Somatostatin Receptor Imaging in Patients with Suspected Cardiac Sarcoidosis

Investigator-initiated, single-center, prospective, pilot study

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I. BACKGROUND AND SIGNIFICANCE

a. Historical Background

Sarcoidosis is a complex inflammatory disease capable of affecting any body organ, including the heart, for which neither the cause nor the cure is known. The United States adjusted annual incidence of sarcoidosis per 100,000 persons is 35.5 cases in African Americans and 10.9 cases in Caucasians [1]. According to post-mortem studies, cardiac involvement is responsible for up to 50% of the deaths related to sarcoidosis [1-3]. Detection of cardiac sarcoidosis is of extreme clinical importance because implantable cardioverter defibrillators (ICD) are recommended in virtually all of these patients to prevent sudden cardiac death[4]. Unfortunately, ante-mortem recognition is challenging and there is no expert consensus on the optimal diagnostic modality for cardiac sarcoidosis [5, 6].

A novel imaging approach is needed because the clinical diagnosis of cardiac sarcoidosis is cumbersome. Heart biopsy, the natural gold standard, is rarely performed because of the risks involved with the procedure, and its poor sensitivity due to sampling error, given the patchy nature of the disease[7]. Non-invasive imaging modalities such as positron emission tomography (PET) using Fluorine-18 fluorodeoxyglucose (FDG) and cardiac magnetic resonance (CMR) with late Gadolinium enhancement (LGE) have emerged as alternative diagnostic tools for the evaluation of patients with suspected cardiac sarcoidosis[8, 9]. However, these imaging modalities are non-specific for the identification of cardiac sarcoidosis and have logistic and technical limitations, which have prevented these images from becoming standard of care.

b. Previous pre-clinical or clinical studies

Somatostatin receptor-targeted imaging with either Indium-111 Pentreotide (OctreoScan) or Gallium-68 DOTA-Tyr^3-octreotate (DOTATATE) has been used in the past for imaging extra-cardiac sarcoidosis. OctreoScan and DOTATATE are both radiopharmaceuticals that bind preferentially to somatostatin receptor subtype-2 (sst-2) on the cell surface. Octreoscan is Food and Drug Administration (FDA)-approved for localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors. Similarly, DOTATATE, a tracer that is widely used in Europe for diagnosis and monitoring therapy of neuroendocrine tumors, also recently received FDA approval in the U.S. for clinical use.[10]

Importantly, previous immunohistochemistry studies have confirmed that sst-2 is over-expressed in in biopsy-proven sites with sarcoidosis as well [10, 11], and at least 3 studies, including a total of 53 patients demonstrated that OctreoScan uptake was significantly increased in 52 out of 53 of patients with sarcoidosis mainly located in the lung, mediastinal and hilar lymph nodes[12-14]. However, OctreoScan and DOTATATE have not yet been systematically utilized for imaging of cardiac sarcoidosis, although, most recently, the potential feasibility of somatostatin receptor imaging was depicted in a series of cases.[16, 17]

c. Study Rationale

We believe that OctreoScan and/or DOTATATE may be of diagnostic value in cardiac sarcoidosis due to the following: 1) intense OctreoScan uptake has been previously shown in the lung and lymph nodes of patients with sarcoidosis [12-14], 2) recently, a case series showed increased DOTATATE uptake in the heart of patients with inflammatory myocardium, including sarcoidosis[17] 3) unlike LGE-CMR, OctreoScan and DOTATATE can be safely used in patients with cardiac devices, and/or renal failure, and 4) unlike FDG-PET, OctreoScan has an advantageous biodistribution for cardiac imaging due to a seemingly low level uptake under baseline conditions (Figure 1)[18,19].

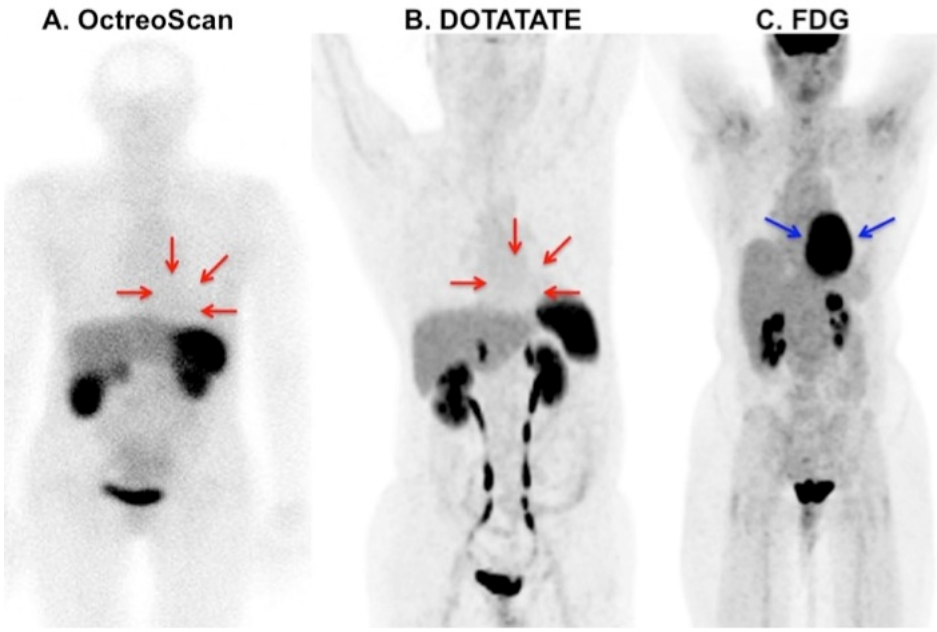


Figure 1. Please notice the low-level OctreoScan (A) and DOTATATE (B) cardiac uptake similar to blood pool of patients A and B, contrasting with the diffuse intense uptake of FDG in the entire heart of patient C despite prolonged fasting and dietary modifications in an attempt to suppress physiologic FDG myocardial uptake

However, to date no studies have systematically evaluated the level of uptake of somatostatin receptor ligands in the heart under baseline conditions, which is necessary before investigating any pathologic accumulation.

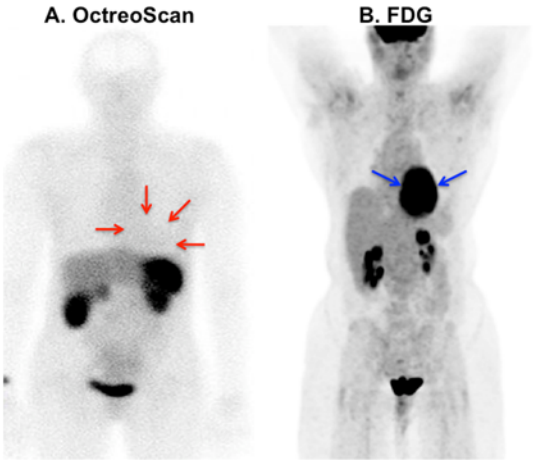


Figure 1.
Please notice the low-level OctreoScan cardiac uptake (red arrows) similar to blood pool of subject A, contrasting with the diffuse intense uptake of FDG in the entire heart (blue arrows) of subject B despite prolonged fasting and dietary modifications in an attempt to suppress physiologic FDG myocardial uptake. None of these subjects have history of sarcoidosis.

Table 1 **Organ (n = 15)**	T-BP Ratio	SD	Min	Max	P value
Septum	1.02	0.15	0.79	1.33	
Inferior wall	1.03	0.13	0.86	1.32	0.0004
Lateral wall	0.92	0.15	0.69	1.15	
Anterior wall	0.81	0.15	0.65	1.09	
Total LV	**0.94**	**0.17**			
Lung, right	0.28	0.14	0.11	0.57	0.32
Lung, left	0.30	0.11	0.15	0.49	
Total lung	**0.29**	**0.12**			
Liver, right lobe	5.51	1.94	2.76	8.17	0.33
Liver, left lobe	5.73	2.57	2.55	11.61	
Total Liver	**5.69**	**2.21**			
Kidney, right	36	22	14	92	0.38
Kidney, left	36	19	13	75	
Total Kidney	**36**	**21**			
Spleen	**27**	**11**	10	50	n/a

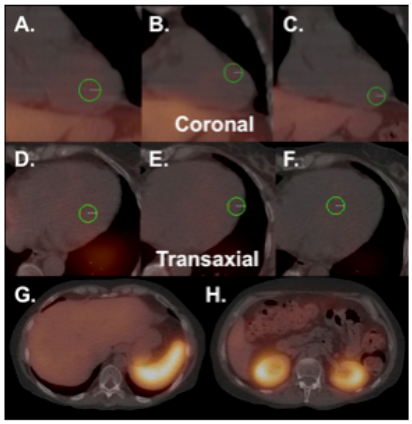


Figure 2. For this reason we studied 15 consecutive adult

patients (7 men and 8 women, mean age 62 years) who underwent OctreoScan with SPECT/CT of the chest for a clinical indication between the periods of April and November of 2013 at the University of Washington in Seattle. Most common clinical indication was detection of local and/or metastatic neuroendocrine tumors. Patients were injected with ~ 6 mCi of OctreoScan, and SPECT/CT of the chest was acquired 24 hr post-injection. OctreoScan uptake was semiquantitatively calculated using a target to blood pool ratio approach. **Figure 2** depicts fused SPECT/CT images of how this was performed. Circular region of interests (ROI) of ~20 mm diameter were applied to left ventricular (LV) cavity blood pool (used as background, 2A and 2D), LV anterior (2B), inferior (2C), lateral wall (2E) and septum (2F), as well as the lungs (not shown), liver (2G), spleen (2G) and kidneys (2H). Results: Visually, the myocardium exhibited indistinguishable activity compared to the LV blood pool. However, there was significant LV regional differences in the uptake ratio/index as shown in **Table 1**. The inferior wall and septum showed higher (above blood pool) and the lateral and anterior walls lower (below blood pool) uptake ratios. This is most likely due to scatter emitted from the liver and spleen (Fig 2G) into the inferior wall (Fig 2C) and, to a lesser extent, the inferior portion of the septum. Likewise, identification of the septal wall (Fig 2F) was difficult given the lack of enough contrast definition on SPECT and CT images, for which an anatomical assumption was made, which makes ROI-based estimates less accurate at this location. These data demonstrated that under baseline conditions, OctreoScan uptake in the heart is indistinguishable from LV blood pool (~ 0.94 ± 0.17). These findings provide solid empirical basis for the work proposed in this project; *the hypotheses are mechanistically plausible, clinically important, and testable*.

d. Differences between OctreoScan and DOTATATE

There are important biological, technical, and practical differences between these radiopharmaceuticals that deserve a brief mention. Like indium-111 pentetrotide (Octreoscan®), 68-gallium dotatate has similar affinity for the same group of somatostatin receptors in inflammatory leukocytes (preferentially somatostatin receptor 2). The availability of 68-gallium dotatate provides several advantages, which are highly beneficial to the patients in this pilot study, including:

a. higher contrast and spatial resolution of PET/CT for detection of small lesions, which we think will result in improved sensitivity as compared to indium-111 pentetrotide SPECT;

b. a nearly 75% reduction in the whole body effective radiation dose to patients from a single administration of gallium-68 dotatate (from 16.4 mSv for Octreoscan to 4.3 with Dotatate);

c. convenience for patients and practical to perform. The entire gallium-68 dotatate PET imaging procedure takes ~2 hours in a single visit, compared to ~24 hours over 2 visits for octreoscan imaging.

II. SPECIFIC AIMS

Aim 1

To investigate if patients with clinically suspected cardiac sarcoidosis exhibit a myocardial OctreoScan or DOTATATE signal high enough (heart-to-blood pool ratio ≥ 2.0) to be visually detected compared to a control group of individuals (expected heart-to-blood pool ratio of ~ 1.0).

Sub-Aim1

To evaluate whether 4-hour (early) compared to 24-hour (delayed) post-OctreoScan injection imaging yields similar lesion detection performance.

Sub-Aim2

To correlate localization and number of increased radiotracer foci between FDG-PET and OctreoScan or between FDG-PET and DOTATATE studies.

Sub-Aim3

To explore the effect of treatment on DOTATATE activity in the heart on follow-up scans

III. SUBJECT SELECTION

We will enroll 30 adult subjects meeting the following inclusion/exclusion criteria.

a. Inclusion Criteria for initial study

- Individuals aged 18 or older

- Documentation of biopsy-proven sarcoidosis OR patients with typical findings on FDG PET and MRI without previous biopsy.

- Clinical suspicion of cardiac involvement defined as the presence of any of the following: high-degree A-V nodal block, complete bundle branch block, reduced left or right ventricular systolic function, any cardiac arrhythmia, and/or unexplained chest pain, dyspnea or syncope

- PET/CT imaging demonstrating abnormal myocardial FDG uptake consistent with active inflammatory myocardium.

b. Exclusion Criteria for initial study

-Initiation of steroids or any other immunosuppressive medication(s) following the completion of FDG-PET, as these medications, in theory, may subsequently suppress OctreoScan or DOTATATE uptake in the heart.

- Patients with history of neuroendocrine tumors (specially insulinomas)

- Patients taking the medication Octreotide

- Patients on total parenteral nutrition (TPN)

- Women who are pregnant or breastfeeding

c. Inclusion Criteria for participation in follow-up study with Dotatate

- Initial dotatate PET scan consistent with active sarcoidosis. Defined as focally increased radiotracer activity in at least one left ventricular wall.

- Being on corticosteroid therapy at a dose of ≥ 10 mg/day of oral prednisone or equivalent for at least 6 weeks since initial dotatate PET scan.

IV. SUBJECT ENROLLMENT

Recruitment Procedures: Potential subjects will be recruited from the following sources: 1) Cardiomyopathy clinic; (2) Sarcoidosis clinic and 2) Nuclear Cardiology Laboratory.

Screening procedures will include daily or weekly queries for potential eligible subjects from lists of patients who have either undergone nuclear imaging or are scheduled to undergo imaging procedures for sarcoidosis. Dr. Bravo will plan on educating the Nuclear Medicine Department staff about the study (recruitment information) as an additional way to ensure potential eligible patients are referred to the study. Our Nuclear Medicine Department staff will be instructed to notify Dr. Bravo if they encounter an abnormal FDG-PET suggestive of active cardiac sarcoidosis, so that the study can be introduced by the nuclear technologists, physiologists or physicians before they leave the Nuclear Medicine facility.

If potential candidate is identified in the sarcoidosis clinic and/or cardiomyopathy clinic, patient's doctor or clinic staff will introduce the study to the patient. If patient is interested in learning more about the study, Dr Bravo will be notified, who will further discuss the study with the patient after the conclusion of his/her appointment with patient's doctor.

If potential patient is identified in the Nuclear Cardiology Laboratory the day of the patient's FDG PET scan, patient will be approached by one of the nuclear technologists, physiologists or physicians before they leave the Nuclear Medicine facility. Only non-study staff members may approach a potential patient in this manner. They can determine whether or not a patient may be interested in finding out more information and can refer him or her to the study team as appropriate. In this setting, the patient may be an inpatient or outpatient.

If deemed eligible, physicians at the Brigham and Women's hospital will be contacted personally and/or via e-mail to explain the purpose of the study, review of its potential risks and discomforts, and the evaluation of whether a patient might be a candidate for the study. After patient's physician agrees to have their patient participate in the study, the patient's physician or inpatient team member will introduce the study to appropriate patients and receive his/her verbal permission to be contacted by study staff. If the patient is an outpatient, the physician can provide the patient a letter describing the study and a copy of the informed consent form. In the letter, potential study subjects will be encouraged to call or email a study coordinator to indicate refusal or willingness to learn more about this study. Interested patients will be contacted by a member of the research study staff to discuss the protocol and to answer any questions regarding the study. Patients who agree to participate will be scheduled for the first study visit and imaging studies, at which point the PI or a co-investigator will review the informed consent form with the patient and answer any additional questions the patient may have.

If the patient is an inpatient, the same recruitment strategy will be followed and the study team will work in coordination with the inpatient team and patient's treating physicians. The physician or inpatient team member will receive verbal permission from the patient to be contacted by study staff. Only once this verbal permission is granted by the patient will study staff approach him/her.

The male/female ratio among the subjects is expected to reflect the approximately prevalence of CAD in the adult population. No specific methods to enhance recruitment of minorities will be used. Minority representation among study subjects is expected to reflect the prevalence of CAD among minorities and the patient population referred to BWH.

b. Procedures for obtaining informed consent

The Principal Investigator or one of the co-investigators will obtain consent during the study-related hospital visit. Consent of subjects who do not speak English will be obtained and documented following the procedures outlined in the PHRC Policy.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured

Enrolled patients will be prospectively imaged after injection of either the radiotracer Indium-111 Penteotride (OctreoScan) or DOTATATE. We expect imaging 10 patients with OctreoScan and 20 patients with DOTATATE. No one will receive both radiotracer injections.

Patients will be scheduled for imaging Tuesday through Friday (no Mondays), since the dose of OctreoScan and DOTATATE must be requested by noon for next day delivery. Subjects will be advised to remain well hydrated prior to and for at least one day after tracer injection, this to reduce radiation exposure.

Women may participate in this study only if they are certain they are not pregnant. If the subject is a woman of childbearing age, a pregnancy test will be performed before OctreoScan or DOTATATE injection unless she has a history of total hysterectomy, is post-menopausal for more than 2 years or post-tubal ligation for more than 1 year.

OctreoScan Protocol

Visit 1 (Screening)

- Review the study with the subject and obtain written informed consent and HIPAA authorization.
- Assign the subject a unique study number.
- Record demographics data.
- Record medical history, including a history of biopsy-proven systemic sarcoidosis, diagnosis date, and prior treatments.
- Record concomitant medications.
- Schedule subject for Visit 2.

Visit 2 (Study Day 1)

- Subject arrives to the Nuclear Medicine Department.
- Concomitant medications review.
- Perform abbreviated physical examination.
- Perform and record vital signs.
- Place a peripheral intravenous (IV) line.
- Perform STAT quantitative serum hCG testing prior to each administration of Octreoscan
- Administer OctreoScan IV.
- Observe patient for 30 minutes post OctreoScan injection.
- Patient is to have a break and return to the Nuclear Medicine Department in 4 hours.
- Perform first set of images (~90 minutes)
- Subject can leave the Nuclear Medicine Department

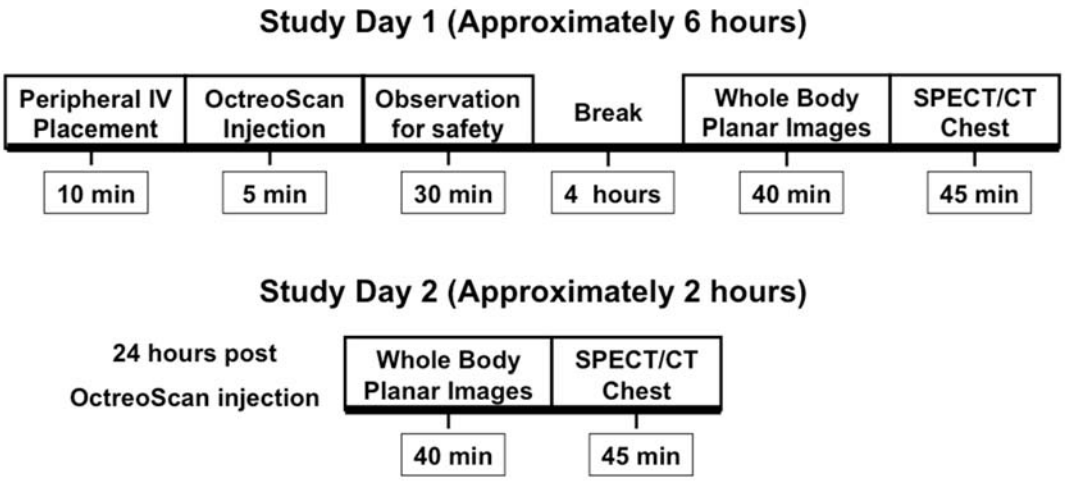
Visit 3 (Study Day 2)

- Subject returns to the Nuclear Medicine Department 24 hours after OctreoScan injection
- Record any Adverse Experiences.
- Perform second set of images (~90 minutes).
- Subject has completed the study protocol at this point.

Follow Up

- All patients will be contacted by telephone at approximately 36-48 hours following the last scan for AE monitoring.

Figure 3. Example of Study Visits for OctreoScan Protocol



DOTATATE Protocol

Visit 1 (Screening)

- Review the study with the subject and obtain written informed consent and HIPAA authorization.
- Assign the subject a unique study number.
- Record demographics data.
- Record medical history, including a history of biopsy-proven systemic sarcoidosis, diagnosis date, and prior treatments.
- Record concomitant medications.
- Schedule subject for Visit 2.

Visit 2 (Study Day 1)

- Subject arrives to the Nuclear Medicine Department.
- Concomitant medications review.
- Perform abbreviated physical examination.
- Perform and record vital signs.
- Place a peripheral intravenous (IV) line.
- Perform STAT quantitative serum hCG testing prior to each administration of DOTATATE
- Administer DOTATATE IV.
- Observe patient for 60 minutes post DOTATATE injection.
- Perform cardiac PET/CT scan (20 minutes)
- Subject can leave the Nuclear Medicine Department

Visit 3 (Study Day 2 - OPTIONAL)

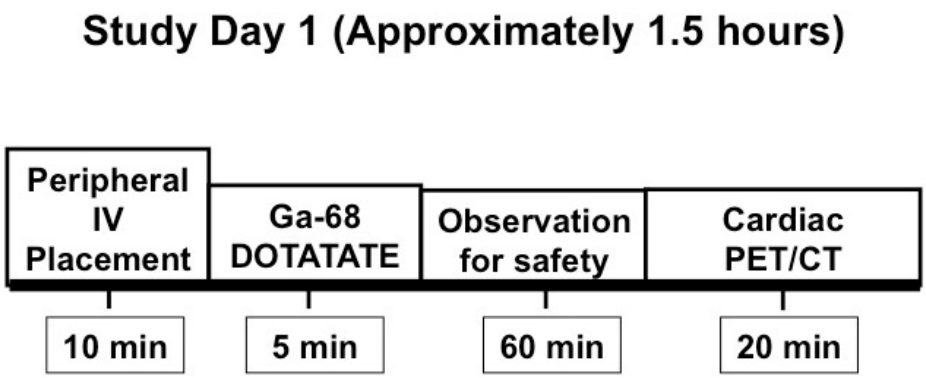
- Subject arrives to the Nuclear Medicine Department.
- Concomitant medications review.

- Perform abbreviated physical examination.
- Perform and record vital signs.
- Place a peripheral intravenous (IV) line.
- Perform STAT quantitative serum hCG testing prior to each administration of DOTATATE
- Administer DOTATATE IV.
- Observe patient for 60 minutes post DOTATATE injection.
- Perform cardiac PET/CT scan (20 minutes)
- Subject can leave the Nuclear Medicine Department

Follow Up

- All patients will be contacted by telephone at approximately 36-48 hours following the last scan for AE monitoring.

Figure 4. Example of Study Visits for DOTATATE Protocol (~1.5 hours)



Schedule of Assessments:

Procedure	Visit 1 Screening (-56 to-1 Days)	Visit 2 Study Day 1	Visit 3 Study Day 2 (OctreoScan only)	Visit 3 Study Day 2 (DOTATATE only)	Telephone Follow-up 36-48 hrs post last injection
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Demographics	X			X	
Medical History	X	X		X	X
Medication History	X	X		X	X
Vital Signs	X	X	X	X	
Pregnancy Test		X		X	
Drug Administration		X		X	

SPECT/CT for OctreoScan		X	X		
PET/CT for DOTATATE		X		X	
AE Monitoring		X	X	X	X

b. Drugs to be used

Study radiopharmaceutical # 1: Indium-111 Penteotride (OctreoScan).

Storage and Dispensing: OctreoScan will be stored at and dispensed from the hospital's radiopharmacy.

Dose and Route of Administration: OctreoScan will be given intravenously per product labeling at the dose (6 mCi) recommended by the manufacturer for evaluation of patients with neuroendocrine tumors.

Study radiopharmaceutical # 2: Ga-68 DOTATATE.

Storage and Dispensing: DOTATATE will be dispensed from Advanced Accelerator Applications USA, Inc., NY 10118.

Dose and Route of Administration: DOTATATE will be given intravenously at the dose of 4.0 mCi (148 MBq).[10]

c. Devices and Procedures

OctreoScan Protocol

Study Day 1 (Early Image Protocol)

Camera type: Imaging will be performed on a Symbia T6 SPECT/CT system (Siemens Medical Solution USA Inc, Knoxville, TN) using a medium energy, low-penetration, parallel-hole collimator, with a 20% energy window centered at 173 keV and 245 keV respectively.

Image acquisition Parameters: Patients will return to the nuclear medicine department 4 hours post-injection and undergo the following protocol: 1. Whole body pass (planar images) in the ANTERIOR and POSTERIOR projection from the top of the head to the mid-femur at 5 cm/min in a 256 x 1024 matrix. Total acquisition time for planar imaging: 40 minutes. 2. SPECT of the chest to include the entire heart. Acquisition parameters: 128 x 128 matrix, 360° of rotation (180°/head), 23 sec per projection, 120 total projections. Total acquisition time for SPECT imaging: 46 minutes. 3. Low-dose CT of the chest for attenuation correction purposes will be performed immediately after SPECT with the following parameters: x-ray tube current-time 50 mAs continuous, voltage 110 kVp. Total acquisition time: 12 seconds.

Imaging Processing:
All SPECT images will be reconstructed with attenuation correction, scatter correction, and the vendor-supplied Flash3D reconstruction algorithm (accounting for spatially dependent resolution response) to create quantitative images of activity concentration (3 iterations, 8 subsets, 5.0mm post-smoothing).

Study Day 2 (Delayed Image Protocol)

Patients will return 24 hours post-injection and the same camera type, image acquisition (whole body planar followed by SPECT/CT of the chest) and processing protocol will be performed as in early imaging.

DOTATATE Protocol

Study Day 1 and OPTIONAL Study Day 2

Camera type: Imaging will be performed on a GE PET-CT scanner (Discovery RX or LightSpeed VCT 64, GE Healthcare, Milwaukee, WI, USA)

Image Acquisition Parameters:
DOTATATE will be given intravenously at the dose of 4.0 mCi (148 MBq). They will then be observed for 60 minutes post DOTATATE injection at the nuclear medicine lab.

Cardiac acquisition: Individuals will be positioned with the help of a CT topogram (grid over the heart, level of the carina), and a low-dose CT scan (120 kVp, 20 – 30 mA) will be acquired for attenuation correction of PET emission data to cover the entire chest. This will be followed by a 20-minute ECG-gated 3-D PET acquisition of the chest and myocardium.

Imaging Processing:
All PET images will be reconstructed with attenuation correction (Matrix 128x128, OSEM, subsets 28, iteration 2, post filter 6.0 mm), and processed and reviewed using the vendor-supplied HERMES software package.

d. Data to be collected and when the data is to be collected

Visit 1. We will collect demographics data, medical history, prior treatments, and concomitant medications, as well as confirm a negative STAT quantitative serum hCG testing prior to the administration of Octreoscan or DOTATATE.

After visit 3 for OctreoScan or after visit 2 for DOTATATE we will analyze and interpret the images as following:

Image Interpretation for OctreoScan:
OctreoScan uptake in the heart will be assessed both qualitative and semi-quantitatively.

1. Qualitative Assessment of OctreoScan cardiac uptake: Two board-certified nuclear medicine physicians will review the early and delayed whole body planar and SPECT/CT images independently of each other and grade each image set based on OctreoScan uptake in the heart as: 1) negative, 2) borderline positive or 3) definitely positive. In this latter case, the number and location (relative to the left ventricular wall position) of positive lesions will be recorded. Similarly, FDG-PET studies (performed as part of the inclusion criteria) will be reviewed and the number and location of FDG-avid lesions recorded.

2. Semi-quantitative assessment of OctreoScan cardiac uptake: A heart to blood pool background ratio will be calculated using a circular region of interests (ROI) applied to each focus of increased radiotracer uptake visualized in the left ventricle on the transverse and/or coronal tomographic slice of the fused SPECT/CT images. A background ROI of the same size will be applied to the blood pool in the left ventricular cavity. In addition, the relative myocardial contrast will be assessed with measurement of myocardial uptake in ROIs positioned in: 1) interventricular septum 2) lateral wall 3) anterior wall and 4) inferior wall. ROI placement will be confirmed via image fusion with the CT portion from the SPECT/CT study (similar to Figure 2). This qualitative and semiquantitative approach will be performed in both early and delayed datasets by 2 separate nuclear medicine physicians.

Image Interpretation for DOTATATE:
DOTATATE uptake in the heart will be assessed both qualitative and semi-quantitatively.

1. Qualitative Assessment of OctreoScan cardiac uptake: Two board-certified nuclear medicine physicians will review the limited whole body and cardiac PET/CT images independently of each other and grade each image set based on DOTATATE uptake in the heart as: 1) negative, 2) borderline positive or 3) definitely positive. In this latter case, the number and location (relative to the left ventricular wall position) of positive lesions will be recorded.

2. Quantitative assessment of DOTATATE cardiac uptake: The axial PET image slice with maximum cardiac uptake will be selected. A standardized 15 mm circular region will be placed over each myocardial wall area with the peak activity. ROI placement will be confirmed via image fusion with the CT portion from the PET/CT study. Each ROI will be used to derive maximum (SUVmax) and mean standardized uptake values (SUVmean). A background ROI of the same size will be applied to the blood pool in the left ventricular cavity, and similarly, SUVmax and SUVmean will be derived to serve as reference. Then, signal-to-background ratios will be calculated.
This qualitative and semi-quantitative approach will be performed in both early and delayed datasets by 2 separate nuclear medicine physicians.

BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study

Please see excel attachments

b. Study endpoints

Primary Endpoint: Positive or abnormal OctreoScan or DOTATATE uptake in patients with cardiac sarcoidosis

Secondary Endpoint: Differences in OctreoScan uptake at 4 hours vs. 24 hours post-radiotracer injection

c. Statistical methods

Data Ascertainment and Analysis:

All statistical analysis will be done using SPSS (version 21.0). A P value <0.05 will be considered statistically significant for all calculations.

Qualitative assessment of OctreoScan or DOTATATE cardiac uptake: First, Cohen's kappa coefficient will be used to examine the visual inter-rater agreement between readers. We expect a kappa of at least 0.9 (excellent). Subsequently, the percentage of patients with abnormal OctreoScan or DOTATATE will be compared between patients with suspected sarcoidosis and those in a control group (Table 1, Figure 2) using chi2.

Semiquantitative assessment of OctreoScan or DOTATATE cardiac uptake: The heart-to-blood pool ratio is a unitless continuous variable. We will use paired t-test to compare within group OctreoScan uptake between early and delayed imaging, and independent-measures t test to compare OctreoScan or DOTATATE uptake between patients with suspected sarcoidosis and the control group.
We will also investigate whether delayed imaging may lead to improved lesion detection performance due to a higher/better target-to-background ratio compared to early imaging. We will employ chi2 to compare if percentage of patients with abnormal OctreoScan varies significantly both on a patient- and lesion-basis between early and delayed imaging in both study groups.
Evaluation of early vs. delay imaging: We will employ chi2 to compare if percentage of patients with abnormal OctreoScan varies significantly both on a patient- as well as lesion-basis between early and delayed imaging in both study groups.

Comparison with FDG-PET: We will also compare if foci of increased OctreoScan or DOTATATE uptake are similar in number and localization compared to FDG-PET scans.

Expected Results:

Our main hypothesis is that OctreoScan or DOTATATE uptake in the heart will be semiquantitatively (heart-to blood pool ratio will be ≥ 2.0) high enough to allow visualization of OctreoScan or DOTATATE activity in patients with cardiac sarcoidosis, compared to the control group, where myocardial uptake will be similar to blood pool activity (heart-to blood pool ratio of ~ 1.0).

We also believe that delayed imaging may lead to improved lesion detection performance due to a higher target-to-background ratio compared to early imaging.

Finally, we hypothesized that OctreoScan or DOTATATE will yield a similar number of abnormal cases (on a patient-basis) compared to FDG-PET.

VII. RISKS AND DISCOMFORTS

Radiation Exposure for OctreoScan Protocol:

1. The radiation dose patients will receive in this study is equivalent to an exposure of 16.4 mSv to the whole body (for one OctreoScan injection and two CT scans). This is more than the 3 mSv that the average person in the United States gets each year from natural sources like the sun, outer space, air, food and soil. It is less than the 50 mSv of radiation that is allowed each year for people who are exposed to radiation in their jobs. Although radiation may cause cancers at high doses and high dose rates, currently there are no data to establish unequivocally the occurrence of cancer following exposure to low doses and dose rates – below about 100 mSv. Therefore, the risks of low-level radiation exposure are not known but are thought to be very low.

Radiation risks are reviewed by the Radiation Safety Committee (RSC) at BWH. Subjects who may be pregnant will be excluded from this study, as radiation may cause physical or genetic damage to a fetus. Calculations are below:

Radionuclide	Activity Each Administration	Compound and Method of Administration	# Administration per Subject	Total Whole-Body Dose per Administration
Indium-111	222 MBq (6 mCi)	Pentreotide	One	12 mSv[17]

Type of exam	# Exams per subject	Total Whole-Body Dose per Exam
Low-dose CT for attenuation correction of the chest	Two	2.2 mSv

Total effective dose estimate = 16.4 mSv (total for study)

Radiation Exposure for DOTATATE Protocol:

1. The radiation dose patients will receive in this study is equivalent to an exposure of 4.3 mSv to the whole body (for one dose of DOTATATE injection and one CT scan). This is more than the 3.0 mSv that the average person in the United States gets each year from natural sources like the sun, outer space, air, food and soil. It is less than the 50 mSv of radiation that is allowed each year for people who are exposed to radiation in their jobs. Although radiation may cause cancers at high doses and high dose rates, currently there are no data to establish unequivocally the occurrence of cancer following exposure to low doses and dose rates – below about 100 mSv. Therefore, the risks of low-level radiation exposure are not known but are thought to be very low.

Radiation risks are reviewed by the Radiation Safety Committee (RSC) at BWH. Subjects who may be pregnant will be excluded from this study, as radiation may cause physical or genetic damage to a fetus. Calculations are below:

Radionuclide	Activity Each Administration	Compound and Method of Administration	# Administration per Subject	Total Whole-Body Dose per Administration
Gallium-68	148 MBq (4 mCi)	DOTA,Tyr^3 octreotate	One	3.1 mSv[20]

Type of exam	# Exams per subject	Total Whole-Body Dose per Exam
Low-dose CT for attenuation correction of the chest	One	1.2 mSv

Total effective dose estimate = 4.3 mSv (total for study)

For subjects participating in the OPTIONAL second DOTATATE scan, the total effective dose will be 8.6 mSv.

2. Side Effects: The following adverse effects have been observed in clinical trials using OctreoScan at a frequency of < 1% of 538 patients: dizziness, fever, flush, headache, hypotension, changes in liver enzymes, joint pain, nausea, sweating, and weakness. These adverse effects were transient in all cases.

According to the package insert, the safety of DOTATATE has been evaluated in three single center studies and in a survey of the scientific literature. No serious adverse reactions were identified, including a small study there were no observed adverse events to the radiopharmaceutical in the immediate or delayed time frames, with a follow-up of 1 year.[21]

3. Venous cathethers: Intravenous (IV) lines are required for OctreoScan or DOTATATE injection. Their placement may cause bruise, temporary clotting, bleeding, redness, swelling, and potentially infection at the insertion site. Some people may feel lightheaded or even faint during IV placement.

4. Invasion of privacy: This is always a potential risk on any research study.

Steps undertaken to minimize risks of harm and to protect subjects' rights and welfare.

1. Radiation exposure: Adequate shielding will be maintained at all times until OctreoScan or DOTATATE is injected to the patient. To help reduce the radiation dose to the thyroid, kidneys, bladder, and other target organs, patients will be encouraged to remain well hydrated before the administration of OctreoScan or DOTATATE, and to increase their fluid intake and void frequency for one day after administration of these drugs.

If the subject is a woman of childbearing age, a pregnancy test will be performed before OctreoScan or DOTATATE at no cost to her unless she has a history of total hysterectomy, is post-menopausal for more than 2 years or post tubal ligation for more than 1 year.

2. Side effects: Patients will be carefully monitored throughout the imaging studies, using blood pressure measurements. Serious adverse events with regard to the study protocol, any other problems or study deviations will be reported to the IRB within 1 week of occurrence/recognition.

3. IV line placement: Only board-certified nuclear medicine technicians, with ample experience in phlebotomy, will perform all peripheral IV line placements.

4. Patients privacy: The patient's personal health information will be kept confidential, and data will be de-identified after the last subject has been imaged. Data will be stored on a computer with access that is password-protected, and inaccessible to those not directly involved in the study. No data will be released unless de-identified as stipulated by HIPAA guidelines. Pregnant women and children will not be included.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

There will be no direct benefits to the study subjects from participating in the study.

b. Potential benefits to society

This is a study aiming at evaluating a potential new imaging modality for the diagnosis of cardiac sarcoidosis. Diagnosis of cardiac sarcoidosis is of paramount importance since these patients are at high-risk of dying suddenly, and currently guidelines advocate for implantable cardioverter defibrillator (ICD) placement in patients with cardiac sarcoidosis. Unfortunately, this condition has been traditionally challenging to detect by standard diagnostic modalities. If our hypothesis is correct, and any of the somatostatin receptor-targeted imaging agents work, this will have a significant impact to the society because it will aid in the identification of patients with cardiac sarcoidosis, a condition that carries significant morbidity and mortality. We believe that the benefits clearly outweigh the risks of the proposed study given the importance of identifying patients with cardiac sarcoidosis.

Our initial preliminary results are rather encouraging as patients who are treatment-naive show comparable levels of DOTATATE uptake/activity in the heart compared to FDG PET (the reference modality). However, it remains to be shown whether DOTATATE can also serve as a marker of therapy response on follow-up scans among those patients with sarcoidosis who showed abnormal cardiac DOTATATE activity in their initial scan.

This is highly clinically relevant as most patients with the diagnosis of active cardiac sarcoidosis based on FDG PET are started on steroids (or other anti-inflammatory drugs) in an attempt to reduce the degree of inflammation since this can be detrimental for the heart function.

Consequently, we would like to explore the effect of treatment on DOTATATE activity in the heart on follow-up scans.

IX. MONITORING AND QUALITY ASSURANCE

a. Safety monitoring

The PI of the study will monitor the overall safety of the study and will report any adverse effect to the IRB immediately. The PI will also monitor this study to ensure that subjects' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol, and study data reported by the investigator/subinvestigator are accurate, complete and verifiable with study-related records such as source documents.

Patients will also be called 36-48 hours after the scan to monitor for any AEs.

Safety data will be obtained at each of the two study visits from the spontaneous reports by patients of adverse events, vital sign monitoring, and focused physical examinations.

Dr. Paco Bravo should be contacted directly at this number to report medical concerns or questions regarding safety.
Phone: (410) 736-0010

b. Data safety monitoring

All safety data will be reviewed by the PI (Dr. Marcelo Di Carli).

c. Discontinuation criteria for individual subjects

Discontinued subjects are those who are enrolled in the study and for whom study treatment is terminated prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

Subjects will be discontinued if:

- Subject experiences a serious or intolerable adverse event
- In the Investigator's opinion, the subject is non-compliant with the protocol requirements
- Subject wishes to withdraw consent
- Investigator elects to end the study

d. Adverse event reporting guidelines

Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one or more of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator

Definition of Serious Adverse Events (SAEs)

A serious AE is any untoward medical occurrence that, at any dose:

- Results in death,
- Is life threatening (an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe),
- Results in persistent or significant disability/incapacity,
- Results in congenital anomaly, or birth defect,

- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, will be considered serious.

Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out."

Causal relationship to the study drug	**Criteria for causal relationship**
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).

Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of adverse events, including abnormal clinical laboratory values.

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator will submit a report through eIRB within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem as per Partners policy.

Follow-up to Adverse Events

All adverse events occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during adverse event follow-up, the adverse event progresses to an ″SAE,″ or if a subject experiences a new SAE, the investigator will immediately report the information to the sponsor.

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