Editorial

Prognosis of Myocardial Damage in Sarcoidosis Patients With Preserved Left Ventricular Ejection Fraction

Always Look at the Bright Side of Cardiovascular Magnetic Resonance

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Sarcoidosis is a systemic granulomatous inflammatory disease of unknown origin, in which myocardial involvement may be part of the systemic process or occur in isolation. The annual incidence of sarcoidosis in the United States has been estimated at 10.9 per 100,000 in whites and at 35.5 per 100,000 in blacks, and the prevalence of cardiac sarcoidosis (CS) in these patients ranges from 4% to 55%. This large range can, in part, be explained by patient selection criteria, different diagnostic methods, and different standards. Nevertheless, the main reason for the differences in the reported prevalence of CS is most likely the fact that the diagnosis of CS is challenging. Some patients may present with conduction abnormalities, ventricular arrhythmias, and symptoms of heart failure, pointing toward potential cardiac involvement of sarcoid disease. However, many patients present with nonspecific symptoms, no relevant ECG abnormalities, and preserved left ventricular ejection fraction (LVEF). Hence, ECG and echocardiography as criteria for CS in these patients might be misleading. Thus, there is a need for a reliable diagnostic tool to identify patients with CS. Cardiovascular magnetic resonance (CMR) as a noninvasive imaging technique delineates both functional and morphological aspects of the heart and, at the same time, provides excellent tissue characterization. One previous study comprising 81 consecutive patients with biopsy-proven extracardiac sarcoidosis and preserved LVEF compared cardiac involvement by late gadolinium enhancement (LGE) CMR with standard clinical evaluation using the consensus criteria (modified Japanese Ministry of Health guidelines 1993). LGE identified CS in 21 patients (26%) compared with 10 (12%; 8 overlapping) using Japanese Ministry of Health criteria resulting in a 2-fold higher rate for LGE. Pathology evaluation in 15 patients (19%) identified 4 with CS; all 4 were positive by LGE-CMR, whereas only 2 of them were positive by the Japanese Ministry of Health guidelines. This landmark study was one of the first to demonstrate the high value of CMR in detection of CS.

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However, histological workup still remains the gold standard for diagnosing CS despite its limitations (eg, invasiveness and potential sampling error). The updated guideline for workup of CS by the Japanese Ministry of Health from 2006 recognized LGE as a minor criterion for the clinical diagnosis group only, requiring another minor criterion, and 1 additional major criterion before the clinical diagnosis of CS can be accepted. In contrast, a current expert consensus article from the Heart Rhythm Society states that CS is probable (and therefore considered adequate to establish a clinical diagnosis of CS) if there is (1) a histological diagnosis of extracardiac sarcoidosis and (2) LGE on CMR (in a pattern consistent with CS), and (3) other causes for the cardiac manifestation have been reasonably excluded. However, the authors had to concede that the LGE pattern in sarcoid patients can be variable, ranging from subepicardial or intramural nonischemic pattern to a more subendocardial, ischemic-type pattern, mimicking previous myocardial infarction.

Perhaps of more relevance than merely diagnosing CS is the prognosis of patients with this disease. CS might result in heart failure, arrhythmias, and sudden cardiac death in these often young individuals. LGE-CMR seems to be a useful predictor of outcome in patients with CS, as well as in other nonspecific myocardial diseases. In the study mentioned above, patients with myocardial damage indicated by LGE-CMR had a 9-fold higher rate of adverse events and an 11.5-fold higher rate of cardiac death compared with patients without LGE. Our group has extended these findings in a larger, international multicenter setting consisting of 155 patients with systemic sarcoidosis who underwent CMR for workup of suspected CS. Patients were followed up for ≥2.6 years, and CMR detected LGE in 39 patients (25.5%). Of note, the presence of LGE yields a Cox hazard ratio of 31.6 for death, aborted sudden cardiac death, or appropriate implantable cardioverter-defibrillator (ICD) discharge and of 33.9 for any event (including ventricular tachycardia [VT] and nonsustained VT). This was superior to functional or clinical parameters, such as LVEF, LV end-diastolic volume, or heart failure presentation, yielding hazard ratios between 0.99 (per % increase LVEF) and 1.004 (presentation as heart failure) and between 0.94 and 1.2 for potentially lethal or other adverse events, respectively.

In this issue of Circulation: Cardiovascular Imaging, Murtagh et al provide further support to the prognostic value of LGE-CMR, investigating 205 patients with
extracardiac sarcoidosis and an LVEF of >50% by CMR, including LGE sequences.

Aims were to (1) determine the prevalence of CS (defined by the presence of LGE), (2) quantify the risk of death/VT, and (3) identify imaging-based covariates that predict which patients are at the greatest risk of death/VT. They found that 41 patients (20%) were LGE positive and 12 patients (6%) died or had VT during follow-up. Of note, 10 of these 12 individuals (83%) were LGE positive. In contrast to previous studies, Murtagh et al. quantified areas of LGE as percentage of LV mass and found that LGE burden was the best predictor of death/VT (area under the curve, 0.80). Interestingly, for every 1% increase of LGE burden, the hazard of death/VT increased by 8%. This finding is of high clinical interest because establishing a critical threshold of LGE burden would make risk stratification much more precise in patients with CS and would facilitate decision making about further patient management, such as whether to implant an ICD. Despite these encouraging results, the study from Murtagh et al. has several limitations: first, although reaching statistical significance, SDs of the means of LGE burden demonstrate a wide range (14.1±10.7 versus 5.1±4.7%; P=0.004) in patients with and without events. Therefore, identifying a definite threshold of LGE burden for predicting serious events remains challenging. Second, the overall number of events is low because only 12 patients of 205 patients (6%) died or had VT during follow-up. Could one really recommend placement of an ICD based on the results of adverse events in 12 individuals? Third, patients with known coronary artery disease were not excluded: 7 of 41 (=17%) LGE-positive patients had coronary artery disease. Three of them reached the end point death/VT, which could be a consequence of their coronary artery disease rather than because of CS. Although the authors provide data that exclude patients with coronary artery disease, LGE-positive patients are still at increased risk of having events, it is a limitation of the present study and is in contrast to previous LGE-CMR studies dealing with prognosis in suspected CS. Fourth, this is a retrospective single-center study with all its associated limitations. Although VT was part of the end point, Holter ECG monitoring was performed in less than a third (29%) of the patients. Thus, in some patients, cardiac arrhythmias may have been missed, which is one possible explanation for the overall low event rate in this patient cohort. Furthermore, the specific cause of death could not be determined in the majority of patients who died. Consequently, it remains elusive if all deaths were from cardiac origin and if cardiac deaths resulted from CS.

The second major finding of the study, beside the role of LGE, is the value of assessment of right ventricular function in patients with suspected CS. The authors state that individuals who died or had VT more frequently had a reduced right ventricular EF compared with patients not having death or VT (45.4±12.3 versus 52.7±27.5%; P=0.037). Again, there is a wide range of SD with the mean of right ventricular EF in patients with and without end point, attenuating the significance of this result.

A key clinical question, thus, is whether sarcoid patients with LGE should receive primary prophylactic ICD implantation. In our opinion, this question cannot be answered on the basis of the data available today. Current American Heart Association guidelines consider CS only a class IIA indication for ICD implant. Further large multicenter studies dealing with LGE-CMR in patients with CS, including quantification of the LGE burden, are needed to sufficiently address this question.

Despite its limitations, the authors should be congratulated on performing this study, which gives much insight into both diagnosis and prognosis of patients with sarcoidosis. Moreover, this group is the first to describe a threshold of LGE burden, by which patients with sarcoidosis are at increased risk of having adverse events.

The future will show if a cutoff of LGE burden can be established to facilitate decision making about prophylactic ICD implant in this per se high-risk population for major adverse cardiovascular events. However, when discussing LGE imaging and its prognostic implications, it should be kept in mind that there is not a one-to-one relationship between the presence of LGE and the occurrence of adverse events in LGE-positive patients, although LGE-positive patients are at increased risk of having an event. Nevertheless, there is much evidence indicating that LGE-negative patients in nonischemic cardiomyopathies tend to have an excellent prognosis consolidating the role of LGE as a gatekeeper for risk stratification in nonischemic myocardial disease.

Disclosures

None.

References


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