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EDITORIAL COMMENT

Emergence of Integrated Cardiac Magnetic Resonance/Positron Emission Tomography Imaging as the Preferred Imaging Modality in Cardiac Sarcoidosis*

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Sarcoidosis is a noncaseating, multisystem granulomatous disease of uncertain etiology that commonly manifests in the perihilar-mediastinal lymph nodes and in the lungs (1,2). The prevalence of sarcoidosis is contingent on ethnicity, sex, and location (2). Involvement of the heart in sarcoidosis has been reported to be quite variable between 20% to 76% (3,4). Cardiac sarcoidosis (CS)-related inflammation and development of myocardial fibrosis-scar tissue may manifest clinically with atrioventricular conductance abnormalities, arrhythmias, such as ventricular tachycardia and/or fibrillation, sudden cardiac death, and congestive heart failure (4). A timely identification of CS, therefore, is of utmost importance, but for the time being remains a difficult challenge due to nonspecific symptoms and low diagnostic yield of endomyocardial biopsy, electrocardiography, and conventional imaging. In this respect, advanced imaging with gadolinium-contrast cardiac magnetic resonance (CMR) and positron emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG-PET) have opened new avenues in the detection of CS and evaluation of response to immunosuppressive treatment (1,4). CMR may detect what may be an active-inflammatory phase and a chronic phase in CS. Early gadolinium enhancement on T1-weighted images, regional wall thickening due to granuloma infiltration and edema in conjunction with wall motion abnormalities on cine images, and an increased signal intensity on T2-weighted images are suggestive of the inflammatory phase of CS. The chronic phase may be identified by late gadolinium enhancement (LGE) on T1-weighted images owing to fibrosis and/or scar tissue in conjunction with regional wall thinning. In contrast, ^{18}F-FDG-PET has evolved as a unique modality to visualize myocardial inflammation as FDG, a glucose analogue, is taken up avidly by infiltrative macrophages (2). The identification of CS with ^{18}F-FDG-PET is commonly conducted in conjunction with scintigraphic myocardial perfusion imaging at rest, and allows the classification of CS into subsequent groups (5): 1) normal perfusion and no inflammation; 2) abnormal perfusion or inflammation; and 3) abnormal perfusion and inflammation.

From a diagnostic point of view, reduced regional perfusion or LGE on T1-weighted CMR images in a nonischemic pattern associated with inflammation (abnormal FDG uptake) denotes a so-called mismatch that can be regarded as widely diagnostic for inflammatory CS. The diagnostic challenge, however, emerges from the "intermediate" classification groups when only 1 component, such as reduced perfusion, early gadolinium enhancement on CMR, or FDG uptake, is present. Although a marked reduction in myocardial perfusion or pronounced LGE can be related to fibrosis and/or scar tissue as a result of previous sarcoidosis activity, isolated FDG uptake or early gadolinium enhancement without any alterations in perfusion may signify an early inflammatory state of CS. In some cases, however, isolated FDG uptake can also represent incomplete suppression of physiologic FDG uptake, despite specific dietary preparation and fasting period, resulting in false-positive findings. Because isolated myocardial FDG

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uptake or regional inflammation may confer a worse clinical outcome (5), the clinical context needs to be given particular consideration and immunosuppressive treatment may be commenced, even in the absence of biopsy-proven cardiac sarcoid disease.

In this direction, help may indeed come from integrated hybrid imaging with CMR/PET (6). The simultaneously acquired imaging data of the integrated CMR/PET afford the combination of excellent soft tissue contrast and detailed image resolution of CMR with metabolic information provided by PET (7). Apart from an accurate co-registration of CMR and PET data, CMR-based motion and attenuation correction of cardiac PET data seem to be feasible (7,8). These features of integrated CMR/PET with the emergence of multiparametric and molecular imaging are likely to open novel pathways in the diagnosis and description of cardiac disease entities such as CS (6,9).

SEE PAGE 94

In this issue of *iJACC*, Dweck et al. (10) report initial results using CMR/PET to diagnose and characterize different scenarios of CS manifestation. In addition, the authors focused on the identification and characterization of isolated inflammatory CS versus false-positive findings. In 25 patients with suspected active CS, hybrid CMR/PET was performed with LGE and FDG to determine the pattern of myocardial injury and disease activity, respectively. Patients were assigned to four groups according to CMR/PET findings as follows: CMR−PET+/+, LGE pattern aligning exactly with increased FDG uptake; CMR−PET+/−, LGE pattern but no increased FDG; CMR−PET−/−, no LGE or increased FDG; and CMR−PET−/+, abnormal FDG uptake in the absence of characteristic LGE. Further, FDG uptake was then quantified using maximum standard uptake values, target-to-normal-myocardium ratio, and the net uptake rate (*Ki*) from dynamic Patlak analysis. Nineteen healthy volunteers were also included to assess the success rate of a low-carbohydrate diet for 24 h followed by a 12-h fasting state before computed tomography/PET examination.

Overall, 8 patients had classical CMR−PET+/+ findings, signifying active-inflammatory CS, 1 patient had CMR−PET+/− findings compatible with inactive CS, and 8 had CMR−PET−/− findings and, thus, were normal. Of particular interest, there were 8 patients with CMR−PET−/+ with global myocardial FDG uptake and focal-on-diffuse uptake. The diffuse FDG uptake was considered a false-positive finding or insufficient suppression of the physiologic glucose and thus FDG uptake (2). In the current study, the reasons for such a high failure rate of 40% to suppress physiologic myocardial FDG uptake in the sarcoid group and even up to 58% in the control group remain uncertain, but they are likely related to suboptimal dietary preparation protocol with low-carbohydrate diet only instead of fatty reach and no carbohydrate meals, a 12-h instead of 16-h fasting state, and failure of patients to fully adhere to the fasting state (2,11). The failed suppression of myocardial glucose uptake (10), however, afforded the opportunity to better characterize and quantify false-positive FDG uptake. The authors observed a 3 times higher standard uptake value when diffusely failed myocardial glucose uptake suppression was assumed in the CMR−PET−/+ versus the CMR−PET+/+ group. Notably, dynamic time-activity curves of FDG uptake revealed a plateau in myocardial FDG activity by 60 min after injection in the CMR−PET+/+ group, whereas in the CMR−PET−/+ group, a continuous increase in FDG activity for more than 70 min was observed. Quantitatively, the Patlak analysis demonstrated higher K_i net uptake rates of FDG in diffuse CMR−PET−/+ versus the CMR−PET+/+ individuals. These observations are unique; they deliver an estimate of maximum standard uptake values and maximum tissue-to-background ratio values, and also a characteristic dynamic FDG uptake pattern that may differentiate between true- and false-positive findings. Yet, false-positive findings may also occur as isolated myocardial FDG uptake. Thus, the current analysis also needs to be expanded to patients with isolated CMR−PET−/+ findings preferentially of the septum with biopsy-proven or -excluded CS.

Isolated acute-inflammatory CS may also be detected by T2-weighted CMR mapping of myocardial edema (12). Accordingly, the authors (10) evaluated the role of T2-weighted mapping in the identification of myocardial edema in CS. T2 mapping values were mildly higher in CS+ (active) than in CS− (nonactive) individuals. One would have expected a more striking difference in T2 values between these 2 groups. The reason remains uncertain but likely is related to the presence of sarcoid-related structural alterations such as fibrosis and/or necrosis characterized by T1-weighted LGE-CMR. Under such circumstances, T2-weighted CMR images may not necessarily tease out the edema (if present) from structural alterations in CS (13). This pattern may also explain the relatively low and nonsignificant correlation between T2 mapping and FDG-PET-determined target-to-normal myocardium ratio values ($r = 0.62$). Thus, the diagnostic value of T2 mapping to identify active-inflammatory CS still needs to be compared head-to-head with FDG-PET in patients with isolated inflammatory CS. The added diagnostic value of

CMR/PET imaging in CS may also derive from the observation that the localization of MR- and PET-measured signals may be quite variable (5,14). Thus, apart from the classical "mismatch" pattern between LGE signal on CMR and corresponding FDG uptake on PET, there may be atypical and noncongruent signal patterns on integrated CMR/PET images in active CS needing better characterization.

Similarly, it may be of great interest to investigate the diagnostic value of CMR T1 mapping-based quantitation of extracellular volume (15) and its relationship to myocardial FDG uptake in the identification of CS in subsequent CMR/PET investigations. Dweck et al. (10) have revealed the unique capability of hybrid CMR/PET in the detection and characterization of different stages (necrosis, fibrosis, edema, and active inflammation) of CS. Yet, the full potential of integrated hybrid CMR/PET imaging with CMR multiparametric imaging and novel radiotracer probes for an optimal identification of CS and also its treatment response is a matter of ongoing research. Although integrated CMR/PET is likely to evolve as the preferred imaging modality in CS versus standalone CMR or PET, further large-scale clinical investigations are needed to fully explore its potential as the current investigation suggests (10).

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