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Preparation is everything: The impact of a structured preparation protocol on cardiac ^{18}F-FDG PET imaging for cardiac sarcoidosis

Sanjay Divakaran, MD[a], **Michael T. Osborne, MD**[b]

[a]Cardiovascular Imaging Program, Departments of Radiology and Medicine and Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[b]Cardiac MR-PET-CT Program, Department of Radiology and Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Cardiac ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has become an important tool in the diagnosis and management of a number of inflammatory cardiovascular pathologies, including cardiac sarcoidosis.[1,2] The technique utilizes ^{18}F-FDG, a radiolabeled glucose analogue that is avidly taken up by highly metabolic tissues. Sarcoidosis is an inflammatory disorder of uncertain origin that is characterized by the infiltration of ^{18}F-FDG-avid non-caseating granulomas into multiple organs. The disease is thought to affect the heart in at least 20% of patients with sarcoidosis, and its presence in the heart can present with arrhythmia, conduction disease, heart failure, or sudden cardiac death.[3,4] Cardiac involvement is often patchy, and endomyocardial biopsy is therefore notoriously insensitive. As such, early identification of cardiac involvement, a key aspect of disease management, has been improved by the development of non-invasive techniques, such cardiac magnetic resonance imaging and ^{18}F-FDG PET.

A major inherent limitation of cardiac ^{18}F-FDG PET imaging lies in the fact that normal background myocardial uptake of ^{18}F-FDG must be suppressed in order to identify pathologic inflammatory foci that may otherwise obscured. Normal myocardium utilizes glucose in the presence of insulin; however, myocardial metabolism shifts to free fatty acids when insulin levels are low.[5] On the other hand, inflammatory cells only use glucose for energy and do so in an insulin-independent fashion.[6] As such, the metabolism of normal background myocardium must be manipulated in favor of free fatty acid utilization by patient preparation, largely by minimizing systemic insulin levels, prior to injection with ^{18}F-FDG. Such manipulation is fraught with pitfalls and may lead to a non-diagnostic test,

Reprint requests: Michael T. Osborne, MD, Cardiac MR-PET-CT Program, Department of Radiology and Cardiology Division, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., Yawkey 5E, Boston, MA 02114-2750, USA; mosborne@partners.org.

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even when instructions are followed completely, especially among challenging populations such as those being tested as inpatients or those with advanced heart failure or diabetes.[7]

Until recently, there was no consensus on the optimal methods for patient preparation. The existing protocols differed substantially from one institution to another with variable utilization of techniques that included behavioral, dietary, and pharmacologic approaches.[8] Recent reviews and meta-analyses suggested that a combination of a high-fat, low-carbohydrate (HFLC) diet and subsequent fasting may be most effective for the suppression of glucose utilization by normal myocardium.[8,9] Therefore, the 2018 Joint Society of Nuclear Medicine and Molecular Imaging (SNMMI)/American Society of Nuclear Cardiology (ASNC) consensus document for ^{18}F-FDG PET imaging of cardiac sarcoidosis recommended one of two options for patient preparation: (1) at least two high-fat (>35 g), low-carbohydrate (<3 g) meals the day before the ^{18}F-FDG PET with a fast of 4–12 hours prior to ^{18}F-FDG injection or (2) a fast of at least 18 hours prior to ^{18}F-FDG injection. Based on the existing evidence, the same document stated that adjunctive heparin injection may be used and urged that diabetic patients minimize their use of insulin and antihyperglycemic therapies on the day of testing but otherwise follow the same methods of preparation as individuals without diabetes. Importantly, the document instructed patients and laboratories to log the preparation used to ensure adherence and consistency.[10]

In this edition of the *Journal of Nuclear Cardiology*, Christopoulos and colleagues provide the first description of the effectiveness of implementing this recommended protocol for patient preparation at the Mayo Clinic.[11] In this well-executed study, the effectiveness of ^{18}F-FDG PET using a prior institutional protocol was retrospectively compared to the effectiveness of a novel institutional protocol based largely upon the recent 2018 Joint SNMMI/ASNC consensus document. The prior protocol consisted of communication with the patient with instructions 24 hours prior to the ^{18}F-FDG PET, a HFLC diet for 24 hours prior to imaging, fasting for at least two hours of imaging, and no instructions on exercise. Patients scanned using the new protocol were prepared by communication 48 hours prior to imaging and were provided written details about permissible foods. They were given two options: (1) two HFLC meals on the day prior to imaging followed by at least 15 hours of fasting (preferred) or (2) fasting alone for at least 18 hours. All patients were urged not to exercise for the 24 hours prior to imaging. The quality of patient preparation was reviewed in detail by imaging staff on the day of the ^{18}F-FDG PET prior to ^{18}F-FDG injection. Importantly, individuals who were identified as having not adhered to the preparation protocol were rescheduled. An impressive 91% of individuals who were prepared with this new protocol had adequate myocardial suppression, a significant improvement beyond the 78% of individuals who were prepared with the prior protocol, which matches recently reported data using a similar protocol.[12] Furthermore, almost one-third of the patients with inadequate suppression using the new protocol were only partially adherent to the preparation protocol, suggesting that full adherence may yield even greater efficacy.

The important findings presented by Christopoulos and colleagues not only confirm the efficacy of a preparation strategy adopted based upon the 2018 Joint SNMMI/ASNC consensus document but also suggest several strategies beyond those presented by that document that may have further augmented the efficacy of the new patient preparation

protocol. In this study, the duration of fasting was at least 15 hours, which was greater than the duration that had been recommended in the consensus document. Further, patients were provided with detailed instructions about permissible foods and behaviors 48 hours before testing. In addition, patients were asked to avoid exercise for 24 hours prior to imaging. Finally, all patients were screened by staff for adherence to the preparation instructions prior to ^{18}F-FDG injection, and those who had not adhered to a satisfactory degree were rescheduled. This attention to detail certainly contributed to the success of the new preparation strategy, and the techniques employed merit consideration for broader implementation (Table 1).[11]

While they are unlikely to explain the entirety of the difference in the success of the preparations, two other factors may be important contributors to these results. Inpatients, although only 5% of the population, were overrepresented in the group prepared with the prior protocol in a relatively small sample. The preparation of inpatients is quite challenging, as its success relies upon a collaboration between patients, dieticians, pharmacists, nurses, and physicians. Furthermore, inpatients often have comorbidities (e.g., cardiomyopathy, diabetes) and treatments (e.g., corticosteroids, insulin) that can adversely affect proper suppression of background myocardial glucose uptake. In addition, several patients in the study underwent imaging with both protocols and 15% of these subjects had inadequate suppression with the prior protocol and adequate suppression with the new protocol. It is possible that the learning experience of having had prior imaging with inadequate suppression was as valuable as the change in preparation protocol for this population. Nevertheless, the strengths of the findings from this study outweigh these considerations.

Looking towards the future, several important questions remain unanswered. It is critical to demonstrate that such a protocol for preparation can be implemented broadly across institutions with the same beneficial impact as that seen at the Mayo Clinic. Similarly, a standardized definition of adequate suppression is needed, as the current criteria remain variable and, at times, subjective. Additional study will be needed to determine the efficacy of such a strategy in challenging populations, such as inpatients, those with dietary restrictions, and those with diabetes (particularly insulin-dependent diabetes) or severe heart failure. There should also be an effort to minimize the number of patients who are required to reschedule due to non-adherence with preparation, as this potentially represents a substantial burden for affected patients. Finally, there should continue to be investigations of novel tracers that do not require preparation to suppress background tracer uptake to identify cardiac sarcoidosis, as well as improve PET's specificity for the disease process to match its current sensitivity.[13]

In closing, Christopoulos and colleagues make important progress towards improving the utility of ^{18}F-FDG PET for the diagnosis and management of cardiac sarcoidosis. Patient preparation is challenging for clinicians and for patients. The test can take a half-day of the patient's time, generate significant cost, and result in radiation exposure with little benefit if thoughtful and careful preparation is absent. By demonstrating the effectiveness of the preparation strategy recommended by the 2018 Joint SNMMI/ASNC consensus document, this study is a call to action for physicians and medical centers to improve patient-centered

care rather than a request for improved patient adherence. Preparation is everything, and the responsibility belongs to us.

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Table 1.

Opportunities for optimization of patient preparation prior to ^{18}F-FDG PET for cardiac sarcoidosis

	Outpatients	Inpatients
Patient education	Call/speak to patients 48 hours prior to ^{18}F-FDG PET	Call/speak to patients 48 hours prior to ^{18}F-FDG PET
Nurse education	–	Speak to nurse 48 hours prior to ^{18}F-FDG PET Review drips and intravenous medications that need to be discontinued or modified 24 hours prior to ^{18}F-FDG PET with nurse
Diet options	Provide patients with a list of permissible foods/meals Allow 18-hour fast if food/meal options are not suitable due to dietary restrictions	Provide patients with a list of permissible foods/meals available on the hospital menu Allow 18-hour fast if food/meal options are not suitable due to dietary restrictions
Exercise	No exercise 24 hours prior to ^{18}F-FDG PET	–
Breakfast	Nothing to eat the morning of ^{18}F-FDG PET	Nothing to eat the morning of ^{18}F-FDG PET
Food log/drips	Review food log prior to start of ^{18}F-FDG PET	Review food log and medications prior to start of ^{18}F-FDG PET

^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography