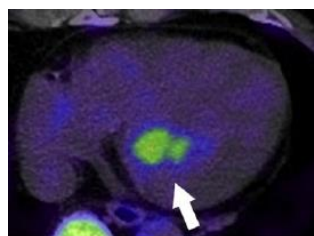# Cardiac Sarcoidosis

Standard Operating Procedure and Case Report Form for Interpretation for Hermes Corridor 4-DM Software

1. Exclude coronary artery disease (CAD)

In the normal myocardium, 50-70% of total myocardial energy requirement is obtained from fatty acid oxidation in the fasting condition. In the setting of myocardial ischemia, glucose becomes the primary substrate instead of fatty acid. Therefore, patients with significant coronary arterial disease (CAD) may demonstrate focal FDG uptake in the culprit lesion.
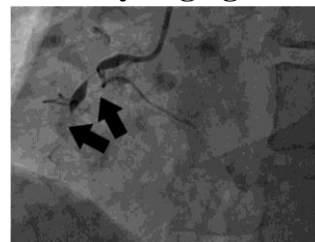
It is necessary to rule out the presence of ischemia to interpret FDG-PET images appropriately.

FDG-PET   **Coronary angiogram**

Focal FDG uptake   **Significant stenosis**

**in the posterior septum of the LV**   **in the proximal RCA**

Egashira T et al. Int J Cardiol 2014; 172: e401-2.

2. Physiological FDG distribution in the heart

Patients undergo perfusion imaging, FDG cardiac and whole body imaging as per the standard operating procedure protocol. Pre-test preparation includes fasting > 12hours prior to PET scan appointment, low dose unfractionated heparin (UFH) administration, and dietary modification (low carbohydrate, high fat and protein permitted diet the last night prior to the scan). This approach has effectively suppressed the physiological FDG uptake. However, some patients may show the physiological FDG uptake in the heart as follows;

Physiological FDG uptake in the LV (normal variation)

Diffuse pattern
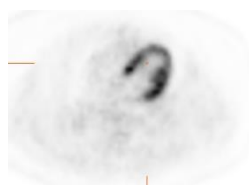
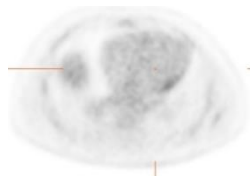Trans-axial view   Short axis   Horizontal long axis   Vertical long axis
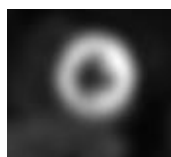
Isolated lateral wall and/or basal pattern

 Isolated lateral wall pattern

Trans-axial view   Short axis   Horizontal long axis   Vertical long axis
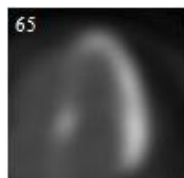
 Isolated lateral wall and basal pattern

Trans-axial view   Short axis   Horizontal long axis   Vertical long axis

In cases with isolated lateral wall and basal pattern, typical cases show FDG uptake in the basal segments like ring.
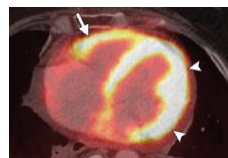
Diffuse pattern
Acute myocarditis (viral infection)   **Chemotherapy induced myocarditis**

Trans-axial view   Trans-axial view

 Takano H et al. *Int J Cardiol* 2008;130:e11-13.   James OG et al. *Radiographics* 2011;31:1271-86.

Diffuse pattern is observed in healthy subjects, however it can be seen in patients with myocarditis.

If CS is highly suspected and FDG-PET images show physiological uptake, consider repeat scan with strict pre-test preparation (long fasting, dietary modification and heparin administration).

2. How to set-up the images

On the HERMES GOLD-3 browser:

Whole body images
        a. Select "**WB 3D MAC**" and "**WB STANDARD**" and open on the hybrid viewer by clicking "**FUSION 1**".
        b. Adjust color contrast as "Absolute" until physiological liver uptake of FDG is visible.

Cardiac images
        a. Select suitable files for cardiac PET images: for interpretation we use resting perfusion images (either

Rubidium-82 or 13-Ammonia) with a **12mm** reconstruction filter for static images as well as ECG-gated perfusion images with a **16mm filter.** For FDG we use either **10mm or 12mm** reconstructed images. ECG-gated images are not available in cases where there is no myocardial uptake. All images are reconstructed using iterative reconstruction. When the appropriate images have been selected, click the 4-DM PET icon.

 b. Ensure that the perfusion and FDG PET are correctly co-registered with the CT attenuation correction scans using the hybrid viewer. If this does not open automatically select the static perfusion and FDG images as well as the CT STD Rest and CT STD FDG and open the hybrid viewer. Note should be made of tracer-avid structures that may be adjacent to the myocardium (e.g. intense liver uptake with Ammonia-13) as these may impact on image interpretation.

 c. If the image co-registration is satisfactory then return to the 4-DM images. Our convention is to have resting perfusion images in the upper rows and FDG images in the lower rows. This can be modified by selecting "User Defined" from the tab in the upper panel on the screen.

 d. Click on the "SETUP" icon on the top of the icon panel on the left of the screen to ensure the images are aligned appropriately (both for static and ECG-gated images). Use the spectrum 10 step color scale for set-up.

 e. <u>VLA, HLA orientation:</u> long axis through the center of the apex
  <u>SA:</u> axis centered in the mid-LV cavity
 f. <u>Apical limit</u>: set it to the mid-apical myocardium
  <u>Basal septum</u>: set to the 50% uptake threshold (i.e. the point where the septal uptake is 50% of the maximal myocardial uptake) (NOTE in cases where the septal uptake is reduced this method does not apply and the positioning should be done based on visual impression)

 g. Click on the "Process" button: verify the orientation of the LV. If it does not appear to be correct, go back to the "Setup" tab to modify the positioning again.

 h. <u>Pmap QA tab</u>: verify that the LV base is at the @50% threshold activity of the basal septum. If not, modify using the control line.

 i. Use **"Gray scale"** for FDG image interpretation while the Spectrum 10-step scale should be used to grad the resting perfusion images.
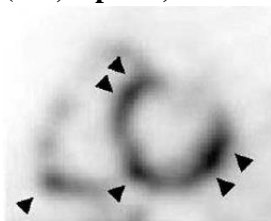
3. Image interpretation

3.1 Visual interpretation of FDG-PET whole body images

While the whole body images are reported separately by Nuclear Medicine, a visual assessment of cardiac uptake can be made from these images. There are 5 patterns of FDG uptake in the heart for patients with suspected cardiac sarcoidosis: "No uptake"; "Diffuse"; "Focal"; "Focal on diffuse" and "Isolated lateral wall and or basal" pattern (refer to section 2).

A "Focal" or "focal on diffuse" pattern is considered as a positive finding of active cardiac involvement by sarcoidosis. Focal uptake in the right ventricle should also be noted if present as this has been associated with adverse outcomes.

Focal pattern
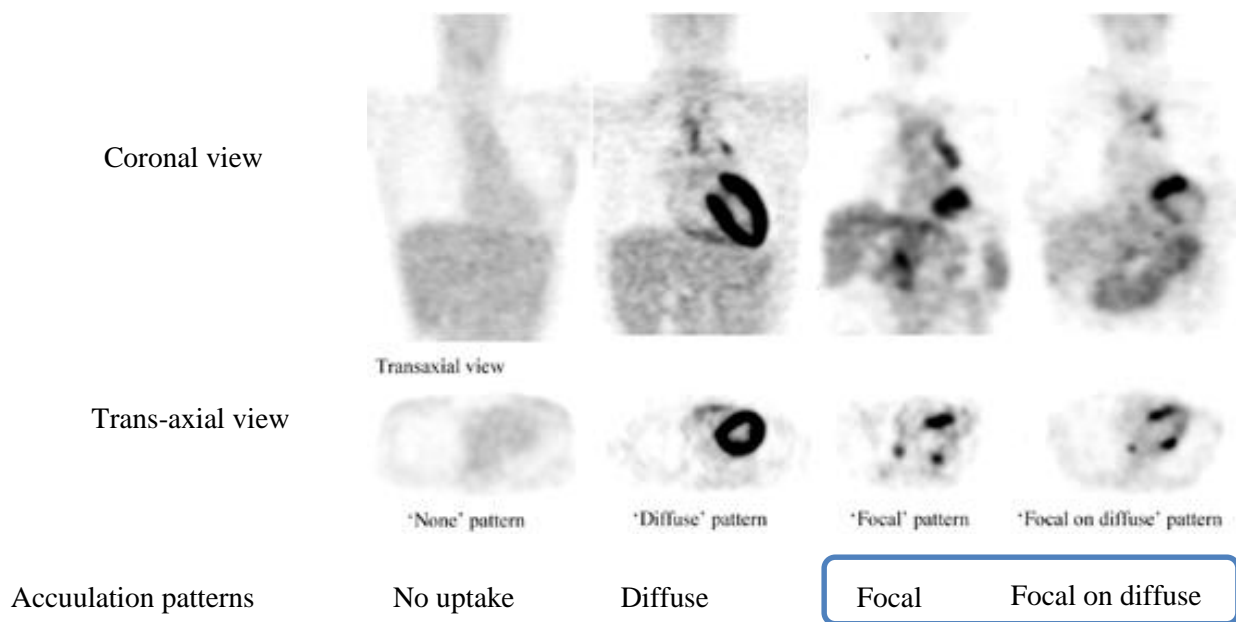**(RV, septum, interior and lateral walls)**

Short axis view

Focal on diffuse pattern

Short axis view

Ohira et al. *EJNMMI*, 2008; 35:933-41.   Blankstein et al. *JACC*, 2014; 63:329-36.

| Coronal view | | | | |

Transaxial view

| Trans-axial view | | | | |

| | 'None' pattern | 'Diffuse' pattern | 'Focal' pattern | 'Focal on diffuse' pattern |

| Accuulation patterns | No uptake | Diffuse | Focal | Focal on diffuse |

Ishimaru et al. *Eur Heart J*, 2005;26:1538-43.

- However if focal FDG uptake is present, but is of lower intensity than the liver (based on maximal SUV value), then this might be due to physiological FDG uptake. This can be confirmed by drawing a Region of interest (ROI) around the area of maximal uptake in the myocardium and another ROI within the liver on the hybrid viewer. Since increased FDG uptake in the lateral wall of the LV is observed in some healthy subjects, cases with focal uptake only within the lateral wall of the LV should not be classified as "focal" or "focal on diffuse" pattern.

3.2 Visual interpretation of cardiac images

- On the 4DM images static resting perfusion should be analyzed firstly. These should be interpreted in the same manner as the rest perfusion portion of a viability study. The location of perfusion defects as well as their extent and severity should be reported based on the 17-segment model of the LV.

- The FDG images are then analyzed visually. As with the whole body images there are 5 patterns of FDG uptake with focal and focal on diffuse uptake being suggestive of active sarcoidosis. The location and extent of focal FDG uptake should be reported based on the 17-segment model of the LV. Focal uptake of FDG in the right ventricle should also be reported. Increased FDG uptake only within the lateral wall should not be classified as "Focal" or "Focal on diffuse" pattern as it is observed in some healthy subjects.

- ECG gated images should then be evaluated. The resting perfusion images are the preferred method for evaluation of LV function as in the absence of diffuse uptake, the FDG images are not likely to be reliable. Once the appropriate setup has been confirmed then the computer-generated values for Ejection fraction as well as end-systolic and end-diastolic volumes should be reported. Visual analysis of regional wall motion should also be performed and the location and severity of abnormalities should be reported similarly to conventional perfusion imaging.

- CONCLUSION: After reporting the location/severity/extent etc for both the perfusion and FDG images as well as the LV functional information, an impression as to whether or not the findings are consistent with cardiac sarcoidosis should be reported. In cases where serial imaging to assess response to treatment is being performed then a comparison with previous imaging as well as an impression as the whether there is ongoing active disease vs. residual scar without active inflammation should be reported.

Since diffuse uptake can be seen in patients with myocarditis, all of the clinical information (symptoms, history, ECG, blood tests and other imaging modalities) should be taken into account in the clinical setting.

3.3 Qualitative analysis

In contrast to its use in oncology, Standardized uptake value (SUV) has not been validated in patients with sarcoidosis.
Therefore, SUV in this field should be used for research purposes:

- **Determining Maximum SUV for the LV in the reading room:** Determination of the MAXIMUM SUV should be performed using the fused CT STD FDG and the static 12mm FDG images displayed on the Hybrid Viewer.
- The "Quick ROI" tool (set to SUV value) can be used to identify the area with the highest SUV value within the myocardium on the transaxial images. The location of this uptake can be accurately determined based on the CT images.
- Once the maximum uptake has been determined this should be confirmed on both the sagittal and coronal images to ensure that it is a true maximum and that it truly lies within the myocardium.
- This value should then be recorded as well as the location of the segment where this area lies.

- **Determining the Mean SUV for the LV in the core labo:** This value can be determined using "Flow-Quant" software, which was developed at our institution.

- Firstly select appropriate static FDG (12mm filter with iterative reconstruction) images and then click on the FlowQuant icon on the upper toolbar of the GOLD-3 browser.

- Once the main screen appears select "comparison" (Figure 1).

- Then select the "Study Settings icon" from the upper toolbar (last icon on the right) (Figure 2). Under the list of study options click on the "Preferred Uptake Units" option and select SUV bw (g/mL). To obtain SUV in the RV, check "Process RV" in the study options. Under the 'Default Analysis Options' change Species to "Human" and Tracer to" FDG", then type 6 in the 'Uptake frames' field. Press the OK button on the Study Settings window for the changes to take effect (Figure 3).

- Next click on Process. All files in the bottom left corner of the screen. The RE-orientation tool will then appear where the program will create an ROI within the LV in three planes (transaxial, mid-VLA, mid-HLA, and basal SA). These should be inspected and if it does not delineate the LV accurately both the size of the ROI and its location can be modified. Where possible this should be done on the transaxial image only but if the program cannot accurately locate the LV on the other images despite manipulating the transxial image then the others can be altered individually in turn.

- Once satisfied with the ROI's then click Accept. An LV Model Tool will then appear. The LV model can be manipulated moving the blue dots on both the HLA and VLA images. The dots should be moved to include all the LV walls and once satisfied then press accept.

- Polar maps of the LV with an SUV scale will then appear on screen (Figure 4).

- The results of the mean SUV values for each of the 17-segments of the LV, and 5-segments of the RV automatically appear on the screen (Figure 5). Coefficient of variation (COV) of the RV and LV are also automatically obtained.

- If you'd like to obtain the results as an EXCEL sheet, click "Data" on the toolbar on the main screen and next click :Export KM results" (Figure 6).

- On the next menu click on the "Uptake" checkbox. Under "Number of Segments" select 17 and under

"Number of Rings" select 16. Segment summary operation should be Mean. Then click "OK".

- A Prompt should then appear to say the operation is complete. Select "open file" to view an Excel spreadsheet with the mean SUV values for each of the 17 segments. This value can then be averaged to give a mean value for the LV.

- Using the EXCEL sheet, the standard deviation of the 17 segments of the LV and 5 segments of the RV can also be calculated and the ratio of the SD and the mean, termed the Coefficient of variation (COV), can also be calculated. This is an index of heterogeneity of FDG uptake and is higher in patients with cardiac Sarcoidosis and should be recorded also.

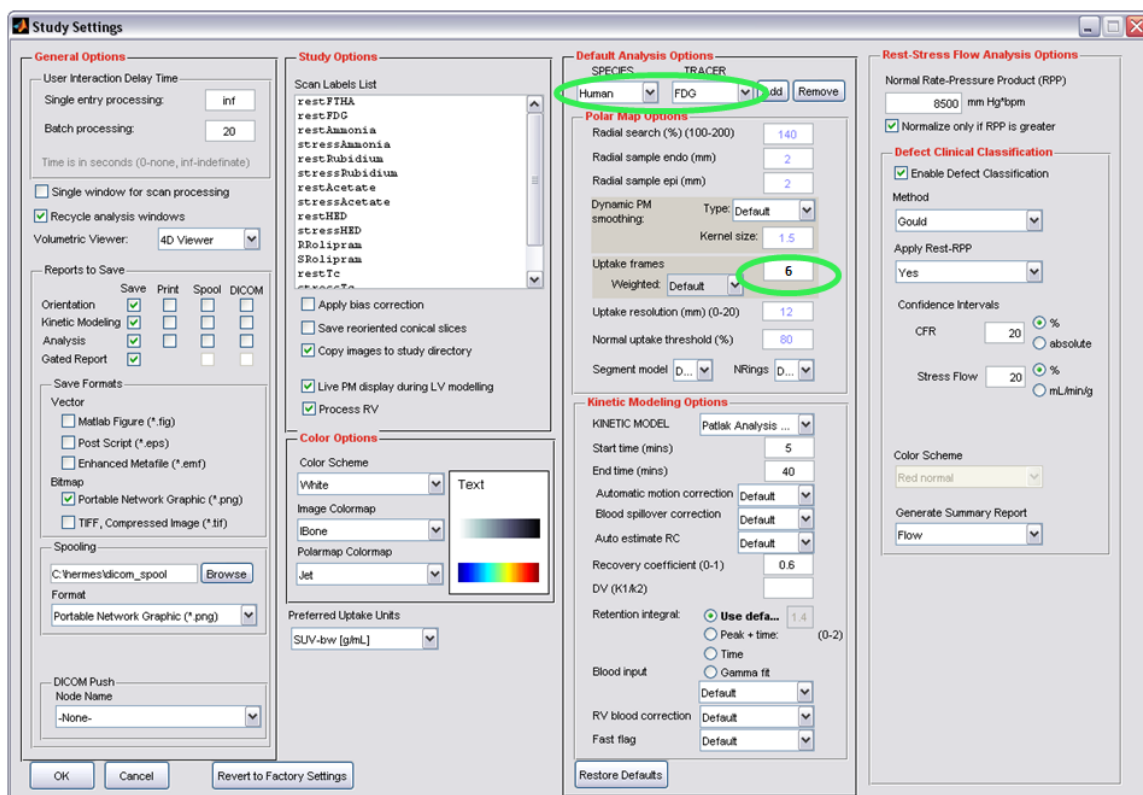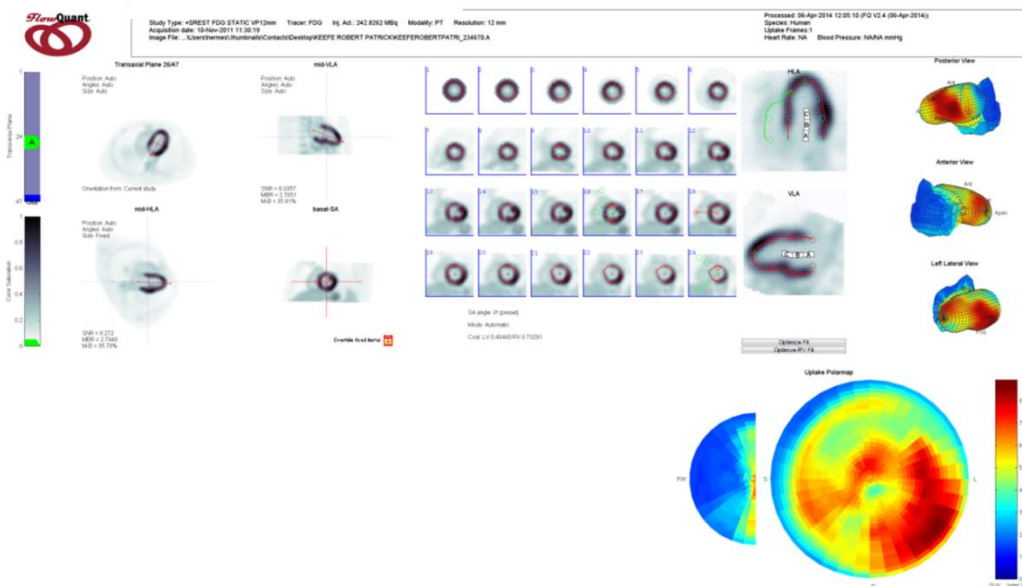Figure 1
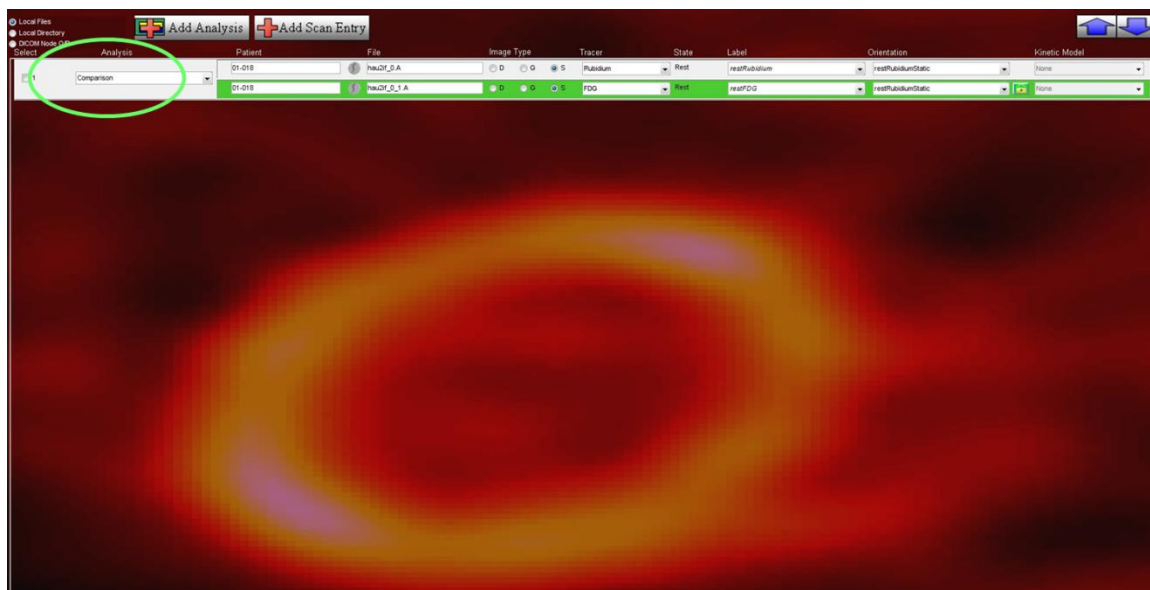
Figure 2
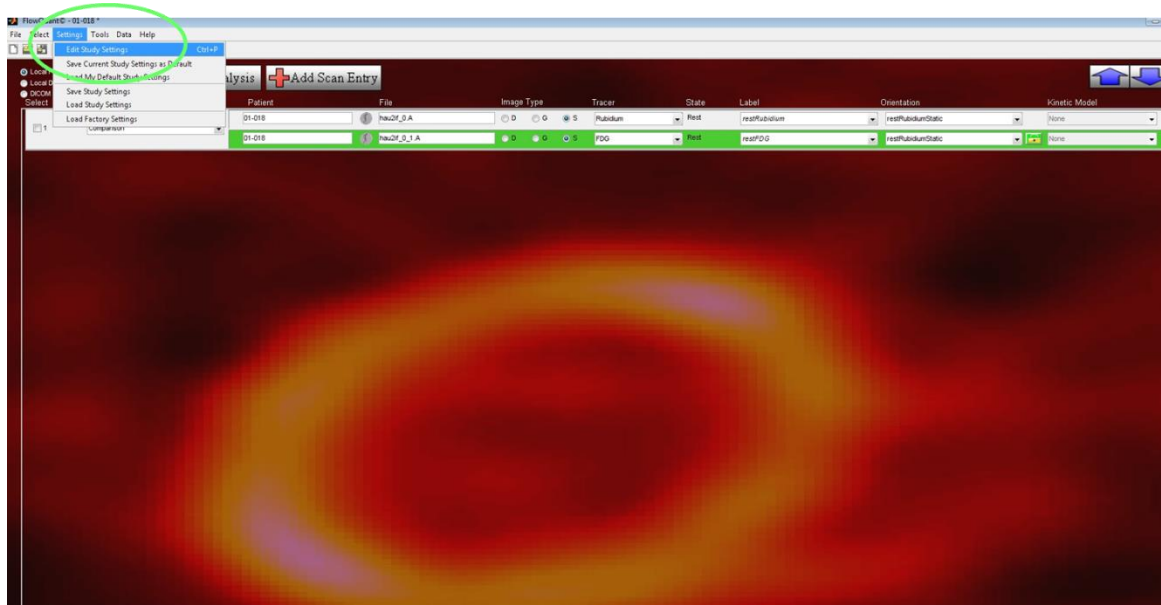
Figure 3

Figure 4

Image showing the process on "Flow-Quant" software
Polar maps showing the RV and LV with SUV (minimum, maximum, and mean SUV value) on "Flow-Quant" software.
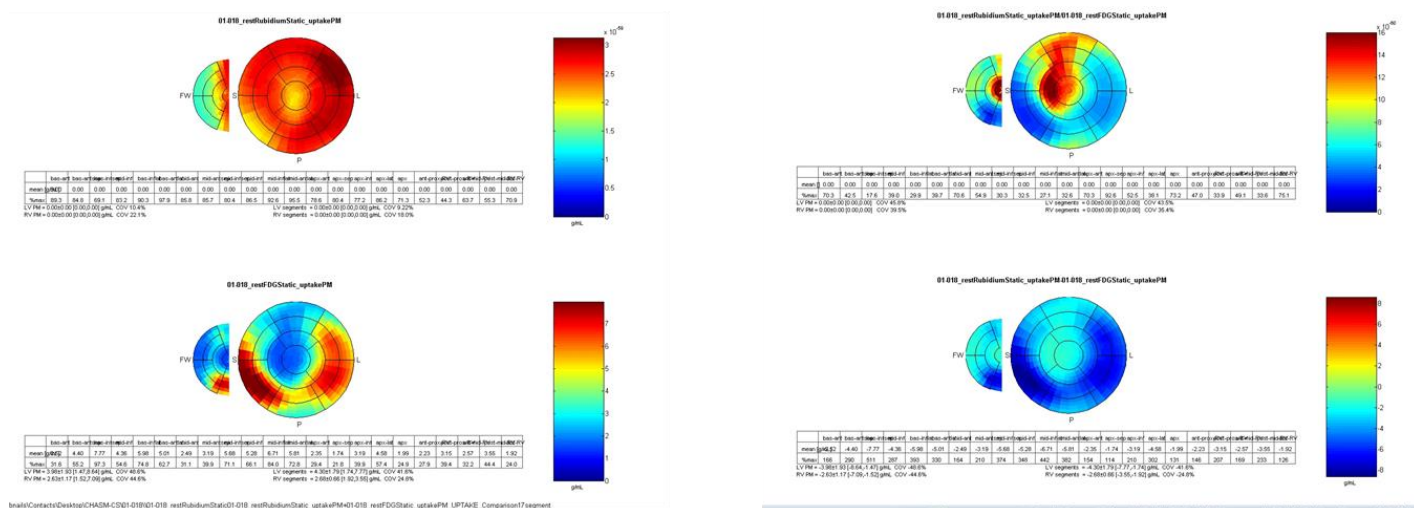
Figure 5

Figure 6

Filename:					
Segments:	17	Rings:	16	Operation	Mean
TAC sheet	Filename	UPTAKE-bas-ant_mean	UPTAKE-bas-antsep_mean	UPTAKE-bas-infsep_mean	UPTAKE-mid-inf_mean
		g/mL	g/mL	g/mL	g/mL
	_restFDGStatic_uptakePM.ma	4.680456994	5.065752969	6.186440712	6.190356818

A part of the report showing the mean SUV for each 17-segments of the LVobtained by "Export KM results".

Appendix A. FDG-PET scan at presentation form

Patient ID ☐☐☐ ☐☐☐

Site #   Pt #

FDG-PET / MRI SCAN AT PRESENTATION FORM

Did the patient have one of the following 2 scans:

FDG/PET at Presentation: ☐ Yes   ☐ No   **If YES, site to complete Section 1**

If yes: ☐   **Standard PET**

☐   **PET/CT**

☐   **PET/MR**

AND/OR

MRI at Presentation: ☐ Yes   ☐ No   **If YES, site to complete Sections 5, 6**

> Presentation is defined as follows:
>
> Group A – Date of first test documenting 2nd or 3rd degree AV block or VT. All tests performed within 6 months before and after presentation should be included on the presentation CRFs.
>
> Group B – Date patient seen by cardiologist for assessment of possible cardiac involvement. All tests performed within 12 months before and 6 months after date of presentation should be included in presentation CRFs.

SECTION 1: PRE-SCAN PREPARATION FOR FDG-PET (SITE TO COMPLETE)

Date of Baseline scan: **Day**   **Month**   **Year**

☐☐   ☐☐   ☐☐☐☐

Heparin: ☐ Yes   ☐ No

Fasting 12 hours: ☐ Yes   ☐ No   Number of hours fasted: ____

Fatty diet as per protocol: ☐ Yes   ☐ No   Blood Glucose Level: ____.___ mmol/L

Time of the meal last evening: ____:____ (24hr clock)   ☐ unknown

How long fasting since the last meal: _____ hrs

Did the evening meal include carbohydrate: ☐ Yes   ☐ No ☐ unknown

If yes, what did the patient eat:

_____

Did the patient eat something after the last meal: ☐ Yes   ☐ No ☐ unknown

 If yes, what: _____

Did the patient receive diet instruction: ☐ Yes   ☐ No   ☐ unknown

Patient ID □□□   □□□
Site #   Pt #

Perfusion Tracer given: □ Rubidium-82   □ Thallium-201

(Select only ONE)   □ N-13 Ammonia   □ Tc-99m Sestamibi

                              □ O-15 water   □ Tc-99m Tetrofosmin

                              □ Other _____   □ Not applicable

Tracer Activity   □□□□ MBq

Attenuation Correction: □ Yes   □ No

FDG Tracer given:

Tracer Activity   □□□□ MBq

---

*Note: Please send copy of de-identified FDG-PET scan report labeled with patient
        ID to the coordinating centre AND

Complete the IMAGE TRANSFER FORM for transfer of PET scan to the Core Lab

---

Completed by:

Site Investigator/Delegate Printed Name: _____

Site Investigator/Delegate Signature: _____

Date: _ _ / _ _ / _ _ _ _ (dd/ mm/ yyyy)
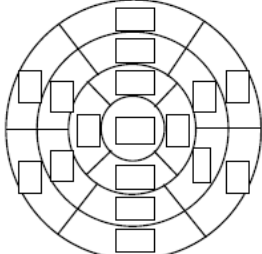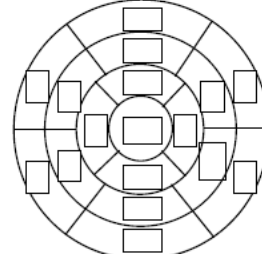
Patient ID
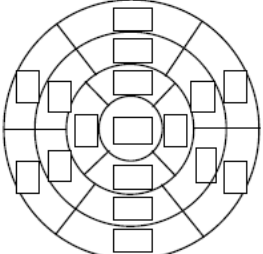
Site #   Pt #

SECTION 3: PET INTERPRETATION - CARDIAC FINDINGS (CORE LAB TO COMPLETE)

CADRE ID #: _ _ - _ _ _ - _ _ _ _ (UOHI site only)

3.0.1 Coronary artery calcification: ☐ Yes   ☐ No

3.1 **FDG Uptake**	3.2 **Perfusion Defect Scoring**	3.3 **Regional Wall Motion - from Perfusion scan**
FDG Score: 0 = No uptake 1 = Equivocal 2 = Positive	0 = Normal 1 = Mild 2 = Moderate 3 = Severe 4 = No uptake	1 = Normal 2 = Hypokinesis 3 = Akinesis 4 = Dyskinesis 5 = Aneurysm
Regional Pattern (choose one): No uptake ☐☐ Isolated lateral wall and or basal ☐☐ Diffuse ☐☐ Focal ☐☐ Focal on diffuse ☐☐ If focal hotspots, how many? ____	**3.2.1** **Summed Rest Score (SRS):**	**OR** ☐ All Normal **3.3.1** **Ejection Fraction** ___ % Or ☐ Not available
3.1.1 **Number of ↑ abnormal segments**		**3.3.2** **EDV**
3.1.2 Mean LV SUV ___.___		**Or** ☐ Not available

Cardiac Sarcoidosis Multi-Center Cohort
FDG-PET/MRI Scan at Presentation
Version October 6, 2014

Page 3 of 7

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 58 • No. 8 • August 2017   Ohira et al.

Patient ID

Site #   Pt #

3.1.3

Max LV SUV ☐☐.☐☐

in segment: ☐☐

3.1.4 COV of the segmental mean values

☐☐.☐☐

3.1.5 RV Uptake

☐ Yes   ☐ No

3.1.6

Max RV SUV ☐☐.☐☐

3.4 Classification of Segments

Please summarize the number of segments into the following 4 types:

Normal Segment (normal FDG uptake with normal perfusion) ☐☐

Abnormal Segment (abnormal FDG uptake with abnormal perfusion) ☐☐

Abnormal Segment (normal FDG uptake with abnormal perfusion) ☐☐

Abnormal Segment (abnormal FDG uptake with normal perfusion) ☐☐

(Total 17)

3.5 Comments:

Patient ID							
	Site #				Pt #		

3.6 CORE LAB INTERPRETATION OF CARDIAC PET SCAN (choose one)

❑ Negative scan not consistent with active cardiac sarcoidosis (no uptake, diffuse, isolated lateral wall)

❑ Positive scan consistent with active cardiac sarcoidosis (if CAD excluded)

❑ Equivocal scan

❑ Non-diagnostic scan (e.g. inadequate pre-test preparation)

❑ Positive scan for other cardiac disease

Comments:

Core Lab Reader Initials:

SECTION 4: PET INTERPRETATION – NON-CARDIAC FINDINGS (CORE LAB TO COMPLETE)

Please select one for _EACH_ item on the list:

	Normal FDG Uptake	Equivocal	Abnormal FDG Uptake
Lung	☐	☐	☐
Lymph Nodes: Neck	☐	☐	☐
Thorax	☐	☐	☐
Abdominal	☐	☐	☐
Skin	☐	☐	☐
Hepatic or GI	☐	☐	☐
Ocular	☐	☐	☐
Salivary	☐	☐	☐
Brain/CNS	☐	☐	☐
Renal	☐	☐	☐
Bone or Joint	☐	☐	☐
Other: _____	☐	☐	☐

Cardiac Sarcoidosis Multi-Center Cohort
FDG-PET/MRI Scan at Presentation
Version October 6, 2014

Page 5 of 7

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 58 • No. 8 • August 2017   Ohira et al.

Cardiac Sarcoidosis Multi-Center Cohort

Patient ID

Site #   Pt #

Overall interpretation:

☐ Cancer ☐ Infection ☐ Extra-cardiac sarcoidosis ☐ Normal

Comments:

Core Lab Reader # 1 (Fellow):

Initials:

Signature: _____

Date: _ _ / _ _ / _ _ _ _
       (dd / mm/ yyyy)

Core Lab Reader # 2 (Staff Physician):

Initials:

Signature: _____

Date: _ _ / _ _ / _ _ _ _
       (dd / mm/ yyyy)

Patient ID

Site #   Pt #

SECTION 5: CARDIAC MRI (SITE TO COMPLETE)

Date of Cardiac MRI   **Day**   **Month**   **Year**

*Note: Please send copy of de-identified Cardiac MRI report labeled with patient ID
         to the coordinating centre AND

Complete the IMAGE TRANSFER FORM for transfer of MRI scan to the Core Lab

SECTION 6: THORAX MRI (SITE TO COMPLETE)

Date of Thorax MRI   **Day**   **Month**   **Year**

*Note: Please send copy of de-identified Thorax MRI report labeled with patient ID
         to the coordinating centre

Completed by:

Investigator/Delegate Printed Name: _____

Investigator/Delegate Signature: _____

Date: _ _ / _ _ / _ _ _ _
         (dd/ mm/ yyyy)

- Maximum SUV in the heart should be obtained using the Hybrid Viewer.
- Mean SUV in the heart should be evaluated using "Flow Quantification" in the core lab.
- SUV of the extra-cardiac involvement can be described based on the clinical report by radiologist.

Appendix B. Blood-Pool and Liver SUV as a reference (research purpose)

Reference Range for Intrapatient Variability in Blood-Pool and Liver SUV for ^{18}F-FDG PET

Raef R. Boktor[1], Gregory Walker[1], Roderick Stacey[1], Samuel Gledhill[2], and Alexander G. Pitman[1,3]

[1]Lake Imaging Department of Positron Emission Tomography and Nuclear Medicine at St. John of God Hospital, Ballarat, Victoria, Australia; [2]Medical Imaging and Radiation Sciences Department, Monash University, Melbourne, Victoria, Australia; and [3]University of Notre Dame, New South Wales, Australia

^{18}F-FDG PET qualitative tumor response assessment or tumor-to-background ratios compare targets against blood-pool or liver activity; standardized uptake value (SUV) semiquantitation has artifacts and is validated by a stable normal-tissue baseline.
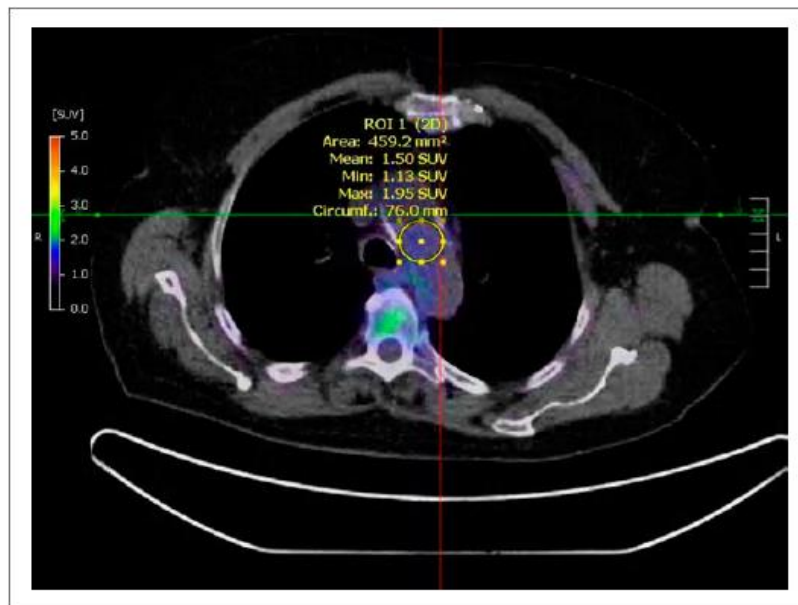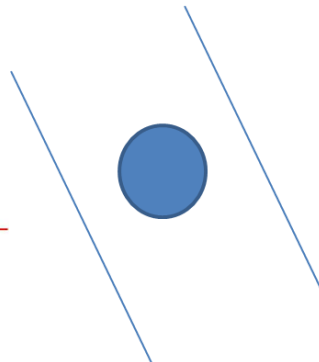
FIGURE 1. Two-dimensional circular region of interest placed on blood pool in aortic arch.

dose CT scan used for anatomic localization was a 3-mm cube. A qualitatively reproducible, 2-dimensional circular region of interest was placed on the blood pool in the aortic arch, avoiding any abnormalities (Fig. 1). A qualitatively reproducible, 2-dimensional circular region of interest was placed on the right lobe of the liver, avoiding abnormal areas (such as cysts or metastases) and well away from diaphragmatic motion artifacts (Fig. 2). In patients

Based on the article above, we will use **3-dimensional circle region of interest (VOI)**.

VOI should be placed on the blood pool in the aortic arch, avoiding aortic wall. Diameter should be adjusted with **one-third** of the size of the aortic arch.
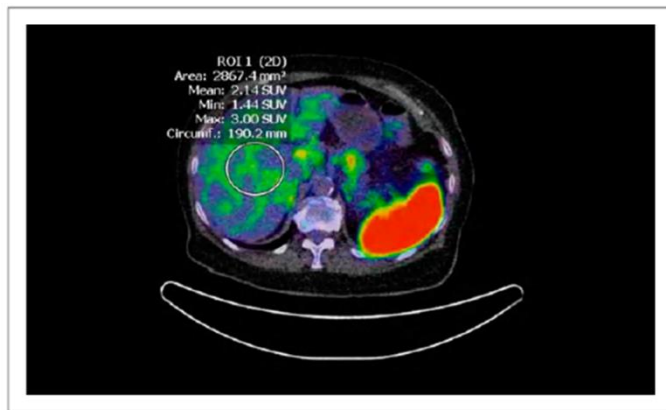

FIGURE 2. Two-dimensional circular region of interest placed on right lobe of liver.

dose CT scan used for anatomic localization was a 3-mm cube. A qualitatively reproducible, 2-dimensional circular region of interest was placed on the blood pool in the aortic arch, avoiding any abnormalities (Fig. 1). A qualitatively reproducible, 2-dimensional circular region of interest was placed on the right lobe of the liver, avoiding abnormal areas (such as cysts or metastases) and well away from diaphragmatic motion artifacts (Fig. 2). In patients

Based on this article, we will use 3-dimensional circle region of interest (VOI). VOI should be placed on the right lobe in the **liver**, avoiding abnormal areas (such as cysts or SOL). Diameter of VOI should be adjusted with 30mm.

Representative case for positive FDG-PET scan.

This case was reported as focal FDG uptake in the basal to apical segments of the anteroseptal wall and septum. Perfusion scan was reported as normal.