Opening the door to noninvasive assessment of cardiac transplant rejection: It's all in the preparation

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INTRODUCTION

The evaluation of cardiac inflammatory conditions can be undertaken with several noninvasive imaging modalities, including Fluorine-18 fluorodeoxyglucose (¹⁸FDG) positron imaging (PET). ¹⁸FDG-PET is a well-established and sensitive imaging modality for the evaluation of inflammatory conditions such as cardiac sarcoidosis and neoplastic disorders. It is now emerging as a potential method for the evaluation of cardiac allograft rejection in cardiac transplant recipients.¹ There are many challenges encountered with ¹⁸FDG-PET imaging, one of which includes the implementation of preparation protocols to differentiate the identification of pathological inflammation within cardiac tissue from physiological uptake. While several preparation protocols have been proposed and are now included in widely used guidelines, the effectiveness of these strategies for detecting cellular rejection within transplanted hearts remains largely untested and is a novel use for this imaging modality. The key to adequate image quality still remains the ability to distinguish physiological myocardial uptake from inflammation-

related ¹⁸FDG uptake, and the preparation protocols are a key factor in determining this.²

In this issue of the *Journal of Nuclear Cardiology*, Felix et al aimed to elucidate the effectiveness of three types of pre-¹⁸FDG-PET preparation protocols in cardiac transplant recipients in the detection of cellular rejection.³ The key to an effective preparation protocol is finding a method to optimally suppress physiological myocardial ¹⁸FDG uptake in order to allow ¹⁸FDG detection in pathological myocardium.⁴

THE ROLE OF PREPARATION PRIOR TO PET IMAGING

The underlying mechanism of pre-PET preparations is to suppress physiological myocardial glucose uptake, usually via high-fat, low-carbohydrate diets, such that if there is glucose uptake, the ¹⁸FDG then acts as a surrogate marker for pathological metabolism.⁵ Apart from glucose utilization by myocardium as fuel, other metabolic factors also play a role, including myocardial blood flow, insulin concentrations, and serum availability of metabolic substrate. These pathways of energy utilization are less well characterized and thus are not incorporated into standard imaging preparation protocols.⁶ Optimizing protocols has resulted in several studies with the aim of producing the best preparation possible for physiological suppression of cardiac glucose and therefore FDG uptake. The ideal preparation will completely suppress cardiac uptake in the normal heart, both transplanted and nontransplanted (see Figures 1 and 2).

The use of ¹⁸FDG-PET in the diagnosis, prognosis, and therapeutic monitoring of inflammatory conditions such as sarcoidosis is well established.^{5,7} Various

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Figure 1. Cross section of the heart (nontransplanted) using ^{18}F FDG-PET/CT demonstrating appropriate physiological FDG cardiac suppression following the administration of a high-fat, low-carbohydrate preparation protocol in a noncardiac transplant patient.

Figure 2. Coronal section of a noncardiac transplant patient undergoing ^{18}F FDG-PET/CT with adequate suppression of myocardial FDG uptake with the same preparation protocol as Fig. 1. Note the homogeneous physiological FDG uptake in the liver compared to the heart, which demonstrates suppressed uptake.

preparation protocols have been described: one such method is a high-fat, low-carbohydrate diet with prolonged fasting to identify FDG uptake in myocardial granulomas given that inflammatory cells tend to have high glycolytic activity.⁸ The current American society of Nuclear Cardiology (ASNC) guideline outline three preparations for suppressing physiological myocardial FDG uptake and enhancing image quality of inflammatory disorders. These preparations include (1) fat enriched diet, low in carbohydrates 12-24 hours prior to the scan (2) a 12-18 hours fast, and (3) a fast with or without the use of intravenous heparin.⁹ The role of heparin lies in its ability to activate lipoprotein lipase which leads to an increase in the supply of fatty acids.¹⁰ ^{18}F FDG PET images are subsequently interpreted using a variety of methods, including visual review of the ^{18}F FDG images, a semiquantitative scale and standardized uptake values (SUVs).

PET AND THE POST-TRANSPLANT POPULATION

The role of ^{18}F FDG-PET is less well characterized in the postcardiac transplant population. Its potential roles include the detection of extra-cardiac malignancy, infection, and less commonly cellular rejection in this specialized patient cohort. Early studies by Rechavia et al established in a relatively small cohort of patients, the homogeneous increase in ^{18}F FDG uptake in rejecting transplanted hearts,¹¹ opening the door for the institution of protocols to suppress physiological cardiac ^{18}F FDG uptake in order to accurately observe rejection using this imaging modality.¹¹ The use of ^{18}F FDG for the diagnosis and monitoring of cardiac transplant is certainly novel. Currently, evidence of its efficacy is scarce within the literature, and the study by Daly et al has managed to use this as a viable imaging option in murine models.¹² A recent study by Nensa et al evaluated the efficacy of > 24 hours high lipid, diet with prolonged fast and a heparin preparation in a population of patients suspected to have myocarditis, cardiac neoplasms, sarcoidosis, and cardiac allograft rejection. Nensa and colleagues cast the net wide, observing a wide range of cardiac inflammatory conditions; the overall result being that of sufficient myocardial ^{18}F FDG uptake suppression with the use of this strict protocol.¹³ It should be noted that this study only included four patients with suspected myocardial transplant rejection, thus opening the door further for assessment of this technique in a larger patient population.

Felix et al's 3-year prospective study³ compared the effectiveness of three preparations in suppressing physiological myocardial ^{18}F FDG uptakes in all 10 cardiac

transplant recipients, with each patient having three studies over 12 months and receiving the preparation choice in random order. The preparations included (1) high-fat, low-carbohydrate diet (2) prolonged fasting (> 12 hours), and (3) low-carbohydrate diet with intravenous heparin. This study also involved the cohort of patients undergoing routine endomyocardial biopsies with microscopic investigation for cellular rejection. The effect of myocardial ^{18}F FDG suppression was assessed using visual scores determined by two blinded investigators and consisted of both a 'semiquantitative' visual analysis score (SVAS), with and without CT attenuation correction, and a 'qualitative' visual analysis score (QVAS). The eventual conclusion from this study was that two of the preparations adequately suppressed physiological myocardial ^{18}F FDG uptake, specifically (1) a high-fat, low-carbohydrate diet and (2) prolonged fasting (> 12 hours). A low-carbohydrate diet along with heparin was deemed to be least effective, although not statistically significant, possibly related to low patient numbers. Interestingly, all patients had either low-grade or absent amounts of inflammation when cellular rejection was classified at the microscopic level. Hence, no conclusion can be made from their study to correlate uptake with the severity of rejection. The degree of inflammation observed in these patients will also be influenced by external factors such as level of immunosuppression. The use of a sensitive imaging modality to diagnose cardiac transplant rejection noninvasively certainly warrants further investigation. The use of endomyocardial biopsies, despite being the gold standard investigation, has issues with sampling error, interobserver variability,¹² and, of course, being invasive in nature.

The authors themselves acknowledge the limitations. Given the small sample size it was not technically feasible to have a control group, who had no preparation. Also, the use of a nondedicated PET camera likely hindered the resolution of the images interpreted by the two evaluators and the visual scores subsequently derived from this. The majority of the patients also had absent or minimal cellular rejection on microscopy (66% and 34%, respectively). The lack of microscopically significant rejection allows no conclusions to be drawn in ^{18}F FDG-PET imaging identifying any patient with significant rejection.

This aside, the team should be commended for opening the door for the noninvasive assessment of transplant rejection in a clinical heterogeneous group of patients. This not only potentially serves as a way of reducing the morbidity, mortality, and healthcare costs associated with invasive monitoring for myocardial rejection, but also forms a framework for potentially modifying immunosuppressive treatment in light of

results obtained from this imaging modality. What is clear so far is that a 'gold-standard' preparation prior to ^{18}F FDG-PET is yet to emerge, which suppresses completely physiological myocardial ^{18}F FDG uptake, with minimal artifact and maximum sensitivity.

CONCLUSION

The use of ^{18}F FDG-PET in cardiac transplant recipients remains uncharted territory. Increasing the sensitivity and specificity of ^{18}F FDG-PET for the detection of cardiac inflammatory conditions are reliant on preparation protocols and adequate patient adherence to those protocols. Felix et al³ have demonstrated in their small trial that the use of ^{18}F FDG-PET is potentially a feasible monitoring modality in cardiac transplant recipients. We look forward to emerging trials to evaluate further assessment of patient preparation protocols in cardiac transplant recipients with varying degrees of rejection. The door has now been opened!

Disclosure

The authors have no relevant disclosures.

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