FDG PET imaging in suspected cardiac sarcoidosis: diagnosis vs. prognosis

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Though diagnosing cardiac sarcoidosis remains a challenge, knowledge of the clinical entity has increased over time. The differential diagnosis for a patient with new conduction disease, ventricular arrhythmias, or heart failure with abnormal imaging findings often includes cardiac sarcoidosis. Because the diagnostic yield of endomyocardial biopsy remains poor, clinicians continue to heavily rely on advanced cardiovascular imaging, namely cardiac magnetic resonance imaging (MRI) and/or ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET), to help make the diagnosis. Though guidelines recommend that cardiac MRI or FDG PET imaging findings be coupled with extracardiac biopsy-proven sarcoidosis to make the diagnosis,¹ in clinical practice patients are sometimes given the diagnosis based on clinical presentation and abnormal imaging findings alone. Moreover, extracardiac biopsy is not always feasible, especially in cases of suspected isolated cardiac sarcoidosis.² This further underscores

the diagnostic importance of high-quality cardiac MRI and FDG PET in suspected cardiac sarcoidosis.

Previous studies have also identified the prognostic importance of specific cardiac MRI and FDG PET findings in cases of suspected cardiac sarcoidosis. A study that prospectively studied 81 consecutive patients with biopsy-proven extracardiac sarcoidosis found that patients with late gadolinium enhancement (LGE) on cardiac MRI had a ninefold higher rate of adverse events (all-cause death, defibrillator shock, or pacemaker requirement) and an 11.5-fold higher rate of cardiovascular death than patients without LGE.³ A systematic review and meta-analysis that included seven studies of 694 subjects with suspected cardiac sarcoidosis who underwent cardiac MRI found that the pooled relative risk of all-cause mortality was 3.38 ($P = 0.04$) in the LGE-positive group when compared with the LGE-negative group.⁴ The relative risk of a combined endpoint of all-cause death or ventricular arrhythmia was 6.20 ($P < 0.001$).

In a retrospective study from our center that included 118 consecutive patients who were referred for FDG PET for suspected cardiac sarcoidosis, the annualized event rate (all-cause mortality or sustained ventricular tachycardia) was 7.3%, 18.4%, and 31.9% ($P < 0.001$) for patients with normal perfusion and no FDG uptake or diffuse FDG uptake, abnormal perfusion or focal FDG uptake, and abnormal perfusion and focal FDG uptake, respectively.⁵ In a multivariable analysis including left ventricular ejection fraction (LVEF), Japanese Ministry of Health and Welfare (JMHW) criteria, and pattern of FDG PET abnormality, the presence of abnormal perfusion and focal FDG uptake on FDG PET had the strongest association with the composite outcome.⁵ Additionally, in a multivariable model that included focal right ventricular (RV) FDG uptake, LVEF, and JMHW criteria, focal RV FDG uptake remained

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associated with the composite outcome. In this study, 38 patients (34%) met JMHW criteria for the diagnosis of cardiac sarcoidosis, 30 (26%) had biopsy-proven extracardiac or cardiac disease, and 31 (26%) were on steroid therapy at the time of FDG PET imaging.⁵ In a retrospective study of 203 patients referred for FDG PET for suspected cardiac sarcoidosis at the Cleveland Clinic, summed rest score (SRS) in segments with abnormal FDG uptake (perfusion-metabolic mismatch) and the coefficient of variation (a marker of heterogeneous FDG uptake)⁶ were significantly associated with adverse events after multivariable adjustment.⁷ In this study, 30 patients (15%) met JMHW criteria for the diagnosis of cardiac sarcoidosis, 146 patients (72%) had biopsy-proven extracardiac sarcoidosis, and 71 (35%) were on immunosuppressive therapy at the time of FDG PET imaging. Finally, in a study from the Barts Heart Centre that included 51 consecutive patients with suspected cardiac sarcoidosis who underwent simultaneous hybrid cardiac MRI and FDG PET imaging, the presence of LGE on cardiac MRI and RV FDG uptake on FDG PET were independent predictors of adverse events (all-cause mortality, aborted sudden cardiac death, sustained ventricular arrhythmia, complete heart block, or heart failure hospitalization).⁸ In this study, 33 patients (65%) met JMHW criteria for the diagnosis of cardiac sarcoidosis, eight patients (14%) and 44 patients (86%) had biopsy-proven cardiac and extracardiac sarcoidosis, respectively, and 19 patients (37%) were on immunosuppression at the time of hybrid imaging.

In this issue of the *Journal of Nuclear Cardiology*, Patel, Pieper, and colleagues aimed to expand the body of knowledge regarding the role of FDG PET in evaluating prognosis in cases of suspected cardiac sarcoidosis. They specifically asked the following question: in patients with suspected cardiac sarcoidosis *not on immunosuppressive therapy*, what are the FDG PET findings associated with adverse events (all-cause mortality or ventricular arrhythmia)?⁹ The investigators retrospectively studied 197 patients referred for FDG PET at the University of Michigan Hospital. Covariates with significant association ($P < 0.05$) with adverse events were reduced LVEF, history of ventricular arrhythmia, and SRS. Other candidate predictors included atrial FDG uptake ($P = 0.068$) and RV FDG uptake ($P = 0.061$). In multivariable modeling with stepwise forward selection, reduced LVEF, history of ventricular arrhythmia, and SRS remained significantly associated with adverse events. In a subset of patients who met the Heart Rhythm Society (HRS) criteria¹ for the diagnosis of cardiac sarcoidosis ($n = 52$), only SRS was associated with adverse events after multivariable modeling with stepwise forward selection.

There are several notable limitations of this study, which may account for the limited association of FDG PET imaging and adverse events. First, 38 of the 41 (93%) primary endpoint events were ventricular arrhythmia. Accordingly, it may not be surprising that a prior history of ventricular arrhythmia had the strongest association with adverse events. It would have been interesting to see the results of a stratified analysis involving patients with and without a history of ventricular arrhythmia. Additionally, of the 17 patients with RV FDG uptake, 3 (18%) had diffuse (not focal) RV uptake. Diffuse RV FDG uptake can be a non-specific finding and classifying this finding as negative may have changed the univariable and/or multivariable analysis results.

Most importantly, as discussed by the authors, only 19 patients (10%) met JMHW criteria for the diagnosis of cardiac sarcoidosis and only 64 (33%) had biopsy-proven extracardiac sarcoidosis at the time of FDG PET imaging. The number of patients that met HRS criteria post-FDG PET during the study period via abnormal FDG PET or histological assessment did increase to 52 (26.4%). However, this percentage is still much smaller than previously investigated in the studies detailed above. This may be due to increased use of FDG PET among patients with suspected cardiac sarcoidosis, and accordingly a lower yield of identifying patients with active disease. However, it is also possible that only including immunosuppressive therapy naïve patients came at the cost of including more patients without inflammatory cardiomyopathy. This is highlighted by the fact that 73 of the 197 patients (37%) had normal FDG PET findings and alternate diagnoses, as detailed by the authors, for which FDG PET results would not routinely be used to aid in prognostic assessment.

Finally, some of the potential reasons offered by the authors as to why their results differ from prior studies merit further discussion. We really do not know if the cohort included patients “earlier in the disease process” as the natural history of cardiac sarcoidosis is not well-defined and does not seem to have a linear progression (as is seen in other conditions). Also, better dietary preparation prior to imaging was unlikely to be responsible for the results as diffuse, non-specific FDG uptake was not treated as a “positive” result in prior studies. In fact, if prior studies had more non-specific uptake categorized as abnormal, that would lower the prognostic value of FDG PET, whereas prior studies showed a stronger association between metabolic abnormalities and adverse outcomes.

Despite these important limitations, Patel, Pieper, and colleagues have highlighted what we know and what we don't know with regard to prognosis in suspected cardiac sarcoidosis cases. Namely LV systolic

dysfunction, evidence of scar via cardiac MRI or nuclear perfusion imaging, and a history of ventricular arrhythmia are all risk markers for adverse events in this population. Ongoing investigation is needed to study if LV FDG uptake, focal RV FDG uptake, or myocardial perfusion-metabolic mismatch offer incremental value for identifying adverse events, and in which patient populations. Though reduction in intensity and extent of FDG uptake has been shown to be associated with improvement in LV systolic function,¹⁰ data regarding immunosuppressive therapy and improved outcomes in cardiac sarcoidosis remain limited.^{11,12} As we continue to treat patients with evidence of myocardial inflammation, especially in the presence of LV systolic dysfunction, high-grade AV nodal disease, or ventricular arrhythmias, with immunosuppression,¹³ Patel et al. have emphasized the need to carefully examine how various imaging and non-imaging biomarkers perform across different populations of patients with suspected cardiac sarcoidosis.

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