Continuing evolution in preparation protocols for ^{18}F FDG PET assessment of inflammatory or malignant myocardial disease

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Fluorine-18 fluorodeoxyglucose (^{18}F FDG) positron emission tomography (PET) imaging is growing as a standard diagnostic tool in patients with cardiac sarcoidosis (CS)¹ and is an emerging imaging modality in other challenging patient populations including those with myocarditis,² neoplastic cardiac disease,³ and cardiac allograft rejection.⁴ Ultimately, widespread implementation and clinical utilization of ^{18}F FDG PET imaging for these indications is predicated upon both optimization and standardization of patient preparation protocols.⁵ As a result, ^{18}F FDG PET protocol optimization has been an active area of research, with recent publications in *the Journal of Nuclear Cardiology* focusing on preparations to suppress physiologic myocardial glucose uptake. In a recent publication in the journal, Manabe et al.⁶ assessed combined prolonged fasting, low-carbohydrate diet, and heparin administration, whereas in the current issue of the journal, Nensa and colleagues examined the efficacy of a ≥ 24 -hour high-fat, low-carbohydrate, protein-permitted (HFLCPP) diet combined with heparin administration.

The objective of patient preparation protocols in inflammatory cardiac conditions is the suppression of physiologic myocardial ^{18}F FDG uptake, thereby allowing detection of ^{18}F FDG in pathologic tissue.⁷ In the physiologic postprandial state, heightened serum insulin levels stimulate glucose transport 1 and 2 (GLUT 1 and

2) which consequently enhance myocyte glucose importation.⁸ As a result, diffuse myocardial ^{18}F FDG PET uptake after a meal is likely a physiologic response and a nonpathologic finding.⁹ At the same time, inflamed myocardial tissue may also demonstrate enhanced glucose uptake¹⁰ and thus may be indistinguishable from healthy myocytes in a patient who has recently ingested a carbohydrate-rich meal. Proposed means by which to suppress physiologic myocardial glucose uptake include (1) prolonged fasting, (2) low-carbohydrate diet (LCD) with or without high fat,¹¹ and/or (3) the use of intravenous unfractionated heparin (UFH) to increase free fatty acid (FFA) levels via lipolytic activity.¹² Contemporary areas of investigation have focused on potential combinations of these preparation protocols. In this issue of the journal, Nensa and colleagues evaluate the efficacy of a ≥ 24 -hour HFLCPP diet accompanied by administration of UFH for suppression of physiologic myocardial glucose uptake in 89 consecutive patients suspected to have either myocarditis, cardiac tumors, sarcoidosis, or cardiac allograft rejection. Each patient was provided with instructions outlining the appropriate diet, and received UFH shortly before undergoing ^{18}F FDG PET magnetic resonance imaging (MRI). Each study was subsequently evaluated both qualitatively and quantitatively for assessment of sufficient suppression of physiologic myocardial uptake with the authors reporting an 84% success rate.

Nensa and colleagues are commended on several aspects of their work. First, their diligence in creating a patient “menu” for each study participant is a critical first step toward ensuring compliance to the recommended diet and standardization. Second, the authors utilized quantitative assessment of ^{18}F FDG uptake by calculating standard uptake value. In the CS population, use of quantitative ^{18}F FDG PET improves specificity from 46% to 97% without diminishing test sensitivity.¹³ Third, Nensa et al. employed hybrid imaging by

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coupling PET and MRI, thereby allowing the simultaneous coregistration of metabolic/molecular probe imaging provided by PET with the morphologic, functional, and tissue imaging gained by MRI. This is the largest study of CS patients (12 out of the 89 total cohort) that the authors are aware of which uses hybrid PET/MRI technology.

The current investigation also highlights several challenges inherent to studying optimal ^{18}F FDG PET patient preparation protocols for inflammatory cardiac conditions. First, the patient group studied was markedly heterogeneous in nature including those with suspected CS, myocarditis, cardiac neoplasms, and transplant rejection. While ^{18}F FDG PET could potentially benefit each of these patient groups, it has only been extensively studied in the CS patient population to the degree in which it has been incorporated into recent diagnostic guidelines.¹ Furthermore, it is unclear from this study what diagnostic “gold-standard” was utilized to confirm the varied diagnoses in each patient subgroup. Moreover, as recognized by the authors as a limitation, a control group could have been employed to compare efficacy of the current preparation protocol. The initial demonstration of the efficacy of this protocol in suppressing physiologic ^{18}F FDG uptake in a healthy patient population prior to introducing the potential confounding of diseased tissue would have been ideal.

An initial step in determining the efficacy of any patient preparation protocol involving dietary manipulation is verifying compliance. Dietary manipulations are particularly challenging in this regard as they generally lack standardization and often pose confusion to the patient. While Nensa and colleagues are commended for providing specific dietary instructions to patients undergoing ^{18}F FDG PET imaging, their diet includes meat and pork, and may not be followed by patients unable to consume these ingredients, which could reduce compliance and pose challenges for widespread applicability of their approach. Furthermore, actual compliance to this diet was self-reported by patients with the potential that some patients may knowingly or unknowingly misreport compliance with the protocol. Thus, this first step of verifying compliance in this study may be suboptimal. On the other hand, their study probably reflects real-life clinical practice whereby specific dietary preparations are required prior to testing and raises the issue of whether prolonged fasting may be simpler and equally, or perhaps even more effective, both in compliance and myocardial glucose suppression, than a HFLCPP diet. Certainly, fasting poses neither patient confusion nor issues related to ingredients that might affect patient compliance to specific diets. Based on published literature, the efficacy of prolonged fasting protocols is reported to be in the range of 62%-90%.¹⁴⁻¹⁷

Thus, comparison of the HFLCPP diet to fasting is an important step that was not addressed by Nensa and colleagues. On the other hand, criticisms of prolonged fasting protocols also include patient compliance^{18,19} and potential harm from hypoglycemia.⁶ Nevertheless, future studies of dietary preparations should include a cohort of patients undergoing prolonged fasting.

The specific protocol supplied by Nensa et al., although termed an HFLCPP diet, permits up to 20 grams of carbohydrates in the form of vegetables, is another variant of the HFLCPP diet, and raises an important issue regarding standardization of these patient preparation protocols within and across institutions. This is an important step for the nuclear cardiology community to address in order to provide further standardization and greater use of ^{18}F FDG PET for inflammatory conditions and has significant implications on test interpretation. Currently lacking are specific guidelines on the exact amount of fat, carbohydrates, and protein, along with the impact of the diabetes mellitus, serum blood glucose and FFA levels, and steroid therapy. These are some important issues not addressed in the study by Nensa and colleagues.

The current work by Nensa et al. also employs the use of intravenous UFH (50 IU/Kg) which is administered 15 minutes prior to the patients receiving ^{18}F FDG. Cardiac myocytes may utilize various sources of potential fuel sources such as FFA, glucose, or ketones.²⁰ Various physiologic factors including myocardial blood flow, serum availability of various potential metabolic substrates, and insulin concentration influence which fuel source is preferentially chosen.²¹ UFH increases the serum availability of FFA via stimulation of lipoprotein lipase resulting in increased lipolytic activity.²² Prior ^{18}F FDG optimization protocols have demonstrated that administration of UFH does indeed increase FFA levels.^{15,23} However, the resulting effectiveness in suppressing physiologic myocardial uptake remains unclear based on conflicting reports in the literature suggesting either beneficial suppression of ^{18}F FDG uptake¹⁴ or on the contrary no evidence of benefit.^{15,16,23} In the current study by Nensa and colleagues, there is not a control group which did not receive UFH to allow a direct comparison. However, as noted by the authors, the reported success rate of their protocol (HFLCPP + UFH) was similar to a prior study that used HFLCPP without UFH suggesting that UFH did not add additional benefit. While further studies are needed to clarify this issue, evidence appears to be mounting that UFH may not be as useful an adjunct in ^{18}F FDG preparation protocols as previously thought.

It is also important to critically appraise the definition of successful suppression of physiologic myocardial ^{18}F FDG uptake with the various protocols to

date. Nensa and colleagues defined success as “homogenous suppression of myocardial ^{18}F FDG below liver uptake with or without focal ^{18}F FDG uptake.” While this definition aligns with the recommendations of the Japanese Society of Nuclear Cardiology, recent investigations have demonstrated the ability to completely suppress ^{18}F FDG myocardial uptake.⁶ Ultimately, suppressing ^{18}F FDG uptake to the greatest extent possible, potentially to below the level of the blood pool, rather than just below hepatic uptake, should be the objective. Achieving complete or near-complete suppression of ^{18}F FDG would likely improve inter-observer variability and enhance both the reproducibility and clinical utility of ^{18}F FDG PET for assessing cardiac inflammation. In the study by Nensa and colleagues, failure of myocardial suppression was recorded if ^{18}F FDG uptake was noted in the lateral wall or the entire base of the heart without collaborating MRI abnormalities such as delayed enhancement, edema, or wall motion abnormalities. While a major strength of hybrid imaging is the simultaneous comparison of corresponding pathologic findings between two modalities, in this case, PET and MRI, the use of this hybrid approach for identification of the various cardiac conditions in this cohort has not been systematically studied. Specifically, prior studies of quantitative ^{18}F FDG PET in CS detection have demonstrated a sensitivity of nearly 90%²⁴ and a specificity of 97%.¹³ In contrast, the reported sensitivity and specificity of cardiac MRI in CS detection is 75%.²⁵ Therefore, some of the patients in Nensa’s study who were defined as having failed myocardial suppression due to contradictory MRI findings may indeed have had true pathologic disease accounting for ^{18}F FDG uptake. Furthermore, this investigation designated diffuse uptake of myocardial ^{18}F FDG as a failure of adequate suppression. While we expect focal uptake in the CS population, the current study included patients with myocarditis who indeed may have had true diffuse disease resulting in more homogenous ^{18}F FDG uptake, in which case, underestimation of the true success rate of myocardial suppression could have occurred. Furthermore, the authors report a successful ^{18}F FDG myocardial suppression rate of 84% (75/89). However, if the six patients who were excluded from the final study analysis due to deviation from preparation protocol in addition to the two patients who could have been excluded due to inability to undergo MRI, then success rate drops to 77% (75/97). This brings the success rate of this protocol in suppressing myocardial physiologic myocardial glucose uptake perhaps closer to that of the fasting protocol. Another potential limitation in assessing successful suppression in the study by Nensa and colleagues relates to the use of PET/MRI. The development of practical and effective methodology to remove the adverse effects

of cardiac and respiratory motion on PET image quality and quantitation in PET/MR imaging is a subject of intense investigation but is not yet consistently successful. This factor could lead to errors in image interpretation and misclassification of suppression failure vs success.

The need for ongoing research into patient preparation optimization prior to PET imaging for cardiac inflammatory conditions is essential. Specifically, means by which to ensure patient compliance to preparation protocols, comparison of fasting vs different dietary recommendations, challenging the theoretical benefit of UFH, and ensuring both qualitative and quantitative assessment of physiologic ^{18}F FDG suppression are crucial to achieving the objective of creating a standardized preparation protocol that can be utilized across institutions ultimately promoting greater utility of ^{18}F FDG PET imaging for more novel indications.

Disclosures

The authors have nothing to disclose.

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