Optimizing myocardial metabolism for fluorine-18 fluorodeoxyglucose positron emission tomography imaging of cardiac inflammation

Efstathia Andrikopoulou, MD,[a] and Pradeep Bhambhvani, MD[b]

[a] Division of Cardiovascular Disease, Department of Medicine, The University of Alabama at Birmingham, Birmingham, AL
[b] Division of Molecular Imaging and Therapeutics, Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL

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Inflammation-related hot spot imaging along with suppression of physiologic myocardial glucose metabolism forms the basis of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) imaging of inflammatory cardiomyopathies, infections of intracardiac devices, and prosthetic valves and vulnerable coronary plaques. Adequate attenuation of physiologic myocardial glucose uptake that ensures high-quality FDG-PET images, however, can be challenging, especially since glucose can be physiologically taken up by the cardiomyocytes under certain conditions. In order to maximize suppression of normal glucose uptake, a number of different interventions have been proposed and are utilized by PET laboratories, without there being a consensus on the most effective one.

To better appreciate the different suppression techniques available, a basic understanding of myocardial metabolism is essential.[1,2] A variety of different metabolic substrates can be utilized by the myocardium depending on fasting vs post-meal state and underlying viability. More specifically, during fasting state, there is a predominant (90%) utilization of free fatty acids (FFAs) and to a much lesser extent glucose and lactate.[1] In contrast, post-meal and in cases of ischemic/viable or dysfunctional myocardium, energy consumption is primarily dependent on glucose utilization.[2] Therefore, suppression of physiologic myocardial glucose metabolism and augmentation of FFA utilization are *sine qua non* in obtaining high-quality FDG-PET images of myocardial inflammatory disorders.

To this extent, a variety of different interventions have been explored, and they can be broadly categorized into dietary and pharmacologic manipulations. The dietary ones include ingestion of a high fat-low (less than 5 g) or even no carbohydrate diet, consumption of a drink rich in FFAs (in addition to the aforementioned diet) just prior to FDG administration and in some cases strict fasting for 4 to 18 hours. The pharmacologic interventions are based on (a) stimulation of lipolysis via injection of intravenous unfractionated heparin (UFH), which can result in up to fivefold increase in the levels of FFAs[3] and (b) decrease in myocardial uptake of FDG by administration of calcium channel blockers.[4,5] In addition, patients are also instructed to avoid strenuous physical activity 12 to 24 hours prior the study, so as to inhibit catecholamine surge and resulting increase in glucose uptake and utilization by skeletal muscle.[6] A list of the different types of interventions and their respective effects in myocardial substrate utilization is shown in Table 1.

In the current issue of Journal of Nuclear Cardiology, Giorgetti et al. conducted a retrospective study to explore whether anticoagulants other than UFH, namely lower molecular weight heparin (LMWH) and warfarin, could also suppress physiologic myocardial glucose utilization.[7] They studied a cohort of patients without evidence and history of cardiac diseases, who were already on LMWH or warfarin as treatment for other comorbidities, and who were also asked to fast for at least 12 hours prior to the study.[7] Patients were divided

Reprint requests: Pradeep Bhambhvani, MD, Division of Molecular Imaging and Therapeutics, Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL; *pbhambhvani@uabmc.edu*
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Table 1. Dietary and pharmacologic interventions and their effects to optimize cardiomyocyte FDG uptake

Intervention	Effect
High fat-low (or no) carbohydrate diet	Stimulate lipolysis, increase blood FFAs, and diminish insulin and glucose levels
Consumption of a high-fat drink prior to FDG injection in addition to high fat-low (or no) carbohydrate diet	Further increase FFA levels
Strict fasting for 4 to 18 hours	Minimize insulin and glucose and increase FFAs
Avoidance of strenuous activity prior to FDG injection	Attenuate catecholamine-induced glucose uptake and oxidative metabolism by skeletal muscle
Unfractionated heparin (UFH)	Increase lipolysis and blood FFAs
Calcium channel blockers	Decrease myocardial FDG uptake

into two groups: those who fasted but were not receiving any anticoagulation vs those who fasted and continued taking their outpatient regimen of either LMWH or warfarin.[7] The investigators found that a significant proportion of patients who were on LMWH or warfarin exhibited optimal suppression of 18F-FDG myocardial uptake (combined: 78%; LMWH: 78%; warfarin: 77%) vs only 13% of those who did not receive any anticoagulants ($P < 0.001$).[7] This is the first study showing that a combination of fasting along with chronic anticoagulation, other than UFH, can provide optimal quality FDG-PET images in a vast majority of patients.[7] Their observations potentially expand the pharmacologic options that can be utilized to improve quality and diagnostic yield of FDG-PET myocardial imaging and promote patient safety, since patients already on LMWH and warfarin should not need an additional dose of UFH, with its potential increased risk of bleeding.

Currently, no consensus exists as to the single most efficacious preparation strategy for patients undergoing FDG-PET imaging of myocardial inflammation. The guidelines set forth in 2016 by SNMMI/ASNC/SCCT recommend a choice of one or more interventions including fasting for 12 to 18 hours or a high fat/low carbohydrate diet for 2 meals followed by an overnight fast with or without IV UFH.[8] A number of studies that have been carried out either compared different methods of patient preparation—mostly dietary and to a lesser extent pharmacologic—[5,9–20] or report suppression rates of a single protocol in patients under evaluation for cardiac sarcoidosis [21,22] or undergoing imaging of vulnerable coronary plaques.[23] Only three of them are randomized,[5,10,15] and small to moderate in size (N range 36 to 153), while the remainder are non-randomized.

Tang et al. carried out a meta-analysis of patients undergoing FDG-PET for cardiac sarcoidosis and aimed at assessing the impact of different patient preparations on the sensitivity and specificity of FDG-PET.[25] A total of 16 studies and 559 patients were included in the final analysis, which showed that intravenous heparin and duration of fasting were positively associated with the diagnostic odds ratio (coefficient, 2.90; $P = 0.04$ and coefficient, 0.282; $P = 0.01$ respectively), as opposed to a high fat-low carb dietary preparation (coefficient, 1.71; $P = 0.17$).[25] Despite its thought-provoking findings, the meta-analysis did have some noteworthy limitations. First, it only included studies assessing patients with suspected or known sarcoidosis; second, the lack of a diagnostic reference standard for cardiac sarcoidosis makes the findings on sensitivity and specificity of FDG-PET somewhat challenging to interpret; and third, the majority of the studies included were small and the preparation methods employed were widely variable.[24,25]

In a comprehensive review of the literature, including the vast majority of the aforementioned studies,[5,9–19,21–23,25] Osborne et al. concluded that the optimal dietary preparation would be ingestion of one or two high fat-no carbohydrate meals followed by a fast of at least 4 hours in duration (longer fasting does, however, seem to be associated with better results).[24] This practice had an 85% to 90% rate of efficacious glucose suppression in most of the studies.[24] An alternative approach would be a combination of high fat-low carbohydrate diet (one meal) followed by fasting and intravenous UFH just prior to FDG injection, which was shown to correlate with a success rate of 88% to 100% in two studies.[18,19,24] On the other hand, strategies which were not shown to correlate with high-quality FDG-PET imaging were fasting of short duration devoid of any dietary preparation, administration of a high-fat drink closely prior to the exam, and addition of calcium channel blocker, namely verapamil.[24]

The study by Giorgetti et al. in the current issue of the journal references prior studies that show improved

myocardial glucose uptake suppression with dietary restriction in addition to prolonged fasting.[7,12,19] The investigators also provide further insight into the effect of pharmacologic interventions showing that anticoagulants other than the traditionally used UFH, i.e., LMWH and warfarin are also associated with satisfactory cardiomyocyte FDG suppression and optimal image quality in a significant majority of patients.[7] There are, however, certain limitations worth noting. First, its retrospective design and the fact that additional important information that could have shed some more light into the effect of LMWH and warfarin was unavailable. For example, it would have been helpful to have data on the levels of plasma FFAs, insulin, and C-peptide levels, especially since warfarin is thought to have an antilipolytic effect and would not have been expected to correlate with high-quality FDG-PET images. Moreover, data on suppression rates with use of UFH and comparing them to the LMWH and warfarin groups would have added to the diagnostic efficacy of LMWH and warfarin was not in the study design. In addition, as the authors themselves state, there was a noteworthy failure rate (suboptimal myocardial FDG suppression) of 22% in patients on LMWH or warfarin should be taken into account when planning patient preparation protocol.[7] Finally, this was a study performed on patients without any evidence of cardiac disease. It would have been interesting to examine these interventions in a more heterogeneous population, such as patients with and without myocardial inflammation.

The ideal preparation method for FDG-PET imaging would result in 100% suppression of physiological 18F-FDG myocardial uptake. So far, no single protocol has shown a definitive and significant superiority compared to others, and different centers follow different strategies. Osborne et al rightfully point to the possibility of incomplete suppression of physiologic myocardial glucose uptake in a small proportion of studies despite all interventions.[24] Thus, it is essential for each institution to continuously review the adequacy of physiological myocardial FDG uptake suppression and adjust accordingly to improve quality of FDG-PET imaging. In addition to development of alternate and more specific inflammation imaging radiotracers, more research is needed to further optimize the diagnostic yield of FDG-PET in myocardial inflammation. To name a few:

(a) Larger randomized studies comparing different approaches, not just dietary but also combined with pharmacologic interventions, as evidenced by the number of questions arising from the current study.
(b) A reference standard for sensitivity and specificity of FDG-PET scans needs to be defined, and to achieve this, different patient populations need to be studied, e.g., patients with inflammatory cardiomyopathies other than just sarcoidosis, infections of intracardiac devices and prosthetic heart valves and patients evaluated for the presence of vulnerable coronary plaque.
(c) There needs to be a consensus on the definition of adequacy of myocardial FDG suppression, as opposed to each study using differing definitions, which rarely is ''complete suppression'' of FDG uptake.
(d) Regarding pharmacologic interventions to optimize suppression, several questions remain unanswered:

1. What is the optimal dose of UFH to achieve adequate suppression? The published studies with UFH that were successful in suppressing myocardial FDG uptake have been carried out at higher anticoagulant doses, i.e., 50 U kg^{-1} intravenously.[16,18,19] Are lower and potentially safer UFH doses (for example 5 to 10 U U kg^{-1}) as effective?
2. Given the somewhat improved risk profile of LMWH compared to UFH,[26] what is the effectiveness of a single dose of LMWH compared to UFH? Also what should be the optimal dose, route of injection and timing before FDG injection?
3. How to approach patients that may be on novel oral anticoagulants, such as dabigatran, apixaban, and rivaroxaban?
4. Finally, when comparing all the different dietary and pharmacologic interventions available, it would be of particular clinical importance for future studies to start including patient adherence to and preference of different protocols in their outcomes.

Clearly, there is a lot more to learn.

Disclosure

The authors have no conflicts of interest to disclose. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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