Multimodality imaging in the diagnosis and management of cardiac sarcoidosis

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Sarcoidosis is a multisystem disorder that is characterized histologically by non-caseating, non-necrotic granulomas. Although it most commonly manifests in the lungs or with lymphadenopathy, it can affect any organ. Cardiac Sarcoidosis (CS) occurs with an incidence of 5%-39% depending on detection method, and has a wide range of clinical manifestations, from no symptoms to sudden cardiac death.[1] CS is considered to be the second leading cause of death by sarcoidosis in the United States,[1] making diagnosis and monitoring the progression of disease of utmost importance.

Guidelines of the Japanese Ministry of Health and Welfare (JMHWG) from 2006 have gained wide acceptance as a reference standard for diagnosing CS.[1] They outline diagnostic criteria that include histologic confirmation of CS by myocardial biopsy or clinical confirmation based on a combination of major and minor criteria, which include Gallium-67 uptake as a major criteria.[2] Gallium-67 has since been shown to be inferior in its sensitivity and diagnostic accuracy for CS as compared to Fluorine-18-fluorodeoxyglucose Positron Emission Tomography (FDG-PET), which is not mentioned in the criteria. Additionally, diagnosing CS via myocardial biopsy is unreliable due to the characteristic skip lesions of CS and sampling error.[1-3]

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Multiple studies have evaluated the use of FDG-PET and Cardiac Magnetic Resonance (CMR) in diagnosing CS and predicting adverse outcomes. However, a diagnostic gold standard has yet to be identified. Given the multimodality imaging landscape, it is important to understand the underlying imaging concepts and capabilities of each modality.

FDG-PET

FDG-PET employs a glucose analog to identify areas with increased inflammation. Areas with active cardiac inflammation have increased glucose metabolism and increased activity on PET.[4] Myocardial perfusion imaging (MPI) is routinely performed in conjunction with FDG-PET to detect areas of myocardial scar. MPI can be obtained from a resting Single-Photon Emission Computed Tomography (SPECT) study using common Technetium-99m or Thallium-201 radiotracers, or with PET perfusion imaging using Rubidium-82.[2] Areas of apparent scar can also result from significant inflammation due to localized edema and compression of adjacent vasculature. In serial follow-up with appropriate treatment, one may see improvement in both areas of active inflammation on FDG-PET as well as areas of apparent scar on MPI.[2] Depending on the degree of active inflammation on FDG-PET and resting perfusion defects on MPI, disease can be classified as normal (no inflammation or scar), early stage (active inflammation with mild or no scar), progressive disease (active inflammation with moderate scar), or fibrous disease (minimal or no inflammation with severe scar).[2] This method of classification highlights the combined use of metabolic and perfusion imaging in the clinical management of CS.

FDG-PET has been shown to be useful for diagnosing CS as well as predicting adverse outcomes. A recent meta-analysis[5] analyzed 7 studies with a total of 164 patients to determine the accuracy of FDG-PET for diagnosing CS when using JMHWG as a gold standard.

This study reported a range of sensitivities and specificities of 79%-100% and 38%-100%, respectively, for diagnosis of CS by FDG-PET.[5] Despite outlier data that affected specificity, likely related to physiologic glucose metabolism, the study demonstrated high diagnostic accuracy.[5]

Blankstein and colleagues demonstrated the ability of FDG-PET to predict adverse events with a study of 118 patients without coronary artery disease who underwent PET with MPI.[6] Adverse events (death or sustained ventricular tachycardia) significantly correlated with positive findings on MPI and FDG-PET despite adjusting for left ventricular ejection fraction and clinical criteria. Interestingly, the investigators observed a discrepancy between FDG-PET and JMHWG, noting a higher event rate in patients with positive imaging findings and negative clinical criteria than in patients with negative imaging findings and positive clinical criteria.[6]

FDG-PET does have disadvantages and limitations. One obvious disadvantage is the exposure to ionizing radiation. However, another that is unique to FDG-PET is the effect of physiologic glucose metabolism on results. Physiological glucose metabolism of myocytes can be heterogeneous and can lead to false positive FDG-PET results.[1] Hence, suppression of background glucose metabolism is integral to differentiating areas of active inflammation from normal myocardium. There is no consensus on a standard protocol prior to FDG-PET to best suppress background glucose metabolism. The lack of standardization limits the ability of meta-analyses and multi-center trials to effectively gauge the diagnostic accuracy of FDG-PET as compared to clinical criteria and other imaging modalities.

Recent studies have proposed alternate tracers that may bind more specifically to inflammatory cells. Gormsen and colleagues[7] compared PET imaging with ^{68}Ga-DOTA-NaI-octreotide (^{68}Ga-DOTANOC) and FDG-PET in 19 patients using JMHWG as a reference standard. ^{68}Ga-DOTANOC binds to somatostatin receptors on inflammatory cells in sarcoid granulomas. PET with ^{68}Ga-DOTANOC had better diagnostic accuracy and inter-observer agreement than FDG-PET.[7] Another novel PET tracer, ^{18}F-fluoromisonidazole (FMISO), was reported by Manabe and colleagues.[8] FMISO is widely used in PET for visualizing and quantifying regional hypoxia, and has been shown to have increased uptake in malignant tumors expressing hypoxia-inducible factor (HIF)-1a and vascular endothelial growth factor (VEGF), also observed in granulomas of sarcoidosis.[8] Evaluation of these novel PET tracers leads the way for future investigation with hopes of improving the diagnostic performance of PET for CS.

CARDIAC MAGNETIC RESONANCE

CMR is routinely used in the evaluation and management of patients with CS. The ability of CMR to detect CS is based on the presence of late Gadolinium enhancement (LGE).[9] Being an extracellular contrast agent, Gadolinium has a slower washout period from areas of scar, a property that allows it to highlight even the smallest areas of fibrosis.[10] As formation of non-caseating granulomas takes place, there is an increase in the amount of LGE as a result of extracellular space expansion and scar formation.[10] When compared to the gold standard (JMHWG), Smedema and colleagues reported CMR with LGE to be 100% sensitive for CS, making it the preferred initial imaging modality for patients with extracardiac sarcoid undergoing a workup for suspected CS.[9] The most common areas of LGE were the basal and lateral aspects of the left ventricle, both of which correlated well with the autopsy specimens in patients with CS.

Since cardiovascular mortality is the most common cause of death in patients with extracardiac sarcoidosis,[11] it can be expected that the presence of LGE in myocardial tissue would portend a poorer overall prognosis. The prognostic value of LGE in patients with extracardiac sarcoidosis has been well established. Patel and colleagues reported a 26% incidence of myocardial LGE in patients with systemic sarcoidosis undergoing CMR.[11] Those patients who exhibited delayed enhancement had an 11.5 times higher rate of cardiac death compared to patients without enhancement. More recently, Murtagh and colleagues evaluated the prognostic role of LGE in patients with sarcoidosis and preserved left ventricular ejection fraction.[12] In their series, the 41 patients (20%) who exhibited LGE on CMR had a 20 times higher likelihood of experiencing cardiac death or sustained ventricular tachycardia. Strikingly, none of the patients with LGE who died would have been classified as having CS based on JMHWG.

Despite its high sensitivity and significant prognostic value, the specificity of CMR for CS is only around 78%.[9] Non-coronary patterns of LGE can be exhibited by cardiomyopathies unrelated to sarcoidosis. LGE alone also fails to differentiate between the active inflammatory and chronic fibrotic phase of CS.[10,13] As a result, adjunctive MR imaging sequences that are sensitive for acute inflammation are needed to differentiate between the two.

One such technique is T2-weighted imaging, in which increased signal is observed from areas of increased free water content as would occur in the setting of edema and inflammation.[10] Crouser and colleagues initially demonstrated that T2-weighted

Table 1. Imaging follow-up of cardiac sarcoidosis

Study	Number of patients	Modality	Baseline imaging abnormalities	Median follow-up	Imaging parameters	Impact of treatment on imaging parameter	Clinical endpoints	Comments
Lee et al.[17]	16 Patients 2-6 serial scans per pt 38 study intervals	FDG-PET	N/A	8.7 months	FDG uptake	(See comments)	Symptoms physical exam NYHA classification EKG changes	17 study intervals with clinical improvement and decreased FDG uptake 10 study intervals with clinical stability and reduced FDG uptake 11 study intervals with clinical worsening and increase in FDG uptake
Orii et al.[14]	10	FDG-PET	8/10 patients	N/A	FDG uptake	Reduction of FDG uptake in all 8 patients	Complete heart block	Resolution of CHB in 6/8 patients following treatment During 26 months follow-up CHB recurred in 50% of patients
Osborne et al.[18]	23	FDG-PET	18/23 patients	6.5 months	FDG uptake		Ejection fraction	7.9% increase in EF per 10 g·mL-1 reduction in SUV
Yamagishi et al.[19]	17	FDG-PET	14/17 patients	1 month	FDG uptake	Reduction of FDG uptake in 5/7 patients	None; 7 patients treated with Steroids	7 patients treated with steroids: 5 had reduction of FDG Uptake 2 had complete resolution of uptake
Crouser et al.[15]		CMR		>4 months	T2 signal	15.4% reduction in T2 signal	Cardiac arrhythmias	83% improvement in cardiac arrhythmias
Matoh et al.[20]	4	CMR	4/4 Patients	2-12 months	LGE	Reduction in the % LGE in 3/4 patients	Ejection fraction	EF improved in one patient with reduction in LGE
Vignaux et al.[21]	12	CMR	11/12 (T2), 10/12 (LGE)	12 months	T2 signal, LGE	Resolution of MRI findings in 2 patients Improvement in MRI findings in 4 patients Stable MRI findings in 3 patients Worsening MRI findings in 3 patients	Serum ACE levels high resolution CT extra-thoracic involvement	2 pts with resolved MRI findings—both cleared clinically 4 pts with improved MRI findings—1 cleared clinically, 3 improved clinically 3 patients with stable MRI findings—all 3 stable clinically 3 patients with worsening MRI findings—all 3 worsened clinically

signals appeared more frequently than LGE in patients with extracardiac sarcoidosis suspected of having myocardial involvement, although the clinical significance was unclear.[13] Orii and colleagues subsequently compared the results from FDG-PET and CMR (both LGE and T2-weighted sequences) in patients with CS presenting with complete heart block.[14] Patients with complete heart block had higher FDG uptake ($P = 0.001$) as well as increased T2 activity ($P = 0.0001$) in the interventricular septum compared with patients without block, although there were no differences in the degree of LGE ($P = 0.232$). The authors concluded that myocardial inflammation rather than fibrosis was responsible for complete heart block in patients with CS. This study supported the hypothesis that T2-weighted imaging may have a role in identifying the acute inflammatory phase of CS.

Crouser and colleagues recently evaluated the role of CMR T2 signal in patients undergoing immunosuppression therapy for CS.[15] Peak myocardial T2 signals were significantly lower following treatment as compared to the pretreatment values (59.2 ± 6.1 vs 70.0 ± 5.5 ms, $P = 0.017$, respectively), suggesting that CMR with T2 weighting may be useful in monitoring patient response to treatment. However, direct comparison of T2-weighted imaging to FDG-PET in a broader patient population would be useful. Despite significant advances in CMR T2-weighted imaging, FDG-PET remains the imaging modality of choice for detecting active inflammation in patients with CS.

HYBRID PET/MR

The recent emergence of hybrid imaging with FDG-PET and CMR provides an exciting direction for future investigation. This can be achieved by either co-registering separately acquired scans, or using a PET-CMR hybrid scanner. This novel method combines the strengths of both imaging techniques to provide a wealth of information on cardiac function, burden of scar/fibrosis, as well as presence and extent of active inflammation.[3] An example of this method of hybrid imaging with FDG-PET and CMR was recently described by White et al.[16] Hybrid imaging with CMR and FDG-PET, along with the emergence of novel tracers and CMR-conditional defibrillators provides multiple avenues of investigation with hopes of improving our ability in diagnosing this disease and perhaps, some day, designating a gold standard for diagnosis and follow-up.

DISCUSSION

In this issue, Lee and colleagues have successfully demonstrated that FDG-PET correlates well with treatment response emphasizing the role of diagnostic imaging in both the diagnosis and management of patients with CS.[17] CS is a disease process laden with diagnostic challenges, a wide range of clinical presentations, and potential for cardiomyopathy, cardiac arrhythmias, and/or sudden cardiac death. Therefore, the ability to diagnose CS and initiate early effective treatment is of utmost importance. JMHWG has gained wide acceptance as a clinical reference standard for diagnosing CS but has its limitations. While CMR and FDG-PET have their respective advantages and disadvantages, both imaging modalities have been shown to have utility in diagnosing CS and providing important prognostic information.[2,10] Once treatment is initiated, monitoring for improvement or progression of disease is important for guiding further therapy. Lee and colleagues showed a significant correlation between serial FDG-PET imaging and clinical parameters in patients being followed for CS.[17] Prior studies have shown correlation between serial imaging with FDG-PET or CMR and the effect of treatment on indices such as ejection fraction and cardiac arrhythmias (Table 1). However, these studies have not specifically evaluated the impact of treatment on clinical parameters such as heart failure status and subjective symptoms. By correlating the radiographic disease burden with these clinical parameters, Lee and colleagues illustrated that it is feasible to use serial FDG-PET imaging in assessing patient's treatment response to therapy. Still, there is much work to be done in order to improve these imaging modalities and further define their diagnostic and prognostic capabilities. Given the complimentary nature of both imaging modalities, future guidelines on the diagnosis and management of cardiac sarcoidosis are likely to employ the combination of both CMR and FDG-PET in their algorithms.[10]

Disclosure

The authors report no conflict of interest.

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