical condition and further supporting studies. 2) The n of our population is low, and therefore, we cannot make any statistical comparisons across both groups of patients in the study (i.e., with SS and with no history of SS). 3) While our patient population is small, given that CS is an uncommon condition, our findings provide relevant diagnostic information according to previous publications.

CONCLUSIONS
We performed a PET following a CMR in our patient population with suspected CS and inflammation to estimate the potential for CS. After combining late enhancement patterns by CMR and perfusion patterns/FDG by PET, none of the patients received immunosuppressants. In the absence of a gold standard, it is suggested that the diagnosis of CS should be based on probabilities according to specific imaging patterns and clinical features for potential treatment guidance.

Conflicts of interest
None declared.

(See authors’ conflict of interests forms on the web/Additional material.)

REFERENCES
of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. Eur Heart J 2007;28:1076–93. https://doi.org/10.1038/eurheartj.esh456.


