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EDITOR'S PAGE

The Challenges of Diagnosing Cardiac Sarcoidosis

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Despite various advances in cardiovascular imaging and blood-based biomarkers, the detection of cardiac sarcoidosis can be incredibly challenging, as there is no single reliable test for diagnosing this condition. Endomyocardial biopsy has limited sensitivity to detect cardiac involvement, in part because of the focal nature of this disease, and various proposed clinical criteria have uncertain diagnostic accuracy and have not been adequately validated. Consequently, imaging plays a central role in evaluating patients with known or suspected sarcoidosis. Yet, because of the absence of a reliable gold reference standard, the true diagnostic accuracy of various tests is unknown, and therefore, there has been significant debate regarding what is the most optimal initial imaging test to detect cardiac sarcoidosis. Because of the uncertainty that exists with various clinical criteria and imaging findings, and because of marked variability in the natural history, presentation, and outcomes of patients with cardiac sarcoidosis, multiple recent studies have focused on elucidating the prognostic value of various test results rather than trying to determine their diagnostic accuracy.

Yet identifying the likelihood of disease involvement remains an important clinical question that perplexes clinicians, imagers, and patients alike. Although there are significant data that cardiac magnetic resonance (CMR), by being able to detect late gadolinium enhancement (LGE), provides high sensitivity to detect cardiac involvement and that the absence of LGE is associated with a favorable prognosis (1,2), this test is more expensive and less available than echocardiography. Thus, some have argued that echocardiography may be a useful initial test for patients suspected to have cardiac sarcoidosis.

In this issue of *iJACC*, Kouranos et al. (3) report data from a 2-center retrospective study that evaluated 321 consecutive patients with biopsy-proven cardiac sarcoidosis. Cardiac sarcoidosis was diagnosed in 30% of the patients on the basis of the Heart Rhythm Society (HRS) consensus criteria. To understand this proportion, it is important to recognize that among patients with histological diagnoses of extracardiac sarcoidosis, the HRS criteria use a definition of "probable cardiac sarcoidosis" when the likelihood of cardiac involvement is >50%. This criterion, and others, acknowledges the fact that there often remains uncertainty regarding the diagnosis of cardiac sarcoidosis and that various imaging findings

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and clinical criteria inform the likelihood of cardiac involvement rather than providing a precise binary diagnostic result.

Compared with the HRS criteria, CMR had sensitivity of 97% and specificity of 100%, whereas transthoracic echocardiography had sensitivity of 27% and specificity of 98%. When echocardiography was combined with symptoms, electrocardiographic changes, or Holter monitor findings, the sensitivity increased considerably (ranging from 70% to 84%), but the higher sensitivity was due to the inclusion of symptoms and Holter monitor findings, and in fact, echocardiography did not appear to improve the sensitivity of detecting cardiac sarcoidosis when added to clinical data.

Although the HRS criteria represent a valid reference standard for the purposes of diagnostic studies, they certainly have important limitations. First, these criteria do not allow the detection of isolated cardiac sarcoidosis unless there is histological diagnosis from the heart (4). Although this limitation does not apply to the study by Kouranos et al. (3), in which all patients had biopsy-proven sarcoidosis, it is noteworthy that in the setting of positive findings on extracardiac biopsy, any LGE on CMR would be sufficient to result in a diagnosis of "probable cardiac sarcoidosis" (and thus the 100% specificity observed in this study). However, this potential limitation does not significantly impact the results, as there were 44 patients with abnormal CMR findings but normal echocardiographic findings, further supporting the notion that regardless of what reference standard we consider, CMR has higher sensitivity than echocardiography to detect cardiac involvement.

So does there remain a role for echocardiography in evaluating patients with cardiac sarcoidosis? Absolutely! Symptomatic patients who are found to have cardiac involvement by sarcoidosis may benefit from echocardiography when there is possible involvement of the pericardium or valves. In addition, in patients who are found to have left ventricular dysfunction, echocardiography may be useful for serial evaluation of ejection fraction, especially as many such patients are candidates for device implantation. Finally, patients with pulmonary sarcoidosis also benefit from echocardiography if there are signs or symptoms that suggest right heart failure, as right ventricular dysfunction, although rare, can occur even in patients who do not have cardiac sarcoidosis. However, when it comes to screening patients with suspected but no known disease, echocardiography seems to be significantly inferior to CMR.

One of the reasons CMR is preferable to echocardiography for screening for cardiac disease in symptomatic patients is that if no abnormalities are detected on echocardiography (i.e., "negative" results), the post-test likelihood of disease is not sufficiently lowered, and additional testing, such as CMR or in some cases positron emission tomography may still be required. Because the proportion of cardiac involvement in patients with suspected cardiac sarcoidosis is about 25% to 30%, most patients with suspected cardiac involvement will not have any disease, and thus if echocardiography were to be used as the initial screening test, most patients would still require further testing.

However, there are limitations of CMR in evaluating patients with suspected cardiac sarcoidosis. First, the finding of LGE, even in patients with biopsy-proven extracardiac disease, is not always specific to cardiac sarcoidosis. Second, the finding of LGE does not provide information on whether myocardial inflammation is present and thus should be used for deciding on the role of anti-inflammatory therapies or for assessing for response to therapy (5).

As advanced imaging modalities have become more available, an important question that remains is which patients should be screened for cardiac sarcoidosis. Several recent multisociety consensus statements (5) have suggested that screening should be performed in patients with signs or symptoms of possible disease. These statements reflect the fact that it is unclear whether there is any value for routine screening for cardiac sarcoidosis in patients with extracardiac sarcoidosis who have no symptoms or signs of cardiac involvement. The main concern with such screening approaches is that they may identify findings that have uncertain diagnostic or prognostic value, potentially leading to increased use of advanced imaging and/or immunosuppressive therapies, in cases in which there may not be any benefit. For the time being, further studies are needed to determine the role, if any, of screening asymptomatic subjects with normal electrocardiographic findings who have no signs or symptoms of cardiac involvement.

Although cardiovascular imaging has taught us a great deal about cardiac sarcoidosis over the past decade, the thoughtful use of multimodality imaging for this condition has also shown us why it is important to study how different imaging tests compare when evaluating various cardiac conditions. The lessons include the following: 1) imaging plays an especially important role in conditions for which there are no reliable clinical or blood-based biomarkers to detect disease; 2) different imaging modalities may be best suited to evaluate different attributes of the same disease (e.g., in cardiac

sarcoidosis, magnetic resonance imaging is best suited for detecting scar, while ^{18}F-flurodeoxyglucose positron emission tomography remains the most robust test for detecting and quantifying the amount of myocardial inflammation [6]); 3) although imaging can be incredibly helpful at estimating the likelihood of disease, imaging is not the same as a tissue diagnosis, but when such a diagnosis cannot be made, imaging—often in combination with other clinical data—may represent the best option for detecting disease; and 4) imaging may be useful for identifying patients who are most likely to respond to therapies and at times provides a useful method to assess response to treatment.

Although comparative effectiveness trials are often needed for ultimately evaluating the efficacy of different diagnostic or treatment algorithms, there remains an important need for well-conducted registries that can further define how different imaging and treatment approaches compare. For instance, future studies are needed regarding the potential role of echocardiography to evaluate treatment response, especially using strain-based quantitative approaches, and how such findings may compare with serial testing with serial ^{18}F-flurodeoxyglucose positron emission tomography or blood-based markers. In addition, future studies should use imaging to evaluate how different types of immunosuppressive therapies compare in reducing myocardial inflammation. Finally, future studies must recognize the diagnostic uncertainly that often remains even when using various expert consensus statements and advanced imaging modalities. To that end, we should recognize that although we might not always know the exact histological diagnosis, imaging ultimately remains the best method for identifying the likelihood of cardiac sarcoidosis and can be used to identify patients who are at increased risk for adverse events.

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