

18F-FDG PET/CT in Diagnosis, Therapeutic Evaluation and Definition of Management in Cardiac Sarcoidosis: Learn From This Case Report

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Introduction

Sarcoidosis is a non-caseating granulomatous inflammatory disease of unknown etiology. The presentation can range from an asymptomatic condition with nonspecific findings on chest radiography to organ failure. Any part of the body can be affected, but the most common sites are the mediastinal lymph nodes and the lungs, followed by the skin and ocular structures such as the uvea. Other systems, such as the nervous, endocrine, gastrointestinal, urinary, musculoskeletal, and cardiovascular systems, can also be affected.¹

Cardiac sarcoidosis is a disease that is still under-researched in cardiology. It is related to cardiomyopathy conditions that can be confused with hypertrophic, infiltrative, or even ischemic cardiomyopathy, and it courses with ventricular arrhythmias and conduction disorders with possible progression to heart failure and/or sudden death. It is worth emphasizing that cardiac sarcoidosis is responsible for up to 35% of cases of complete atrioventricular block (CAVB) in patients under 60 years of age.¹ These patients benefit from the implantation of a pacemaker and implantable cardioverter defibrillator (ICD). Immunosuppressive therapy is indicated to control the inflammatory process.²

Positron emission tomography with computed tomography (PET/CT) using fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) is a hybrid imaging method that provides anatomical and molecular information of diseases in a non-invasive and objective manner. The degree of ¹⁸F-FDG uptake in the regions affected by sarcoidosis reflects the inflammatory intensity of the disease.³ In this context, ¹⁸F-FDG PET/CT is able to identify early the presence and extent of intra- and extracardiac involvement, thus being able to guide and monitor the

therapeutic response. Furthermore, early diagnosis of cardiac sarcoidosis is essential, since late diagnoses are related to greater cardiac damage and worse prognosis.⁴

The objective of this article is to demonstrate that presumptive diagnosis of cardiac sarcoidosis is possible, based on clinical and radiological criteria, especially with the use of ¹⁸F-FDG PET/CT. Furthermore, in this report we show how ¹⁸F-FDG PET/CT assists therapeutic monitoring and definition of conduct.

Case description

We describe the case of a 39-year-old male patient who was hospitalized with recurring “off-on” syncope. The 24-hour Holter showed frequent ventricular extrasystoles and intermittent episodes of CAVB, with pauses of up to 14.5 seconds. On echocardiography, the left ventricle (LV) was dilated with segmental and global dysfunction (LV ejection fraction 43%). Coronary angiography did not show obstructive coronary lesions. Cardiac magnetic resonance imaging (CMR) showed structural heart disease with a non-ischemic enhancement pattern, predominantly in the basal region of the septum, with a large quantity of fibrosis. In this context, the diagnostic hypothesis of cardiac sarcoidosis was considered as the cause of intermittent CAVB and ventricular dysfunction, and implantation of a permanent dual-chamber pacemaker with ICD was performed to treat bradyarrhythmia and prevent sudden death.

As a diagnostic complement, ¹⁸F-FDG PET/CT was performed, revealing a focal increase in glycolytic metabolism throughout the entire length of the basal region of the LV (anterior, anteroseptal, inferoseptal, inferolateral, and anterolateral segments). Whole body imaging also showed pulmonary, lymph node, and bone involvement, in addition to diffuse increase in the arm muscles (Figure 1). Resting myocardial perfusion scintigraphy (Figure 2) showed abnormally low tracer concentration in the apical region (match of ^{99m}Tc-sestamibi and ¹⁸F-FDG: did not show uptake of either tracer, suggesting an area of fibrosis without inflammation) and in the basal segment of the LV anteroseptal wall (mismatch of ^{99m}Tc-sestamibi and ¹⁸F-FDG: no uptake of ^{99m}Tc-sestamibi and uptake of ¹⁸F-FDG, suggesting an area of fibrosis with local inflammation).

Keywords

Sarcoidosis; Positron-Emission Tomography; Fluorodeoxyglucose F18

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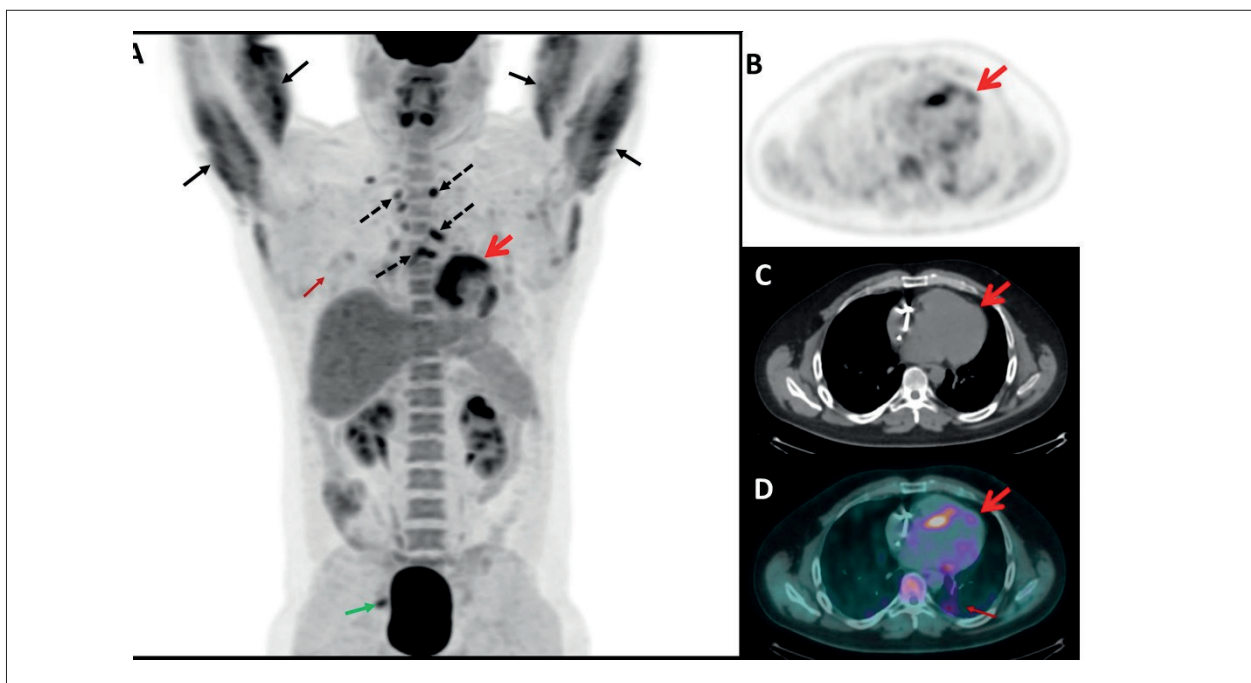


Figure 1 – ^{18}F -FDG PET/CT scan showing increased glycolytic metabolism in several mediastinal lymph nodes (black hatched arrows) with ^{18}F -FDG standardized uptake value (SUV) of up to 5.9, in small, grouped reticulonodular lung opacities (thin red arrow), with lymphatic distribution, some with foci of calcifications, sparse in both lungs (SUV of up to 3.6), in the left ventricular myocardium (thick red arrow), with heterogeneous pattern (SUV = 6.7), in the right iliac bone marrow (green arrow), next to the right sacroiliac joint (SUV = 4.6) and in the musculature of both arms (black arrows), mainly biceps and triceps, which were hypertrophied, with a heterogeneous pattern that was a little more intense in the right arm (SUV = 5.5). In A, 3-dimensional full-body maximum intensity projection of ^{18}F -FDG PET imaging; in B, coronal section of the chest from PET with ^{18}F -FDG at the cardiac level; in C, computed tomography; in D, PET/CT fusion.

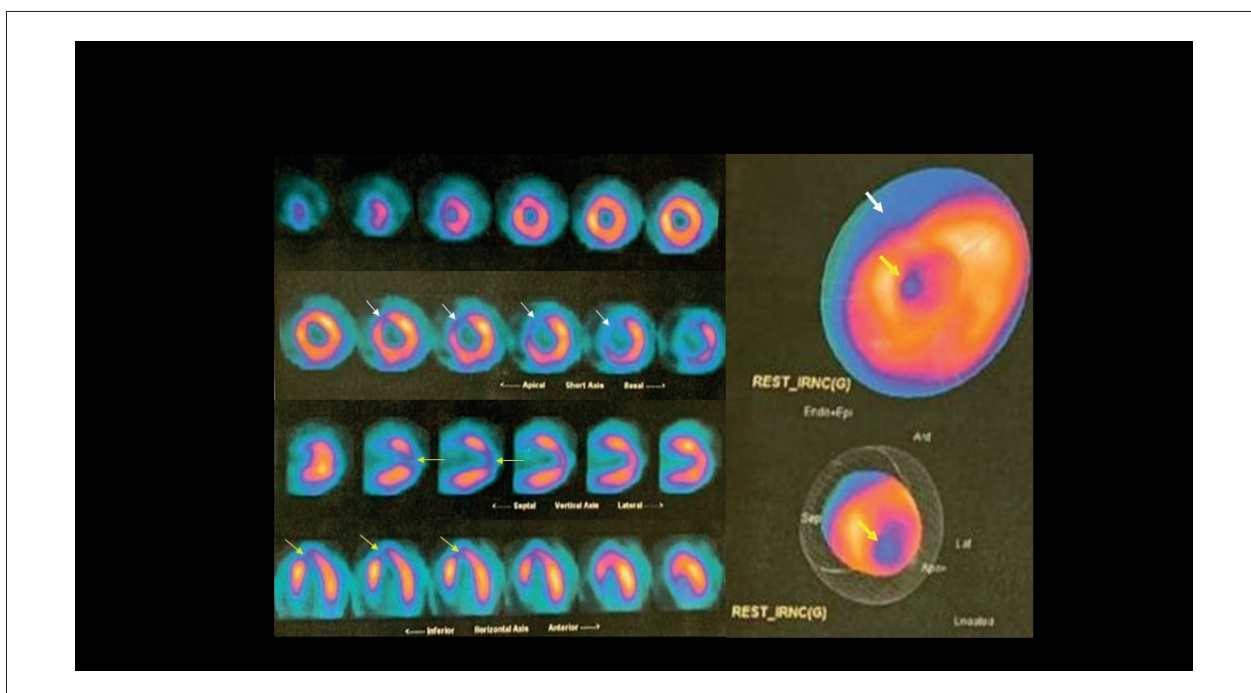


Figure 2 – Resting myocardial perfusion scintigraphy with $^{99\text{m}}\text{Tc}$ -sestamibi showing abnormally low tracer concentration in the basal anteroseptal (white arrows) and apical (yellow arrows) segments of the LV, suggesting fibrosis.

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Corticosteroid therapy was initiated at a dose of 40 mg of prednisone orally for 3 months. After this period, the steroid dose was progressively reduced. The patient complained of dyspnea on routine exertion and atypical chest pain. He was completely dependent on the pacemaker (CAVB no longer intermittent). A new Holter revealed normal functioning pacemaker rhythm, frequent ventricular extrasystole, and episodes of accelerated idioventricular rhythm. A new ^{18}F -FDG PET/CT was carried out, showing persistence of cardiac and extracardiac inflammatory activity. Due to the maintenance of cardiac inflammation, methotrexate 15 mg orally once a week was added, in addition to optimization of therapy for heart failure.

To assess the therapeutic response, approximately 8 months after starting methotrexate, a new PET/CT showed complete resolution of cardiac uptake of ^{18}F -FDG and improvement in heart failure with increased LV ejection fraction, but the patient remained dependent on the pacemaker. The other regions showed persistence of inflammatory disease activity (Figure 3).

Discussion

Cardiac involvement by sarcoidosis is characterized by the presence of non-caseating granulomas in the myocardium and/or pericardium. Clinical manifestations depend on the location and intensity of the granulomatous inflammation.¹

The diagnostic definition of cardiac sarcoidosis is based on expert consensus recommendations. Diagnosis can be histological, identifying the presence of non-caseating

granuloma in the heart, or clinical, based on imaging tests.¹ Myocardial biopsy is the gold standard; however, in addition to the fact that it is an invasive procedure, its sensitivity does not exceed 30%.⁵ Table 1 summarizes the criteria applied for diagnosing cardiac sarcoidosis according to the 2016 update of the Japanese Circulation Society guideline.⁶ According to these criteria, this patient fulfilled the criteria for systemic sarcoidosis with cardiac involvement.

Considering the typical findings of sarcoidosis on CMR and ^{18}F -FDG PET/CT scans, associated with the lack of experience in performing myocardial biopsy in cardiology and thoracic surgery services in Brazil, the use of ^{18}F -FDG PET/CT has become popular among cardiologists.⁷ A meta-analysis published in 2012, with data from 164 patients, showed that ^{18}F -FDG PET/CT has a sensitivity of 89% and specificity of 83% for diagnosis of cardiac sarcoidosis.⁴

It is, nonetheless, worth noting that the test should be performed in specialized centers, given that findings of cardiac sarcoidosis can be confused with other cardiac conditions, such as hibernating myocardium in patients with ischemic heart disease, or active myocarditis in systemic rheumatic conditions.⁷ For this reason, the interpretation of the exam by an excellent professional is fundamental in order to avoid diagnostic errors.³

In addition to assisting diagnosis, these advanced imaging modalities play a key role in monitoring the therapeutic response, as they are capable of detecting the inflammatory state before and after the start of therapy. The use of these exams can guide safer professional decisions, such as when

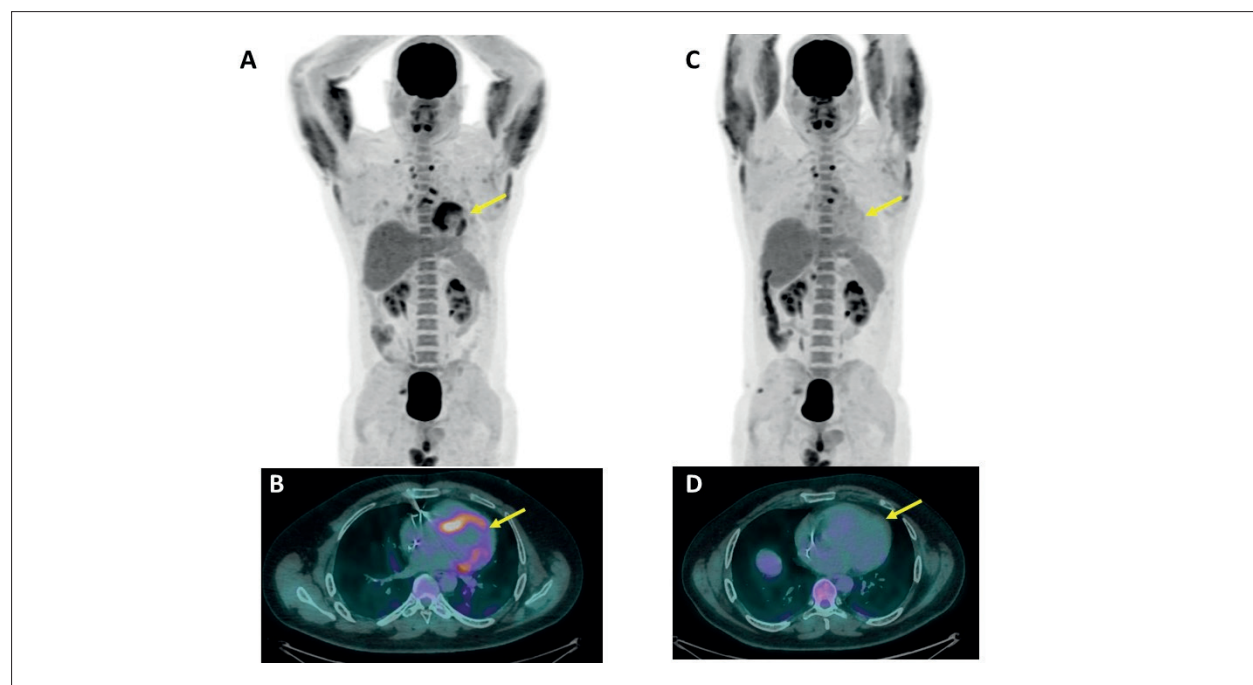


Figure 3 – ^{18}F -FDG PET/CT scans performed before (A and B) and after (C and D) initiation of methotrexate. A and C show 3-dimensional full-body maximum intensity projection images of ^{18}F -FDG PET; B and D show axial slices (PET/CT) of the chest at the heart level. About 8 months after starting methotrexate, PET images showed complete resolution of ^{18}F -FDG uptake in the left ventricular myocardium (yellow arrows). The other regions (arm muscles, mediastinal lymph nodes, lungs, and right iliac region) show persistence of ^{18}F -FDG uptake.

Table 1 – Criteria for defining cardiac sarcoidosis according to the Japanese Circulation Society (JCS)

Japanese Circulation Society criteria for clinical diagnosis of cardiac sarcoidosis		
Criteria for clinical definition of pulmonary sarcoidosis ¹	1. Bilateral hilar lymphadenopathy 2. CT or high-resolution CT images showing thickened interstitium surrounding the bronchial vascular bundles and multiple nodular opacities along lymphatic vessels*	
Laboratory/imaging criteria characteristic of sarcoidosis and clinical findings strongly suggestive of cardiac involvement ²	1. Bilateral hilar lymphadenopathy 2. High serum angiotensin-converting enzyme activity or elevated serum lysozyme levels 3. High serum levels of SIL-2R 4. Increased uptake of tracers for inflammation such as gallium-67 citrate on conventional scintigraphy or ¹⁸ F-FDG on PET/CT 5. High percentage of lymphocytes with a CD4/CD8 ratio of > 3.5 in the bronchoalveolar lavage fluid	
	Major criteria	Minor criteria
Criteria for clinical definition of cardiac sarcoidosis ³	1. High-grade atrioventricular block (including CAVB) or fatal ventricular arrhythmia (for example, sustained ventricular tachycardia, and ventricular fibrillation) 2. Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional thickening of the ventricular wall) 3. Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50%) or focal ventricular wall asynergy 4. Scintigraphy with gallium-67 or ¹⁸ F-FDG PET/CT revealing high tracer uptake in the heart 5. CMR with gadolinium revealing delayed contrast enhancement in the myocardium	1. Abnormal ECG findings: ventricular arrhythmias (nonsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves 2. Perfusion defects on resting myocardial perfusion scintigraphy.

1. The clinical definition of pulmonary sarcoidosis* depends on the presence of at least 1 of the 2 criteria listed; 2. At least 2 out of 5 laboratory/imaging criteria characteristic of sarcoidosis and clinical findings strongly suggestive of cardiac involvement; 3. The clinical definition of cardiac sarcoidosis requires the presence of 2 or more major criteria or 1 major criterion plus 2 or more minor criteria. CAVB: complete atrioventricular block; CMR: cardiac magnetic resonance imaging; CT: computed tomography; ECG: electrocardiogram. *Multiple nodular opacities along the lymphatic vessels may be found in the central and/or peripheral parts of the lobules along the pleura, interlobular septa, and bronchopulmonary arteries. Source: Terasaki et al.⁶

to start weaning from a certain medication or when to add or withdraw certain drugs (Figure 4).³

It is important to emphasize that all of this patient's ¹⁸F-FDG PET/CT scans were performed strictly following the preparation protocol for physiological suppression of glucose uptake by cardiomyocytes (Figure 5).⁷

¹⁸F-FDG PET/CT is indicated for evaluation of inflammatory disease activity in patients with persistent symptoms or clinical worsening and evaluation of the therapeutic response.⁴ Accordingly, the PET/CT scan was important in confirming cardiac sarcoidosis, in the systemic staging of the disease, in therapeutic monitoring, and in determining management.

In sarcoidosis, nonspecific chest pain, dyspnea, and fatigue are common symptoms that are generally associated with extracardiac disease.⁵ In all ¹⁸F-FDG PET/CT scans performed, extracardiac disease persisted. For these patients, extracardiac involvement is common; however, it is practically restricted to low-grade

lung injury and almost never symptomatic involvement of other organs.⁷

Conclusion

This case report has illustrated how ¹⁸F-FDG PET/CT can be useful in confirming cardiac and extra-cardiac sarcoidosis, avoiding endomyocardial biopsy and serving to evaluate therapeutic response and determine management.

Author Contributions

Conception and design of the research: Brandão SCS, Lucena MVA, Wiefels C, Mesquita CT, Rezende MF, Mastrocolla F; acquisition of data: Brandão SCS, Lucena MVA, Da Silva PHR, Mastrocolla F; analysis and interpretation of the data: Brandão SCS, Lucena MVA, Mastrocolla F; writing of the manuscript: Brandão SCS, Lucena MVA, Da Silva PHR; critical revision of the

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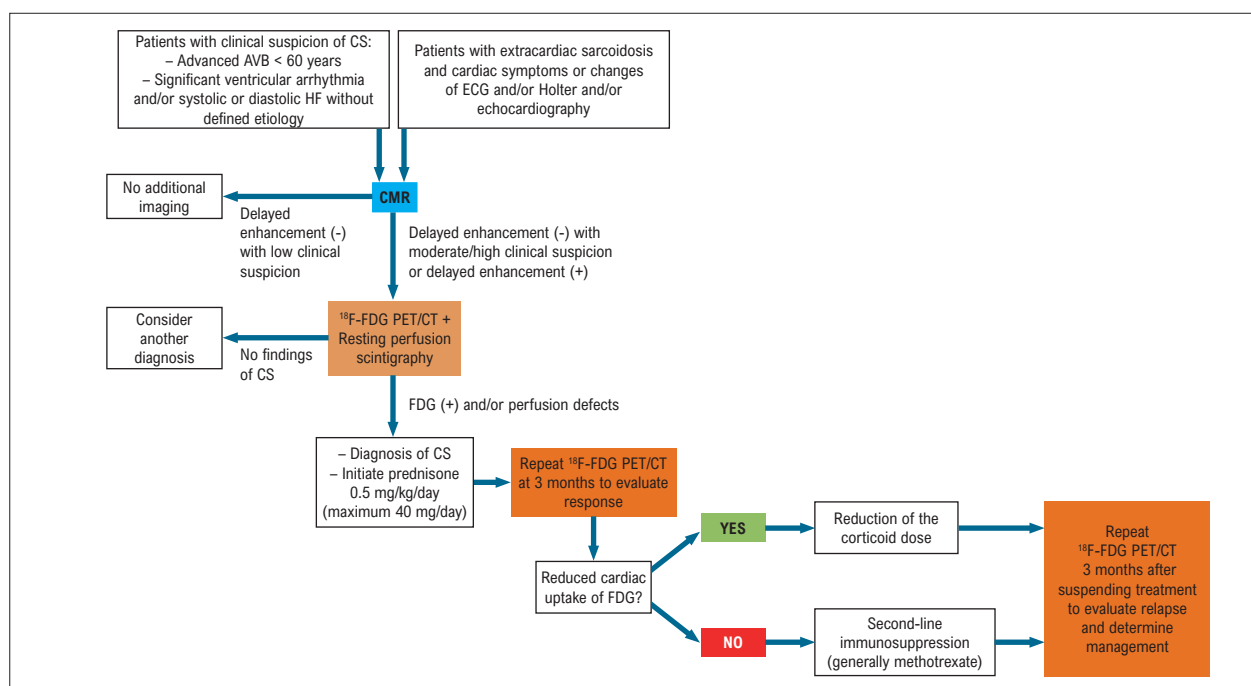


Figure 4 – Algorithm for investigation and therapeutic monitoring of cardiac sarcoidosis according to data from the literature and the authors' experience with the use of ^{18}F -FDG PET/CT. AVB: atrioventricular block; CMR: cardiac magnetic resonance imaging; CS: cardiac sarcoidosis; ECG: electrocardiogram; HF: heart failure; FDG: fluorodeoxyglucose.



Figura 5 – ^{18}F -FDG PET/CT in the investigation of cardiac sarcoidosis. Whole-body imaging is required to screen for systemic disease, and cardiac acquisition synchronized with the electrocardiogram is required to evaluate the heart in greater detail. In this figure, we summarize the preparation for the exam: 1. The day before the scan (at least 24 hours before), the diet should be low in carbohydrates and high in fat to stimulate the consumption of fatty acids by the heart muscle; thus, the diet is based on proteins and fibers and is rich in fat. 2. Fast for at least 12 hours (preferably 18 hours), except water, which can be consumed without restriction. 3. Avoid physical activity 24 hours before the scan. 4. Get a good night's sleep. 5. In the case of patients with diabetes using insulin, insulin use is not permitted on the day of the scan. 6. Serum glucose level must be below 180 mg/dL. 7. In some centers, unfractionated heparin 50 IU/kg is administered intravenously, 15 minutes before the ^{18}F -FDG injection. Source: Kumita et al.⁷

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da UFPE under the protocol number 6.222.794. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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