The role of late gadolinium enhancement in predicting arrhythmic events in cardiac sarcoidosis patients – A mini-review

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Abstract
Sarcoidosis is a multisystem inflammatory disorder with an unknown origin. Symptomatic cardiac involvement is rare and occurs in about 5% of patients with sarcoidosis. Fatal ventricular arrhythmias are the most severe clinical presentation of the disease. Cardiac magnetic resonance (CMR) is a useful noninvasive tool for the risk stratification of ventricular arrhythmias and sudden cardiac death (SCD) in patients with cardiac sarcoidosis (CS). More specifically, late gadolinium enhancement (LGE), a CMR tool for scar detection, has been found to be significantly associated with arrhythmic events in CS patients. This review aims to present the existing evidence regarding the association of LGE with adverse events and especially with fatal ventricular arrhythmias.

Keywords: cardiac magnetic resonance; Late gadolinium enhancement; Cardiac sarcoidosis; ventricular arrhythmias; Sudden cardiac death

Introduction

Sarcoidosis is an inflammatory disorder that affects mainly the lungs, but any organ can be involved [1]. Clinically manifested cardiac involvement is rare and is estimated to occur in about 5% of patients with sarcoidosis [2, 3]. The clinical presentation of cardiac sarcoidosis (CS) ranges from clinically silent cases to heart failure, conduction anomalies and severe forms with ventricular arrhythmias and sudden cardiac death [2, 4]. An analysis of nationwide clinical and cause-of-death registries showed that high-grade atrioventricular block was the most common presentation of CS followed by heart failure, unexpected fatal or aborted sudden cardiac death (SCD) and sustained ventricular tachycardia [4]. Criteria for the diagnosis of sarcoidosis have been developed [5-7]. However, a study that compared the performance of the diagnostic criteria showed that a high proportion of patients clinically judged to have CS were unable to be classified according to the three main diagnostic criteria. Interestingly, the low concordance between the criteria was revealed [8]. The risk stratification of SCD plays a significant role in the management of CS patients. Reduced right and left ventricular ejection fraction, positive electrophysiology study and standardized uptake value in FDG PET scan have been proposed as valuable tools for the risk stratification of CS patients [9-12]. Cardiac magnetic resonance (CMR) is a radiation-free noninvasive method for diagnosing and evaluating cardiomyopathies and valve diseases [13-15]. This review aims to summarize the role of CMR and especially the association of late gadolinium enhancement (LGE) with adverse outcomes in CS patients.

The role of LGE in predicting arrhythmic events in CS patients

We performed a comprehensive search in the Medline and Cochrane databases to retrieve the studies that provide data about the role of LGE presence in the future adverse outcomes of CS patients (supplementary data). The main characteristics of the retrieved studies and the outcomes of our interest are summarized in table 1.

The cardiac involvement in the clinical setting of sarcoidosis includes three successive histological stages: edema, granulomatous inflammation, and fibrosis (scar) [16]. Various patterns of LGE have been described in CS patients, but findings are usually patchy and multifocal with subendocardial sparing. Occasionally CS may demonstrate subendocardial LGE mimicking a prior myocardial infarction. Specifically, typical LGE patterns in CS patients include subepicardial and mid-wall LGE along the basal septum, while an extension into the right ventricular insertion points as well as the inferolateral wall can be noted [17, 18]. The

presence of LGE is associated with a worse prognosis and arrhythmic risk. Discrimination of edema from a myocardial scar is crucial for prognostic purposes. A CMR examination when the patient is no longer in the acute phase or a multiparametric mapping with T2 can help to confirm the scar-related LGE by identifying areas of reversible myocardial tissue pathology, including edema and inflammation [19]. Regarding the pathophysiology of arrhythmogenesis in the setting of CS, scar formation instead of active inflammation seems to serve as the main arrhythmogenic substrate [20, 21]. Specifically, one study showed that among the seven CS patients with sustained ventricular tachycardia (VT), only one patient had cardiac inflammation by Gallium-67 citrate scintigraphy [21]. Similarly, another study included CS patients with VT history who underwent CMR, PET, and electroanatomical mapping [20]. The authors found that myocardial segments with abnormal electrograms tended to have more scar as depicted by CMR and less inflammation by PET [20]. On the other hand, a retrospective study showed a significant association between focal FDG uptake on cardiac PET (a marker of inflammation) with future VT or death [22]. However, the retrospective nature of this study makes it unclear if inflammation and not a downstream scar formation is the primary pathophysiological mechanism of VT occurrence in CS patients[22].

The existing data provide evidence that LGE can be a valuable tool for the risk stratification of CS patients. Cain et al., in a retrospective study, examined the distribution of atrial and ventricular arrhythmias in patients with and without LGE in the CMR examination [23]. Interestingly, they found that both atrial and ventricular arrhythmias were more frequently observed in LGE-positive patients. Moreover, in the subgroup of LGE-positive patients with implantable cardioverter defibrillators (ICDs), 30.8% received therapies, 1.5% of which were inappropriate for atrial arrhythmias [23]. In another observational study, the authors found a strong association of myocardial scar with potentially lethal events [24]. Specifically, LGE patients had a 31.6 times greater risk for death, aborted SCD, or appropriate ICD discharge compared to patients without myocardial scar [24]. Nadel et al., in a retrospective study, provided data about the incidence of adverse cardiovascular events in CS as depicted by the presence of LGE on CMR compared to patients with extracardiac sarcoidosis [25]. The authors found that patients with CS had significantly higher rates of the combined endpoint consisting of SCD and VT as well as higher rates of SCD or ICD aborted SCD compared to patients with extracardiac sarcoidosis [25]. Interestingly, in the CS subgroup, patients without an ICD were more likely to die of SCD compared to patients with an ICD implanted [25]. Another study found that LGE burden was the best predictor of death/VT, and interestingly for every 1% increase of LGE burden, the hazard of death/VT increased by 8%

[26]. Another interesting finding of this study was also that sarcoidosis patients with LGE are at significant risk for death/VT, even with preserved left ventricular ejection fraction [26]. The routine measurement of LGE in CS patients is also supported by the findings of another observational study that aimed to investigate the role of CMR in predicting adverse outcomes [27]. More specifically, the authors found that the extent of LGE was the only independent predictor of outcome events on CMR imaging, with a hazard ratio of 2.22 per tertile [27]. Another interesting finding was that an extent of LGE >22% (the tertile with the higher scan burden) had positive and negative predictive values for serious cardiac events of 75% and 76%, respectively [27]. The distribution and the percentage of myocardial scar seem to be correlated with the type of adverse outcomes in CS patients. Okada et al. showed that patients with atrioventricular block had a higher percentage mass scar in the anterior and anteroseptal walls while patients with ventricular arrhythmias had a higher percentage scar in the basal inferoseptum [28]. Furthermore, a scar in the anteroseptal wall was significantly associated with the combined endpoint consisting of death, heart transplantation and arrhythmic events [28]. Moreover, it was found that in patients with CS, left ventricular fibrosis mass and localization of LGE defined as the sum of LGE in left ventricular basal anterior and basal anteroseptal areas, or the right ventricular area were significantly associated with increased prevalence of ventricular arrhythmias [29].

Beyond the CMR abnormalities of the left ventricle, right ventricular abnormalities, including right ventricular systolic dysfunction and right ventricular LGE, have also been found to have a prognostic role in CS patients [30]. Interestingly, right ventricular systolic dysfunction but no LGE was independently associated with all-cause death. In contrast, right ventricular LGE but not systolic dysfunction was associated with the arrhythmic endpoint (SCD or ventricular arrhythmia) [30]. Similar results were reported recently by another observational study. Specifically, this study included patients with definite and probable CS. The authors showed that decreased right ventricular ejection fraction or the presence of right ventricular LGE were associated with major adverse cardiac events, while the combined analysis of right ventricular systolic dysfunction and LGE showed better risk stratification for cardiac events [31].

Positron emission tomography (PET) has been reported to have a prognostic value in CS patients [22]. However, the combined use of both LGE and fluorodeoxyglucose (FDG) PET has been reported not to have an incremental prognostic value than LGE alone [32]. Notably, a study showed that LGE-positive/abnormal-FDG and LGE-positive/normal-FDG patients had

a comparable risk of events (deaths and ventricular arrhythmias) [32]. These data support the unique role of LGE in the risk stratification of CS patients. Similarly, Kouranos et al. highlighted the valuable role of CMR in the diagnosis and prognosis of CS patients [33]. CMR was the most accurate diagnostic modality regarding CS diagnosis compared to the other tests, including cardiac symptoms, electrocardiogram, transthoracic echocardiography, and Holter monitoring [33]. Specifically, CMR showed a sensitivity of 96,9%, a specificity of 100% and an area under the curve of 0,984. An interesting finding was the limited diagnostic value of echocardiography as a screening test [33]. In the same study, LGE was an independent predictor of the primary outcome that consisted of the composite of all-cause mortality, sustained VT and hospitalization for heart failure [33]. Finally, the role of LGE was studied in a meta-analysis designed to investigate the predictive value of LGE in CS patients [34]. The authors found that LGE-positive patients had approximately three times higher risk of all-cause mortality, 10.7 times higher risk of cardiovascular mortality and 19.5 times higher risk of ventricular arrhythmias [34].

Current recommendations for implantable cardioverter-defibrillator (ICD) implantation in CS patients

According to the 2017 AHA/ACC/HRS Guideline Recommendations for ICD Implantation in cardiac sarcoidosis, an ICD is recommended (Class I) in patients with spontaneous sustained ventricular tachycardia (VT) or SCD and in patients with a left ventricular ejection fraction (LVEF) < 35%. An ICD should be considered (IIa) in patients with LVEF>35% with one of the following characteristics: a) syncope, b) need for a pacemaker, c) inducible sustained VA, d) any LGE [35]. A retrospective study that evaluated the 2017 AHA/ACC/HRS recommendations showed that all patients with an arrhythmic event had a class I or IIa indication for ICD placement [36]. Furthermore, patients that fulfill one of the following two indications: LVEF >35% with a need for a permanent pacemaker and LVEF >35% with LGE >5.7%, had high annualized event rates [36].

A recent meta-analysis including 585 patients with a mean LVEF of 38.4% and an ICD implanted showed a high incidence of ICD treatments in CS patients. Specifically, the pooled analysis showed that appropriate and inappropriate ICD treatments were reported in 39% and 15%, respectively [37]. Another meta-analysis showed that patients who received an appropriate therapy were younger, more likely to be male, had a lower LVEF, had a higher rate of complete heart block and more frequently had ventricular pacing [38].

Conclusions

Existing evidence highlights the prognostic role of LGE in CS patients. The presence of any LGE, if it represents scar as opposed to edema, is associated with worse arrhythmic risk. Future studies can focus on determining whether the LGE on a single scan represents edema or scar and identify a potential threshold or location associated with significant risk to guide management. More data are needed for developing a reliable CMR-derived risk score for identifying those patients who will benefit from an implantable cardioverter-defibrillator.

Conflicts of interest
The authors declare no conflicts of interest

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References

[1] Llanos O, Hamzeh N. Sarcoidosis. Med Clin North Am. 2019;103:527-34.
[2] Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac Sarcoidosis. J Am Coll Cardiol. 2016;68:411-21.
[3] Birnie DH, Kandolin R, Nery PB, Kupari M. Cardiac manifestations of sarcoidosis: diagnosis and management. Eur Heart J. 2017;38:2663-70.
[4] Ekstrom K, Lehtonen J, Nordenswan HK, Mayranpaa MI, Raisanen-Sokolowski A, Kandolin R, et al. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. Eur Heart J. 2019;40:3121-8.
[5] Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, et al. The WASOG Sarcoidosis Organ Assessment Instrument: An update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31:19-27.
[6] Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, et al. JCS 2016 Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis- Digest Version. Circ J. 2019;83:2329-88.
[7] Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11:1305-23.
[8] Ribeiro Neto ML, Jellis C, Hachamovitch R, Wimer A, Highland KB, Sahoo D, et al. Performance of diagnostic criteria in patients clinically judged to have cardiac sarcoidosis: Is it time to regroup? Am Heart J. 2020;223:106-9.
[9] Chiba T, Nakano M, Hasebe Y, Kimura Y, Fukasawa K, Miki K, et al. Prognosis and risk stratification in cardiac sarcoidosis patients with preserved left ventricular ejection fraction. J Cardiol. 2020;75:34-41.
[10] Okada DR, Smith J, Derakhshan A, Gowani Z, Zimmerman SL, Misra S, et al. Electrophysiology study for risk stratification in patients with cardiac sarcoidosis and abnormal cardiac imaging. Int J Cardiol Heart Vasc. 2019;23:100342.
[11] Flores RJ, Flaherty KR, Jin Z, Bokhari S. The prognostic value of quantitating and localizing F-18 FDG uptake in cardiac sarcoidosis. J Nucl Cardiol. 2020;27:2003-10.
[12] Mehta D, Mori N, Goldbarg SH, Lubitz S, Wisnivesky JP, Teirstein A. Primary prevention of sudden cardiac death in silent cardiac sarcoidosis: role of programmed ventricular stimulation. Circ Arrhythm Electrophysiol. 2011;4:43-8.
[13] Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, et al. Association Between Midwall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients With Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction. Circulation. 2017;135:2106-15.
[14] Vassiliou VS, Perperoglou A, Raphael CE, Joshi S, Malley T, Everett R, et al. Midwall Fibrosis and 5-Year Outcome in Moderate and Severe Aortic Stenosis. J Am Coll Cardiol. 2017;69:1755-6.
[15] Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, et al. Outcome in Dilated Cardiomyopathy Related to the Extent, Location, and Pattern of Late Gadolinium Enhancement. JACC Cardiovasc Imaging. 2019;12:1645-55.
[16] Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiac sarcoidosis-state of the art review. Cardiovasc Diagn Ther. 2016;6:50-63.
[17] Komada T, Suzuki K, Ishiguchi H, Kawai H, Okumura T, Hirashiki A, et al. Magnetic resonance imaging of cardiac sarcoidosis: an evaluation of the cardiac

segments and layers that exhibit late gadolinium enhancement. Nagoya J Med Sci. 2016;78:437-46.
[18] Smedema J-P, Ainslie G, Crijns HJGM. Review: Contrast-enhanced magnetic resonance in the diagnosis and management of cardiac sarcoidosis. Progress in Cardiovascular Diseases. 2020;63:271-307.
[19] Jackson E, Raman S, Crouser ED. Resolution of Cardiac Magnetic Resonance T2 Signal Following Immune Suppression for Cardiac Sarcoidosis: A Case Series. C40 SARCOIDOSIS: UNDERSTANDING THIS MULTI-SYSTEM DISORDER. p. A5025-A.
[20] Muser D, Santangeli P, Liang JJ, Castro SA, Magnani S, Hayashi T, et al. Characterization of the Electroanatomic Substrate in Cardiac Sarcoidosis: Correlation With Imaging Findings of Scar and Inflammation. JACC Clin Electrophysiol. 2018;4:291-303.
[21] Banba K, Kusano KF, Nakamura K, Morita H, Ogawa A, Ohtsuka F, et al. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. Heart Rhythm. 2007;4:1292-9.
[22] Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol. 2014;63:329-36.
[23] Cain MA, Metzl MD, Patel AR, Addetia K, Spencer KT, Sweiss NJ, et al. Cardiac sarcoidosis detected by late gadolinium enhancement and prevalence of atrial arrhythmias. Am J Cardiol. 2014;113:1556-60.
[24] Greulich S, Deluigi CC, Gloekler S, Wahl A, Zurn C, Kramer U, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. JACC Cardiovasc Imaging. 2013;6:501-11.
[25] Nadel J, Lancefield T, Voskoboinik A, Taylor AJ. Late gadolinium enhancement identified with cardiac magnetic resonance imaging in sarcoidosis patients is associated with long-term ventricular arrhythmia and sudden cardiac death. Eur Heart J Cardiovasc Imaging. 2015;16:634-41.
[26] Murtagh G, Laffin LJ, Beshai JF, Maffessanti F, Bonham CA, Patel AV, et al. Prognosis of Myocardial Damage in Sarcoidosis Patients With Preserved Left Ventricular Ejection Fraction: Risk Stratification Using Cardiovascular Magnetic Resonance. Circ Cardiovasc Imaging. 2016;9:e003738.
[27] Ekstrom K, Lehtonen J, Hanninen H, Kandolin R, Kivisto S, Kupari M. Magnetic Resonance Imaging as a Predictor of Survival Free of Life-Threatening Arrhythmias and Transplantation in Cardiac Sarcoidosis. J Am Heart Assoc. 2016;5.
[28] Okada DR, Xie E, Assis F, Smith J, Derakhshan A, Gowani Z, et al. Regional abnormalities on cardiac magnetic resonance imaging and arrhythmic events in patients with cardiac sarcoidosis. J Cardiovasc Electrophysiol. 2019;30:1967-76.
[29] Yasuda M, Iwanaga Y, Kato T, Izumi T, Inuzuka Y, Nakamura T, et al. Risk stratification for major adverse cardiac events and ventricular tachyarrhythmias by cardiac MRI in patients with cardiac sarcoidosis. Open Heart. 2016;3:e000437.
[30] Velangi PS, Chen KA, Kazmirczak F, Okasha O, von Wald L, Roukoz H, et al. Right Ventricular Abnormalities on Cardiovascular Magnetic Resonance Imaging in Patients With Sarcoidosis. JACC Cardiovasc Imaging. 2020;13:1395-405.
[31] Kagioka Y, Yasuda M, Okune M, Kakehi K, Kawamura T, Kobuke K, et al. Right ventricular involvement is an important prognostic factor and risk stratification tool

in suspected cardiac sarcoidosis: analysis by cardiac magnetic resonance imaging. Clin Res Cardiol. 2020;109:988-98.
[32] Bravo PE, Raghu G, Rosenthal DG, Elman S, Petek BJ, Soine LA, et al. Risk assessment of patients with clinical manifestations of cardiac sarcoidosis with positron emission tomography and magnetic resonance imaging. Int J Cardiol. 2017;241:457-62.
[33] Kouranos V, Tzelepis GE, Rapti A, Mavrogeni S, Aggeli K, Douskou M, et al. Complementary Role of CMR to Conventional Screening in the Diagnosis and Prognosis of Cardiac Sarcoidosis. JACC Cardiovasc Imaging. 2017;10:1437-47.
[34] Hulten E, Agarwal V, Cahill M, Cole G, Vita T, Parrish S, et al. Presence of Late Gadolinium Enhancement by Cardiac Magnetic Resonance Among Patients With Suspected Cardiac Sarcoidosis Is Associated With Adverse Cardiovascular Prognosis: A Systematic Review and Meta-Analysis. Circ Cardiovasc Imaging. 2016;9:e005001.
[35] Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018;138:e272-e391.
[36] Kazmirczak F, Chen KA, Adabag S, von Wald L, Roukoz H, Benditt DG, et al. Assessment of the 2017 AHA/ACC/HRS Guideline Recommendations for Implantable Cardioverter-Defibrillator Implantation in Cardiac Sarcoidosis. Circ Arrhythm Electrophysiol. 2019;12:e007488.
[37] Halawa A, Jain R, Turagam MK, Kusumoto FM, Woldu HG, Gautam S. Outcome of implantable cardioverter defibrillator in cardiac sarcoidosis: a systematic review and meta-analysis. J Interv Card Electrophysiol. 2020;58:233-42.
[38] Azoulay LD, Waintraub X, Haroche J, Amoura Z, Cohen Aubart F. Factors associated with implantable cardioverter defibrillators appropriate therapy in cardiac sarcoidosis: a meta-analysis. Sarcoidosis Vasc Diffuse Lung Dis. 2020;37:17-23.