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Myocardial Delayed Enhancement by Magnetic Resonance Imaging in Patients With Chagas' Disease

A Marker of Disease Severity

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OBJECTIVES We sought to investigate whether myocardial delayed enhancement (MDE) by magnetic resonance imaging (MRI) could quantify myocardial fibrosis (MF) in patients with Chagas' heart disease (CHD), thus defining the severity of the disease.

BACKGROUND Myocardial fibrosis secondary to ischemic disease can be imaged using MDE. Advanced CHD is characterized by progressive MF.

METHODS Fifty-one patients with CHD were enrolled: 15 seropositive asymptomatic participants in the indeterminate phase (IND); 26 patients with known clinical CHD; and 10 patients with known CHD and ventricular tachycardia (VT). Using a 1.5-T MRI system, we acquired left ventricular (LV) short-axis slices using cine-MRI (LV function) and inversion-recovery gradient-echo (MDE).

RESULTS Myocardial fibrosis by MRI was present in 68.6% of all patients, in 20% of IND, 84.6% of CHD, and 100% of VT ($p < 0.001$). Quantified MF increased progressively across disease severity subgroups (0.9 ± 2.3% in IND; 16.0 ± 12.3% in CHD; and 25.4 ± 9.8% in VT, $p < 0.001$) and New York Heart Association functional classes (I: 7.5 ± 9.5%; II: 21.9 ± 13.8%; and III: 25.3 ± 9.9% of LV mass, $p < 0.001$). Left ventricular ejection fraction and MF had significant negative correlation ($r = -0.78$, $p < 0.001$), similar to the segmental MF and function: 4.9 ± 15.1% of MF in normal function, 32.5 ± 32.5% in mildly hypokinetic, 57.8 ± 31.4% in severely hypokinetic, and 72.3 ± 36.2% in akinetic and dyskinetic segments, respectively ($p < 0.001$).

CONCLUSIONS In CHD, MDE by MRI quantifies MF that not only can be detected in the early asymptomatic stages but parallels well-established prognostic factors and provides unique information for clinical disease staging. (J Am Coll Cardiol 2005;46:1553–8) © 2005 by the American College of Cardiology Foundation

Chagas' disease is a chronic disease that is caused by *Trypanosoma cruzi* infection (1), a pathogen that has been afflicting humans for millennia (2). The disease currently affects 4% to 7% of Latin Americans, with 200,000 new cases annually (3). Chagas' heart disease (CHD) is the most serious complication, striking approximately one-third of seropositive individuals and is a main cause of death from heart failure in Latin America.

After infection with *T. cruzi* (4), the asymptomatic phase can last for decades (indeterminate) until unknown triggers initiate disease progression to heart failure and arrhythmias in a subset of patients. Pathologic studies of advanced CHD have shown prominent myocardial fibrosis (MF) (5–7). However, serial in vivo quantification of MF across different stages of Chagas' disease has not been previously performed.

Myocardial delayed enhancement (MDE) by magnetic resonance imaging (MRI) is the best noninvasive method to evaluate MF or necrosis caused by acute, chronic myocardial infarction (8–11) or non-ischemic myocardial disease (12).

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We hypothesized that MDE quantifies myocardial damage caused by CHD at different stages of disease severity. Our objectives were to evaluate the extent, location, and frequency of MF in Chagas' disease and to determine its relation to established parameters of disease severity.

METHODS

We evaluated 51 seropositive patients for Chagas' disease without history of myocardial infarction and at low risk for coronary artery disease (CAD). All patients signed an InCor-approved consent form. Exclusion criteria were previous infarction or CAD, >2 CAD risk factors, valve disease, and MRI contraindications. We enrolled three subgroups at distinct stages of disease progression (Table 1) based on well-recognized markers of worse prognosis (New York Heart Association [NYHA] functional classification, left ventricular [LV] ejection fraction [LVEF], LV volumes, electrocardiogram abnormalities, and ventricular tachycardia) (4,13–15). They consisted of: 1) an indeterminate group (IND group) of 15 asymptomatic patients without signs of cardiac involvement by CHD with normal echocardiography, MRI, electrocardiogram, and chest X-ray; 2) a CHD group of 26 consecutive patients with known heart involvement by CHD defined as abnormal electrocardio-

Abbreviations and Acronyms

CAD = coronary artery disease
CHD = Chagas' heart disease
IND = indeterminate phase group
LV = left ventricular
LVEF = left ventricular ejection fraction
MDE = myocardial delayed enhancement
MF = myocardial fibrosis
MRI = magnetic resonance imaging
NYHA = New York Heart Association
VT = ventricular tachycardia

gram (typically, right bundle branch block with left anterior hemiblock) and/or LV dysfunction; and 3) a ventricular tachycardia (VT) group comprising 10 patients with known CHD, with previously documented episode of ventricular tachycardia, and with normal coronary angiography. All patients in the VT group underwent coronary angiography and electrophysiologic studies within one year from the MRI study.

Magnetic resonance imaging methods. All patients had MRI examination on 1.5-T GE CV/i System (Wakeusha, Wisconsin). Left ventricular short-axis and long-axis imaging planes were obtained, during an 8- to 15-s breath-hold, by two electrocardiogram-triggered pulse sequences at the same exact locations, allowing precise comparisons between LV function and myocardial structure.

A gradient-echo (steady-state free precession) was used for LV function evaluation, and an inversion-recovery prepared gradient-echo was used for MDE (10 to 20 min after intravenous bolus of 0.2 mmol/kg of gadolinium-based contrast), with the following parameters, respectively: repetition time 3.9/7.1 ms, echo time 1.7/3.1 ms, flip angle 45°/20°, cardiac phases 20/1, views per segment 8/16 to 32, matrix 256 × 128/256 ×192, slice thickness 8/8 mm, gap between slices 2/2 mm and field of view 32 to 38/32 to 38 cm, inversion time none/150 to 250 ms, receiver bandwidth 125/31.25 kHz, number of excitations 1/2, acquisition every heart beat for both.

Data analysis. End-systolic, end-diastolic LV volumes, and LVEF were measured by MASS-plus Analysis software (Leiden, the Netherlands), applying Simpson's method. On the MDE short-axis images, LV mass and total extent of MDE (as percent of LV mass) were measured using

Table 1. Patient Characteristics

	All (n = 51)	IND (n = 15)	CHD (n = 26)	VT (n = 10)	p Value
Male gender	19 (37.3)	2 (13.3)	12 (46.2)	5 (50.0)	0.068*
Age (yrs)	50.4 ± 12.9	46.5 ± 12.0	49.3 ± 12.7	58.9 ± 12.0	0.049†
LVEF (%)	49.0 ± 17.8	65.7 ± 7.5	45.7 ± 16.0	32.3 ± 12.7	<0.001†
ESV (ml/m^2)	43.9 ± 33.8	20.3 ± 7.0	48.3 ± 36.1	68.0 ± 32.0	<0.001‡
EDV (ml/m^2)	77.4 ± 35.8	58.3 ± 14.3	80.7 ± 41.0	97.7 ± 32.2	0.005‡
LV mass (g/m^2)	64.6 ± 23.5	57.5 ± 16.0	61.2 ± 25.5	83.9 ± 18.2	0.005‡
Mean NYHA functional class	1.5 ± 0.6	1.0 ± 0.0	1.5 ± 0.6	2.2 ± 0.6	<0.001‡
NYHA functional class >I	20 (39.2)	0	11 (42.3)	9 (90)	<0.001*
BMI (kg/m^2)	24.1 ± 4.0	24.2 ± 3.4	24.5 ± 4.7	22.8 ± 2.8	0.523‡
Hypertension	1 (2.0)	0	1 (3.9)	0	1.000*
Diabetes	1 (2.0)	0	0	1 (10)	0.196*
Hypercholesterolemia	7 (13.8)	2 (13.3)	3 (11.54)	2 (20.0)	0.864*
Current smoker	1 (2.0)	1 (6.7)	0	0	0.490*
CAD family history	1 (2.0)	0	0	1 (10)	0.196*

Data are expressed as mean ± SD or number (%) for discrete variables. *Fisher's exact test. †One-way analysis of variance (ANOVA). ‡One-way analysis of variance by ranks-Kruskal-Wallis test.

BMI = body mass index; CHD = Chagas' heart disease; EDV = end-diastolic volume; ESV = end-systolic volume; IND = indeterminate; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VT = ventricular tachycardia.

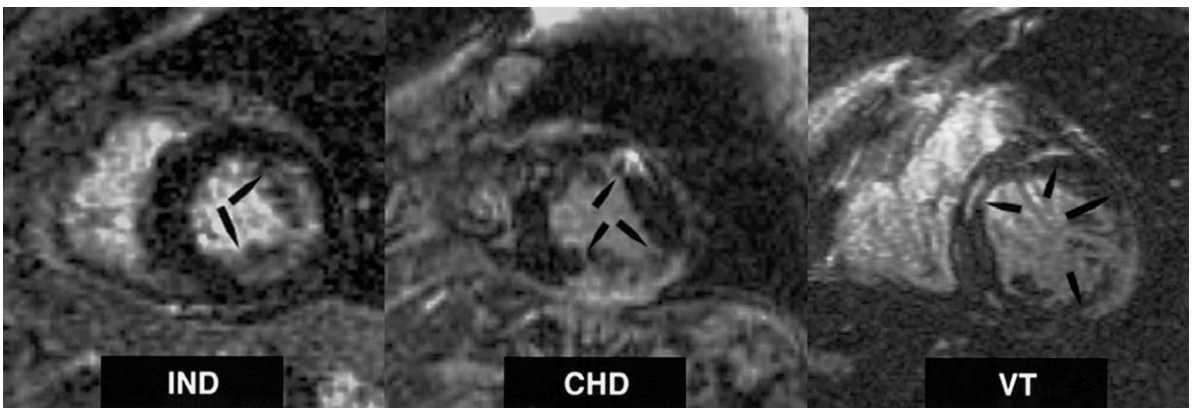

Figure 1. Myocardial delayed enhancement **(arrowheads)** on left ventricular short-axis slices in different stages of Chagas' disease. CHD = Chagas' heart disease group; IND = indeterminate phase group; VT = Chagas' heart disease with ventricular tachycardia group.

Table 2. Myocardial Fibrosis by MRI

	All (n = 51)	IND (n = 15)	CHD (n = 26)	VT (n = 10)	p Value
With MF	35 (68.6)	3 (20.0)	22 (84.6)	10 (100)	
Without MF	16 (31.4)	12 (80.0)	4 (15.4)	0 (0)	< 0.001*
MF (% of LV mass)	13.4 ± 13.2	0.9 ± 2.3	16.0 ± 12.3	25.4 ± 9.8	< 0.001†

Data are expressed as mean ± SD or number (%) for discrete variables. *Fisher's exact test; †one-way ANOVA with Bonferroni multiple (3) comparison test; IND vs. CHD = $p < 0.001$, IND vs. VT = $p < 0.001$ and CHD vs. VT = $p = 0.044$. Adjusted p value for significance is $p < 0.05/3$ or $p < 0.016$.
MF = myocardial fibrosis by magnetic resonance imaging [MRI]; other abbreviations as in Table 1.

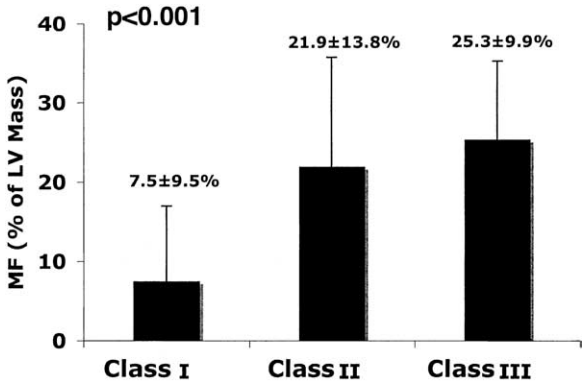

Figure 2. Increase in myocardial fibrosis (MF) over New York Heart Association functional classes ($p < 0.001$ by analysis of variance). Class I had less MF than classes II and III (multiple [3] comparisons by Bonferroni test, with adjusted p value for significance $p < 0.016$: I vs. II $p < 0.001$; II vs. III $p = 1.0$; I vs. III $p = 0.012$). LV = left ventricular.

NIH-Image software (U.S. National Institutes of Health, Bethesda, Maryland). Segmental MDE transmurality and myocardial function were scored (by two observers) using standard LV 17-segment model (16), as the visual percent area enhanced (<25%, 26% to 50%, 51% to 75%, and >75%) and as normal, mild hypokinesia, severe hypokinesia, and akinesia or dyskinesia. Additionally, pattern of MDE was classified as subendocardial, midwall, subepicardial, or transmural.

Statistical analysis. Comparisons of normally distributed continuous variables were performed by the Student *t* test and one-way analysis of variance with Bonferroni test for multiple comparisons. The Fisher exact test was used for proportions comparisons. The nonparametric test for discrete variables and non-normal continuous variables was Kruskal-Wallis rank test. Normality was determined by Shapiro-Francia W' test. Simple linear regression was used between the MF mass and LVEF, end-diastolic volume, and end-systolic volume. For the segmental analysis, we

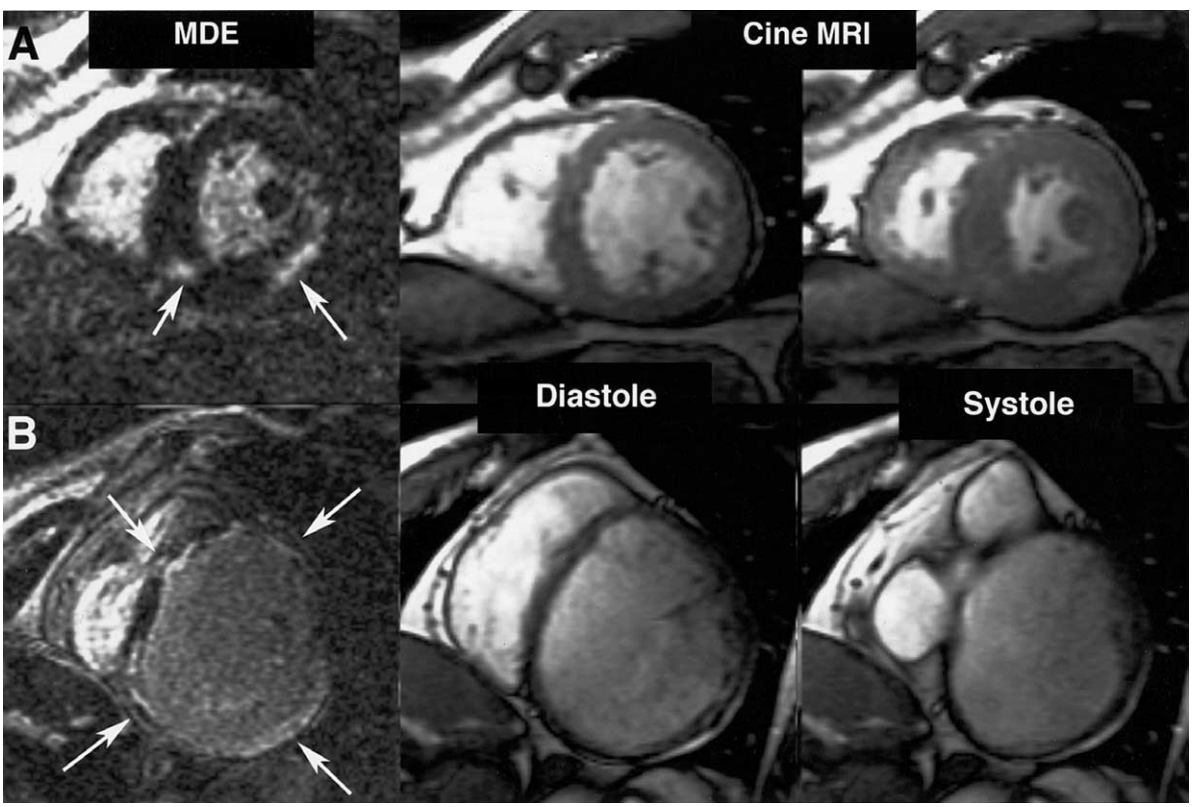

Figure 3. Extent of myocardial fibrosis (MF) **(arrows)** and left ventricular function. **(A)** Patient with small area of MF (8.2%) and normal left ventricular ejection fraction (65.5%). **(B)** Patient with large area of MF (23.8%) and severe left ventricular dysfunction (left ventricular ejection fraction 19.2%). MDE = myocardial delayed enhancement; MRI = magnetic resonance imaging.

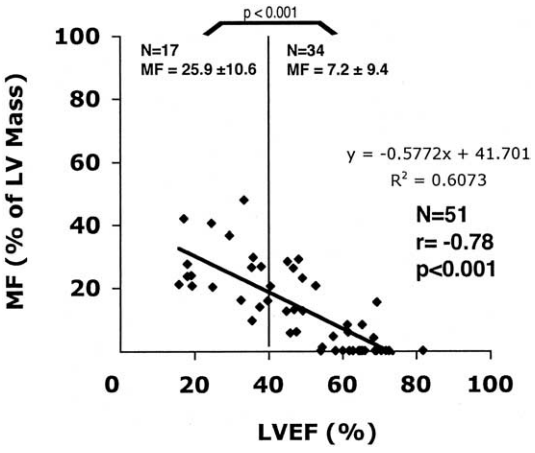

Figure 4. Good correlation between left ventricular ejection fraction (LVEF) and myocardial fibrosis (MF). Patients with LVEF >40% had less quantified MF than those with LVEF ≤40% (Student *t* test).

used ordered logistic regression with standard errors adjusted for clustering on patients to consider the non-independence of the segmental measurements. Interstudy reproducibility was measured by mean differences and repeatability coefficient (2 SD). Stata 8.0 (Stata Corp., College Station, Texas) was used, and $p < 0.05$ (two-tailed) considered statistically significant.

RESULTS

Myocardial fibrosis was detected in 35 of 51 patients (68.6%), in all groups (Fig. 1), and with a progressively higher proportion of patients with MF from IND to CHD and VT groups (Table 2). Similarly, the magnitude of MF increased progressively (Table 2).

Clinical status. Quantitative MF also increased progressively from NYHA functional class I to II and III patients (Fig. 2). Among patients without MF, only 12.5% (2 of 16) were in NYHA class >I compared with 51.4% (18 of 35) of those with MF ($p = 0.012$, by the Fisher exact test).

Global LV function. Patients with small areas of MF showed preserved LV function, whereas patients with large areas of MF had severe LV dysfunction (Fig. 3, Video 1 [accompanying videos can be viewed with the online version of this article]). Patients with LVEF >40% had significantly less MF than those with LVEF ≤40%, with a significant inverse correlation between MF and LVEF (Fig. 4). End-diastolic and end-systolic volumes indices also correlated directly with MF ($r = 0.57$ and $r = 0.65$, $p < 0.001$).

Segmental LV function and MF. Segmental MF (269 of 867) and dysfunction (290 of 867) were unequally distributed (apex, inferior, inferolateral segments significantly more involved; Fig. 5). Importantly, there was no segmental dysfunction in IND group, even in segments with MF, which tended to be of limited degree.

Although atypical MDE patterns were observed in 46.9% of LV segments (126 of 269: subepicardial, 12.3%; midwall, 34.6%), 53.1% were subendocardial or transmural, indistinguishable from infarction caused by CAD. Small, heterogeneous and diffuse MF patterns also were observed.

The more severe the degree of segmental dysfunction, the greater the percent area of LV segmental enhancement observed (Fig. 6). Myocardial fibrosis increased progressively from segments with normal function to those with mild hypokinesia, severe hypokinesia, akinesia, and dyskinesia ($p = 0.0001$ by Kruskal-Wallis test). Reanalysis, using ordered logistic regression with clustering on patients to adjust for the non-independence of the data, also showed statistical differences for all groups ($p < 0.001$) and between each group ($p < 0.03$ for all comparisons).

Reproducibility and coronary angiography (VT group). Five patients with MDE had a second MRI examination 1.5 to 6 months later. Myocardial fibrosis mean difference between the second and first examination was $-1.4 \pm 1.7\%$ ($18.5 \pm 11.2\%$ vs. $17.0 \pm 10.5\%$, respectively, $p = NS$ by *t* test). The repeatability coefficient was 3.4%, and MDE

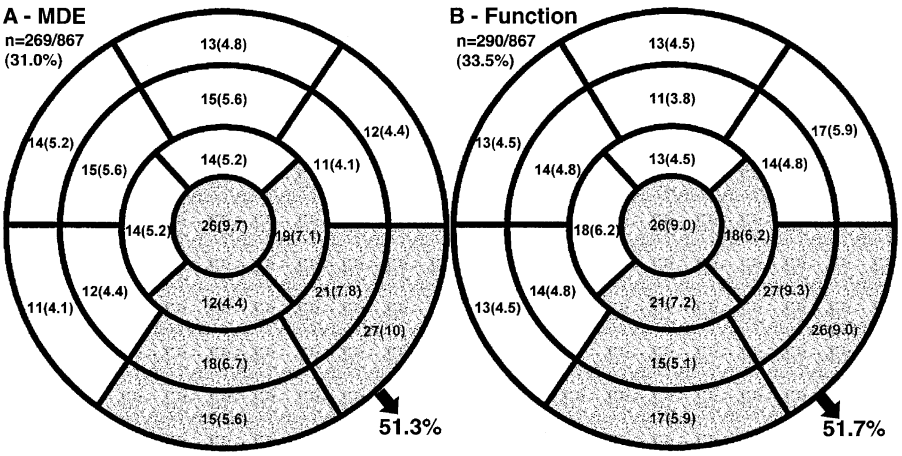

Figure 5. Left ventricular 17-segment model showing concentration on apex, inferolateral, and inferior segments **(shaded area)** of regional myocardial delayed enhancement (MDE) **(A)** (51.3%, $p < 0.001$ by the Fisher exact test and $p = 0.002$ by logistic regression) and wall motion abnormality **(B)** (51.7%, $p < 0.001$ by the Fisher exact test and by logistic regression). Absolute number of segments and (percent values) are shown.

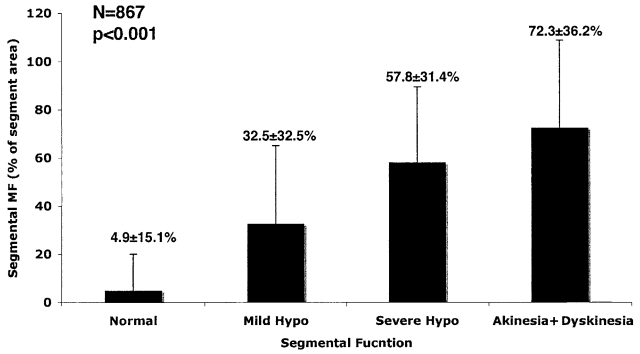

Figure 6. Segmental left ventricular function and extent of myocardial fibrosis (MF). A progressive and significant increase of MF along with the loss of segmental contractile activity can be observed.

segment distribution, size, and shape of areas were identical in both examinations. All patients in the VT group had extensive MF (25.4 ± 9.8%) but no obstructive CAD by angiography (Fig. 7, Video 2 [accompanying videos can be viewed with the online version of this article]).

DISCUSSION

This study is the first to quantify myocardial fibrosis in vivo by delayed enhanced MRI in patients with CHD. We demonstrate that the degree of MF increases progressively from the mildest to the most severe disease stages. Additionally, MF correlates inversely with LVEF and clinical status, which agrees with previous biopsy study, relating interstitial collagen deposition to LV dysfunction (5). The good correlation between the degree of MF by MDE and established prognostic factors in CHD supports the role of MRI-defined fibrosis as a marker of disease severity. Moreover, MRI provides evidence of myocardial involvement among seropositive patients without clinical symptoms or wall motion abnormality, which further supports the use of MRI-defined MF as a subclinical marker of disease severity.

The segmental MDE analysis indicates the LV apex and inferolateral regions as preferable sites for MF, in accordance with previous pathological studies (5–7,17). This distribution supports the concept that MF develops in regions of distal circulation due to *T. cruzi*-mediated microvascular disease, causing impaired perfusion to watershed myocardial territories (6,17).

Persistent MDE from repeated MRI studies accompanied by chronic elevation of biomarkers (18,19), myocardial perfusion abnormalities by scintigraphy, and normal coronary arteries by angiography (20) reflect the effect of continued myocyte loss with relentless replacement by MF as defined by previous pathological studies (6,17).

On the basis of the clinical profile of our study population (relatively young, low risk for CAD, no previous infarction or CAD), the high incidence of MF (84.6% [22 of 26],

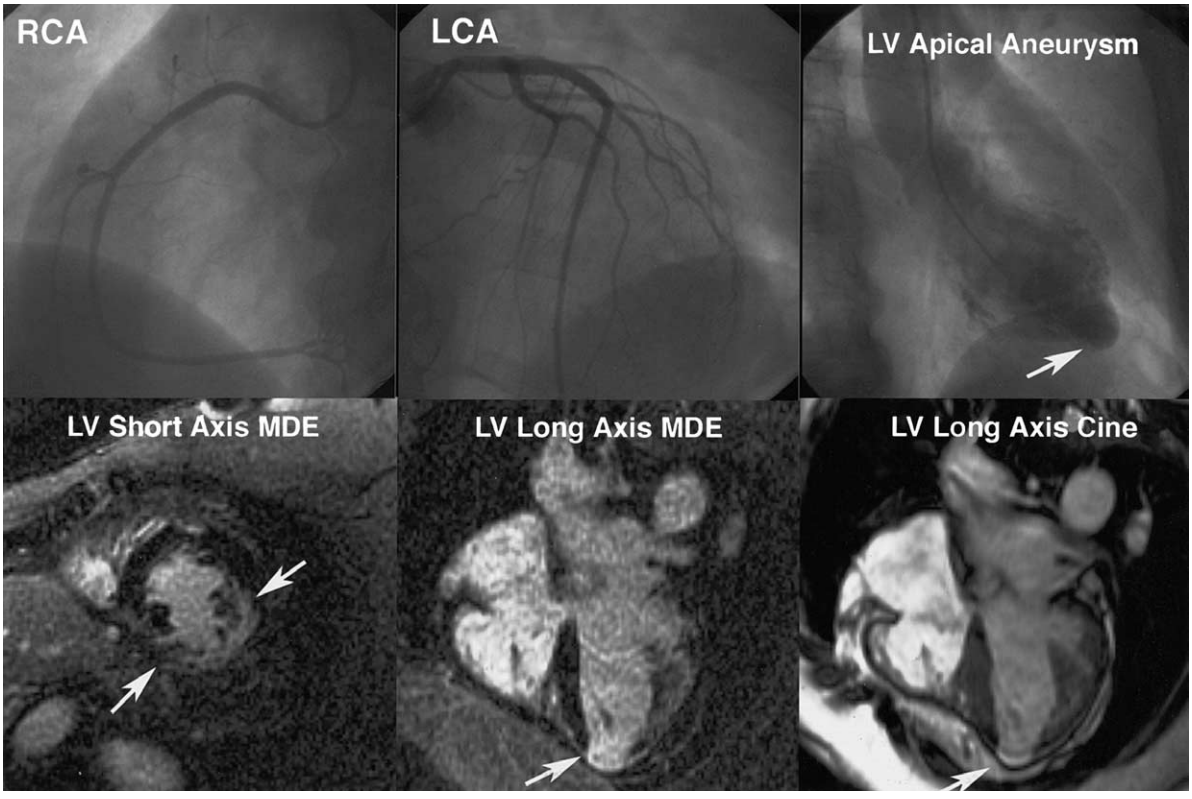

Figure 7. A ventricular tachycardia group patient with typical apical and inferolateral myocardial fibrosis by magnetic resonance imaging **(arrows in bottom, middle, and left columns)** and normal coronary arteries by angiography **(top, middle, and left columns)**. The left ventricular (LV) apical aneurysm (vorticilar) observed on the ventriculogram **(arrow, top right column)** and cine-magnetic resonance imaging **(arrow, bottom right column)** is a classical finding of Chagas' heart disease. MDE = myocardial delayed enhancement; RCA = right coronary artery/

CHD group), and the atypical pattern of MF when compared with CAD (predominantly midwall and subepicardial and encompassing multiple coronary territories) we feel confident that the MDE regions documented in this study are caused by CHD and not by CAD. To further exclude CAD, all patients in the group with documented VT showed no obstructive CAD by angiography despite the presence of large areas of MF (25.4 ± 9.8%).

Conclusions. Magnetic resonance imaging tissue characterization by MDE enables the quantification of MF, which adds important information on disease severity to the assessment of patients with CHD. These results also provide novel pathophysiologic insights into our current understanding of CHD, particularly into indeterminate phase and arrhythmias, which hopefully could be used to guide the future development of new therapeutic interventions designed to halt myocardial fibrosis early in the subclinical phases of the disease process.

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APPENDIX

For accompanying videos, please see the online version of this article.