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PET-CT Sarcoidosis-A Brief Review and Consideration For PET-CT Patient Workflow

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Cardiovascular disease continues to lead as one of the greatest contributors to mortality [1]. Cardiac sarcoidosis is a lesser known but highly lethal clinical condition that has been increasing in incidence and prevalence globally [1]. Within the radiologic modalities, both cardiac magnetic resonance imaging (MR) and positron emission tomography-computed tomography (PET-CT) have emerged as ideal imaging modalities used in evaluating and assisting with treatment considerations for cardiac sarcoidosis. MR and PET-CT are complementary in regards to imaging capabilities but certain patient population considerations lend themselves to favoring PET-CT over MR, In particular, although an increasing number of implanted cardiac defibrillators (ICDs) are MR-compatible, many patients do not have MR-compliant devices and are unable to have MR for sarcoidosis evaluation due to the dangers inherent to the MR's magnetic field and the ferromagnetic properties of ICDs. Cardiac MRI is unable to differentiate between active or inactive cardiac sarcoid. However, PET-CT allows the identification of active cardiac sarcoid; information necessary to guide the clinical management of patients. Furthermore, for patient safety, cardiac PET-CT may be the only effective imaging option available. To date, PET has not been widely used for cardiac sarcoidosis [2]. This has largely been due to the limited availability of PET-CT imaging devices, the primacy of oncology for existing PET-CT scanner use and for many imaging departments, lack of knowledge base for optimized cardiac PET-CT and patient protocols. This review of PET-CT cardiac sarcoidosis will provide an overview of key considerations and provisions necessary for high-quality PET-CT cardiac sarcoidosis imaging. Chief considerations reviewed will include physiologic mechanism of radiopharmaceutical localization, imaging protocol, patient throughput, patient dietary preparation, medication adjuncts for optimization, optimal uptake times, and considerations for departmental collaboration and staffing.

1. PET radiopharmaceuticals and the physiologic mechanism of cardiac sarcoidosis

In the fasting state, myocardial cells will primarily use fatty acids while sarcoid myocardial cells remain in a highly glycolytic state [3]. If the patient can fast

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sufficiently, normal myocardial cells will shift to metabolizing fatty acids while sarcoid affected myocardium will continue using glucose. F-18 fluorodeoxyglucose (FDG) is a glucose analog with a radiologic half-life of 109 minutes that can be administered and correspondingly phosphorylated and trapped in the cell. This will reveal the active inflammatory cells and is valued by the patient's clinician for identifying the extent and severity of active cardiac sarcoid. A patient protocol is outlined in the next paragraph.

2. Imaging protocol

A complete cardiac sarcoidosis protocol may take upwards of 4 hours to complete. This time interval is inclusive of the Rb-82 perfusion imaging, fatty acid optimization, F-18 FDG uptake, imaging and processing. Figure 1 depicts an example of a complete protocol timeline in common use in a multidisciplinary cancer center that also supports cardiology and neurology.

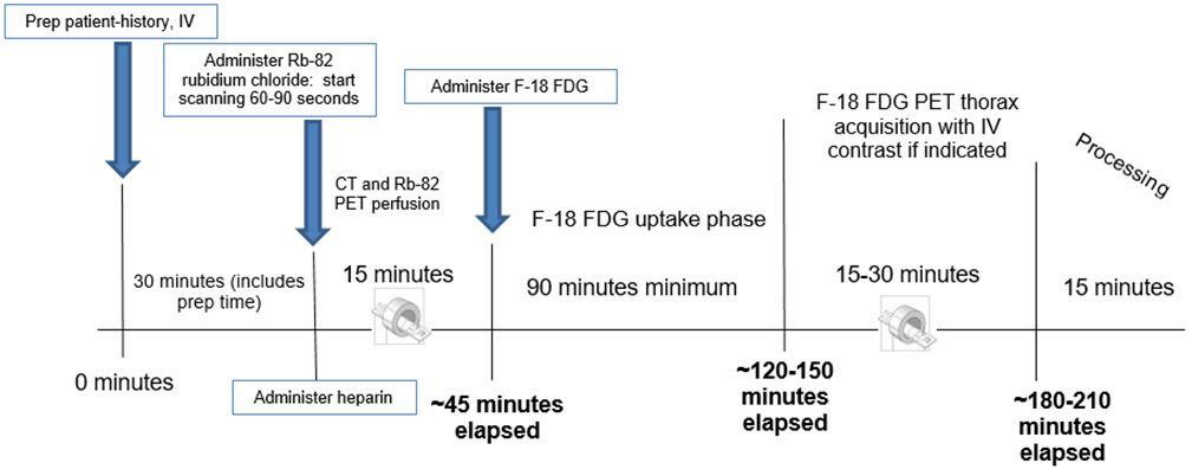


Figure 1: Preparation, acquisition, and processing sequence for Rb-82 rubidium chloride myocardial perfusion and F-18 FDG metabolism imaging.

Importantly, the above regimen allows Rb-82 rubidium chloride perfusion imaging, heparin fatty acid mobilization, F-18 FDG injection, uptake and imaging along with appropriate processing and technologist image quality control considerations. Performing baseline Rb-82 rubidium chloride perfusion imaging is important for identifying baseline alterations in perfusion and comparing to subsequent F-18 FDG metabolism images. Rb-82 rubidium chloride is a potassium analog with a radiologic half-life of 75 seconds. Its uptake in the myocardium is proportionate to the patient's resting perfusion. Typical protocol parameters include the following:

- Patient preparation and fasting: Patient is instructed to follow a low carbohydrate, high fat diet for 48 hours followed by an 18-hour fasting regimen.
- Baseline laboratory values: Blood glucose values should be less than 200 mg/dL. Blood glucose values greater than 200 mg/dL should be verified with a cardiologist or radiologist within the scope of the protocol.
- Radiotracer perfusion dosing: Rb-82 rubidium chloride at 4.44 mBq per kilogram (0.12 mCi per pound)
- Radiotracer metabolism dosing: F-18 FDG at 5.18 mBq per kilogram (0.14 mCi per pound)
- Attenuation correction mode: CT is used for attenuation correction for both Rb-82 rubidium chloride perfusion and F-18 FDG metabolism imaging.

- Imaging mode: Dynamic and gated mode followed by rebinning into static images for tomograms. Image framing rate (number of bins)=8.
- Breathing protocol: Patient is instructed to breath normally during CT. This will ensure that the CT matches the free-breathing PET as closely as possible for optimal attenuation correction.

3. Patient throughput-challenges in supporting multiple service lines in a busy PET-CT laboratory

One challenging aspect of supporting cardiac PET-CT may be the minimal availability of scanner time for cardiac patients. This is the case because many PET-CT scanners are principally used for oncology and neurology making the time available for cardiac imaging less likely. This is especially true in states with restrictive certificate of need (CON) laws and statutes that limit the availability of more expensive imaging equipment consistent with limiting medical imaging costs. Likewise, the primacy of single photon emission computed tomography (SPECT) typically is a better known and conventionally reimbursed imaging strategy. This is despite the available literature describing the higher resolution and capabilities of PET-CT myocardial imaging. This has resulted in continued promotion and use of SPECT [2]. Providers who insist on PET-CT may find themselves in protracted peer-to-peer interactions that harm productivity and available time resources in their practice.

In terms of a mixed PET-CT imaging regimen including cardiology, neurology and oncology, one useful strategy is to perform cardiac PET-CT in dedicated slots that account for patient dietary prep and prolonged fasting as well the need for oncology imaging. Practically, this could mean scheduling cardiac sarcoid tests for the earliest appointment to allow time for the Rb-82 rubidium chloride blood flow images, fatty acid potentiation with heparin and optimal 90 minute or longer F-18 FDG uptake times.

4. Patient dietary preparation

Several strategies have been used to promote fatty acid metabolism in normal myocardial cells and visualization of high glycolytic mode in the sarcoid tissue [4]. Chief among these methods is a prolonged low-carbohydrate, high-fat regimen of at least 24 hours and upwards of 48 hours along with water only for at least 18 hours prior to the F-18 FDG imaging. This will suppress myocardial glucose uptake except for inflammatory cells (active sarcoid). Patient compliance and education are among the greatest impediments to successful myocardial suppression and corresponding image quality [3]. Osborne et all have described lack of suppression and non-diagnostic imaging outcomes in as many as 30% of cardiac sarcoidosis imaging attempts [4]. Figure 2 shows a patient whose myocardium is not adequately suppressed due to improper preparation. The patient's study was repeated with appropriate low carbohydrate diet preparation with resulting favorable myocardial suppression. Figure 3 reveals tomographic versions of the projection images for comparison:

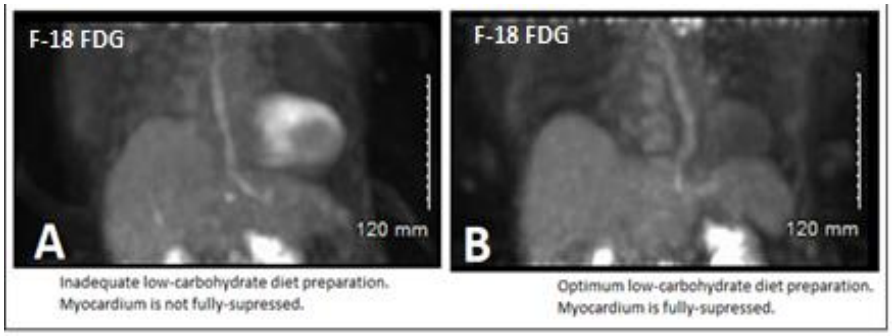


Figure 2: The effect of patient low carbohydrate diet on myocardial suppression. The image on the left (A) represents a patient's maximum

intensity projection (MIP) F-18 FDG with inadequate low carbohydrate diet. The image on the right (B) reveals the same patient repeated with appropriate 48-hour low carbohydrate and excellent suppression of myocardium.

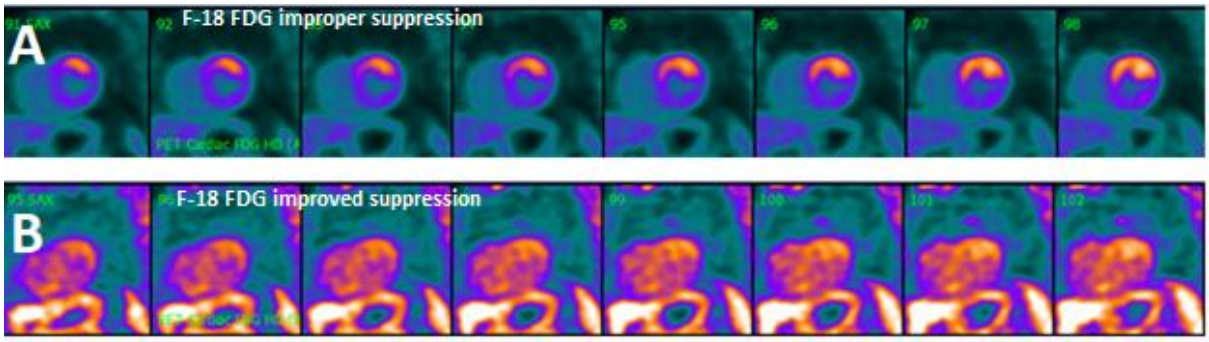


Figure 3: A: Short axis views of inadequate suppression. B: Short axis views of optimum suppression. Note that in some cases, a substantial amount of left ventricular blood pool may be present and require image intensity adjustment for proper interpretation.

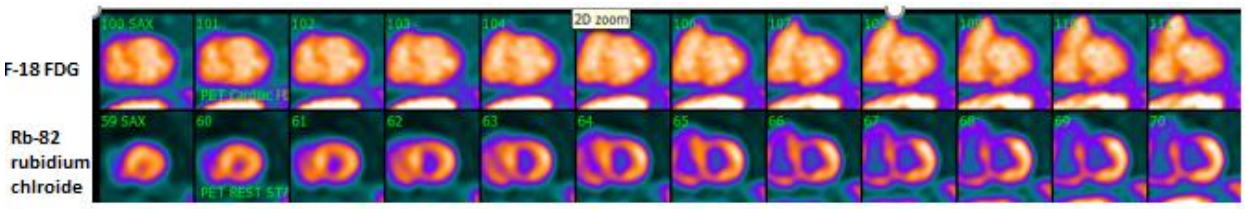
Patients with diabetes or impaired fasting glucose trends will require special attention and coordination with referring and primary care provider. This entails adjusting and adapting insulin or oral diabetes medications to complete the low-carbohydrate, high-fat diet while maintaining safe and near euglycemic blood glucose ranges.

5. Adjunct medications for imaging optimization

Most protocols for optimal myocardial suppression rely on patient fasting and low-carbohydrate, high-fat consumption for an extended period prior to cardiac imaging. However, mobilization of fatty acids and concomitant suppression of the myocardium may be enhanced using unfractionated heparin provided 15 to 30 minutes prior to F-18 FDG injection [5]. Heparin promotes increased lipolysis along with an increase in circulating plasma fatty acids as well as increased utilization of fatty acids by the myocardium. An important consideration will be screening the patient for coagulopathies that may render heparin contraindication. This includes platelets <50 x10*3/µL, heparin induced thrombocytopenia (HIT), or allergy to heparin.

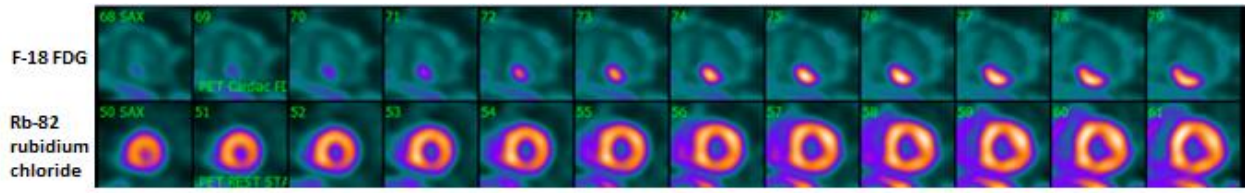
6. Uptake times

It is noteworthy that performing F-18 FDG imaging sooner than 60 minutes may result in images that are difficult to read. This is because the target-to-background and visualization of the suppressed myocardium may be difficult to visualize in comparison to the remaining F-18 FDG in the myocardial left ventricle. Waiting a full 90 minutes is preferred whenever possible for images that provide the interpreting provider with the best opportunity for visualizing the myocardial wall F-18 FDG avidity and corresponding inflammatory tissue. Figure 4 provides a corresponding example of uptake time that was too short as well as optimum 90-minute uptake time:



60-minute F-18 FDG short axis myocardial metabolism images. Blood pool was intense at this earlier uptake

time hampering interpretation and localizing of sarcoid regions of the myocardium.



90-minute F-18 FDG short axis myocardial metabolism images. Blood pool was markedly reduced resulting in more favorable reviewability.

Figure 4: 60 versus 90-minute delay F-18 FDG. Proper patient preparation and myocardial suppression combined with ideal uptake time are important considerations for optimized imaging. Note the diminishing cardiac blood pool in the 90-minute images compared to 60-minute images. It is noteworthy that clearance from myocardial blood pool is not linear and improves significantly as a function of radioisotope decay and 109-minute half- life of F-18 FDG.

In some instances, despite the patient's best efforts at adhering to the myocardial suppression diet and adherence to strict technical criteria, blood pool activity may interfere with favorable visualization. Figure 5 provides a relevant example of proper patient preparation and greater than 90-minute uptake time but excessive blood pool.

7. Interdepartmental collaboration: Cardiology and Radiology

Patients may also have pulmonary or extra-cardiac sarcoidosis that requires evaluation as part of best practices and standard of care. Therefore, it is ideal to also characterize the lung fields, lymphatics and adjacent structures to enhance the referring provider's understanding of the extent of the patient's active sarcoidosis. Correspondingly, optimized CT imaging and intravenous contrast may be used to according to the imaging laboratory's capabilities and within available time constraints. Principally, this will require technologists who are certified in computed tomography and IV contrast usage. Radiologists will need to be engaged for soft-tissue interpretation and collaboration with cardiologists in reporting criteria and practices will be vital for delivering a unified and coherent narrative describing both cardiac and extra-cardiac anatomy via CT and metabolism via PET. Increasingly, radiologists are completing additional training and fellowships in multi-modality cardiac imaging. Ideally, these practitioners can independently provide complete assessments of cardiac anatomy and function in an integrated manner.

8. Staffing

A successful PET-CT cardiac team is comprised of the appropriate compliment of staff for optimum patient care and generating quality images. At a minimum, technologists, registered nurses (RNs) and radiologists and/or cardiologists collaborate for patient preparation, imaging, interpretation and final reporting. Ideally, the technologist should have a background in both nuclear medicine and computed tomography (CT). This is an especially important consideration if optimized images of the hilum and mediastinum will be rendered for characterization of extra-cardiac sarcoidosis such as is likely to occur in pulmonary or lymphatic regions. Importantly, concurrent characterization of lymph adenopathy will incorporate administration of intravenous contrast. Corresponding CT technologist skillsets necessary for IV contrast administration, considerations for contrast induced nephrotoxicity and reconstruction methodologies will all need to be completed by competent and capable nuclear medicine staff [6].

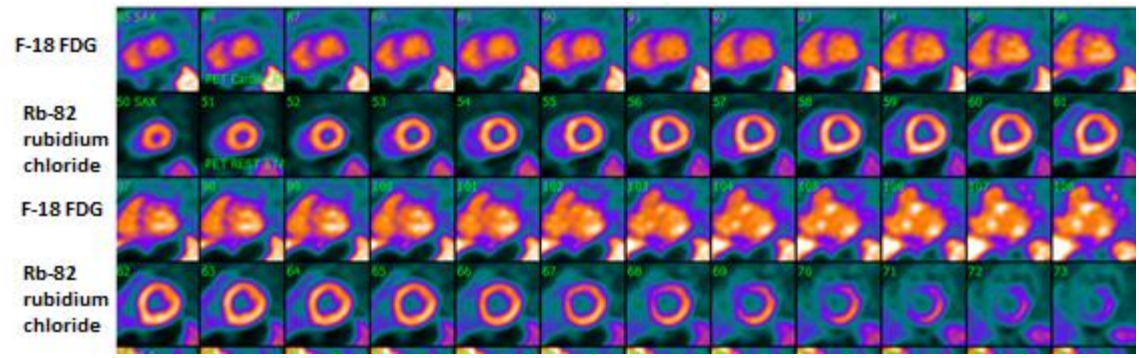


Figure 5: Short axis images following patient fasting for 18 hours, 48 hours of low-carbohydrate, high-fat diet and 100 minutes of uptake time. Relevant patient criteria: 64-year-old female, F-18 FDG dose=525 mBq (14.2 mCi), Rb-82 rubidium chloride dose=736.3 mBq (19.9 mCi), weight=172 pounds (78.2 kilograms), height=62 inches (157 centimeters), BMI=31.

Similarly, the RN complements the efforts of the technologists including administration of adjunct medications such as heparin for myocardial fatty acid optimization and any rescue medications in the event of a patient IV contrast reaction or extravasation. Although dedicated RNs are not required on staff, they will need to be available as resource for administering heparin. Correspondingly, a 2nd RN is highly recommended for medication validation consistent with best practices for administration of high-risk medications such as heparin [7]. Finally, the cardiologist/radiologist team will need to be closely aligned and supportive of the technical and nursing team. This undoubtedly will include direction to technical staff on ideal image reconstruction, IV contrast timing for the CT and continual feedback to technical staff for image quality assurance related to motion correction, image normalization and slice alignment. This trifecta of technologist, RN and radiologist/cardiologist will form the core of safe, effective and high-quality imaging and patient care.

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