

# Cardiac Sarcoidosis: A Picture May Be Worth a Thousand Words, But Do We Need More?

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Cardiac sarcoidosis is a potentially life-threatening granulomatous disorder of the myocardium. It is an inflammatory process that can become destructive and result in extensive myocardial scarring. Depending on the location and amount of myocardial involvement, the clinical presentation may range from being asymptomatic to more severe forms such as decompensated heart failure, malignant arrhythmias, or even sudden cardiac death.<sup>1</sup> Early detection and prompt initiation of treatment with immunosuppressive therapy is believed to be crucial to reduce the morbidity and mortality associated with cardiac sarcoidosis. The diagnosis of cardiac sarcoidosis can be very challenging because it is known to mimic many other cardiac conditions and often involves only a small amount of the myocardium that may not be readily detectable using clinical tools such as physical examination, ECG, or echocardiography.<sup>2</sup> Even endomyocardial biopsy is insensitive for the detection of cardiac sarcoidosis because the myocardial involvement is often patchy and the diseased regions may go unsampled.<sup>3</sup>

During the past 25 years, late gadolinium enhancement cardiac magnetic resonance (CMR) and cardiac <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (CPET) imaging have increasingly been used to identify not only patients with cardiac sarcoidosis<sup>4,5</sup> but also individuals at high risk for arrhythmias<sup>6–10</sup> and to monitor response to immunosuppressive therapy.<sup>11</sup> Figures 1 and 2 show CMR and CPET images from 2 patients with cardiac sarcoidosis. Both CMR and CPET play integral roles in the clinical algorithms now used to diagnose cardiac sarcoidosis.<sup>12</sup> Together, the 2 imaging modalities provide a comprehensive understanding of the overall burden and disease

stage of cardiac sarcoidosis.<sup>13–16</sup> CMR is a sensitive technique for identifying even small areas of myocardial damage or scar tissue associated with cardiac sarcoid; in addition, it provides accurate assessment of left and right ventricular function. The areas of myocardium with scar tissue serve as a nidus for the development of arrhythmias.<sup>17</sup> Importantly, the scar tissue detected using CMR does not typically disappear even after the underlying myocardial inflammation has subsided. Patients who have an increased burden of myocardial scar tissue or who have scar tissue in the presence of left or right ventricular dysfunction are at the highest risk of developing sustained ventricular tachycardia. These patients often require an implantable cardioverter-defibrillator<sup>12</sup> to reduce their risk of sudden cardiac death. In contrast, CPET allows for the identification of patients who have regions of myocardium that are actively inflamed by cardiac sarcoidosis and who may benefit from immunosuppressive therapy by improving their symptoms and their ejection fraction.<sup>11</sup> Despite the progress made in the detection, treatment, and risk stratification of patients with cardiac sarcoidosis, diagnosing the condition remains difficult in the absence of known extracardiac sarcoidosis in part because of the absence of pathognomonic imaging features.

In this issue of the *Journal of the American Heart Association (JAHA)*, Okasha and colleagues<sup>18</sup> attempted to define the distribution of myocardial damage that occurs in cardiac sarcoidosis, with the hope of identifying patterns that are strongly associated with the diagnosis. The authors used an innovative methodological approach in which they performed a meta-analysis of published gross pathology images of cardiac sarcoidosis samples collected from necropsy or following heart transplantation. They identified 33 articles with images from 49 unique hearts and found that nearly all the hearts had multifocal involvement of the left ventricular epicardium, septum, and/or right ventricular free wall. These data provide an important basis for suspecting the diagnosis of cardiac sarcoidosis when such a pattern of myocardial damage is present in a noninvasive imaging test, even in the absence of known extracardiac sarcoidosis. Conversely, the published images did not comprise many cases of cardiac sarcoidosis without gross myocardial involvement, nor did they contain many examples without septal involvement or with involvement that was limited to 1 area of the left ventricle. In addition, few of the images

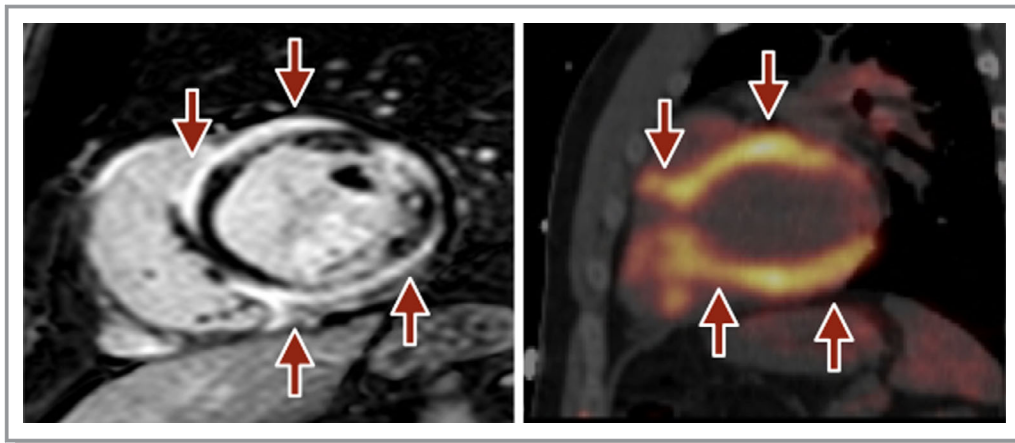
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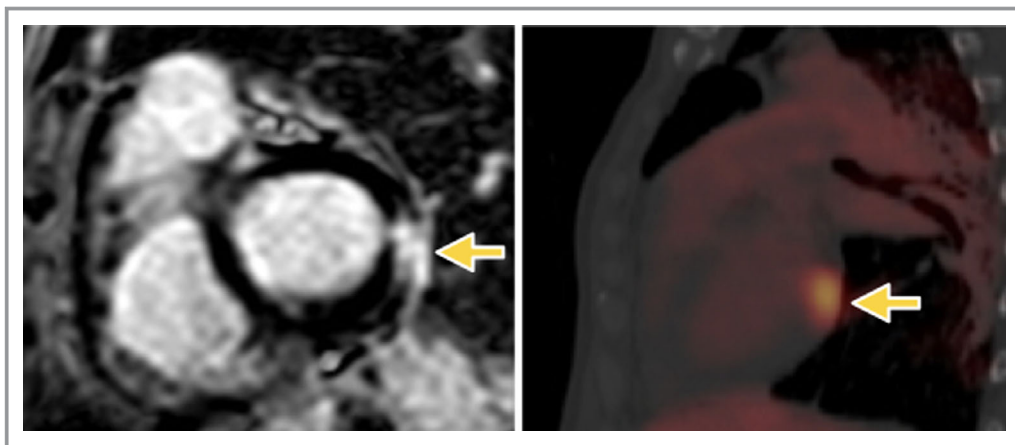
**Figure 1.** Pattern of extensive cardiac sarcoidosis. Late gadolinium enhancement cardiac magnetic resonance (left) and cardiac <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (right) images from a patient with extensive cardiac sarcoidosis. The arrows point to areas with myocardial involvement by sarcoidosis.

demonstrated isolated left ventricular scarring in a midmyocardial, subendocardial, or transmural pattern. A possible interpretation of this observation is that the presence of one of these rare patterns of myocardial damage on noninvasive imaging may not be as strongly associated with the diagnosis of cardiac sarcoidosis.

Although the findings reported by the authors are important and very interesting, a few issues should be considered when interpreting these results. First, the results are significantly affected by a disease-severity bias because all images were acquired from patients who died or underwent heart transplantation. Consequently, the published images represent only what cardiac sarcoidosis looks like in its end stages. At this very advanced stage, it is likely that both goal-directed heart failure therapy and use of immunosuppressive agents would be less effective. It is not hard to believe that initiating

treatment at an earlier stage of cardiac sarcoidosis would be more successful than initiating it once a significant amount of myocardial damage has already occurred. The methods used in this article to create a picture of cardiac sarcoidosis may not help us understand what cardiac sarcoidosis looks like during its earlier stages when treatment may have the most impact. Rather, the patterns of cardiac sarcoidosis described by the authors are likely to reflect what the disease looks like in the highest risk patients. Perhaps patients who have these patterns of cardiac sarcoidosis should be considered for early referral for implantation of an implantable cardioverter-defibrillator or for evaluation of heart transplantation.

Another important issue to consider is that this meta-analysis of published images is likely affected by image-selection bias. It is probable that the authors of each article included as part of the meta-analysis selected their most



**Figure 2.** Pattern of focal cardiac sarcoidosis. Late gadolinium enhancement cardiac magnetic resonance (left) and cardiac <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (right) images from a patient with only a small focal area of cardiac sarcoidosis. The arrows point to areas with myocardial involvement by sarcoidosis.

impressive images for publication. Such a bias likely favors the selection of cases with more extensive myocardial involvement. Although it is helpful to see examples of such cardiac sarcoidosis cases, from a clinical perspective, patients with less extensive findings are more challenging to diagnose using our current diagnostic tools. The imaging findings in this more common situation can be fairly nonspecific with significant overlap with numerous other conditions, especially when the patient does not have known sarcoidosis already involving another organ system. This commonly encountered situation is likely significantly underrepresented in this study because of the methods used. A major finding of this study is that the various patterns of isolated or focal left ventricular involvement are rarely seen; however, this conclusion must be tempered because the impact of image selection bias is unknown and may have systematically led to the underrepresentation of these more focal variants.

Although the study by Okasha and colleagues has some important limitations, the authors should be congratulated for the use of an innovative methodology to begin unraveling some of the major challenges in detecting cardiac sarcoidosis. Their findings not only improve our understanding of cardiac sarcoidosis but also provide a framework with which to educate clinicians about some of the higher risk patterns of myocardial damage that occur with cardiac sarcoidosis. Importantly, the authors describe several patterns of myocardial damage that should raise the suspicion of cardiac sarcoidosis, potentially even in the absence of known extracardiac sarcoidosis. Nevertheless, it is also important to remember that other clinically important patterns of cardiac sarcoidosis exist and are likely underrepresented in the study published in this issue of *JAHA*. Figure 1 shows an example of CMR and CPET images from a patient who has a pattern of cardiac sarcoidosis described by the authors. In contrast, Figure 2 shows an example of a patient with cardiac sarcoidosis who has a pattern of myocardial involvement that is not well represented in the published images but that is commonly encountered in clinical practice.

## Disclosures

None.

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**Key Words:** Editorial • cardiac sarcoidosis • myocardial structure