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EDITORIAL COMMENT

Quantitative Assessment of Myocardial Blood Flow in Cardiac Sarcoidosis

A Potential Next Step in the Further Integration of FDG-PET in Imaging Management?*

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Sarcoidosis is a noncaseating granulomatous disease of uncertain etiology predominantly involving the pulmonary system. Cardiac involvement is variable, ranging from 20% to 76% (1,2) and accounts for up to 85% of sarcoid-related deaths in certain populations (1,3).

Accurate diagnosis of cardiac sarcoidosis (CS) is critical but is limited by the nonspecific presentation of CS and the low sensitivity of endomyocardial biopsy, electrocardiography, and conventional imaging (4). Further confounding factors include the small sample size of studies of this relatively uncommon disease and the lack of prospective validation of the diagnostic criteria (3). Advanced imaging for CS with cardiac magnetic resonance and fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) have emerged and hold great promise for improved diagnostic capabilities. Specifically, a meta-analysis of 7 small studies of PET in 164 patients reported a pooled sensitivity of 89% and specificity of 78% for diagnosing CS (5) using the Japanese Ministry of Health and Welfare Criteria (6) as the gold standard. Given this high diagnostic accuracy, ^{18}F-FDG-PET is now included in a contemporary diagnostic algorithm for CS (7). Consequently, there is growing interest in using ^{18}F-FDG-PET in diagnosing, managing, and risk stratifying patients with suspected or known CS.

Assessment of CS using ^{18}F-FDG-PET is generally performed in conjunction with a resting myocardial perfusion scan, which permits differentiation of the spectrum of CS. Focal ^{18}F-FDG uptake with or without a perfusion defect is compatible with active inflammation. The presence of perfusion defect(s) in the same or other region(s) suggests compression of the microvasculature by either inflammation and/or granulomas. A resting perfusion defect without ^{18}F-FDG uptake is compatible with either scar or with effectively treated CS. The presence of both abnormal myocardial perfusion and ^{18}F-FDG uptake has the worst outcome among the PET patterns and is associated with a 4-fold increase in the annual rate of ventricular tachycardia or death compared with that of patients with normal imaging (8). Patient preparation prior to ^{18}F-FDG administration is also critical for achieving adequate suppression of physiological myocardial glucose uptake to visualize inflammation. The current approach in a number of institutions is to require 2 high-fat, low-carbohydrate meals followed by a long fast of at least 12 h before the PET study (9). In addition to cardiac ^{18}F-FDG imaging, limited whole-body ^{18}F-FDG imaging from the base of the skull to the upper thighs is highly recommended because the presence of extracardiac sarcoidosis is important for the diagnosis of CS and for guiding management.

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Whereas visual assessment of resting perfusion has thus far been used in conjunction with ^{18}F-FDG imaging of CS, absolute quantification of myocardial blood flow (MBF), stress perfusion, and calculation of myocardial flow reserve (MFR) are also possible with PET. PET MBF quantification is highly reproducible and accurate and adds incremental diagnostic and prognostic value in patients with known or suspected coronary artery disease (10,11). In this issue of *iJACC,* Kruse et al. (12) characterized absolute resting and

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hyperemic PET MBF and MFR in a small CS population to determine the relationship between MBF and inflammation and the impact of suppression of inflammation via corticosteroid therapy on MBF. This retrospective study included 32 consecutive patients with "known or suspected" CS referred for ^{18}F-FDG-PET. In their study, patients consumed a very high-fat, low-carbohydrate diet the day prior to the study followed by a prolonged fast of >12 h. Image acquisition was carefully performed, and images initially interpreted independently by 2 experienced readers with consensus reading to resolve any differences. The ^{18}F-FDG PET analysis also included calculation of standard uptake values (SUV) to provide a measure of the severity or amount of inflammation. PET MBF quantification was performed using ^{13}N-ammonia and a 2-compartment tracer kinetic model at rest and during regadenoson stress, and MFR was calculated. Of the original cohort of 32 patients, 13 underwent a total of 18 repeat examinations for assessment of MBF and MFR. In their analysis, Kruse et al. (12) divided the original 32 patients into 2 groups: those with abnormal ^{18}F-FDG uptake and no resting perfusion defects; and those with both abnormal ^{18}F-FDG uptake and perfusion defects. They subsequently compared ^{18}F-FDG-positive to ^{18}F-FDG-negative regions and demonstrated that resting MBF was similar regardless of the presence or absence of inflammation (inflammation defined as increased SUV uptake). However, with hyperemia, ^{18}F-FDG-positive regions in all patients demonstrated decreased MBF and a lower MFR than ^{18}F-FDG-negative areas did. Thirteen patients underwent repeat studies and results suggest that global MFR decreased in "nonresponders" compared with "responders" to immunosuppressive therapy. These findings led the investigators to conclude that "sarcoid-mediated myocardial inflammation is associated with regional impairment of coronary circulatory function."

Kruse et al. (12) are commended for many aspects of their study. First, they have conducted a novel study, the only one we are aware of in the published reports, to investigate MBF and MFR measurements in CS and to examine possible treatment effects and inflammatory response on these measurements. Their investigation reaches beyond typical CS studies, which generally assess only resting perfusion. Second, they used ^{13}N-ammonia for MBF quantification, which has been shown to be highly reproducible and prognostic (10,13,14). Third, they used a preparation that combines both a high-fat, low-carbohydrate diet and extended fasting to optimize ^{18}F-FDG imaging for CS. Fourth, the study used contemporary PET/computed tomography technology and extended imaging to the whole body for evidence of active extracardiac sarcoidosis. Lastly, the investigators also assessed the impact of immunosuppressive therapy on MBF. Ultimately, as acknowledged by Kruse et al. (12), their greatest contribution to the published data is to hopefully serve as a catalyst for further larger investigations not only to corroborate their findings but to answer critical questions prompted by their study.

Several important issues arise, however, when assessing the current study. First, was the study population truly homogenous in regard to including only sarcoid patients? The investigators note that by using the Japanese Ministry of Health and Welfare Criteria (6) only 59% of their patients were considered to have CS. Furthermore, as alluded to previously, newer CS diagnostic criteria have been proposed (7) and it would be interesting to apply the criteria to the current study population. Next, the investigators eliminated patients who did not have sufficient preparation but the actual number of eliminated patients is unclear. Indeed, recent reviews of the published data (15) have noted significant variability in the rate of successful preparation dependent on differing prescribed dietary instructions. In addition, even though the patient preparation in the current study indicated a "very high-fat, low-carbohydrate, protein-permitted diet," the exact amount of fat, carbohydrate, and protein was not specified and as such, it is unclear whether the exact same preparation was replicated. This could certainly affect results not only in the initial identification of ^{18}F-FDG-positive and ^{18}F-FDG-negative regions but also in assessing ^{18}F-FDG uptake in the follow-up studies. Similarly, the use of pharmacologic stress prior to the ^{18}F-FDG administration and concomitant PET acquisition could increase regional myocardial ^{18}F-FDG uptake due to ischemia, perhaps due to disruption of the coronary circulation by CS through a variety of mechanisms including inducing microvascular constriction. In this situation, the increased regional myocardial ^{18}F-FDG uptake would not be due to inflammation, but rather due to underlying ischemia. Furthermore, the very small sample size of patients in each group and in those with follow-up studies adds another significant limitation to the study. Based on these limitations, the study results should be cautiously interpreted and any conclusions carefully considered.

The study by Kruse et al. (12) also raises additional questions related to PET imaging of CS. It did not address a portion of the CS population with scar or "burnt-out" sarcoidosis where perfusion defects would occur in an area of little or no ^{18}F-FDG

uptake. It would be critical to ask how this population might affect the overall MBF and MFR assessment. Similarly, it also would be important in future studies to examine the potential incremental diagnostic and prognostic role of quantitative MBF and MFR in CS. Furthermore, whereas SUV-based quantitative metrics have been described for interpreting ^{18}FDG-PET imaging for CS and some measurements may perform better than visual analysis, there is no SUV that can distinguish CS from normal myocardium. Although the use of ^{13}N-ammonia for MBF quantification in this study is a strength, the investigators' findings may have greater applicability if similar results could be replicated with the more commonly used PET perfusion tracer, rubidium-82, which possesses slightly less favorable properties than ^{13}N-ammonia for MBF quantification but still has robust MBF quantification. Considering MBF, it is of interest that this was normal in the study population at rest regardless of the presence of inflammation and only with hyperemia became abnormal. It could be surmised that similar to obstructive or microvascular atherosclerotic disease, autoregulation works to achieve appropriate regional MBF at rest but the ability to maintain MBF when under hemodynamic stress is compromised. Lastly, it appears that the definition of "responder" versus "nonresponder" was based on imaging criteria alone and it would be of interest to correlate this information with clinical response or lack thereof.

Kruse et al. (12) have revealed important preliminary data in furthering our ability to assess the pathophysiologic consequences of CS by using advanced noninvasive imaging techniques. Given the small size of the current as well as previous studies, it is clear that larger meaningful investigations will require a concerted and collaborative effort among centers of excellence.

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