

THE UTILITY OF DELAYED-ENHANCEMENT MAGNETIC RESONANCE IMAGING FOR IDENTIFYING NONISCHEMIC MYOCARDIAL FIBROSIS IN ASYMPTOMATIC PATIENTS WITH BIOPSY-PROVEN SYSTEMIC SARCOIDOSIS

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ABSTRACT. *Background:* The pathophysiology of sarcoidosis includes infiltrative inflammatory injury, as well as interstitial fibrosis formation. Delayed-enhancement (DE) magnetic resonance imaging (MRI) techniques have been shown to identify fibrotic tissue as areas of hyperenhancement. To test the hypothesis that DE-MRI can be used to identify myocardial fibrosis resulting from cardiac sarcoidosis, we assessed this method in asymptomatic patients with biopsy-proven systemic sarcoidosis. *Methods:* Thirty-one patients with biopsy-confirmed systemic sarcoidosis and no known history of heart disease or sarcoid cardiac involvement underwent DE-MRI after gadolinium-chelate administration. The location and extent of DE were quantified by 2 radiologists experienced at evaluating cardiovascular MRI images. *Results:* According to DE-MRI, 8 (26%) of the 31 patients had nonischemic fibrosis, as evidenced by abnormal DE patterns. Unlike characteristic ischemic injuries, most of the fibrosis was mid-myocardial, extending to the adjacent endocardium, epicardium, or both. The most frequent site of fibrosis was the basal inferoseptum, followed by the basal inferolateral wall. *Conclusions:* In asymptomatic patients with systemic sarcoidosis, DE-MRI may provide a novel, noninvasive method for the early identification of myocardial fibrosis. (*Sarcoidosis Vasc Diffuse Lung Dis* 2009; 26: 39-46)

KEY WORDS: sarcoidosis, cardiac, cardiac magnetic resonance imaging, delayed enhancement

INTRODUCTION

Sarcoidosis is a systemic inflammatory disease characterized by noncaseating granulomas in the affected organs, most commonly the pulmonary system (1). The exact etiology of sarcoidosis is unknown.

The granulomas may resolve without producing symptoms, or a persistent inflammatory response may lead to fibroblast proliferation, collagen production, and progressive fibrosis (2). The exact prevalence of cardiac involvement also is not clear. Some studies suggest that it may be as high as 50% in patients with sarcoidosis, although only 5% of these patients may have clinical symptoms (3-6). In the United States, 13% to 50% of deaths in patients with sarcoidosis are due to cardiac sarcoidosis (CS) (7, 8), the mortality being primarily related to electrical conduction abnormalities, ventricular dysrhythmias, and congestive cardiac failure. In Japan, CS is the major cause of sarcoid-attributed death (9).

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Cardiac magnetic resonance imaging (MRI) has emerged as the gold standard for evaluating ventricular function, and it plays an increasingly important role in assessing various cardiomyopathies. Its primary advantages are that it is noninvasive, has excellent spatial resolution, is highly reproducible, uses a non-nephrotoxic contrast agent (gadolinium [Gd]-chelate), and involves no ionizing radiation (10-14).

A number of MRI approaches have been proposed to identify cardiac sarcoid involvement. T2-weighted, spin-echo-based imaging sequences have been proposed to identify the myocardial edema caused by the inflammatory response in CS (15). Recently, the advent of delayed-enhancement (DE) MRI has made it possible to identify myocardial fibrosis with exquisite spatial and contrast resolution (16). To date, several anecdotal and retrospective studies have suggested that DE-MRI may be an effective tool for evaluating myocardial fibrosis due to CS (15, 17-23).

In the current study, we used DE-MRI to prospectively evaluate the presence of myocardial fibrosis in patients with biopsy-confirmed systemic sarcoidosis and no known history of heart disease. A secondary goal was to characterize the volume, pattern, and location of myocardial fibrosis in these patients.

METHODS AND MATERIALS

Study Group

From August 2003 to June 2006, 58 consecutive patients with biopsy-proven sarcoidosis were screened for inclusion in this study after being referred for cardiac MRI examination from a local tertiary pulmonary and critical care clinic. Patients with a previous history of heart disease were excluded from the study. Before MRI was performed, each patient underwent 12-lead electrocardiography to exclude potential confounding factors such as left ventricular (LV) hypertrophy, which could give rise to myocardial hyperenhancement in DE-MRI. Other exclusion criteria included known or suspected ischemic heart disease, tachyarrhythmias, MRI-incompatible devices or implants, a serum creatinine level of >1.5 g/dl, extreme obesity, or claustrophobia

that might prevent successful MRI. Thirty-one of the 58 patients fulfilled the acceptance criteria. Our hospital's institutional ethics committee approved the study, and all the subjects gave written informed consent. One year after the MRI examination, a follow-up telephone interview was conducted with the patients.

Image acquisition and postprocessing

Imaging was performed with a 1.5T commercial scanner (Philips NT-Intera or Philips Achieva; Philips Medical Systems, Cleveland, Ohio, USA) equipped with a 5-element cardiac coil for signal reception and vectorcardiographic gating.

Initially, we obtained standard survey images of the thorax in 3 orthogonal directions. Using these images, we then obtained conventional bright-blood (steady-state free-precession [SSFP]) cine images of the heart in standard orientations, including vertical long-axis, 4-chamber, and LV outflow-tract views. In addition, we acquired 10 to 12 contiguous short-axis imaging slices that covered the entire left ventricle from base to apex. The following acquisition parameters were used for SSFP cine imaging: repetition time/echo time, 3.4/1.7 msec; flip angle, 55°; temporal resolution, 36 to 40 msec; and in-plane resolution, 1.5 to 1.75 mm² (depending on the patient's size). A parallel imaging technique called sensitivity encoding (SENSE) was used to reduce the acquisition time to 5 to 6 heartbeats per image slice.

The DE-MRIs were acquired 15 minutes after administration of an MRI contrast agent (gadoversetamide, 0.2 mmol/kg) (OptiMARK®, Mallinckrodt Corporation, Hazelwood, Missouri, USA), using an inversion-recovery-prepared, T1-weighted, gradient-echo sequence. After the inversion pulse, 16 to 24 gradient echoes (repetition time/echo time/flip angle, 7.0 msec/2.0 msec/15°) were collected per heartbeat during diastole, with an inversion delay that was iteratively adjusted to optimally null the signal from normal myocardium. The total acquisition time was 16 heartbeats per image slice. Selected 8-mm-thick, long-axis slices were acquired along with a series of contiguous short-axis slices, so as to cover the entire left ventricle. The images were acquired in the same orientations as the cine SSFP sequences.

Data Analysis

Data were transferred to a commercially available postprocessing workstation (ViewForum; Philips Medical Systems, Best, The Netherlands) for analysis. Two experienced cardiovascular imagers (SDF and BC) drew the endocardial and epicardial contours of each section of the left ventricle at end-diastole and end-systole. The pixels circumscribed by these contours were summed and multiplied by the slice thickness (voxel-summation method) to obtain global parameters such as end-diastolic volume (EDV), end-systolic volume (ESV), and LV mass. From the EDV and ESV, secondary parameters such as the stroke volume ($SV = EDV - ESV$) and LV ejection fraction ($LVEF = SV/EDV$) were calculated for each patient.

The regions that showed hyperenhancement within the myocardium were quantified by using a semiautomated thresholding algorithm. An experienced observer circumscribed the endocardial and epicardial boundaries on the short-axis DE-MRIs. This observer also selected a small region of interest ($\sim 75 \text{ mm}^2$) in a normal remote portion of the myocardium. The signal-intensity statistics computed from this region characterized normal remote myocardium. Within the circumscribed myocardial boundaries, all signal intensities greater than 2 standard deviations above the mean signal intensity were thresholded to identify myocardial fibrosis. From the number of fibrotic voxels and the total number of myocardial voxels, LV fibrosis was calculated as a percentage of the total LV mass.

Statistics

All data are presented as mean \pm standard deviation. We used a paired Student *t* test to assess continuous variables and a χ^2 test to assess categorical variables.

RESULTS

All 31 patients completed the MRI study. Table 1 shows the demographic and quantitative LV functional data for patients with DE compared to those without DE. The baseline characteristics between the 2 groups were similar. The 9 men and 22 women

Table 1. Associated conditions and left ventricular quantitative variables*

Variables	Patients with DE (n=8)	Patients without DE (n=23)	P Value [†]
Age (y)	58 \pm 16	50 \pm 11	0.11
Males	3 (37.5%)	6 (26%)	0.50
Hyperlipidemia	4 (50%)	6 (26%)	0.21
Diabetes mellitus	2 (25%)	2 (8.6%)	0.24
Hypertension	4 (50%)	8 (35%)	0.44
Smoker	1 (12.5%)	0	0.08
End-diastolic volume (ml)	144 \pm 48	133 \pm 24	0.39
End-systolic volume (ml)	70 \pm 43	56 \pm 14	0.18
Stroke volume (ml)	75 \pm 13	77 \pm 14	0.70
Cardiac output (l/min)	5.6 \pm 1.1	5.5 \pm 1.2	0.70
Ejection fraction (%)	54 \pm 10.0	58 \pm 5.3	0.17
LV mass (g)	92 \pm 28	83 \pm 21	0.32

DE, delayed enhancement; LV, left ventricular

*Associated conditions are expressed as number (percent) of patients, and left ventricular quantitative values are expressed as the mean \pm standard deviation.

[†] χ^2 test for categorical variables and Student *t*-test for continuous variables.

had a mean age of 52 \pm 13 years (mean \pm standard deviation). The majority of the patients (26/31; 84%) had pulmonary sarcoidosis, and the rest had biopsy-proven cutaneous, hepatic, or gastrointestinal sarcoidosis.

With respect to global LV function, including EDV and LVEF, there was no significant difference between the patients with and without DE. Those with DE tended to be older (58 \pm 16 vs. 50 \pm 10 years; $P=NS$). There was no correlation between the duration of the disease and the extent of DE.

Eight patients (26%) had DE in the left ventricle. Table 2 shows the locations and amount of DE, expressed as a percentage of the total LV mass. The most common location for DE was in the basal inferoseptum (75%; 6/8 patients), followed by the basal inferolateral wall (38%; 3/8 patients). Of the 31 patients, only 2 had evidence of right ventricular (RV) involvement; both of these patients also had DE in the left ventricle.

Whereas none of the patients with evident or suspected heart disease were included in the study, 33% of the patients (numbers 5, 7, and 8, Table 2) in the DE group underwent X-ray coronary angiography as part of a pulmonary transplant evaluation within 6 months after MRI. All 3 patients had no evidence of obstructive CAD.

Table 2. Location and degree of left ventricular hyperenhancement

Patient	Location of LV Hyperenhancement	Degree of LV Enhancement (%)
1	a) Basal inferoseptum, epicardium b) Basal inferolateral wall, mid-myocardium	2
2	Proximal 2/3 of inferoseptum, mid-myocardium to subepicardium	1
3	Middle 1/3 of inferoseptum, mid-myocardium to subepicardium	1
4	Proximal 2/3 of inferoseptum, mid-myocardium to subepicardium	2
5	Basal inferoseptum, mid-myocardium to epicardium	0.5
6	a) Basal inferolateral wall, subendocardium b) Basal inferolateral wall, mid-myocardium to subepicardium	2
7	a) Basal inferolateral wall, mid-myocardium to subendocardium and subepicardium and involving adjacent basal inferior wall b) Basal inferoseptum, mid-myocardium to subepicardium c) Basal right ventricular inferior wall	7
8	a) Predominantly transmural in distal 2/3 of anteroseptum b) Distal anterior wall extending into anterolateral wall, mid-myocardium to subendocardium and subepicardium c) Basal inferoseptum, epicardium d) Basal right ventricular inferior wall	10

Twelve patients had active pulmonary sarcoidosis, and all were receiving medical treatment, including steroid therapy with or without oral methotrexate. Delayed enhancement was more common in patients with active disease who required medical treatment than in patients without active disease ($P=0.04$).

One year after MRI, 30 (97%) of the 31 patients were interviewed by phone, and 1 patient was lost to follow-up. Of the 30 remaining patients, 1 was admitted to the hospital for exacerbated pulmonary sarcoidosis within the 12-month follow-up period and subsequently died of a pulmonary embolism while waiting for lung transplantation. The other 29 patients were asymptomatic from a cardiovascular standpoint.

DISCUSSION

In sarcoidosis, cardiac involvement is difficult to diagnose. In 1929, Bernstein and coworkers (24) published the first description of such involvement. The first necropsy series was performed in 1952. According to unselected autopsy series, up to 27% of patients with sarcoidosis have cardiac involvement

(5). Patients with CS frequently present with electrocardiographic abnormalities, including non-specific ST-T-wave changes and first-degree atrioventricular conduction abnormalities, as well as left anterior hemiblock and right-bundle-branch block (25). However, CS is diagnosed clinically in only a small number of cases, partly because the myriad clinical manifestations of the disease (papillary muscle dysfunction, conduction abnormalities, ventricular arrhythmias, pericarditis or effusion, and congestive heart failure) are often nonspecific and attributable to other disease entities.

Cardiac sarcoidosis has a predilection to occur in the interventricular septum (mid-myocardial). Because CS can be diffuse, a target for a transvenous myocardial biopsy is hard to localize. Neither echocardiography nor thallium-201 scanning is sensitive or specific for CS, so these methods have a limited role in its diagnosis (26). Thus, antemortem diagnosis of CS remains a challenging clinical problem. Other investigators have also described the use of position-emission tomography for the detection of CS (27, 28).

From a pathologic standpoint, noncaseating granulomas and other inflammatory infiltrates may result in fibrosis, as well as permanent tissue damage

(29). In this regard, MRI offers 3 prominent means for identifying CS:

1) Inflammatory changes appear as regions of increased signal intensity in T2-weighted spin-echo images. Therefore, conventional tissue-characterization techniques, such as those based on T2-weighted spin-echo, can be used to identify myocardial inflammation. However, the information provided by a T2-weighted imaging sequence is often nonspecific (15, 17-21). When De Cobelli and colleagues (30) used cardiac MRI to evaluate patients with biopsy-proven myocarditis, DE detected the myocarditis in 70% of the patients, but a T2-weighted sequence detected it in only 22%. Spin-echo, with or without fat suppression sequences, was not performed in our study because the patients were asymptomatic from a cardiovascular standpoint, so myocardial edema (suggesting active disease) would have been unlikely to be present.

2) Cardiac cine MRI can reveal focal regional wall-motion abnormalities caused by CS. However, this finding is also nonspecific, and often the SSFP sequences used for cine imaging do not provide sufficient tissue contrast to differentiate myocardial CS-affected regions from unaffected regions.

3) DE-MRI identifies fibrotic regions with exquisite spatial and contrast resolution. It is specific in identifying fibrosis. It is a simple imaging technique that requires intravenous administration of an extravascular MR contrast agent such as Gd-chelates, followed by an imaging sequence that provides very high T1-weighted contrast. Typically, this process involves an inversion-recovery-prepared, segmented k-space gradient-echo technique with cardiac gating. Regions of fibrosis have a greater accumulation of Gd-chelates because there is more interstitial space in fibrotic regions than in normal myocardium. The DE technique exploits this differential accumulation of Gd-chelates in fibrotic and normal regions of myocardium (31). On the resultant images, scarred or fibrotic tissue appears bright, and normal, viable tissue is dark. This difference in signal intensity allows normal myocardium to be differentiated from scarred or fibrotic tissue, which could indicate sarcoid granulomatous infiltrates.

The DE-MRI technique has been well validated in animal models. In a canine study, Kim and colleagues (16) demonstrated a near-perfect correlation between the extent of fibrous scarring stained by

2,3,5-triphenyltetrazolium and that obtained with DE-MRI; subsequent investigators have confirmed these initial observations (32, 33). One of the primary advantages of DE-MRI is its fine spatial resolution, which is typically 1 to 2 mm in-plane. When this resolution is combined with the technique's excellent contrast resolution, even fibrosis or small infarctions can be readily identified (32, 34). Because of its ease of clinical use and its higher spatial and contrast resolution in comparison to nuclear methods, DE-MRI is an attractive clinical option. Moreover, cardiac MRI can also detect extracardiac manifestations of sarcoidosis.

In 2003, Serra and colleagues (35) published a case report documenting the use of DE-MRI to detect CS. Since then, several other groups have used this method to detect CS in a limited number of patients (36-38).

In our study, the pattern of CS involvement was usually patchy and involved 1 or more focal areas of the myocardium (Table 2). The most commonly affected area was the basal inferoseptum (6/8 patients; 75%), followed by the basal inferolateral wall (3/8 patients; 38%). Representative images are shown in Figures 1 and 2. These findings are consistent with those described by Tadamura and colleagues (36) and by Smedema and coauthors (37). With respect to the location of sarcoid involvement, it would be

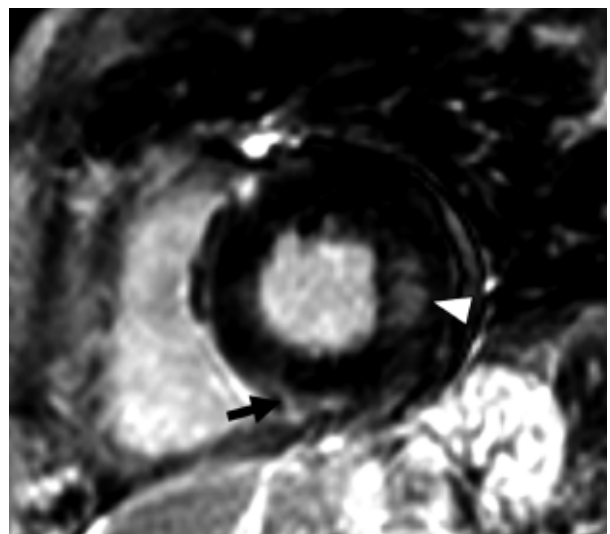


Fig. 1. Cardiac magnetic resonance image showing delayed hyperenhancement of the basal inferoseptum (black arrow) and the basal inferolateral wall (white arrowhead)

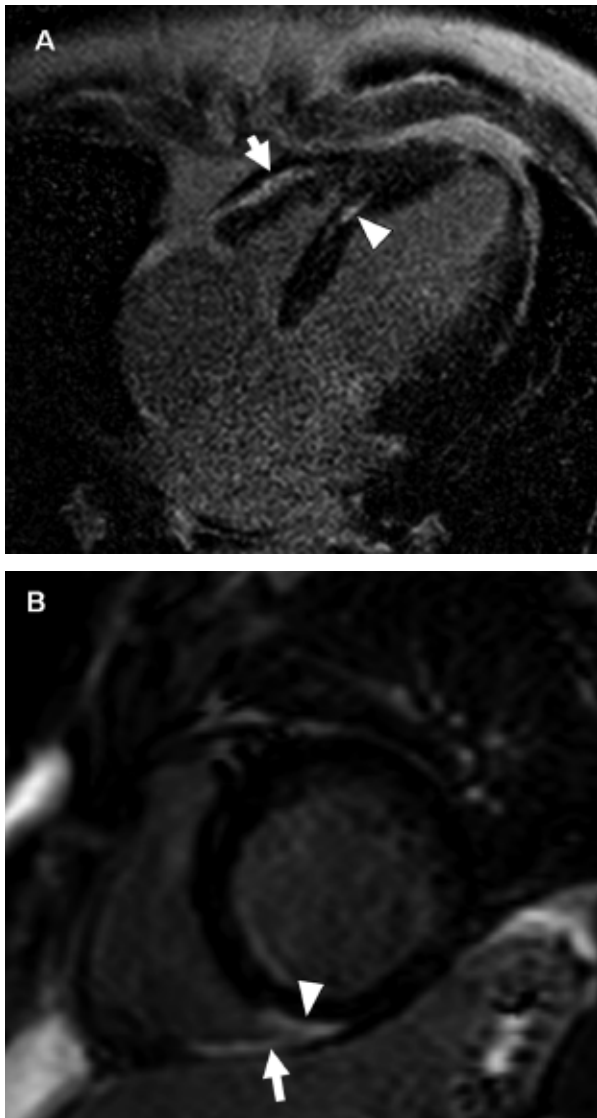


Fig. 2. Cardiac magnetic resonance image from another patient, showing delayed hyperenhancement (A) of the right ventricle (arrow) and the interventricular septum (arrowhead) and (B) of the basal inferoseptum (arrowhead) and the adjacent inferior wall of the right ventricle (arrow)

difficult to compare our study directly with previous studies, as some of the researchers did not use a standard 16- to 17-segment model for reporting (15, 17-19). It is unclear why CS tends to involve the basal septum.

In all 8 of our patients with myocardial DE, the pattern of involvement either was confined to the mid-myocardium or extended from the mid-myocardium to the epicardium, endocardium, or both.

In addition, 2 patients had areas of DE involving the epicardium alone. The 2 patients with RV involvement also had the largest amount of DE involving the left ventricle.

Fibrosis resulting from ischemic cardiomyopathy nearly always involves the endocardium and corresponds well to the affected coronary artery distribution. However, the pattern of fibrosis associated with CS is distinct from that of ischemic cardiomyopathy. Because of the limited number of patients in our study, we were unable to reach definitive conclusions regarding the pattern of DE in patients with CS.

In prospectively using DE-MRI to identify myocardial fibrosis, our study was somewhat different from previous studies described above. For example, although the series reported by Smedema and associates (37) had a larger number of patients, only 16 of them underwent DE-MRI sequencing. The study was conducted between 1998 and 2004, but the authors do not clarify whether it was retrospective or prospective. Moreover, in the study performed by Schulz-Menger and colleagues (23), all 31 patients in the study group had cardiac symptoms.

There are currently no large prospective randomized studies that have evaluated the optimal treatment of symptomatic and asymptomatic patients with CS. On the basis of small series, some authors have recommended early initiation of corticosteroid therapy (17, 20, 39, 40) and they have reported clinical and laboratory improvements on follow-up examination of these patients. Our current prospective study concentrated on imaging CS by means of DE-MRI, and the evaluation of treatment of CS is beyond the scope of this article. Nevertheless, the high spatial resolution and reproducibility of cardiac MRI, as well as the lack of radiation and potentially nephrotoxic contrast agents, make cardiac MRI a unique modality for the diagnosis and long-term follow-up evaluation of patients with CS.

LIMITATIONS

Our study's main limitation is the lack of independent confirmation of the presence of CS by means of an endocardial biopsy. However, all of our patients were asymptomatic from a cardiovascular

standpoint, so an invasive biopsy procedure (which could have entailed serious complications) would have been hard to justify on either medical or ethical grounds. Moreover, the patchy nature of CS would have made the results vulnerable to sampling errors. Similarly, other noninvasive methods such as echocardiography or nuclear perfusion studies were not mandated in our series. Because DE may also occur in myocardial infarction, hypertrophic cardiomyopathy, and other nonischemic forms of cardiomyopathy, we purposely excluded patients who had cardiac symptoms or known cardiac disease in order to minimize confounding factors. For similar reasons, because all patients in the study group were asymptomatic from a cardiovascular standpoint, neither coronary angiography nor noninvasive stress testing was mandated. Although some of the study patients had other comorbidities such as diabetes and hypertension, these disease processes typically give rise to mid-myocardial DE and spare the subendocardium and subepicardium. Furthermore, none of our patients had LV hypertrophy, as determined by measurement of the LV mass. Therefore, we believe that the fibrosis seen on DE-MRI in this study was likely due to sarcoidosis.

CONCLUSION

In our prospective series of 31 patients with biopsy-proven systemic sarcoidosis and no history of cardiac involvement, 8 patients (26%) had DE in the left ventricle, right ventricle, or both, suggesting sarcoid involvement. Typically, the fibrosis characterized by DE was located in the mid-myocardium and extended to the adjacent epicardium and endocardium, predominantly affecting the basal inferoseptum and basal inferolateral wall. Because of DE-MRI's exquisite spatial and contrast resolution in identifying fibrosis, this method may potentially be useful for diagnosing CS.

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