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Delayed Gadolinium-Enhanced Cardiac Magnetic Resonance in Patients With Chronic Myocarditis Presenting With Heart Failure or Recurrent Arrhythmias

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OBJECTIVES We evaluated the effectiveness of contrast-enhanced cardiac magnetic resonance (CE-CMR) in detecting chronic myocarditis (CM).

BACKGROUND Chronic myocarditis represents a common evolution of acute myocarditis. Although CE-CMR has been revealed to be effective in identifying areas of myocardial damage in acute myocarditis, its role in the diagnosis of chronic myocardial inflammation has not yet been investigated.

METHODS Twenty-three patients with CM underwent CE-CMR and endomyocardial biopsy (EMB). Chronic myocarditis was defined by the presence of: 1) chronic (>6 months) heart failure symptoms and/or repetitive ventricular arrhythmias; 2) no history of recent flu-like symptoms or infections; and 3) histologic evidence of active myocarditis (AM) or borderline myocarditis (BM) according to Dallas criteria. Contrast-enhanced cardiac magnetic resonance included black-blood T2-weighted (BBT2w) images without and with fat saturation and delayed three-dimensional T1 turbo field-echo inversion-recovery sequences obtained 15 min after gadolinium injection.

RESULTS Histology showed AM in 14 patients and BM in 9 patients. FatSat BBT2w revealed the presence of edema in five (36%) patients with AM but not in BM patients. Areas of late enhancement (LE) were observed in 12 (84%) subjects with AM and in 4 (44%) cases with BM. A mid-wall LE pattern was the most frequent finding in both groups while a subepicardial distribution of LE was observed only in patients with AM.

CONCLUSIONS Contrast-enhanced cardiac magnetic resonance identified areas of myocardial inflammation in up to 70% of patients with biopsy-proven CM. We suggest that CE-CMR may be a useful non-invasive diagnostic tool in patients with CM, and it may indicate and even guide the execution of left ventricular EMB with relevant prognostic and therapeutic implications. (J Am Coll Cardiol 2006;47:1649–54) © 2006 by the American College of Cardiology Foundation

Clinical manifestations of myocarditis are extremely various, ranging from asymptomatic state to fulminant acute heart failure, conduction disturbances, or ventricular tachyarrhythmias (1,2), and even global biventricular dysfunction in patients with coronary artery disease (3).

A spontaneous recovery may occur in the acute phase in up to 50% of patients (4), but chronic inflammatory cardiomyopathy and dilated cardiomyopathy sustained by both viral persistence and autoimmune self-perpetration represent a common evolution of the disease (5–7). The diagnosis of myocarditis has relevant therapeutic implications as immunosuppressive therapy and interferon-beta administration has been revealed effective in autoimmune and viral myocarditis, respectively (6,7). Unfortunately, laboratory tests, serologic studies, and non-invasive tools are unable to provide a definite diagnosis of myocarditis that still relies on endomyocardial biopsy (EMB) (5–7). Cardiac magnetic resonance (CMR) imaging with gadolinium late enhancement (LE) may identify areas of myocardial damage in myocardial infarction (8), hypertrophic and dilated cardiomyopathies (9,10). Recent studies (11,12) have demonstrated that contrast-enhanced cardiac magnetic resonance (CE-CMR) may be useful in non-invasive recognition of myocardial inflammation in patients with acute myocarditis (AM). However, the sensitivity of CE-CMR in detecting myocardial inflammation in patients without clinical evidence of AM remains unknown.

In the present study we sought to investigate whether CE-CMR may allow the non-invasive recognition of myocardial inflammation in patients with chronic myocarditis (CM).

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METHODS

Patient population. Twenty-three consecutive patients with CM were submitted to CE-CMR before EMB. Chronic myocarditis was defined by the presence of the following

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Abbreviations and Acronyms

AM = active myocarditis
BBT2w = black-blood T2-weighted
BM = borderline myocarditis
CE-CMR = contrast-enhanced cardiac magnetic resonance
CM = chronic myocarditis
CMR = cardiac magnetic resonance
EF = ejection fraction
EMB = endomyocardial biopsy
LE = late enhancement
LV = left ventricle/ventricular
PCR = polymerase chain reaction
RV = right ventricle/ventricular

criteria: 1) chronic (>6 months) heart failure symptoms and/or repetitive ventricular arrhythmias (Lown class III to IVa) with or without left ventricular (LV) systolic dysfunction; 2) no history of recent flu-like syndrome or gastrointestinal or upper respiratory infection; 3) evidence of AM or borderline myocarditis (BM) according to Dallas criteria (13) on EMB. Patient population included 8 women and 15 men. Clinical presentation was represented by symptoms of heart failure in 9 patients and repetitive ventricular arrhythmias in 14 patients. These 14 patients presented persisting ventricular ectopic beats at three consecutive electrocardiographic Holter monitoring executed monthly. No patient experienced sustained ventricular tachycardia requiring direct current shock or implantable cardioverter defibrillator implantation. No patient showed pericardial effusion nor troponin I elevation.

CMR imaging acquisition and analysis. Cardiac magnetic resonance was performed before cardiac catheterization on a 1.5-T whole-body scanner (Gyroscan Intera Master; Philips Medical Systems, Best, the Netherlands) by using an enhanced gradient system (maximum gradient strength: 30 mT/m; maximum gradient slew rate: 150 $mT \cdot m^{-1} \cdot s^{-1}$) and a five-element cardiac phased-array coil (SENSE Cardiac, Philips Medical Systems, Bothell, Washington).

Morphologic images in the cardiac short-axis, four-chamber long-axis, and two-chamber long-axis planes were acquired by using black-blood T2-weighted (BBT2w) sequences without and with fat suppression; BBT2w images with fat suppression were visually evaluated to detect areas of hyperintensity suggesting the presence of edema.

In the same planes cine-magnetic resonance imaging was performed by using a breath-hold steady-state free precession (SSFP) sequence with parallel imaging (SENSE, Philips Medical Systems, Best, the Netherlands) as previously described (14).

Left ventricle end-diastolic and -systolic volumes, stroke volume, ejection fraction (EF) cardiac output, and myocardial mass were calculated from a stack of sequential short-axis cine loops (8 to 12 contiguous slices) by semi-automatic segmentation (EasyVision; Philips Medical Systems) of endocardial and epicardial borders on each frame as previously described (14).

The LE short- and long-axis images were acquired 10 to 15 min after peripheral bolus injection of gadolinium-DTPA (Shering AG, Berlin, Germany) (0.2 mmol/kg of body weight) by using a three-dimensional TFE-inversion-recovery T1-weighted sequence (repetition time: 3.8 to 4.1 ms; echo time: 1.2 ms; flip angle: 15°, inversion time: 200 to 300 individually optimized to null myocardial signal, matrix: 256; thickness: 5 mm).

The extension of LE was planimetered by an experienced operator on 20 contiguous short-axis images, summed up to a volume and expressed as a percentage of total myocardium.

The location and the pattern (subendocardial, mid-wall, subepicardial, or transmural) of LE were assessed by the consensus of two expert observers unaware of the pathological findings.

Cardiac catheterization and EMB. All patients were submitted to cardiac catheterization, coronary angiography, LV and right ventricular (RV) angiography with end-diastolic pressure measurements and biventricular EMB. Endomyocardial biopsies (three to four from each ventricle) were performed in the septal-apical region; two to three samples were immediately frozen in liquid nitrogen for molecular studies. The remaining tissue specimens were fixed in 10% buffered formalin and embedded in paraffin wax. All invasive cardiac procedures were performed after informed patient consent and approval by the ethics committees of our institutions.

Histology and immunohistochemistry. Four to six samples from each patient were processed for histology and immunohistochemistry. All samples from the same patient were analyzed together. The diagnosis of myocarditis was made according to Dallas criteria (13) and by immunohistochemical characterization of inflammatory infiltrates (6). The presence of inflammatory infiltrates with foci of necrosis of adjacent myocytes in at least one specimen was diagnostic for AM. Morphometric quantification of fibrosis was performed on Masson's trichrome sections using an automated system (Nikon, Japan).

Molecular biology studies. Two frozen myocardial specimens from each patient were used for polymerase chain reaction (PCR) and reverse transcriptase PCR analysis. Ten primer pairs were used to detect cardiotropic viruses' deoxyribonucleic and ribonucleic acid. The purified PCR products were sequenced directly on an automated ABI (Foster City, California) model 310 A sequencer, as previously described (2,6).

RESULTS

Cardiac catheterization and EMB findings. All patients presented normal epicardial coronary arteries and increased LV end-diastolic pressure (19.3 ± 3.6 mm Hg, range 14 to 25 mm Hg). Histology showed the presence of AM in 14 patients: inflammatory infiltrates were present in both LV

and RV myocardial samples in 5 patients, only in LV samples in 8 cases, and only in RV samples in 1 case. The remaining nine patients showed histological evidence of BM: inflammatory infiltrates were present in both LV and RV myocardial samples in three cases, confined to LV samples in five patients, and to RV samples in one case. At immunohistochemistry, inflammatory infiltrates were mainly represented by activated T-lymphocytes (CD 45RO+) in all patients. Morphometric studies showed that in BM patients interstitial and replacement fibrosis extent was significantly higher than in AM patients (18 ± 5% vs. 7 ± 2%, $p < 0.05$).

MOLECULAR BIOLOGY STUDIES. Polymerase chain reaction on frozen myocardial samples detected the presence of viral genome in five patients with AM and in four patients with BM (Table 1).

CMR results. Systolic function (EF <50%) was depressed in the 9 patients with heart failure symptoms and normal (EF >50%) in the remaining 14 patients (Table 1).

FatSat BBT2w image analysis revealed the presence of areas of hyperintensity in the myocardium in only 5 of 23 patients (22%), all presenting AM.

Contrast-enhanced CMR analysis showed LE in 16 of 23 patients (70%) (Figs. 1 and 2). A mid-wall distribution was observed in 10 patients (62.5%), and a subepicardial distribution was observed in 6 cases (37.5%). There was no correlation between the presence/absence of LE or its extent (mean ± SD, 7.3 ± 6.4%, range 0% to 19%) and any functional or hemodynamic parameters.

Comparison of contrast-enhancement versus EMB findings. AM GROUP. Areas of LE were observed in 12 of 14 patients with a sensitivity of CE-CMR in detecting AM of 86%. In particular, LE was present in 12 of 13 patients with evidence of LV or biventricular myocarditis (92%) (Fig. 3), but was absent in the remaining patient with isolated RV involvement. In six cases LE showed a mid-wall and in six a subepicardial distribution with the mid-posterior and mid-lateral LV walls being the most frequently involved segments. Patients with LE subepicardial distribution presented heart failure symptoms in three cases and repetitive ventricular arrhythmias in the other three. In six patients with evidence of mid-wall LE, two subjects had symptoms of heart failure and four had an arrhythmic presentation.

BM GROUP. Areas of LE were present only in four cases (44%), always with a mid-wall pattern (Fig. 3); in these patients clinical presentation was represented by ventricular arrhythmias in three cases and heart failure in one. Histological analysis showed in all cases inflammatory infiltrates associated with extensive areas of replacement fibrosis suggesting a healing phase of the inflammatory process.

DISCUSSION

Myocardial inflammation represents a potentially treatable cause of chronic cardiac symptoms, but its non-invasive identification is still difficult. In the present study we show that CE-CMR may detect LE areas in up to 70% of patients with biopsy-proven CM presenting with heart

Table 1. Clinical, Histological, and CMR Features of Patient Population

Patient	Gender	Age (yrs)	EF (%)	Clinical Presentation	Histology	PCR	Affected Ventricle	LE Pattern	LE (%)
1	M	30	64.2	VA	AM	AV	RV	—	—
2	F	31	21.1	HF	BM	EBV	LV, RV	MS	12
3	F	29	66.6	VA	AM		LV	SS	11
4	M	70	58.0	VA	AM	AV	LV	MS	4
5	M	44	58.0	VA	AM		LV, RV	SS	4
6	F	50	69.8	VA	AM	EV	LV, RV	MS	3
7	M	37	59.8	VA	BM		LV, RV	—	—
8	F	18	47.2	HF	AM		LV, RV	MS	17
9	M	37	48.6	HF	AM	AV	LV, RV	SS	10
10	F	37	55.5	VA	BM	EBV	LV	MS	11
11	F	48	78.8	VA	BM	AV	LV	—	—
12	M	59	47.4	HF	AM		LV	—	—
13	M	63	58.8	VA	AM	EV	LV, RV	MS	11
14	M	37	45.1	HF	BM		LV	—	—
15	M	56	55.5	VA	BM	EBV	LV, RV	MS	14
16	M	58	28.8	HF	AM		LV	SS	9
17	M	26	51.5	VA	BM		LV	—	—
18	F	31	57.6	VA	AM		LV	SS	17
19	M	36	29.4	HF	BM		RV	—	—
20	M	52	40.2	HF	AM		LV	MS	13
21	M	19	57.1	VA	BM		LV	MS	19
22	F	25	43.9	HF	AM		LV	SS	7
23	M	41	61.0	VA	AM		LV	MS	6

AM = active myocarditis; AV = adenovirus; BM = borderline myocarditis; CMR = cardiac magnetic resonance; EBV = Epstein-Barr virus; EF = ejection fraction; EV = enterovirus; HF = heart failure; LE = late enhancement; LV = left ventricle; MS = mid-wall striae; PCR = polymerase chain reaction; RV = right ventricle; SS = subepicardial striae; VA = ventricular arrhythmias.

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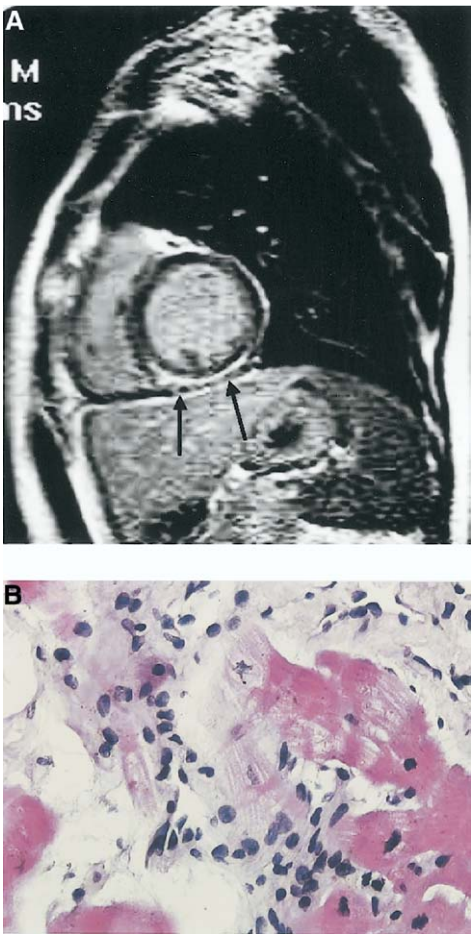

Figure 1. Patient with active myocarditis. Contrast-enhanced cardiac magnetic resonance short-axis imaging **(A)** shows a subepicardial late-enhancement stria in the posteroinferior left ventricular wall **(arrows)**. **(B)** Left ventricular endomyocardial biopsy shows clusters of lymphocytic inflammatory infiltrates associated with necrosis of adjacent myocytes (hematoxylin and eosin, original magnification ×400).

failure or ventricular arrhythmias. These findings were observed in patients submitted to biventricular EMB with extensive sampling and immunohistochemical and molecular biology studies increasing the diagnostic sensitivity of the procedure. In particular, LE was observed in 86% of patients with histologic evidence of AM and in 44% of patients with BM. The percentage of patients with AM presenting LE of the LV increases to 92% when excluding one patient with AM confined to the RV. These findings are consistent with the recently reported sensitivity of the CMR in detecting AM (11,15).

The high percentage of patients with positive LE findings in the AM group compared with patients with BM suggest that LE is mainly related to myocardial necrosis and edema characterizing the active phase of the inflammatory process and representative of an ongoing myocardial inflammation. Conversely, the extensive areas of replacement fibrosis observed at histology appear to be the most likely substrate of LE in patients with BM.

The presence of a different LE substrate in the two groups is also suggested by the different LE pattern ob-

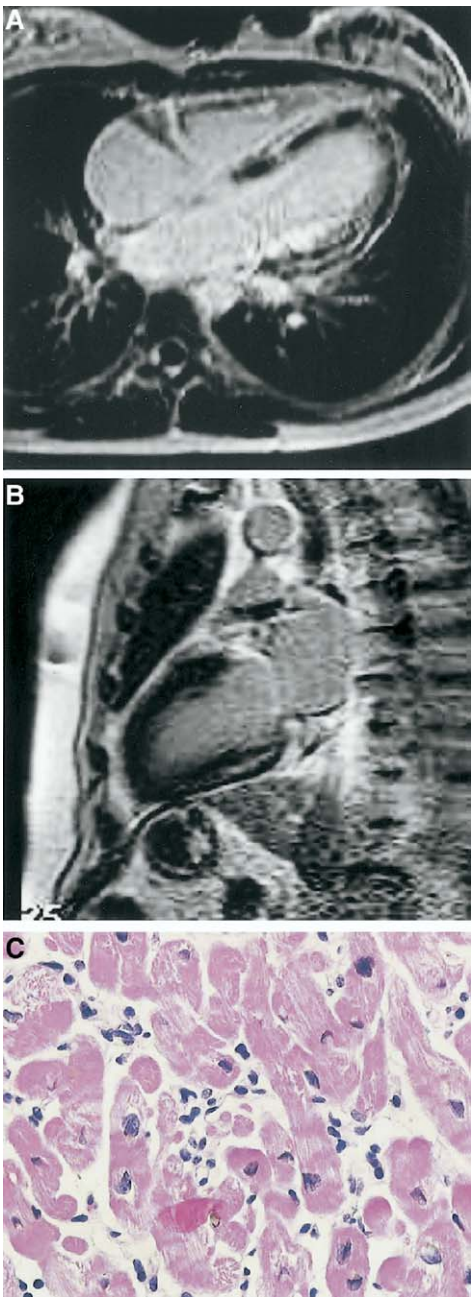

Figure 2. Patient with borderline myocarditis. **(A)** In the TFE-inversion recovery T1-weighted long-axis four-chamber view, a mesocardial late-enhancement stria in the lateral medio-basal wall and small late-enhancement foci in interventricular septum are present. Long-axis two-chamber image **(B)** shows a mid-wall late-enhancement stria in the inferior medio-basal left ventricular wall. Left ventricular endomyocardial biopsy **(C)** showing sparse inflammatory infiltrates without myocyte necrosis indicating a borderline myocarditis (hematoxylin and eosin, original magnification ×250).

served in our series. In fact, although a mid-wall pattern was the most frequent finding in both groups, a subepicardial distribution of LE was observed only in patients with AM, while all BM patients showed a mid-wall pattern, commonly observed in dilated cardiomyopathy as reported by McCrohon et al. (10). With regard to this, the evidence of a similar LE pattern suggests that an underlying chronic

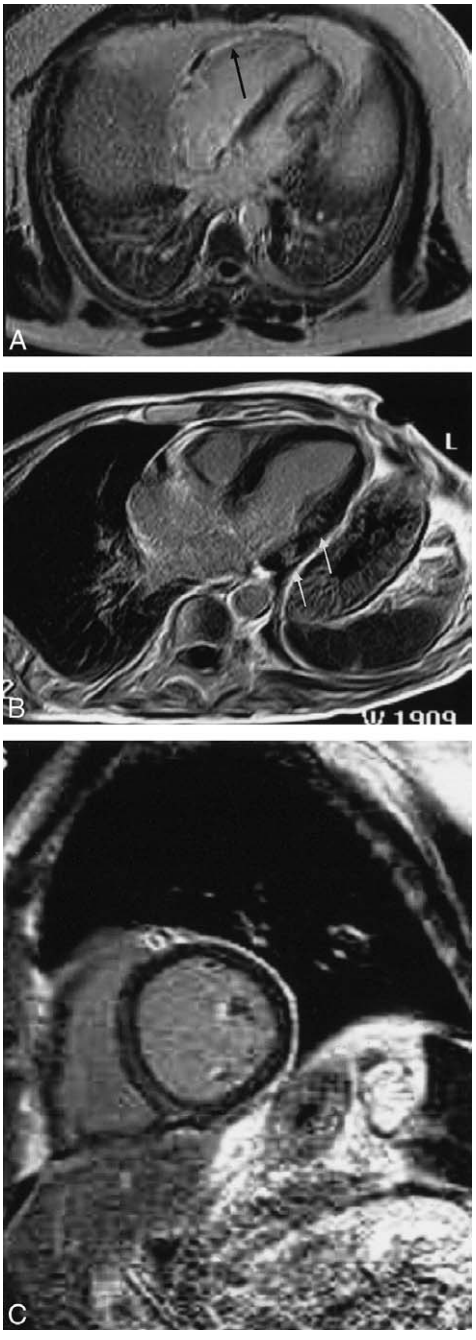

Figure 3. Different patterns of late enhancement. **(A)** TFE-inversion recovery T1-weighted images shows late-enhancement stria in right ventricular free wall **(arrow)** in a patient with active myocarditis involving both ventricles. **(B)** Contrast-enhanced cardiac magnetic resonance showing late-enhancement foci in the lateral wall in active myocarditis. **(C)** TFE-inversion recovery T1-weighted images showing a mid-wall late-enhancement stria located in the medial interventricular septum in a patient with heart failure and borderline myocarditis.

BM may be present in some patients with non-invasive diagnosis of dilated cardiomyopathy; the distinction between these two entities, detectable through EMB, is relevant as effective therapeutic strategies may be adopted in the presence of chronic myocardial inflammation and/or viral infection (6,7).

In contrast with the recently reported high sensitivity of T2-weighted sequence in diagnosing AM (12), in our study, using a similar technique, FatSat BBT2w images revealed the presence of hyperintensity only in 22% of patients, all with AM. These findings reflect the different underlying pathologic substrate of CM characterized by myocardial edema mostly in the presence of consistent areas of cell necrosis. Therefore, considering the low sensitivity of T2-images observed in our series, this part of CMR evaluation appears to be ancillary in the diagnostic evaluation of patients with CM.

Our findings have relevant clinical implications as the recognition of myocarditis may be easy in the acute phase when myocardial inflammation is often accompanied by fever, troponin, and inflammatory marker elevation in peripheral blood, but it is more difficult when the process becomes chronic because of viral persistence or autoimmune evolution. In these settings, the execution of CE-CMR may represent a useful non-invasive tool in indicating and even guiding the execution of EMB.

In fact, the diagnosis of CM, mostly when accompanied by assessment of myocardial presence of viral genome and evaluation of autoimmune activation, may have relevant prognostic and therapeutic implications as a selective treatment with immunosuppression (6), immunoadsorption (16), high-dose immunoglobulin (17), or beta-interferon (7), which may provide recovery of cardiac function.

In conclusion, CE-CMR in patients with chronic cardiac symptoms in the absence of coronary artery disease may non-invasively identify areas of myocardial damage suggesting the presence of a myocardial inflammatory process.

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