PET/MR imaging of inflammatory cardiomyopathy as a two for one deal: Great value or too good to be true?

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Sarcoidosis is a granulomatous condition of unknown etiology that can affect any organ system. The prevalence of cardiac sarcoidosis (CS), a major cause of morbidity and mortality, is not well known and is estimated around 25% based on autopsy studies[1] and up to 55% based on advanced imaging in patients with biopsy known extra-cardiac sarcoidosis.[2] Endomyocardial biopsy is insensitive, thus a true gold standard for diagnosis of cardiac CS does not exist. Advanced imaging with 18F-FDG cardiac PET and MRI (CMR) has become crucial in diagnosis, management, and long-term follow-up in patients with suspected and confirmed inflammatory cardiomyopathy, in particular CS.[3]

In CS, cardiac PET and MRI image complementary but distinct pathophysiologic processes. PET, a metabolism-based test, uses radiolabeled 18F-FDG to image-enhanced glucose metabolism in the areas where myocardial inflammation is present. CMR, on the other hand, traditionally uses pre and post-gadolinium-based contrast tissue characterization techniques to image areas of increased interstitial edema and fibrosis or scar.[3,4] Gadolinium is an extracellular contrast agent, thus areas of increased gadolinium concentration in the myocardium suggest expansion of the myocardial extracellular volume (ECV) due to inflammation, infiltration, infarction, or fibrosis. CMR does provide diagnostic value regarding active edema/inflammation, but the diagnostic accuracy of CMR-based techniques for inflammation is inferior to PET and less useful clinically. Although both CMR and PET have diagnostic and prognostic implications individually,[4–7] they have complimentary value in diagnostic accuracy and management of CS.[8] Expert centers use either CMR or PET for initial diagnosis of inflammatory cardiac disease such as sarcoidosis, although CMR is favored due to having zero radiation and being highly sensitive. On the other hand, clinicians generally employ PET to clarify difficult diagnostic cases or for serial imaging and to evaluate response to therapy (Figure 1). This concept has sparked interest in hybrid imaging techniques using PET/MRI and development of integrated scanner platforms, which have been rapidly expanding in research and clinical arenas ever since their introduction in 2010. The question has remained if the hybrid PET/MRI platform is able to provide the convenience of a single scan without sacrificing the quality of the individual components.

In this issue of the Journal, Wisenberg et al. prospectively evaluated the imaging characteristics and diagnostic information obtained in a cohort of ten patients with suspected CS who underwent same-day PET/CT and PET/MRI.[9] They demonstrate similar presence/absence and distribution of 18F-FDG uptake in all subjects, with improved contrast between areas of enhanced myocardial uptake compared to background in patients who underwent PET/MRI. This observation is attributed to greater clearance of tracer from the blood pool and longer scan acquisition times which were used

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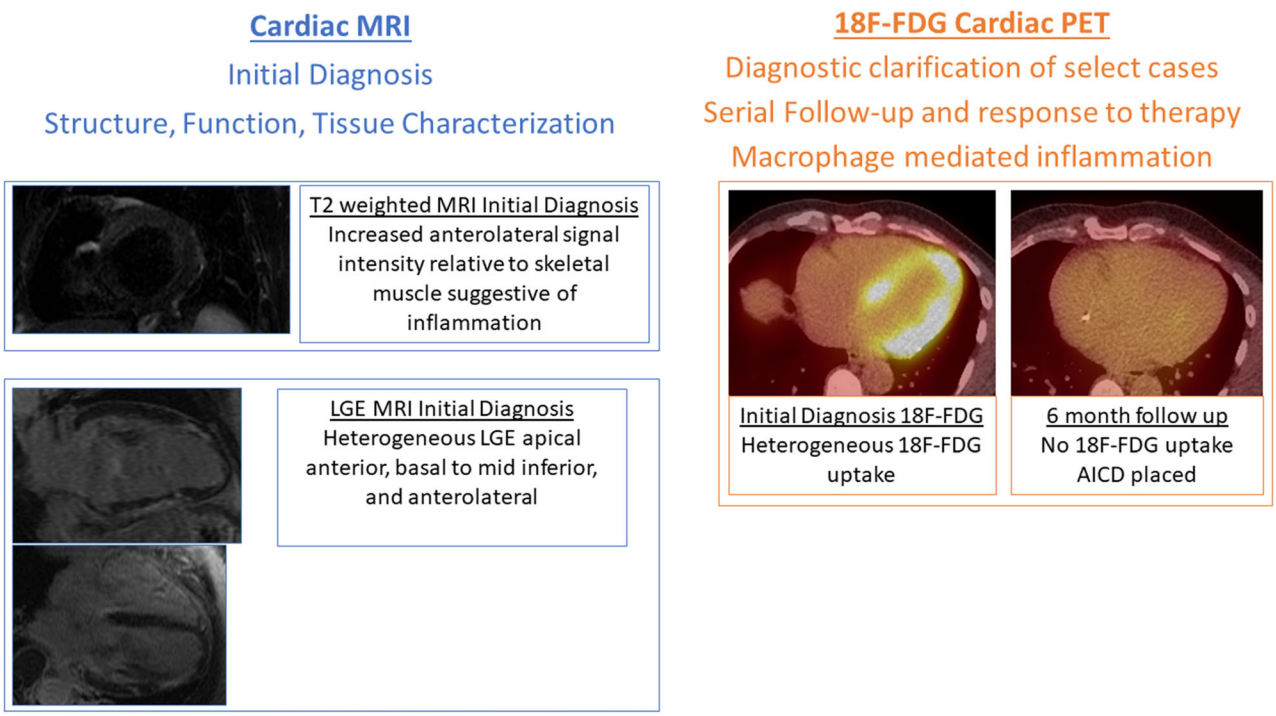

Figure 1. Cardiac MRI and 18F-FDG cardiac PET of a patient with cardiac sarcoidosis. The T2-weighted MRI images demonstrated increased myocardial signal intensity relative to skeletal muscle suggestive of inflammation. However, the inflammation demonstrated by 18F-FDG cardiac PET is more accurate and reliable. Late gadolinium enhancement (LGE) images demonstrated heterogeneously focal abnormal signal in a non-coronary distribution indicative of expansion of the myocardial extracellular volume due to fibrosis in this case. Initial 18F-FDG cardiac PET/CT images demonstrated heterogeneous cardiac uptake as well as extra-cardiac uptake consistent with acute inflammation due to active cardiac sarcoidosis that was confirmed by lymph node biopsy. Six-month follow-up PET/CT after prednisone therapy demonstrated resolution of abnormal 18F-FDG uptake. *AICD*, automated internal cardiac defibrillator.

to compensate for the decay given that PET/MRI was performed after the PET/CT. In eight patients who had prior cardiac MRIs, the regions of delayed myocardial enhancement correlate between the dedicated cardiac MRI and the PET/MRI, with the latter providing improved image quality due the use of a 3 T magnet rather than the 1.5 T dedicated unit.

Although eloquently designed, the study is limited by all the weaknesses of a small sample size. Given only ten patients, significant heterogeneity of imaging findings exists, and it is difficult to speculate whether these are related to the imaging technique and quality or heterogeneous pathophysiology and disease activity of the subjects. Despite the heterogeneity, the authors are able to demonstrate a significant inverse linear relationship between metabolically active volumes (MAV) in the thorax and left ventricular ejection fraction (LVEF), with an $R^2 = 0.86$, $P < .01$, which has known implications in management and prognosis of CS.[5] The generalizability of these findings, however, is limited by the small sample size. Despite the limitations of a small study design, the authors accomplished the goal of demonstrating that combining PET and MRI imaging in evaluation of cardiac sarcoidosis does not result in degradation of imaging quality adding to the growing body of literature supporting this trend (Table 1).

Although the hybrid PET/MRI technique has sparked tremendous interest and enthusiasm, it is important to pause and ask certain questions regarding the benefits, disadvantages, applicability, accessibility, and cost effectiveness of this technology. The current PET/MRI scanners maintain the advantages of the individual techniques by allowing high spatial and temporal resolution, soft tissue characterization, motion correction and soft tissue discrimination, coupled with ability to characterize inflammation.[10] One of the clear benefits of the hybrid PET/MRI is the ability to decrease the amount of ionizing radiation the patients are exposed to by cutting out the CT scan. Dweck and colleagues reported average radiation exposure of 8.2 mSv in their

Table 1. Reprinted with permission from Robson et al[10]

	CT	MR	PET	PET/CT	MR/PET
Anatomic imaging					
Spatial resolution	Strong	Strong	Weak	Strong	Strong
Soft tissue contrast	Weak	Strong	NP	Weak	Strong
Molecular and functional imaging					
Molecular imaging	NP	NP	Strong	Strong	Strong
Exogenous contrast tissue imaging	Moderate	Strong	NP	Moderate	Strong
Tissue characteristics	Weak	Strong	NP	Weak	Strong
Temporal resolution	Moderate	Strong	Moderate	Moderate	Strong
Other					
Complexity	Strong	Moderate	Moderate	Moderate	Weak
Scan time	Strong	Weak	Moderate	Moderate	Weak
Cost	Strong	Moderate	Weak	Moderate	Weak
Robustness of imaging	Strong	Moderate	Moderate	Moderate	Weak
Potential					
Research potential	Moderate	Strong	Weak	Moderate	Strong
Translatability	Strong	Moderate	Weak	Strong	Moderate

CT, computed tomography; *FDG*, fluorodeoxyglucose; *NP*, not possible

PET/MRI patients vs 12.3 in the PET/CT group.[11] This is especially important in patients who are young and require repeat imaging, such as those with CS. Additionally, in combining the two imaging techniques, the total scan time is decreased from multiple scans on separate days and efficiency and patient comfort are improved.

With these advantages, however, come several disadvantages. The limitations of the individual imaging techniques still remain. The hybrid PET/MRI scan continues to be limited by an inability to study patients with advanced kidney disease due to risk of nephrogenic systemic fibrosis for gadolinium when glomerular filtration rate is below 30 mg/dL. A major drawback to hybrid PET/MRI scanner is the additional challenge presented when imaging via PET/MRI versus PET/CT in the presence of implantable cardiac devices, which are frequently found in patients with CS. Implantable device management of heart block is common and the Heart Rhythm Society recommends considering preventive defibrillator implantation for patients with CS due to high incidence of ventricular arrhythmia and sudden cardiac death. Although MRI-conditional pacemaker/ICDs may be safely scanned, they still require pre- and post-scan interrogation for MRI imaging, additional precautions, and contain metal that results in more significant image artifacts on PET/MRI versus PET/CT. Failed myocardial FDG uptake suppression which is reported anywhere from 30 to 50%,[11,12] in addition to limiting adequate assessment of inflammation, creates a clinical conundrum in the small subset of patients who have increased myocardial FDG uptake but normal MRI imaging. Although less common, early myocardial inflammation detected by PET but not by MRI cannot be fully ruled out in this setting. This drawback is very relevant in patients with CS whose insulin sensitivity maybe altered by steroid treatment. Many operational obstacles further impede the technology. These include the cost of purchasing and operating the integrated scanners, as well as the limited availability of technologists trained in both modalities which have resulted in a limited availability of the PET/MRI systems, as summarized by Dr. Robson et al. (see Table).[10]

The true generalizability of hybrid PET/MRI for CS, therefore, remains in question. Although the potential benefits are undeniable, the practical value in patients with suspected or confirmed CS is yet to be determined. In patients who have normal cardiac MRI, the addition of PET is unlikely to increase the likelihood of detecting active cardiac sarcoidosis other than for selected cases. This was demonstrated in a study by Vita and colleagues in which only 2 out of 107 subjects were reclassified as having a high probability of CS given abnormal myocardial FDG uptake in the setting of normal MRI.[8] Additionally, the assessment of CS response to therapy is very robust with PET imaging,[5] with no clear benefit to longitudinal MRI follow-up. The

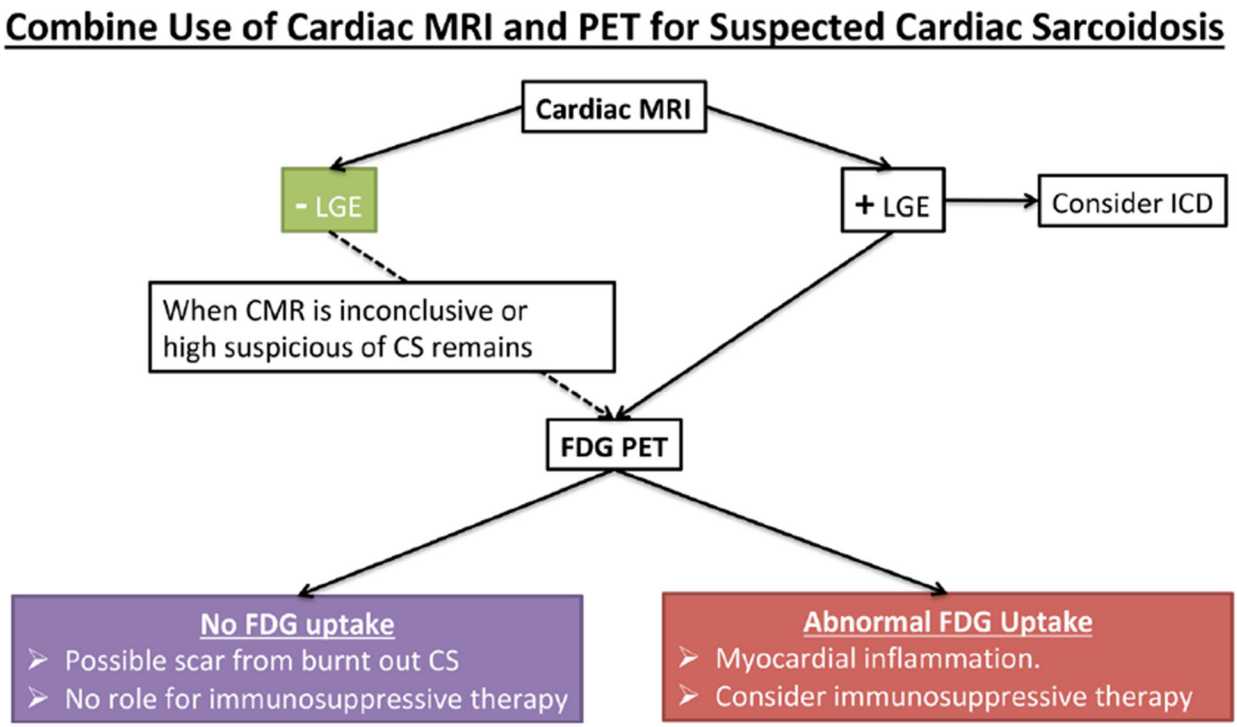

Figure 6. Algorithm for cardiac sarcoidosis (CS) diagnosis. A suggested algorithm for incorporating cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) for evaluating individuals with suspected CS. CMR indicates cardiac magnetic resonance; FDG, F18-fluorodeoxyglucose; and LGE, late gadolinium enhancement.

Figure 2. Reprinted with permission from Vita et al[8].

utility and cost effectiveness of doing simultaneous scans when one can potentially be avoided needs to be further evaluated and a more stepwise imaging approach as suggested by Vita may be more realistic at this time (Figure 2).[8]

It is important to highlight that since the introduction of hybrid PET/MRI scanners, many technological advances have made it more feasible, accurate, and robust and have led to the new applications of this technology. We, therefore, applaud Dr. Wisenberg and colleagues on their contribution in the advancement of this exciting technology. It is only through continued research efforts such as theirs that the previously mentioned challenges can be overcome and the question asked by Dr. Schindler a little over a year ago in this same journal, ''Quo Vadis?'' answered.[13]

Disclosure

No financial conflicts of interest. The views expressed in this article are those of the author and do not reflect the official policy of Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or U.S. Government.

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