Cardiac sarcoidosis: An important niche for PET, but a journey just begun

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Heart failure! From the victim's perspective, the diagnosis has evolved to be as feared as cancer. It is a life-changing diagnosis, a formidable enemy, often a drawn-out ''death sentence''. It affects quality of life, life expectancy, family finances, compliance with multiple medications often taken 2 or 3 times per day, consideration of hardware implants, and frequent tests to help determine etiology and assess response to interventions. From a cardiology practice perspective, heart failure has become a major focus of attention. In the United States alone, some 5.7 million people have heart failure, with approximately 550,000 new cases diagnosed each year. The cost of caring for people with heart failure exceeds $30 billion annually.[1] It should not be surprising that heart failure has become as important a focus for cardiologists in the twenty-first century as coronary artery disease was in the late twentieth century.

Nuclear cardiology is a clinical imaging subspecialty that evolved primarily to address needs in patients with known or suspected coronary artery disease.[2] Education, training, hardware, and software were all fashioned for a specific purpose. In most nuclear cardiology labs, one or two stress protocols, one or two imaging protocols, one or 2 similar SPECT scanners, and one processing and one interpretation tool are used almost exclusively. This does not lend itself well to a more diverse referral indication for cardiovascular radiologic imaging. An important paper in the current issue of Journal of Nuclear Cardiology[3] provides ample demonstration that new imaging equipment and new software tools will be needed if a contemporary nuclear cardiology lab will be a helpful resource to a new era of decision-making.

The paper in question[3] addresses the challenge of following response to therapy for cardiac sarcoidosis using F-18 fluorodeoxyglucose (FDG) PET/CT. Systemic sarcoid is a disease of unknown etiology characterized by development of caseating granulomas in different organs including the heart. Cardiac involvement can occur with and without systemic evidence of the disease. Cardiac involvement may be benign (as autopsy series report presence of clinically unsuspected caseating granulomas in up to 25% of patients with systemic sarcoid[4]), or can be associated with heart block, atrial and ventricular arrhythmias, sudden cardiac death, and systolic and diastolic heart failure.[5] The combination of perfusion imaging using Rb-82 or NH3-ammonia and F-18 FDG has proved helpful in both diagnosing and tracking response to therapy in cases of cardiac sarcoid.[6,7] The information provided relates to an assessment of myocardial fibrosis, active inflammation, left and right ventricular involvement, and left and right ventricular function. Because aggressive therapy with potentially harmful high-dose prednisone and other immunosuppressive agents appear to limit cardiac complications, it is important to both accurately diagnose it and to know when therapies have been effective and can be stopped.

Miller et al[3] used a hybrid PET/CT scanner and a review system that permits both multiplanar co-registration of PET and CT data and quantification of FDG uptake based on standardized uptake values (SUV's). They studied 17 patients meeting clinical criteria for cardiac sarcoid who also had an abnormal baseline PET/CT study both visually and quantitatively with findings consistent with cardiac sarcoid. The patients then

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underwent repeat imaging one or more times during and after therapy. The sequential images were compared visually and quantitatively by 5 different measurements ($SUV_{max,}$ Cardiac Metabolic Volume CMV, Cardiac Metabolic Activity CMA, and measuring volumes of FDG voxels above 2 different thresholds). 8/17 patients were identified as complete responders by visual analysis compared to 10/17 using the best quantified measurements (CMA and CMV). The quantified measurements identified more partial responders than did visual assessment. The authors conclude that visual assessment is insensitive to identify a partial response and that the various quantitative measures have different performance characteristics but overall are more accurate than visual. The paper concludes that the typical software used in a nuclear cardiology lab that has been optimized for perfusion imaging is inadequate for assessment of therapeutic response of cardiac sarcoid.

While an increasing number of nuclear cardiology labs have access to PET scanners, these are usually used for myocardial perfusion imaging in situations where the advantages of PET compared to SPECT are felt to be needed. The software is typically SPECT-centric, with quantitative normal limits modified for differences in the technologies. In perfusion imaging, abnormalities are identified as lower count regions when compared to the best-perfused regions. As the authors point out, hot spot imaging introduces new challenges. Whereas in perfusion imaging, normalization of rest and stress images helps to identify areas of true count deficit, the same normalization procedure for hot spot imaging can lead to noise being amplified such that a normal area can be misinterpreted as abnormal. The authors make a compelling case for the necessity of different software for this different purpose.

There are however several matters specific to this study that need to be emphasized before concluding with certainty that the proposed quantification approaches are revealing disease progression/regression over time, and are superior to visual assessment. First, the study is purely observational in nature, with no ''gold standard'' as to accuracy. There were no outcomes measures such as clinical status, LVEF, or size of perfusion defects to convince that sophisticated and challenging quantitative measurements significantly out-perform informed visual assessment. Second, the patients included in this study mostly had normal left ventricular function (mean LVEF was 53%)—such patients tend to do well over time with greater than 80% survival over 10 years, in sharp contrast to cardiac sarcoid patients with ventricular dysfunction who have a ten-year survival of less than 20%.[8] The lack of change in any measured outcome variable despite changes in quantified measurements suggests that at least in patients resembling those in the study, quantified changes may not be important to management or to outcomes. Further study in patients with more dynamic disease will be important. Third, the authors did not specify a specific patient preparation or image acquisition protocol that they used, nor did they confirm that the exact same protocol was used over the study time-span. The quantification measurements are highly sensitive to blood pool and background counts, such that different protocols over time could as easily explain changes in measurements as changes in disease activity.[9] Finally, the study did not address whether an ECG-gated and attenuation-corrected SPECT perfusion scan co-registered with a non-gated FDG scan acquired in a radiology department would be adequate. Radiology departments typically have PET/CT scanners and the kinds of software needed for SUV measurements, while cardiology departments typically have SPECT scanners and cardiac-dedicated software that does not measure SUV's or permit placement and analysis of reader-selected regions of interest. Multiple bed positions, frequently employed in radiology departments, would also circumvent the problems of normalization identified by the authors. Most cardiology departments would not perform multiple bed position imaging even if they had a PET/CT scanner, because interpretation of findings outside of the heart are beyond their area of expertise. Clearly, for both patient convenience as well as compliance with best practices any such interdepartmental arrangements would need to be carefully crafted so that patients could have both the perfusion and the FDG images performed in close sequence with attention to derivation of maximal information about cardiac structure, function and inflammation as well as information about non-cardiac disease activity. How generalizable such an interdepartmental effort might be is an open question. In conclusion, while it seems likely that quantification measurements will be helpful to visual interpretation, as has been shown for perfusion assessment, the matter is not totally closed by this study and introduces a number of challenging nuances.

The paper raises some interesting questions for nuclear cardiologists. The most important one is whether the findings from this investigation mandate major changes in the structure and operations of a nuclear cardiology lab in order to accommodate current and/or anticipated referrals for diagnosing cardiac sarcoid and, once diagnosed, for following it for therapeutic response. Most nuclear cardiology labs have not yet incorporated PET/CT. The increasing clinical demand related to cardiac sarcoid, myocarditis, device infections, prosthetic valve infections, myocardial viability, and blood flow analysis have convinced this provider that a contemporary cardiology program simply needs access to PET/CT. The education, training, and

proficiencies of most nuclear cardiologists is sufficient grounding for evolution to perfusion PET, assuming an as-of-yet undefined amount of PET-specific exposure. However, inflammation and infection imaging introduce nuances—there are often extra-cardiac in addition to cardiac issues, and hot-spot imaging is substantively different from perfusion (cold-spot) imaging. As such, access to the kind of software used in this study, not typically used in a nuclear cardiology lab, is but one of a number of challenges posed to a contemporary nuclear cardiology lab that agrees to assess such patients.

1. There is currently no CPT code for cardiac sarcoid diagnosis using radionuclide approaches, never mind for follow-up imaging. This provider has been attempting to get a major insurer to cover a follow-up FDG study in a patient with cardiac sarcoid having side-effects from her immunosuppressive therapy. The insurer's position is that this is not a covered indication.
2. Patient preparation is still not standardized, with 20% to 30% of studies deemed definitely or likely non-diagnostic due to failed preparation.[10,11] The issues relate to how strictly and for how long carbohydrates need to be avoided, how long fasting should be before the study, should heparin be used, what should the glucose level be before proceeding with the study, and how long to wait after FDG injection before starting the image. Finally, are there specific criteria on image analysis to confirm an adequate preparation? These are all critically important issues, as the test results will be either non-diagnostic or called into question if there is no ability to make a clear distinction between FDG uptake by normal myocardium as opposed to pro-inflammatory cells.
3. In the absence of a tissue diagnosis, there can be no certainty that the findings on FDG imaging are specific to cardiac sarcoid versus other causes of myocardial inflammation. Criteria likely will depend

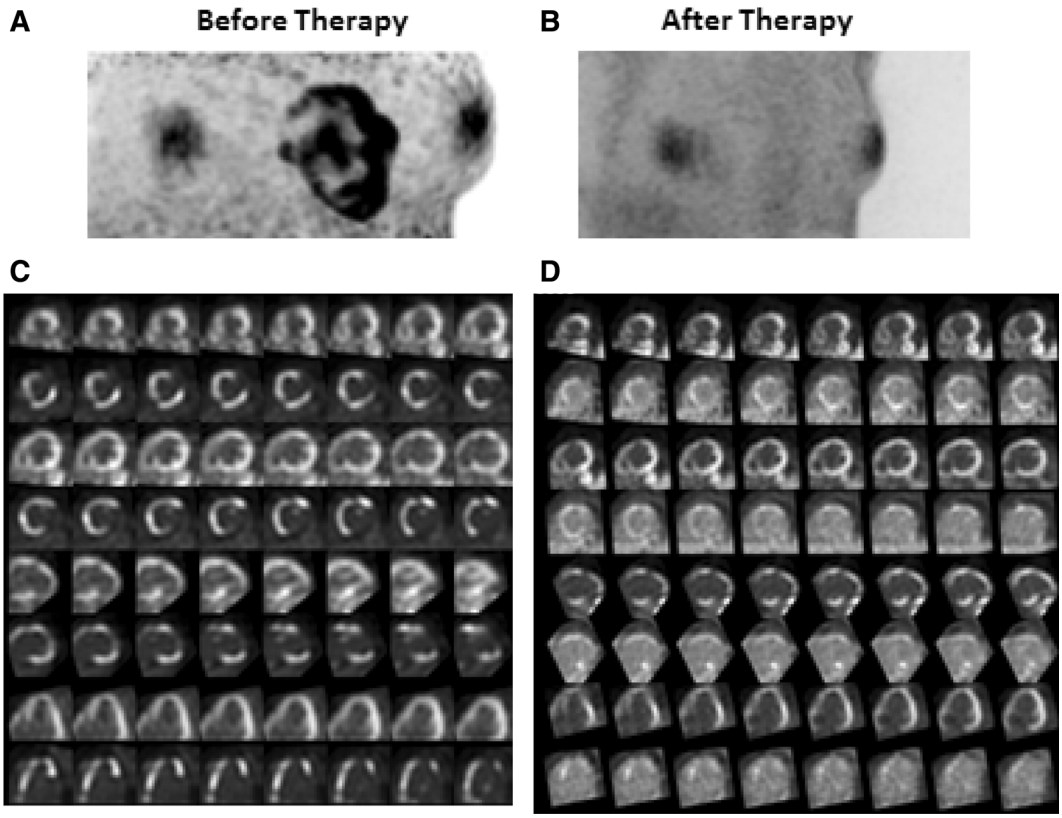

Figure 1. 43 year old female with systemic sarcoid, LVEF 18%, and late gadolinium enhancement on cardiac magnetic resonance. The over-laid FDG and CT images show initial (**A**) extensive cardiac uptake of FDG that is completely resolved on the after therapy (**B**) images. On the bottom row, the normalized Rb-82 (top) and FDG (bottom) images correlate well initially with the co-registered FDG/CT data, but the after therapy images raise uncertainty. The case illustrates well the investigators' contention that quantification techniques need to be validated and incorporated into decision-making.

on correlations with other imaging modalities such as CMR, but have yet to be developed.
4. Optimized software is not yet available for diagnosing and tracking progress/regression of cardiac sarcoid. The authors of the current study have suggested a number of criteria that may be useful, but do not describe a specific package that a nuclear cardiology provider might purchase to facilitate the computations. Importantly, no software has been FDA approved for either diagnosing cardiac sarcoid or tracking its response to therapy.
5. The data available on PET imaging for cardiac sarcoid is based on single-site investigations including small numbers of subjects. No prospective multicenter study has been published or to my knowledge is on-going.
6. The methods described herein utilized a hybrid PET/CT scanner with ECG-gating. While PET/CT scanners are widely distributed across the world, a comparative few are used for cardiovascular imaging. In the United States, likely less than 200 sites have the capability to perform a cardiac sarcoid study as described in this paper, and out of these likely less than a few dozen have attempted this.
7. Concomitant CAD, especially when there is at least one high-grade stenosis, can render this approach non-useful. It is extremely difficult to suppress myocardial FDG uptake in hibernating myocardium, and hence the images cannot distinguish hibernation from inflammation.

Despite these concerns, the authors should be congratulated in advancing concepts about diagnosing and tracking therapeutic responses using PET/CT in patients with known or suspected cardiac sarcoid. Figure 1 shows an example in support of the importance of their work. The co-registered PET and CT images strongly infer that the cardiac sarcoid is in remission, while the normalized Rb-82 and FDG display raises uncertainty. This is a disease that has captured the interest of heart failure and electrophysiology specialists, who will increasingly be looking to PET for answers. Thus far, only a few advanced nuclear cardiology centers are performing and interpreting these kinds of studies. Given the growing interest, studies like this will prove helpful as providers begin to consider what might be needed to address this important cardiac disease.

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