

## Prognostic Value of Myocardial Damage in Patients With Sarcoidosis Is Cardiac Magnetic Resonance What We Need?

Han W. Kim, MD; Raymond J. Kim, MD

Sarcoidosis is a granulomatous disease of unknown pathogenesis that can affect virtually any organ system. Cardiac involvement results in significant morbidity and mortality, with some studies reporting that cardiac involvement accounts for up to 25% of all deaths from sarcoidosis in the United States and more than half of all deaths in Japan.<sup>1-3</sup> Many deaths seem to be arrhythmic in nature and are potentially preventable. For example, recent studies<sup>4,5</sup> in patients with cardiac sarcoidosis (CS) and an implantable cardioverter-defibrillator show high rates of appropriate implantable cardioverter-defibrillator discharges ( $\approx 10\%$ – $15\%$  per year for primary prevention patients), which are more than double that reported in large randomized trials of heart failure patients.<sup>6</sup>

### See Article by Hulten et al

Unfortunately, the diagnosis of cardiac involvement is difficult because the extent of disease is often limited and focal in nature. Necropsy studies have shown that patients with CS frequently have lesions that are small and patchy, leaving much of the myocardium uninvolved.<sup>1,7,8</sup> Hence, although a positive endomyocardial biopsy is confirmatory, a negative biopsy cannot exclude CS because the false-negative rate may be as high as 80%.<sup>9</sup>

Guidelines such as those from the Japanese Ministry of Health and Welfare (JMH)<sup>10</sup> and, more recently, from the Heart Rhythm Society (HRS),<sup>11</sup> have been published for the diagnosis of CS. Unfortunately, the recommendations rely heavily on expert opinion because the level of evidence is low. A particular limitation of the guidelines is that the diagnosis of CS requires the histological confirmation of sarcoidosis—either in the heart or outside the heart. Hence, in the absence of a positive myocardial biopsy, the guidelines do not provide a pathway to diagnose sarcoidosis confined to the heart. This is important because there is growing evidence that isolated CS is not a rare phenomenon. A nationwide study of all patients diagnosed with histologically confirmed CS in Finland suggests that nearly two thirds of patients had clinically isolated CS.<sup>12</sup>

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From the Duke Cardiovascular Magnetic Resonance Center (H.W.K., R.J.K.), Division of Cardiology (H.W.K., R.J.K.), and Department of Radiology (R.J.K.), Duke University Medical Center, Durham, NC.

Correspondence to Raymond J. Kim, MD, Duke Cardiovascular Magnetic Resonance Center DUMC 3934, Durham, NC 27710. E-mail raymond.kim@duke.edu

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The latest guidelines incorporate modern imaging techniques, such as cardiac magnetic resonance (CMR) into their diagnostic and treatment algorithms.<sup>10,11</sup> Studies have shown that late gadolinium enhancement (LGE) identified with CMR can be used to determine cardiac involvement in patients with suspected CS, and there also seems to be an association with prognosis. However, there is uncertainty over CMR's role, particularly with regards to risk stratification, because the available data are from small, single-center studies, and some of the findings are inconsistent.

In this issue of *Circulation: Cardiovascular Imaging*, Hulten et al<sup>13</sup> report the results of a meta-analysis on the prognostic value of myocardial damage diagnosed by LGE in patients with known or suspected CS. The aims of the meta-analysis were as follows:

1. To clarify the association between LGE and poor outcomes
2. To evaluate whether a negative LGE study identifies low-risk individuals.

The authors performed a systematic review of the literature to identify cohort studies of at least 20 patients with suspected or confirmed CS who were referred for CMR with evaluation of LGE. The studies were required to have at least 12 months of follow-up for any of the following end points: all-cause mortality, cardiovascular mortality, ventricular arrhythmia, heart block requiring pacemaker implantation, or heart failure requiring hospital admission.

Seven studies involving a total of 694 patients met the criteria and were included in the analysis. Three studies were prospective and 4 retrospective. The studies ranged in size from 37 to 205 patients and were performed at diverse sites, including Japan, Germany, Australia, and the United States. A standard implementation of the LGE technique was used in 5/7 studies. However, in one study, a fixed inversion time of 300 ms was used for all patients,<sup>14</sup> which is unfortunate because a fixed inversion time is known to potentially result in erroneous findings.<sup>15</sup> In another, details regarding the LGE method were not reported.<sup>16</sup> The individual studies reported a wide range of LGE prevalence from 13% to 70%.

For the total cohort, 199 patients were LGE positive (29%). All-cause mortality occurred in 19 LGE-positive versus 17 LGE-negative patients. Cardiovascular mortality occurred in 10 LGE-positive versus 2 LGE-negative patients. A combined end point of death or ventricular arrhythmias, defined as appropriate implantable cardioverter-defibrillator therapy, ventricular fibrillation, or sustained ventricular tachycardia  $>30$  seconds, occurred in 64 LGE-positive and 18 LGE-negative patients. The event rates among LGE-positive patients as compared with LGE-negative patients were consistently higher and statistically

significant for all outcomes. The relative risk was 3.4 ( $P=0.04$ ), 10.7 ( $P=0.03$ ), and 6.2 ( $P<0.001$ ) for all-cause mortality, cardiovascular mortality, and the combined end point, respectively.

Strengths of the study by Hulten et al<sup>13</sup> include the multiple end points that were tested and the consistency of findings for these end points. There was no evidence of heterogeneity or small study effects for any of the outcomes. The author's conclusion that "LGE is associated with future cardiovascular death and ventricular arrhythmia among patients referred to MRI for known or suspected cardiac sarcoidosis" appears sound. Nonetheless, the number of fatalities is few, and the magnitude of the effect is uncertain. For example, there were only 12 cardiovascular deaths, and the 95% confidence interval for relative risk was broad, ranging from 1.3 to 86.3.

Given the results of the study, is a change in clinical practice warranted? The HRS guidelines already indicate that an evaluation by CMR is appropriate (class 2a) in patients with extracardiac sarcoidosis who have signs or symptoms of cardiac involvement.<sup>11</sup> Still, the findings of the meta-analysis strengthen the body of evidence linking the presence of LGE with adverse outcomes and helps to support the HRS recommendation. Additionally, the meta-analysis highlights the potential role of CMR in influencing patient management. The data show that the absence of LGE was associated with low event rates. The annualized incidence of either death or ventricular arrhythmias was 0.6% in LGE-negative patients compared with 8.8% in LGE-positive patients. Given this reassuring event-free survival, the authors conclude that when LGE is absent, it has sufficiently high negative predictive value that no further testing is needed for the majority of patients. A caveat, of course, is that the warranty period of a normal scan in this patient population is unknown.

The HRS guidelines state that CMR is not recommended (class 3 indication) for patients without abnormalities on initial screening by symptoms (defined specifically as unexplained syncope, presyncope, or significant palpitations lasting >2 weeks), ECG, or echocardiography.<sup>11</sup> It is possible these criteria are too rigid. There are data to suggest that all 3 criteria are insensitive in detecting CS. Patel et al<sup>17</sup> recruited patients out of pulmonary, rheumatology, and general medicine clinics. Patients were not referred clinically for CMR. LGE was positive in 26% of patients, indicating cardiac involvement; however, the majority of these patients were asymptomatic and did not have any conventional signs of cardiac involvement after a thorough clinical evaluation. Murtagh et al<sup>18</sup> studied a cohort restricted to those with preserved left ventricular ejection fraction of >50% and found that 20% of their population was LGE positive. Although data regarding symptoms and signs are not reported, the authors state "a significant portion of the patients underwent the CMR examination as part of widespread screening, despite the absence of symptoms or ECG abnormalities." Nagai et al<sup>14</sup> specifically investigated a cohort without signs or symptoms of cardiac involvement. The prevalence of LGE was 13% in their study.

These 3 studies were included in the meta-analysis by Hulten et al and reflect the heterogeneity in patient populations and different inclusion criteria used by the individual studies. Strictly speaking, it seems the meta-analysis was not limited to patients with known or suspected CS. Although the

meta-analysis could not adjust for various patient factors, such as symptoms and ECG abnormalities, these data raise the possibility that CMR could potentially be used more broadly as a screening test in asymptomatic patients with the diagnosis of extracardiac sarcoidosis.

But if CMR's ability to improve the diagnosis of CS is an important advance, it raises the natural question, what should a clinician do with a positive scan? Although the absence of LGE is reassuring, the magnitude of the effect of a positive scan is less clear, given the wide 95% confidence intervals for relative risks as stated earlier. Certainly, not all patients with LGE develop adverse outcomes, and there are no data to support the routine implantation of implantable cardioverter-defibrillators in this group.

A positive CMR scan needs to be evaluated in context of the clinical scenario. Although CS is considered a serious condition, there are several factors that likely modify the risk entailed by the diagnosis. For example, there seems to be significant differences in mortality depending on ethnicity. Yazaki et al<sup>19</sup> reported an overall survival of 60% at 5 years in Japanese patients. Although not directly comparable, Kandolin et al<sup>12</sup> observed a substantially better prognosis in Finnish patients and reported a transplantation-free cardiac survival of 90% at 5 years. Murtagh et al<sup>18</sup> enrolled patients at the University of Chicago of whom 59% were black. It is notable that within the LGE-positive group, all patients who experienced death or ventricular tachycardia were black.

Left ventricular ejection fraction is also known to modify the risk profile in patients with CS.<sup>4,12</sup> Yet other studies indicate that the extent of LGE is a better predictor of outcome than just simply the presence of LGE.<sup>18,20</sup> Unfortunately, these and many other covariates could not be assessed on a per patient basis in the meta-analysis.

Hulten et al have made an important contribution that extends our knowledge of this enigmatic disease. Their data clearly show that CMR can be used to stratify sarcoid patients with potential cardiac involvement into low- and high-risk categories and, by corollary, influence patient management. Moving forward, it will be important for future studies to precisely assess the adverse risk associated with a positive LGE CMR scan and the effect of other covariates that could modify risk. Also useful will be additional data in patients with isolated CS because the literature provides little guidance in its diagnosis. In the meta-analysis, <2% of patients did not already have a known diagnosis of extracardiac sarcoidosis. Finally, of particular value will be prospective studies in patients with sarcoidosis that evaluate the efficacy of patient management strategies guided by CMR that aim to improve patient outcomes.

## Disclosures

None.

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