# Optimizing radionuclide imaging in the assessment of cardiac sarcoidosis

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Sarcoidosis is a disease of unknown etiology and is characterized by the development of non-caseating granulomas with a predilection for the pulmonary system. Involvement of the cardiovascular system ranges from 20% in the United States to over 75% in Japan.[1] Up to 85% of sarcoid-related mortality results from cardiac sarcoidosis (CS).[2] Observational studies suggest that early initiation of glucocorticoids may inhibit the inflammatory response to CS, thereby limiting fibrotic formation within the heart and ultimately improving long-term survival.[3] Consequently, prompt and accurate diagnosis of CS is critical given its prognostic and therapeutic ramifications. Unfortunately, the diagnosis of CS has proven challenging since approximately half the of patients with CS are initially asymptomatic[1] and, due to heterogenous myocardial involvement, CS detection by endomyocardial biopsy (EMB) has a sensitivity of only 20% to 30%.[4] Gallium ($^{67}$Ga) single-photon emission tomography (SPECT) is specific for CS but has a sensitivity of less than 40%.[5] Non-radionuclide techniques for the diagnosis of CS include echocardiography which has a poor sensitivity (25%)[4] and cardiac MRI which has substantially greater sensitivity for CS detection at 75%[6] but may be contraindicated in some patients with suspected CS such as those with cardiac devices.

Cardiac imaging with fluorine-18 fluorodeoxyglucose ($^{18}$FDG) positron emission tomography (PET) appears to have high diagnostic accuracy for CS as demonstrated in several observational studies.[7] Consequently, experts have recently included cardiac$^{18}$FDG-PET imaging in the standard diagnostic algorithm for CS.[8] The gradual adoption of cardiac$^{18}$FDG-PET imaging as a standard of care in the assessment and treatment of CS underscores the need for studies focusing on standardization of patient preparation, imaging protocols, and interpretation of cardiac$^{18}$FDG-PET imaging for CS.

An important component of cardiac imaging with $^{18}$FDG-PET is patient preparation. The objective of patient preparation for an $^{18}$FDG-PET CS imaging protocol is to suppress physiologic myocardial $^{18}$FDG uptake in order to enhance detection of pathologic $^{18}$FDG uptake in inflamed tissues.[9] Under postprandial conditions, increased serum insulin levels upregulate glucose transporter 1 and 2 (GLUT-1 and GLUT-2) which in turn facilitate myocyte glucose uptake.[10] Therefore, diffuse myocardial $^{18}$FDG uptake in the non-fasting state may be a normal physiologic finding.[11] In some healthy individuals, $^{18}$FDG uptake may be more heterogeneous, and may be present even in the fasting state. At the same time, inflamed tissue, such as that seen in CS, can also increase glucose utilization[12] and result in elevated intramyocardial levels of $^{18}$FDG. The appearance of $^{18}$FDG uptake in inflamed tissues may be indistinguishable from heterogeneous or focal $^{18}$FDG uptake in healthy myocardium, underscoring the importance of suppression of normal physiologic myocardial $^{18}$FDG uptake. Current means of suppressing physiologic myocardial $^{18}$FDG uptake for CS PET imaging include (1) prolonged fasting, (2) low-carbohydrate diet (LCD) with or without high fat,[13] and/or (3) use of intravenous unfractionated heparin (UFH) to stimulate lipolytic activity and increase free fatty acid (FFA) levels.[14] Limited studies suggest varying degrees of efficacy of these protocols. Similarly, prior studies using other means of physiologic suppression such as shorter fasting protocols have noted varying degrees of myocardial $^{18}$FDG uptake in a majority of patients,[15]

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again underscoring the need for additional studies and novel protocols to enhance cardiac $^{18}$FDG-PET as a tool in CS.

In the current issue of the *Journal of Nuclear Cardiology,* Manabe and colleagues assessed both the qualitative and quantitative effects of two patient preparation protocols, an 18-h fast with LCD (<5 gm) vs a minimum 6-h fast without LCD, on diffuse left ventricular (LV) $^{18}$FDG-PET uptake and plasma free fatty acid (FFA) levels in patients with suspected CS. Qualitative assessment by two different blinded nuclear medicine physicians demonstrated complete physiologic $^{18}$FDG suppression in all patients undergoing the 18-h fast with LCD compared to 72% of patients who underwent the 6-h fast only, a difference which was statistically significant ($P = .0041$). Quantitative analysis showed no significant difference in maximal standard uptake value (SUVmax) between the two groups. Furthermore, the authors also noted significantly lower fasting plasma glucose and higher FFA levels in the prolonged fast and LCD group compared to the 6-h fast group. Interestingly, patients with diffuse LV $^{18}$FDG uptake showed significantly lower FFA levels than patients without diffuse LV $^{18}$FDG uptake. Lastly, the current study demonstrated significantly higher FFA levels after vs before UFH administration, but no significant difference in FFA levels between the two preparation groups after UFH administration.

Until now, complete suppression of physiologic $^{18}$FDG uptake in all patients has not been reported in the literature. The results of this study using combined 18-h fast with LCD are highly promising for enhancing the assessment of CS by cardiac imaging with $^{18}$FDG-PET. The authors are also congratulated for adding substantially to the literature in this area, which has been limited. Prior studies have mainly addressed the effect of 18-h fasting preparation on suppression of myocardial physiologic FDG uptake. The current study also addresses the utilization of UFH as a means by which to acutely raise FFA and thereby theoretically suppressing myocardial $^{18}$FDG uptake. Previous reports have demonstrated that fasting was more effective than UFH in suppressing $^{18}$FDG uptake.[16] In the current study, Manabe and colleagues noted that while UFH does increase FFA, it does not effectively reduce diffuse $^{18}$FDG uptake. This is also a crucial finding from the study given the possible risks of UFH administration.

Despite these important findings by Manabe et al, several critical issues remain to be addressed when considering optimizing cardiac $^{18}$FDG-PET protocols. First, while Manabe and colleagues demonstrated the complete suppression of physiologic myocardial $^{18}$FDG uptake, it is unclear whether this finding impacted how CS images were interpreted and the resultant overall accuracy in CS detection by $^{18}$FDG-PET. Providing evidence of clinical utility is an essential step towards developing universal patient preparation protocols for CS detection. Second, as noted by Manabe et al in the limitations section, the exact fasting times for each group were not available. Recent literature has demonstrated poor compliance with fasting instructions and emphasize the need for further patient education.[17,18] Poor compliance with dietary instructions may have led to some patients in the 6-h fasting group to actually fast for longer than advised and those in the 18-h group to fast for less than the recommended time ultimately leading to possible contamination of the study groups. Third, it remains unclear whether the prolonged fast or the LCD was the primary factor in suppressing physiologic $^{18}$FDG uptake or if both were necessary components in achieving complete suppression. If diet is the primary factor, then a prolonged fast could perhaps be avoided. This would be preferable given that one patient in the Manabe study had to be removed due to a low glucose level and given the concerns that a prolonged fast without insulin use (as was the protocol in the current study) might cause untoward complications in patients with insulin-requiring diabetes mellitus. Fourth, the current study spanned over a decade and thereby may have been influenced by changes in practice patterns. For instance, three different PET imaging systems were employed with varied detector crystals and methods of attenuation which could potentially influence image quality and ultimately the interpretation of the presence of $^{18}$FDG uptake. Manabe and colleagues cite a meta-analysis by Youssef et al that utilized different PET systems to analyze CS and suggest that the varied operating systems had little impact upon interpretation.[7] However, it is important to note that the study period of Youssef's work was much shorter (3 years) than the current study and therefore may not have been subjected to as many protocol changes and advancements in technology as the current study. Fifth, as protocols become further refined it will be important to remember that other non-pathologic (papillary muscles, crista terminalis, lipomatous hypertrophy of the left atrial septum) and pathologic (myocarditis and left ventricular hypertrophy) phenomena will impact the pattern of $^{18}$FDG uptake regardless of the preparation protocol used. In the current study patients with coronary artery disease, myocarditis, cardiomyopathy, and valvular heart disease were excluded. These are important considerations when deciding whether or not a protocol has widespread clinical applicability. Furthermore, recent literature advocates the use of a high-fat diet in conjunction with LCD for suppression of myocardial $^{18}$FDG uptake,[13,19,20] a protocol recommended and utilized by many experts. The current study does not incorporate a

high-fat diet with LCD protocol, which should be included in future studies to examine its effectiveness in suppressing myocardial $^{18}$FDG uptake both qualitatively and quantitatively. Lastly, experts advocate the use of $^{13}$N-ammonia in conjunction with cardiac $^{18}$FDG-PET imaging for CS evaluation[21] but the former is yet to be fully investigated to determine its diagnostic accuracy in the CS population.

Given the recent incorporation of cardiac $^{18}$FDG-PET into the Heart Rhythm Society guidelines for the assessment of CS,[8] it is imperative that standardized protocols be developed for cardiac $^{18}$FDG-PET imaging for CS. The findings by Manabe and colleagues represent a significant contribution towards the ultimate goal of creating a universal $^{18}$FDG-PET preparation protocol for CS and is a step in the right direction of optimizing and standardizing PET imaging for the diagnosis and management of CS.

## Disclosures

*The authors have nothing to disclose.*

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