^{18}F-FSPG PET/MRI or PET/CT Imaging of Cardiac Sarcoidosis or Inflammation

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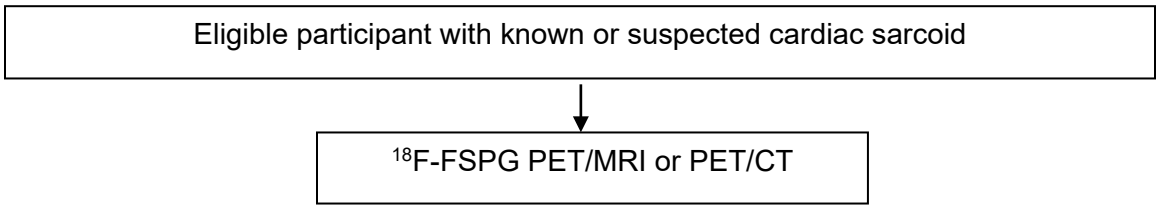
TITLE	^{18}F-FSPG PET/MRI or PET/CT Imaging of Cardiac Sarcoidosis or Inflammation
STUDY PHASE	2
INDICATION	Suspected cardiac sarcoid
INVESTIGATIONAL PRODUCT OR PROCEDURE	^{18}F-FSPG
PRIMARY OBJECTIVE(S)	To evaluate if ^{18}F-FSPG PET/MRI or PET/CT will identify cardiac sarcoid
SAMPLE SIZE	20
GOALS	To allow the referring physicians in the cardiology group to provide their patients a specific molecular imaging test for sarcoidosis. To improve the PET/MRI or PET/CT protocol.

SCHEMA


Eligible participant with known or suspected cardiac sarcoid
^{18}F-FSPG PET/MRI or PET/CT

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

F-18	Fluorine-18
IRB	Institutional Review Board
IV	Intravenous
PET/MRI	Positron emission tomography – magnetic resonance imaging
SUV	Standardized Uptake Value
FSPG	(4S)-4-(3-18F-Fluoropropyl)-L-Glutamate

1. OBJECTIVE

We hypothesize that increased ^{18}F-FSPG uptake will be detected in cardiac sarcoid or inflammation using PET/MRI or PET/CT.

2. BACKGROUND

2.1. Study Disease

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, which can result in myocardial inflammation [1]. Myocardial inflammation can also result from other causes including myocarditis. Identifying cardiac involvement in the setting of sarcoidosis or myocarditis remains challenging. Approximately 5% of patients with sarcoidosis have clinically apparent cardiac involvement, yet autopsy series indicate that cardiac involvement is present in up to 25% of cases [1]. The diagnostic yield of endomyocardial biopsy is reported at less than 20% [2].

Previous studies have demonstrated high diagnostic accuracy of both cardiac magnetic resonance imaging (MRI) [3-5] and 18F-labelled fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) [6, 7] for detection of cardiac sarcoidosis and myocardial inflammation. To date, simultaneous PET/MRI evaluation of cardiac sarcoidosis has only been described in limited case reports [8]. Despite relative success, patient compliance is affected by the need for 12 hours low-carb diet prior to the scan [9]. Therefore, other radiopharmaceuticals should be investigated.

System xC- is composed of xCT and 4F2hc, mediating cellular cystine uptake for glutathione synthesis to protect cells from oxidative stress [10]. System xC- may play a role in the innate and adaptive immune system. Upregulation of system xC- expression was observed in activated macrophages and granulocytes [11]. Induction of system xC-may be an autoprotective mechanism from the high levels of released reactive oxygen species. Activation of T-lymphocytes has been reported to involve expression of system xC- in antigen-presenting cells [12]. Upregulation of xCT occurs during activation and differentiation of B lymphocyte. On the other hand, very low or no expression of xCT was detected in peripheral leukocytes, thymus, spleen, and lymph nodes in humans [13]. These results suggest that system xC-is a key player in the active phase of inflammation.

(4S)-4-(3-18F-Fluoropropyl)-L-Glutamate (18F FSPG) is a L-glutamate derivative that is specifically taken up by system xC- as previously demonstrated in tumor models and cancer patients [14, 15]. 18F FSPG has also demonstrated increased uptake in inflammation and infection [16]. PET imaging with 18F FSPG does not require a diet or special preparation prior to the scan; hence, we expect increased patient compliance when compared to 18F FDG in the evaluation of cardiac sarcoidosis or inflammation.

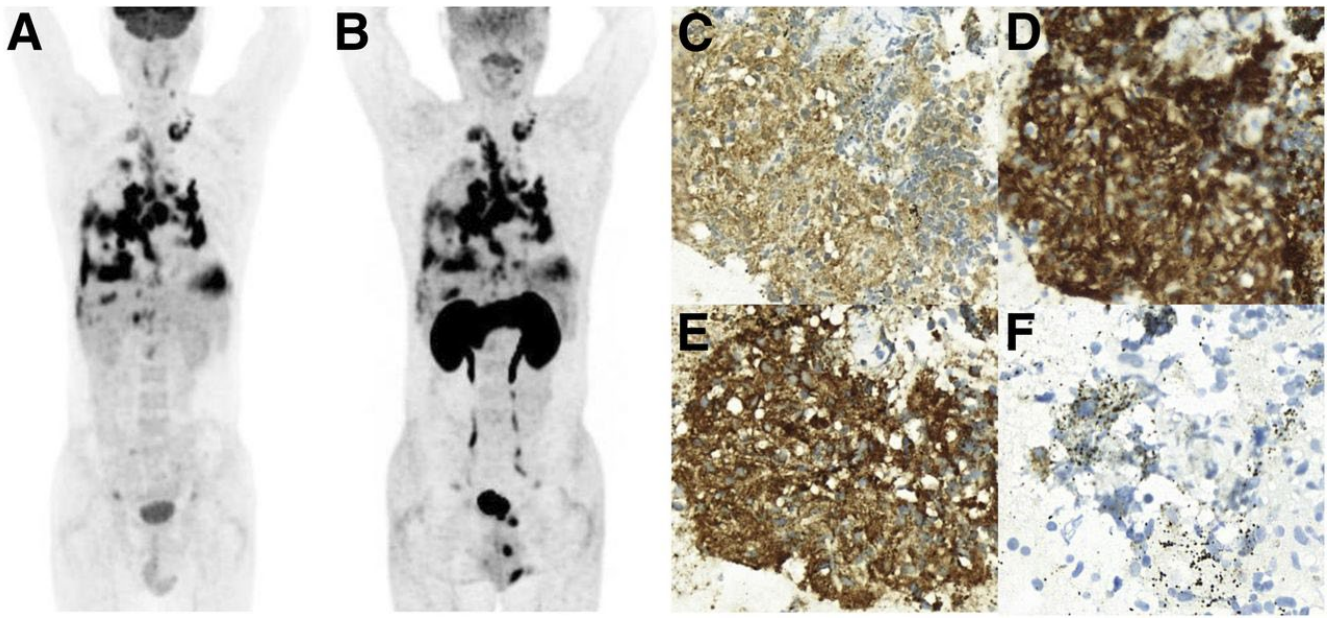


Figure 1. 53 year old man with sarcoidosis: 18F-FDG (A) and 18F-FSPG (B) present similar major uptake involving pleura, supraclavicular lymph nodes, and thoracic lymph nodes. Sun Young Chae et al. J Nucl Med 2016;57:67-69.

2.2. Study Agent/Device/Imaging procedure

^{18}F-FSPG PET/MRI or PET/CT Imaging of Cardiac Sarcoidosis or Inflammation

Methods: Here we will evaluate the detection of cardiac sarcoidosis or inflammation using ^{18}F-FSPG PET/MRI or PET/CT. PET/CT will be used for patients with metal implants who are not eligible for MRI due to safety reasons. We will recruit patients from Division of Cardiology (Sarcoidosis Clinic) at Stanford University. We plan to recruit a total of 50 patients over 4 years who have suspected cardiac sarcoidosis or inflammation, after receiving ^{18}F FDG PET/CT as standard of care. Potential subjects will undergo preliminary evaluation to ensure eligibility, receive and sign an informed consent and be enrolled in the trial.

PET/MRI scans will be performed with a whole-body PET/MR imaging system capable of simultaneous PET and MR imaging (SIGNA, GE Healthcare, Milwaukee, WI), 45-60 minutes after injection of (+/-20%) 8 mCi of ^{18}F-FSPG. The system consists of a 3T MR imager that contains a PET detector based on lutetium oxyorthosilicate scintillators coupled to silicon photomultiplier detector (SiPM) technology. PET events will be detected throughout the entire cardiac MRI acquisition in one bed position centered over the heart. A coronal T1-weighted 3D encoded spoiled gradient-echo sequence will be acquired for attenuation correction.

Cardiac MRI sequences will include breath-hold, ECG-triggered balanced cine SSFP for assessment of ventricular size and function by a stack of short axis slices (slice thickness 8 mm, TR 3.0 ms, TE 1.5 ms, flip angle 50°, temporal resolution 35 ms; in-plane resolution 1.7×1.4 mm), and two-dimensional (2D) turbo inversion-recovery magnitude T2-weighted imaging in short axis for assessment of myocardial inflammation and edema (slice thickness 8 mm, TR 2000 ms, TE 44 ms, flip angle 180°, inversion time 180 ms, in-plane resolution 1.3×1.4 mm). Late gadolinium enhanced (LGE) imaging will be performed 15 minutes following administration

of 0.15 mmol/kg bodyweight of MultiHance (Bracco Diagnostics Inc, Monroe Township, NJ) employing a 2D inversion recovery gradient-recalled echo sequence (IR GRE) in short-axis (slice thickness 8 mm, TR 6.5 ms, TE 1.5 ms; flip angle 20°; inversion times 220-360 ms; in-plane resolution 1.8×1.4 mm). Two-, three- and four-chamber LGE planes will also be obtained.

PET/CT will be performed using Discovery MI PET/CT scanner (GE Healthcare). In brief, PET/CT images will be acquired in 3D mode approximately 45-60 minutes after injection of ^{18}F FSPG. First, a vertex to mid-thighs scan is done, followed by dedicated imaging of the heart over 1 bed. ToF is standard on the digital PET/CT system. Data driven gating will be acquired according to the vendor's protocol (once commercially available). The PET emission scan is corrected using segmented attenuation data of the CT scan. The PET images are reconstructed both with a standard iterative algorithm (OSEM, two iterative steps, 28 subsets), as well as a regularized reconstruction algorithm (Q.Clear®) provided by GE Healthcare.

Interpretation of Results: All images are reformatted into axial, coronal, and sagittal views and viewed with the software available in the Nuclear Medicine and Molecular Imaging Clinic (MIM Vista). PET images will be interpreted by two radiologists in consensus (A.I. and G.D.). A third reader (C.M.) will serve as referee to achieve consensus.

PET image interpretation will begin with identification of areas of myocardial ^{18}F-FSPG uptake on PET/MRI images using multi-planar reformations and maximum-intensity projections. Myocardial ^{18}F-FSPG uptake will be globally classified into one of four patterns (none, diffuse, focal, or focal on diffuse) for each participant. Diffuse, focal and focal on diffuse patterns of ^{18}F-FSPG uptake will be considered to be positive findings indicative of cardiac involvement. Myocardial segments will be evaluated for focal ^{18}F-FSPG activity using the 17-segment model recommended by the American Heart Association (AHA). The presence or absence of RV free wall ^{18}F-FSPG activity will also be evaluated. The whole-body PET/MRI or PET/CT acquisition will be evaluated for findings of extra-cardiac sarcoid.

For cardiac MRI analysis, left and right ventricular (LV and RV) endocardial borders will be manually contoured on short-axis SSFP images to assess for end-diastolic and end-systolic volumes, and ejection fraction (EF). LV epicardial borders will also be manually contoured to assess LV mass. Presence of T2-hyperintensity and LGE will be qualitatively assessed by visual inspection of all available images and will be graded as present or absent using the AHA 17-segment model. The pattern of LGE will be classified as either CAD type or non-CAD type as described previously [17]. The presence or absence of RV free wall LGE was also evaluated.

2.3. Clinicaltrials.gov

The study is registered at ClinicalTrials.gov (NCT03103490).

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1. Inclusion Criteria

• Patient is ≥ 18 years old at the time of the scan
• Patient with known or suspected cardiac sarcoidosis referred for standard of care ^{18}F FDG PET/CT

• Patient is capable of complying with study procedures
• Patient can remain still for duration of imaging procedure

3.2. Exclusion Criteria

• Patient is pregnant or nursing
• Metallic implants (contraindicated for MRI; these patients will get PET/CT)
• History of renal insufficiency (only for MRI contrast administration)

4. STUDY PROCEDURE:

Patients will be injected with ^{18}F-FSPG and undergo the PET/MRI or PET/CT image acquisition after a 45-60 minute delay.

PET/MRI

First, a localizer MRI scan will be performed to define the table positions after correct positioning of the spatial acquisition window. A coronal 2-point Dixon 3-dimensional volumetric interpolated breath-hold T1-weighted MRI sequence will be acquired and used for the generation of attenuation maps and for anatomic allocation of the PET results. Simultaneously with the start of the MRI sequences, the PET acquisition will start at the same table position, thus ensuring optimal temporal and regional correspondence between MRI and PET data. The PET acquisition time will be continuous during the MRI exam, taking delayed acquisition times and radioactive decay into account. The MRI scans will be acquired during breath-hold in the standard cardiac views including 2,3,4 chamber views and stacked axial and short axis views. Some patients may be given an IV (intravenous) gadolinium-based contrast injection as part of the PET/MRI research study to enhance the results of the study. 10 minutes after contrast injection, MRI delayed enhancement images may be obtained in the standard cardiac views. The protocol director or one of the co-investigators will decide the administration of contrast.

PET/CT

First, a vertex to mid-thighs scan is done, followed by dedicated imaging of the heart over 1 bed. ToF is standard on the digital PET/CT system. Data driven gating will be acquired according to the vendor's protocol (once commercially available). The PET emission scan is corrected using segmented attenuation data of the CT scan. The PET images are reconstructed both with a standard iterative algorithm (OSEM, two iterative steps, 28 subsets), as well as a regularized reconstruction algorithm (Q.Clear®) provided by GE Healthcare.

5. ADVERSE EVENTS AND REPORTING PROCEDURES

The administration of the radioactive substance will feel like a slight pinprick when given by IV injection. Patients who are claustrophobic may feel some anxiety while positioned in the scanner. Also, some patients find it uncomfortable to hold one position for more than a few minutes. The subjects will not feel anything related to the radioactivity of the substance in their body. Because the radioactivity is very short-lived, the radiation exposure is low. The substance amount is so small that it does not affect the normal processes of the body.

This research study involves exposure to radiation from one ^{18}F-FSPG PET/MRI scan. The effective dose from one typical administration of ^{18}F-FSPG is 4.5 mSv, approximately equal to 10% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year. This radiation exposure is for research purposes only.

In case you cannot undergo MRI due to metal implants, PET/CT will be done. CT in PET/CT will add 5 mSv for a total of 9.5 mSv, approximately equal to 20% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year.

Adverse events will be graded according to CTCAE v5.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochures, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution and 30 days after the last dose of the study treatment.

6. REGULATORY CONSIDERATIONS

6.1. Data and Safety Monitoring Plan

The principal investigator will be responsible for monitoring the safety of subjects who have enrolled in the study.

6.2. Confidentiality

All data including data forms, PET/MRI reports, and clinical information will be stored in a locked, secure location within the Division of Nuclear Medicine and Molecular Imaging. Data will only be accessed by members of the research team assigned to data collection or analysis. No information derived from this study will be provided to the subject's personal physician, a government agency, or any other person or group.

7. MEASUREMENTS

N/A. This is a pilot study evaluating feasibility of the exam as measured by completed exams and diagnostic quality images.

8. STATISTICAL CONSIDERATIONS

N/A. This is a small pilot study with no statistical analysis included.

8.1. Criteria for future studies

If sarcoid is identified in more than 50% of the cases, a larger study will be planned.

Appendix: Inclusion/Exclusion Criteria Checklist

Protocol Title:	**^{18}F-FSPG PET/MRI or PET/CT Imaging of Cardiac Sarcoidosis or Inflammation**
Protocol Number:	IRB-40376
Principal Investigator:	Andrei Iagaru, MD

Inclusion Criteria – Yes must be checked to be eligible (From IRB approved protocol)	Yes	No	Supporting Documentation
1. Patient is ≥ 18 years old at the time of the scan	☐	☐	☐
2. Patient with known or suspected cardiac sarcoidosis	☐	☐	☐
3. Patient is capable of complying with study procedures	☐	☐	☐
4. Patient can remain still for duration of imaging procedure	☐	☐	☐

Exclusion Criteria – No must be checked to be eligible (From IRB approved protocol)	Yes	No	N/A	Supporting Documentation
1. Patient is pregnant or nursing	☐	☐	☐	☐
2. Metallic implants (contraindicated for MRI; these patients will get PET/CT)	☐	☐	☐	☐
3. History of renal insufficiency (only for MRI contrast administration)	☐	☐	☐	☐

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

i. Statement of Eligibility

By signing this form of this trial, I verify that this subject is [☐eligible / ☐ ineligible] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

PI/ SubPI Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

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