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Myocardial Delayed Enhancement by Magnetic Resonance Imaging in Patients With Muscular Dystrophy

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Objectives This study sought to analyze whether cardiovascular magnetic resonance (CMR) can detect and quantify myocardial damage in the early stages of cardiomyopathy in muscular dystrophies (MD).

Background Muscular dystrophy is a genetic disease that involves skeletal and cardiac tissues of humans. Cardiomyopathy is common, and death secondary to cardiac or respiratory diseases occurs early in life. Cardiovascular magnetic resonance is a reliable method for assessing global and regional cardiac function, allowing also for the detection of myocardial fibrosis (MF).

Methods Ten patients with Duchenne or Becker dystrophies were studied by CMR. Physical examination, Chagas disease serological tests, electrocardiogram, chest radiograph, total creatine kinase, and Doppler echocardiogram were also obtained in all patients.

Results Patients with MF had a lower ejection fraction than those without. Myocardial fibrosis (midwall and/or subepicardial) was observed in 7 of the 10 patients, and the lateral wall was the most commonly involved segment. There was moderate correlation between segmental MF and dysfunction.

Conclusions Cardiovascular magnetic resonance can identify MF and may be useful for detecting the early stages of cardiomyopathy in MD. Future work will be needed to evaluate whether CMR can influence cardiomyopathy and outcomes. (J Am Coll Cardiol 2007;49:1874–9) © 2007 by the American College of Cardiology Foundation

Muscular dystrophy (MD) is a genetically determined group of diseases with progressive degeneration of skeletal muscle. These diseases can be classified based on the pattern of inheritance or on the muscle protein abnormality. The most common X-linked MD is dystrophinopathy (1) caused by the dystrophin gene (Xp21) mutation. Dystrophin is a sarcolemmal protein of skeletal and cardiac muscle cells that triggers complex molecular and biological events (2). The most common forms of MD are Duchenne (1:3,000 men) and Becker (1:30,000 men) diseases, characterized by absence and reduced or abnormal dystrophin, respectively (3,4).

Death secondary to cardiac or respiratory causes typically occurs in the second to third decade in Duchenne and in the fourth to fifth decade in Becker MD (3,4). In MD autopsy, end-stage cardiac disease is characterized by alternating areas of myocyte hypertrophy, atrophy, and fibrosis (5,6). Clinical studies of cardiomyopathy show that the heart disease process is underway long before symptoms appear (7,8).

Cardiovascular magnetic resonance (CMR) is a precise and reliable method for assessing global and regional cardiac function (9,10). Myocardial delayed enhancement (MDE) is the best noninvasive method for evaluating myocardial fibrosis (MF) caused by ischemic (10,11) or nonischemic disease (12,13). We hypothesized that MDE can detect and quantify myocardial damage caused by MD at early stages of disease.

Methods

We evaluated 10 patients with MD (8 Duchenne, 2 Becker) 7 to 18 years old. The dystrophinopathy was established by: 1) DNA analysis of the dystrophin gene (multiplex polymerase chain reaction), and 2) dystrophin immunohistochemical analysis in muscle tissue. In all patients, DNA analysis was performed. Three patients showed deletions in the dystrophin gene, and 4 others had an absence of dystrophin in muscle fibers by biopsy (Table 1). Three patients had no deletions and

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a positive familiar history (Table 1). Two patients were siblings, and presented proximal muscle weakness, hyporeflexia, calf hypertrophy, and onset of symptoms around 10 years old, suggesting Becker MD. One had a classic Duchenne phenotype, an affected brother and a carrier mother with increased serum creatine kinase (CK) level. Thus, these 3 patients had a diagnosis based on age of weakness onset, high CK levels, and an X-linked inheritance pattern.

All patients underwent cardiologic and neurologic evaluation in the outpatient clinic of the Federal University of Minas Gerais, with routine physical examination, electrocardiography, chest radiograph, Doppler echocardiogram, and serum CK levels (Table 1).

Informed consent from patients or their legal representatives preceded CMR evaluation and Chagas disease serological test. Clinical characteristics are shown in Table 2.

CMR methods. The CMR examination was performed on 1.5-T GE Signa LX System (GE Medical Systems, Wakeusha, Wisconsin). Breath-hold left ventricular (LV) short-axis and long-axis images were obtained by 2 pulse sequences, at the same locations, allowing precise comparisons between LV function (gradient-echo sequence, steady-state free precession) and myocardial structure (inversion-recovery prepared gradient-echo sequence, 10 to 20 min after intravenous bolus of 0.2-mmol/kg gadolinium-based contrast), acquired 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 1/1, acquisition every other heartbeat for MDE.

Data analysis. End-systolic LV volume, end-diastolic LV volume, and LV ejection fraction (LVEF) were measured using ReportCard 2.0 software (GE Medical Systems), applying the Simpson method. On the MDE short-axis images, we evaluated the number of LV segments with MF using a standard LV 17-segment model. Two independent observers scored segmental MDE transmurality as the visual percent area enhanced (nontransmural ≤50%, or transmural >51%), and 2 other observers evaluated myocardial function as normal, mild hypokinesia, severe hypokinesia, and akinesia or dyskinesia. Patterns of MDE were classified as subendocardial, midwall, subepicardial, and transmural.

Statistical analysis. Data are presented as mean ± standard deviation. Chi-square analysis was used for comparison between proportions. Student *t* test was used for comparison between groups with and without MF. Simple linear regression was used to compare total CK levels with LVEF. The kappa test was used for agreement between observers and MF versus segmental dysfunction. The Kruskal-Wallis test was used to compare mean scores among different segments. A limitation of the statistical analysis was the small sample size.

Abbreviations and Acronyms

- **CK** = creatine kinase
- **CMR** = cardiovascular magnetic resonance
- **LV** = left ventricle/ventricular
- **LVEF** = left ventricular ejection fraction
- **MD** = muscular dystrophy
- **MDE** = myocardial delayed enhancement
- **MF** = myocardial fibrosis
- **RV** = right ventricle/ventricular

Results

Six of the 8 patients with Duchenne dystrophy were already wheelchair-bound. All patients were negative for Chagas disease. Seven of 10 patients had MF (70%), 6 had Duchenne MD, and 1 had Becker MD (Fig. 1, Table 1). Only 2 patients had an abnormal cardiac silhouette on chest radiograph; both presented MDE. Among the 7 patients with any electrocardiographic abnormality, 5 had MF by CMR. Only 1 patient had a Q-wave suggesting MF.

Global LV and right ventricular (RV) function. Reduced LVEF (<55%) was found in 2 patients by echocardiogram and in 3 patients by CMR. Ventricular morphologic and functional characteristics are shown in Table 3. Patients

Table 1 Muscular Dystrophy Diagnosis and Treatment

Patient #	Age (yrs)	Diagnosis	DNA Deletion	Muscle Biopsy	MF by CMR	Echo	X-Ray	ECG	CK	Steroids	ACEI
1	8	DMD*	No	NA	No	Nl	Nl	Abnl	11,596	Yes	No
2	18	DMD	Yes†	NA	Yes	Nl	Nl	Abnl	1,810	No	No
3	15	DMD	Yes†	NA	Yes	Abnl	Abnl	Abnl	1,495	No	Yes
4	11	DMD	Yes‡	NA	Yes	Nl	Nl	Abnl	1,988	Yes	No
5	10	DMB§	No	NA	No	Nl	Nl	Nl	19,700	No	No
6	13	DMB§	No	NA	Yes	Nl	Nl	Nl	9,908	No	No
7	7	DMD	No	+	Yes	Nl	Nl	Nl	6,248	Yes	No
8	10	DMD	No	+	Yes	Nl	Nl	Abnl	9,420	Yes	No
9	15	DMD	No	+	Yes	Abnl	Abnl	Abnl	6,348	Yes	Yes
10	11	DMD	No	+	No	Nl	Nl	Abnl	4,270	No	No

*Classical Duchenne phenotype, affected brother and carrier mother with increased CK level. †Exons 48, 49, and 50. ‡Exons 51 and 52. §Siblings.

+ = absence of dystrophin; Abnl = abnormal; ACEI = use of angiotensin-converting enzyme inhibitors; CK = creatine phosphokinase (normal values <109 U/l for older and <225 U/l for younger than 12 years); CMR = cardiovascular magnetic resonance; DMB = Becker muscular dystrophy; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; ECG = electrocardiogram; Echo = echocardiography; MF = myocardial fibrosis; Nl = normal; steroids = use of glucocorticoids; X-ray = conventional chest radiograph.

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Table 2 Clinical Characteristics Comparison

	All (n = 10)	With MF (n = 7)	Without MF (n = 3)	p Value
Male	10 (100%)	7 (100%)	3 (100%)	
Age (yrs)	12.5 ± 3.1	13.1 ± 3.6	11.0 ± 0.0	0.35
Weight (kg)	46.7 ± 14.6	46.6 ± 15.1	47.0 ± 16.6	0.97
Height (cm)	150.4 ± 11.4	153.7 ± 12.2	142.7 ± 3.1	0.17
Body surface area (m^2)	1.4 ± 0.2	1.4 ± 0.3	1.4 ± 0.2	0.80
Wheelchair-bound	6 (60.0%)	5 (71.4%)	1 (33.3%)	0.26
Duchenne	8 (80.0%)	6 (85.7%)	2 (33.3%)	0.26
Becker	2 (20.0%)	1 (14.3%)	1 (66.7%)	0.26
Abnormal electrocardiogram	5 (50.0%)	4 (57.1%)	1 (33.3%)	0.50
Abnormal radiograph	2 (20.0%)	2 (28.6%)	0	0.47

MF = myocardial fibrosis.

with MF (Fig. 2) showed a significantly lower LVEF and higher end-systolic volume index than those without (Fig. 3). No differences were found for RV volumes and function (Table 3).

There was a trend to higher levels of total CK in patients with more preserved LVEF ($r = 0.54$, $p = 0.10$). Moreover, patients with fibrosis tended to have lower levels of CK than those without fibrosis (Table 3).

Segmental LV function and MF. For 2 independent observers, segmental MF was present in 33 (19.4%) and 25 (14.7%) segments. Regional dysfunction was present in 25 (14.7%) and in 23 (13.5%) segments. There was good interobserver agreement when analyzing LV function (kappa 0.76, $p < 0.001$) and segmental MF (kappa 0.75, $p < 0.001$). Comparing 340 observations (2 observers combined), we noted moderate agreement between segmental MF and dysfunction, kappa 0.41, $p < 0.001$. Only 10.6% of segments with normal function showed MF, and 43.8% of the dysfunctional segments had no MF. Among 58 MF observations, 27 (56.2%) had abnormal contractility. The agreement between the segmental MF extent and the degree of segmental dysfunction was fair (kappa 0.31, $p < 0.001$). Additionally, there was no segmental dysfunction in 31 (53.5%) of 58 MF observations, particularly with nontransmural MF (26 of 42, 61.9%).

Atypical patterns of MDE occurred in 89% of segments with MF; MF was midwall in 57.8% and subepicardial in 31.1%. Segmental MF was unequally distributed, with lateral segments being most commonly involved for both observers (Table 4), and with the highest score (more MF) for the combined observers ($p = 0.003$ by Kruskal-Wallis test).

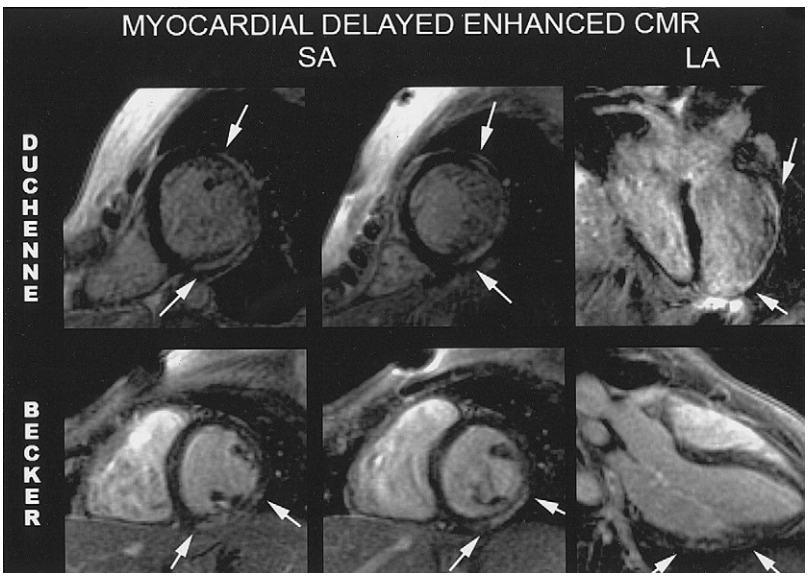

Figure 1 Myocardial Fibrosis in Duchenne and Becker Muscular Dystrophy by CMR

Adjacent short-axis (SA) and long-axis (LA) views of 2 patients with muscular dystrophy (**top**: Duchenne, **bottom**: Becker) by cardiovascular magnetic resonance (CMR) using myocardial delayed enhancement technique. Between **arrows** are regions of myocardial delayed enhancement indicating myocardial fibrosis.

Table 3 Cardiovascular Magnetic Resonance Ventricular Function and Creatine Kinase Levels in Muscular Dystrophy With and Without Myocardial Fibrosis

	All (n = 10)	With MF (n = 7)	Without MF (n = 3)	p Value
LV EF (%)	53.7 ± 12.5	48.3 ± 11.0	66.1 ± 0.6	0.02
LV EDV (ml/m^2)	68.1 ± 17.6	73.7 ± 16.4	55.1 ± 14.6	0.13
LV ESV (ml/m^2)	32.6 ± 14.8	38.5 ± 13.5	18.7 ± 5.4	0.04
LV mass (g/m^2)	106.8 ± 34.6	116.9 ± 36.9	83.3 ± 11.9	0.17
LV EDD (cm)	4.7 ± 0.7	4.8 ± 0.7	4.3 ± 0.3	0.28
LV ESD (cm)	3.4 ± 0.8	3.6 ± 0.9	3.0 ± 0.2	0.23
LV ASWT (mm)	8.6 ± 0.7	8.6 ± 0.5	8.7 ± 1.2	0.86
LV ILWT (mm)	8.5 ± 1.1	8.6 ± 1.3	8.3 ± 0.6	0.77
RV EF (%)	54.8 ± 10.3	51.8 ± 9.3	61.7 ± 10.9	0.18
RV EDV (ml/m^2)	59.0 ± 14.2	58.7 ± 11.6	59.7 ± 22.4	0.93
RV ESV (ml/m^2)	26.6 ± 9.0	28.6 ± 9.5	21.8 ± 6.5	0.30
Total creatine kinase*	7,278.3 ± 5,644.6	5,316.7 ± 3,601.6	11,855.3 ± 7,718.3	0.09

*Normal levels <190 UI/l for men and <225 UI/l for children <12 years old.
ASWT = anteroseptal wall thickness; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; ESV = end-systolic volume; ILWT = inferolateral wall thickness; LV = left ventricular; MF = myocardial fibrosis; RV = right ventricular.

Reproducibility. In 2 patients, we repeated the CMR study 60 days after the first study. Segmental MF had the same location (4 for each patient) and extent for both studies.

Discussion

Dilated cardiomyopathy is an increasing cause of death in patients with Duchenne and Becker MD because of a dramatic improvement in respiratory care in the last 2 decades. The time course for the development of cardiomyopathy has not been well characterized. Data from clinical studies suggest that heart disease is underway long before symptoms appear (7).

We used the ability of CMR to delineate RV and LV morphology, function, and myocardial tissue characteristics in patients with Duchenne and Becker MD. The presence of MF was consistently shown by the MDE technique in our patients with MD.

The frequent finding of MF, even in patients with preserved global LV and RV function, supports the current belief that heart disease begins much earlier than the onset of symptoms (7). Moreover, this observation suggests that CMR can be useful for the early detection of heart disease over and above the sole information on ventricular function provided by the conventional Doppler echocardiogram. We

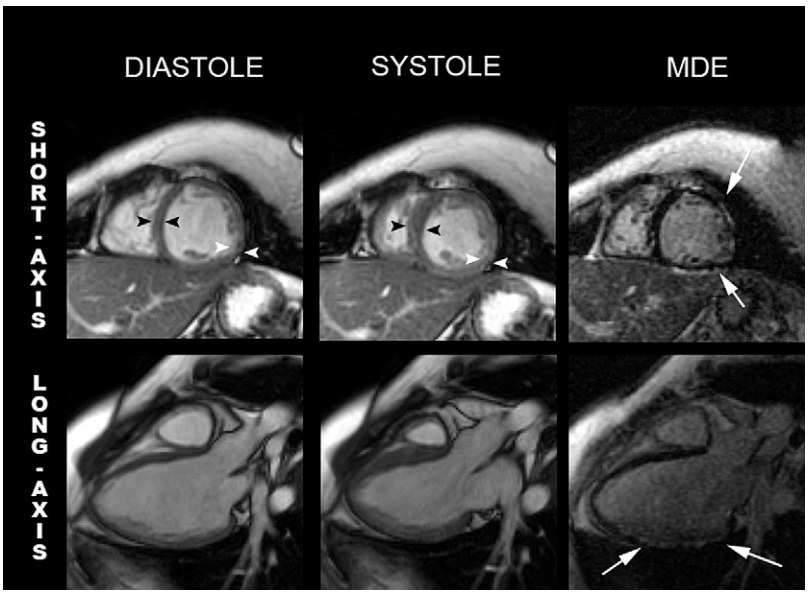

Figure 2 Myocardial Fibrosis and Dysfunction in Muscular Dystrophy by Cardiovascular Magnetic Resonance

A patient example with Duchenne muscular dystrophy showing lateral myocardial delayed enhancement (MDE) and lateral akinesia (compare the wall thickening between septal **[black arrowheads]** and lateral **[white arrowheads]** walls) and global left ventricular dysfunction (left ventricular ejection fraction 41%).

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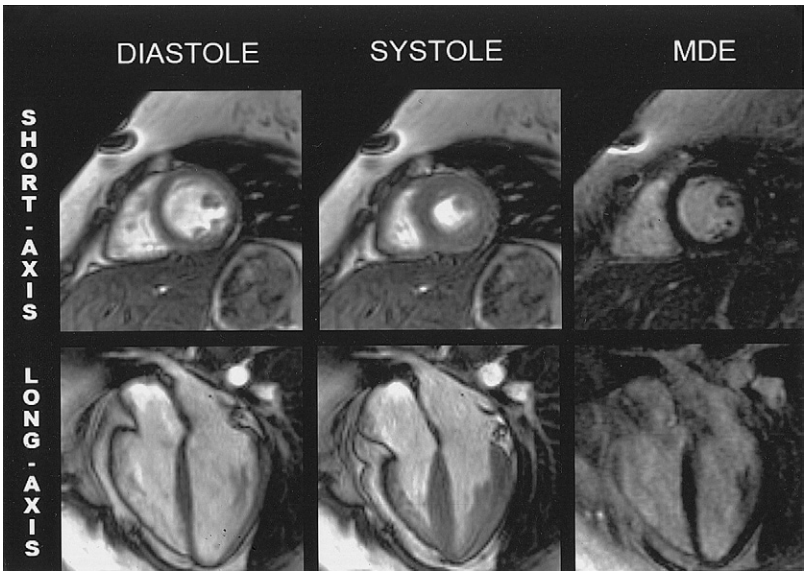

Figure 3 **Absence of Myocardial Fibrosis and Normal Function in Muscular Dystrophy by Cardiovascular Magnetic Resonance**

A patient with Duchenne muscular dystrophy showing no myocardial delayed enhancement (MDE) and normal global and segmental left ventricular function.

also observed that even among patients with MF, the chest radiograph and electrocardiogram were completely normal. Another interesting observation is the detection of myocardial injury at a very young age. We detected MF in 2 of 4 patients ≤10 years old with normal echocardiogram, a time when drug treatment is still not usually indicated (14).

Global LV dysfunction was associated with the presence of MF, indicating an MF role in the development of cardiomyopathy and heart failure in MD. Myocardial delayed enhancement pattern preserving subendocardium and more frequently located in the LV lateral wall has been observed in other cardiomyopathies (12,13). The correlation between segments with MF and dysfunction reinforces the pathophysiological link. In this regard, the dystrophin gene mutation has been associated not only with X-linked dilated cardiomyopathy, but also with sporadic dilated cardiomyopathy (15,16). Previous work has suggested that dystrophin gene exon 51 to 52 mutations protect against the development of dilated cardiomyopathy (17). We had 1 case with this specific mutation and 2 cases with the exon 48, 49, and 50 mutations (Table 1). All 3 of these patients had MF on CMR studies. Moreover, of 7 patients with MF, only 2 had abnormal echocardiography. In light of our data, it is possible that patients with normal echocardiography might already have myocardial injury shown by CMR studies. Therefore, the use of CMR, leading to a more detailed evaluation of these patients, particularly the MF detection, can be useful.

Standard heart failure management, although supported by few data, has been used in this group of patients with suboptimal results (18). Systemic glucocorticoid administration is becoming the standard treatment for skeletal muscle disease, and it may be beneficial to cardiac function. Therefore, further studies are needed to investigate the use of MF by CMR as a surrogate for the beginning of medical therapy for heart failure, with potentially better results. Moreover, the early use of drugs, known to act on the development of MF, such as aldosterone and angiotensin-converting enzyme inhibitors, also needs to be investigated.

Table 4 **Segmental LV MF Distribution**

	Observer 1		Observer 2		
LV Wall	With MF	Without MF	With MF	Without MF	Total
Lateral	19 (38.0)	31 (62.0)	16 (32.0)	54 (68.0)	50 (100)
Septal	6 (12.0)	44 (88.0)	5 (10.0)	45 (90.0)	50 (100)
Anterior	4 (10.0)	36 (90.0)	2 (5.0)	38 (95.0)	40 (100)
Inferior	4 (13.3)	26 (86.7)	2 (6.7)	28 (93.3)	30 (100)
Total	33	137	25	145	170

Absolute frequencies (row percent). $p = 0.001$ for both observers by chi-square test.
Abbreviations as in Table 3.

Conclusions

Cardiovascular magnetic resonance can detect MF in the early stage of cardiomyopathy in patients with MD, when other abnormalities cannot be recognized by a standard cardiologic evaluation. Myocardial delayed enhancement may be useful to further monitor the effectiveness of medical heart failure treatment and to evaluate new strategies targeting the molecular etiology. Whether this approach will influence the cardiomyopathy mortality in patients with MD requires further investigation.

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