

Cardiac Involvement in Myotonic Dystrophy Type 2 Patients With Preserved Ejection Fraction Detection by Cardiovascular Magnetic Resonance

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Background—Myotonic dystrophy type 2 (DM2) is a genetic disorder characterized by skeletal muscle symptoms, metabolic changes, and cardiac involvement. Histopathologic alterations of the skeletal muscle include fibrosis and fatty infiltration. The aim of this study was to investigate whether subclinical cardiac involvement in DM2 is already detectable in preserved left ventricular function by cardiovascular magnetic resonance.

Methods and Results—Twenty-seven patients (mean age, 54±10 years; 20 females) with a genetically confirmed diagnosis of DM2 were compared with 17 healthy age- and sex-matched controls using a 1.5 T magnetic resonance imaging. For myocardial tissue differentiation, T1 and T2 mapping, fat/water-separated imaging, focal fibrosis imaging (late gadolinium enhancement [LGE]), and ¹H magnetic resonance spectroscopy were performed. Extracellular volume fraction was calculated. Conduction abnormalities were diagnosed based on Groh criteria. LGE located subepicardial basal inferolateral was detectable in 22% of the patients. Extracellular volume was increased in this region and in the adjacent medial inferolateral segment ($P=0.03$ compared with healthy controls). In 21% of patients with DM2, fat deposits were detectable (all women). The control group showed no abnormalities. Myocardial triglycerides were not different in LGE-positive and LGE-negative subjects ($P=0.47$). Six patients had indicators for conduction disease (60% of LGE-positive patients and 12.5% of LGE-negative patients).

Conclusions—In DM2, subclinical myocardial injury was already detectable in preserved left ventricular ejection fraction. Extracellular volume was also increased in regions with no focal fibrosis. Myocardial fibrosis was related to conduction abnormalities. (*Circ Cardiovasc Imaging*. 2016;9:e004615. DOI: 10.1161/CIRCIMAGING.115.004615.)

Key Words: arrhythmias, cardiac ■ cardiomyopathy ■ fibrosis ■ magnetic resonance imaging
■ myotonic dystrophies ■ triglycerides

Myotonic dystrophy type 2 (DM2, also known as Ricker disease) is an autosomal dominantly inherited disease, first described as an independent disorder in 1994.¹ The DM2 mutation frequency is ≈1:1800, but the incidence is suspected to be even higher.² Most patients experience first symptoms in their third to fourth decade of life³ with muscle weakness, myotonia, and muscle pain as the most common complaints.¹ Typical myopathological alterations in skeletal muscle are a wide variation in muscle fiber diameters, type 2 fiber atrophy, and centralized nuclei.⁴

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In DM2, the zinc finger protein is genetically changed,⁵ leading to systemic disease with alteration of several organs.

One major feature aspect is its role in the glucose metabolism.⁶ This could explain the development of type 2 diabetes mellitus³ and justified to consider the reduced insulin sensitivity as part of DM2 itself. Furthermore, patients are also experienced hypothyroidism,⁷ hypercholesterolemia, and hypertriglyceridemia.⁸

In a clinical setting, cardiac involvement seems to be rare, but following autopsy data it is underestimated. Already in 1988, before genetic differentiation of subtypes had been introduced, an extended autoptical study reported myocardial fibrosis and local fatty infiltrations in the conduction system of the heart in patients with myotonic dystrophy.⁹ Interestingly, different forms of cardiac arrhythmias are reported showing a large variation of 17% to 36%.^{10–12} Also sudden cardiac death occurred in these patients.¹³

Received November 30, 2015; accepted May 24, 2016.

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Circ Cardiovasc Imaging is available at <http://circimaging.ahajournals.org>

DOI: 10.1161/CIRCIMAGING.115.004615

It is well known that a subclinical detection of myocardial injury applying cardiovascular magnetic resonance (CMR) may help to stratify therapy and has a potential impact on prognosis.¹⁴ In clinical routine, usually echocardiography is used as a first-line method, and in case of decreased left ventricular (LV) function, the diagnosis of myocardial involvement is established. However, one of the major advantages of CMR is the early detection of subclinical myocardial involvement in systemic disorders already in preserved ejection fraction.^{15,16} CMR enables the differentiation of underlying myocardial injuries, including inflammation,¹⁶ focal and diffuse fibrosis,¹⁷ or fatty infiltration.^{18,19} Similar morphological changes were described in DM2 in histological reports.¹³

In this study, we aimed to use the CMR to investigate whether subclinical myocardial alterations in patients with DM2 were detectable in preserved LV function.

Methods

Study Population

The study was approved by the local ethic committee, and all subjects gave written informed consent. We prospectively included patients with a genetically confirmed diagnosis of DM2. A normal global systolic function was required for inclusion (preserved LV ejection fraction defined as $\geq 55\%$ and no wall motion abnormalities). The criteria for exclusion were known vascular or cardiac diseases (eg, coronary artery disease, significant valvular disease, or myocarditis) or life-threatening comorbidities, such as cancer. Furthermore, known contraindications for CMR or contrast media led to exclusion. A detailed medical history was recorded (including comorbidities and medication, family history, and cardiovascular risk factors). Screening for conduction abnormalities was based on a 12-lead ECG and an ambulatory electrocardiography monitoring (Holter-ECG, ≤ 72 hours). Blood sample for hematocrit was taken for the quantification of the extracellular volume (ECV). Blood pressure and heart rate were measured immediately before the CMR scan. As a control group, 17 healthy age- and sex-matched volunteers were included. Exclusion criteria and CMR protocol (except spectroscopy) were equal to the patient group.

Cardiovascular Magnetic Resonance

Scan Protocol

We applied CMR at a 1.5 T Scanner (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany) using a 12 channel surface coil. An overview of the scan protocol is provided in Figure 1.

Cine images in the long and short axis were acquired by applying steady-state free precession sequences to assess cardiac volumes and function (long axis: repetition time, 35 ms; echo time (TE), 1.18 ms; and voxel size, $1.8 \times 1.8 \times 6.0$ mm³ and short axis: repetition time, 62 ms; TE, 1.14 ms; and voxel size, $2.0 \times 1.4 \times 7.0$ mm³).

For myocardial tissue differentiation, we performed T1 and T2 mapping, fat/water-separated imaging, focal fibrosis imaging (late gadolinium enhancement [LGE]), and ¹H magnetic resonance spectroscopy (H-MRS).

Quantitative relaxometry was performed using T2 mapping and T1 mapping in 3 short axes in the basal, medial, and apical level. Analysis was done for each myocardial segment following the AHA model.²⁰

In short, motion-corrected T2 mapping was based on a T2 prepared steady-state free precession technique (3 single-shot images with T2 preparation times of 0/24/55 ms and voxel size of $1.6 \times 1.6 \times 6.0$ mm³).²¹

Furthermore, we performed motion-corrected T1 mapping (based on modified look-locker inversion-recovery²²) to depict diffuse myocardial fibrosis. A sampling protocol with reduced sensitivity to heart rate was used²³ (native T1: 5s(3s)3s and postcontrast: 4s(1s)3s(1s)2s; TE, 1.08 ms; and slice thickness, 6 mm) before and 15 minutes

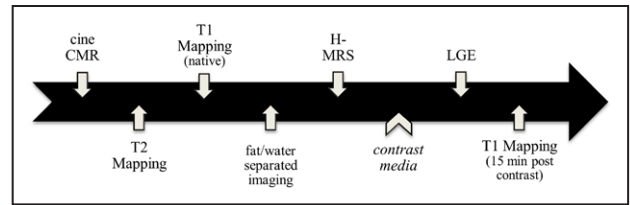


Figure 1. Scan protocol. Cine cardiovascular magnetic resonance (CMR) was performed to quantify left ventricular volumes, mass, and function. Myocardial tissue differentiation started with T2 mapping followed by native T1 mapping and fat/water separated imaging. ¹H magnetic resonance spectroscopy (H-MRS) was performed to determine myocardial triglycerides. After contrast media application (0.2 mmol/kg body weight gadoteridol), we applied late gadolinium enhancement (LGE) imaging and postcontrast T1 mapping.

after contrast media application. We used 0.2 mmol/kg body weight gadoteridol.

We acquired a multiecho sequence for fat/water separation to detect myocardial fat deposits^{19,24} in a 4-chamber long-axis view and 3 short axes. Slice position was similar to the relaxometry acquisition. Sequence parameters were as follows: gradient echo sequence, double inversion recovery dark blood preparation, 4 echos with monopolar readout, TE of 1.53 to 8.22 ms, and slice thickness of 6 mm.

To determine myocardial triglycerides (MTGs), we performed single voxel H-MRS as published recently²⁵ (spin-echo sequence: repetition time, 1600 ms; TE, 35 ms; nonsuppressed spectra: one averaging, 16 series; and water-suppressed spectrum: 96 averaging, one series). The imaging volume was placed as a voxel ($20 \times 15 \times 6$ mm³) in the myocardial septum (Figure 2).

Focal fibrosis imaging by LGE was performed in the same slice positions as cine CMR (gradient echo sequence, breath-held segmented protocol with 10 ms echo spacing, TE of 5.02 ms, and slice thickness of 7 mm) 10 to 15 minutes after administration of contrast media.

The protocol of the control group included cine CMR, fat/water-separated imaging, parametric mapping, and LGE. H-MRS was not performed because own volunteer data were already available as published recently.²⁶

Data Analysis

The readers were blinded to the clinical information. CMR image analysis was performed using the postprocessing software cvi⁴² version 4.1.2 (Circle Cardiovascular Imaging Inc, Calgary, Canada).

Short-axis cine images were used for the calculation of LV volume, mass, and function.²⁷ Both the values of T2 and T1 maps were quantified as previously reported.²⁸ The qualitative survey implied the exclusion of segments in case of artifacts (eg, caused by susceptibility effects or unintended thoracic motion) or wrong motion correction as described recently.²⁸ We performed inter- and intraobserver variability analysis.

In addition, we calculated the ECV by means of native and postcontrast T1 values and the hematocrit as published.²⁹

The visual assessment of the fat/water-separated imaging was based on predefined criteria. A suspected region was considered positive if the intramyocardial fat could be (1) either assured coexistent in the fat-separated image (hyperintense) and in the water-separated image (hypointense) or (2) detected in one of the separated images and in the cine images and the LGE.

The content of MTG was calculated as the percentage of fat to water signal (Figure 2). The signal value was determined by standard line-fitting procedure (Siemens syngo Spectroscopy) as an area under the peaks.

The visual evaluation of the LGE images was performed by 2 independent experienced readers. The qualitative assessment included the presence, number, and transmuralty of focal scar lesions. Unambiguous differentiation of a pathological pattern from

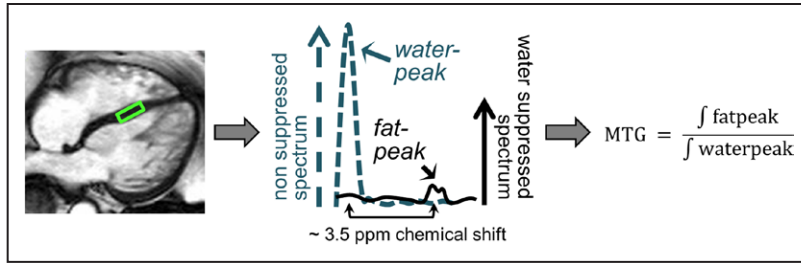


Figure 2. ^1H magnetic resonance spectroscopy: Method. Volume of interest (green box) placed into the myocardial septum to acquire a non-suppressed and a water-suppressed spectrum. The fraction of myocardial triglycerides (MTGs) was calculated as the ratio of the fat peak integral to the water peak integral.

an artifact was permitted during the acquisition by verification in 2 perpendicular slices or by requiring another readout direction.

We evaluated the 12-lead ECGs using the Groh criteria.³⁰ Patients were ranked positive if one of the following criteria was present: no sinus rhythm, PR interval of ≥ 240 ms, QRS duration of ≥ 120 ms, and second- or third-degree atrioventricular block.³⁰ Holter-ECGs were analyzed using the evaluation software CardioDay Standard (GETEMED AG, Teltow, Germany).

Statistical Analysis

All measured values are shown as mean \pm SD. The statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corp). Using 2-sided Mann–Whitney U test, significant values were accepted by $P < 0.05$. Correlation analyses were performed using the Spearman rank correlation coefficients. For intra- and interobserver reproducibility, images were analyzed twice by blinded readers. The results were evaluated by means of Bland–Altman plots and intraclass-correlation coefficients.

Results

We screened 266 patients with different muscular diseases and could prospectively enroll 32 patients with DM2 (age 54 ± 10.6 years, 24 women). Reasons for exclusion were no genetically proven DM2 ($n=154$), medical history ($n=23$), and CMR-related exclusion criteria ($n=7$). Four patients were not able to complete the scan, 2 aborted immediately at the beginning of the scan and 2 before contrast media application. One patient had to be excluded because of newly diagnosed ejection fraction of 42%. Finally, we had 27 complete data sets, 29 data sets were included in the precontrast-analysis. In addition, 17 healthy volunteers were matched for age ($P=0.97$), sex ($P=0.79$), and body mass index ($P=0.83$). Following the inclusion criteria, all patients had a preserved ejection fraction. The ejection fraction of the control group was statistically lower than that of the patient group but within the normal range ($64.5 \pm 5\%$ versus $68.1 \pm 6\%$, $P=0.03$). For the anthropometric characteristics, no significant differences were found besides the diastolic blood pressure (DM2 versus controls: 83 ± 10 mmHg versus 77 ± 10 mmHg, $P=0.03$). None of the subjects had wall motion abnormalities. For detailed characteristics see Table 1. Besides, Table 2 provides a comparison of the findings in DM2 patients with and without type 2 diabetes mellitus.

Myocardial Tissue Differentiation

Analysis of LGE imaging revealed focal myocardial fibrosis in 6 (3 women) of the 27 subjects. These fibrous lesions were mostly localized subepicardial inferolateral in the basal region (Figure 3). No fat deposits were detectable in this region. The presence of focal fibrosis was not significantly different in patients with and without diabetes mellitus (43%

versus 15%, $P=0.29$). Blood pressure did not differ between patients with positive and negative LGE (systolic: $P=0.1$ and diastolic: $P=0.5$; Table 1). No focal fibrosis was detectable in the control group.

T2 maps of 29 patients (438/448 segments) and 17 healthy subjects (263/272 segments) were evaluable. No focal lesions were visually detectable. T2 times of subjects with DM2 were higher compared with healthy volunteers in all slices (basal: 51.0 ± 1.7 ms versus 48.7 ± 1.4 ms, $P < 0.001$; medial: 52.5 ± 2.4 ms versus 48.5 ± 2.6 ms, $P=0.001$; and apical: 55.8 ± 3.4 ms versus 51.5 ± 1.8 ms, $P < 0.001$).

For T1 maps, 1440 segments of 29 patients and 17 healthy subjects were obtained. One hundred ninety-two segments (13%) had to be excluded because of artifacts or inaccurate motion correction. Global native T1 values are given in Table 3. Reliability was sufficient for both inter- and intra-observer evaluations ($r=0.78$ and 0.92 , intraclass-correlation coefficient= 0.83 and 0.96).

The analysis of the T1 maps of patients experiencing DM2 revealed primarily significant differences in the basal segments of the LV lateral wall in comparison with the control group. Both the global basal (control versus DM2: 1006 ± 24 ms versus 1030 ± 29 ms, $P=0.005$) and the global apical native T1 values (control versus DM2: 964 ± 34 versus 1018 ± 48 ms, $P=0.001$) were increased in patients with DM2. No significant difference was found between healthy volunteers and patients with DM2 for the midventricular slice (992 ± 28 ms versus 1013 ± 36 ms, $P=0.054$).

ECV was evaluated in 20 patients with DM2 and in all 17 healthy subjects. Global values of the ECV of DM2 sufferers showed no significant differences to the control group besides the apical slice (DM2 versus controls: basal $26.1 \pm 3\%$ versus $24.7 \pm 4\%$, $P=0.28$; medial $26.7 \pm 3\%$ versus $26.8 \pm 3\%$, $P=0.88$; and apical $29.2 \pm 3\%$ versus $27.0 \pm 3\%$, $P=0.04$). The comparison of the LGE-positive patients to the control group showed elevated values in both the basal and the medial inferolateral segment, where no focal fibrosis was detected (basal inferolateral: $31.7 \pm 6\%$ versus $24.1 \pm 4\%$, $P=0.02$ and medial inferolateral: $29.3 \pm 2\%$ versus $24.1 \pm 3\%$, $P=0.03$). ECV was not different between patients with and without diabetes mellitus (basal: $P=0.86$, medial: $P=0.054$, and apical: $P=0.28$). Detailed ECV values are given in Figure 4.

Compared to LGE-negative patients, LGE-positive patients showed increased T1 values in the medial inferolateral segment of the native T1 maps (1085 ± 85 ms versus 1018 ± 48 ms, $P=0.007$). Similarly, the ECV of LGE-positive patients compared with LGE-negative patients was increased in both the basal and the medial inferolateral segment (basal: $31.7 \pm 6\%$ versus $25.9 \pm 3\%$, $P=0.048$ and medial: $29.3 \pm 2\%$

Table 1. Detailed Patient Characteristics

	All Patients With DM2 (n=27)	Healthy Subjects (n=17)	LGE-Positive Patients (n=6)	LGE-Negative Patients (n=21)
General characteristics				
Female, %	74.1	70.6	50.0	81.0
Age, y	54.0±10.4	54.2±10.0	61.0±9.9	52.0±9.9
BP systolic, mm Hg	133±14	130±20	141±17	131±13
BP diastolic, mm Hg	83±10	77±10*	83±6	83±11
Increased BP, %	40.7	35.3	50.0	38.1
Heart rate, bpm	71±7	75±10	72±9	70±7
BMI, kg/m ²	25±4	24±3	27±5	24±4
General CMR findings				
LV-EF, %	68.0±6	64.5±5*	64.5±6	69.2±6
LV-EDV index, mL/m ²	70±10	65±11	73±15	69±8
LV mass index, g/m ²	53±10	55±6	60±15	51±7
Content of MTG, %	0.49±0.5	Not performed	0.85±0.9	0.37±0.2
Apical fat, n (%)	19.2	0.0	16.7	20.0
Myocardial fibrosis, n (%)	22.2	0.0*	All positive by definition	All negative by definition
Clinical presence of symptoms				
Muscle pain (by NRS)	3.3±3.0	None	3.3±2.8	3.3±3.1
Muscular strength (by MRC)	4.3±0.8‡	Not limited	4.1±0.8	4.3±0.8
Myotonia, %	59.3	None	0.0	76.2†
Fatigue, %	66.7	0.0*	66.7	66.7
Hardness of hearing, %	18.5	5.9	16.7	19.0
Cataract, %	29.6	0.0*	50.0	23.8
Disagreeable palpitations, %	33.3	17.6	33.3	33.3
Further characteristics				
Hypothyroidism, %	14.8	None	16.7	14.3
Hypercholesterolemia or hypertriglyceridemia, %	70.4	11.8*	50.0	76.2
Type 2 diabetes mellitus, %	25.9	None*	50.0	19.0
Smoker, %	22.2	17.6	50.0	14.3
Positive family history for cardiovascular events, %	44.4	35.3	50.0	42.9
Positive Groh criterion, %	23.8	Not performed	60.0	12.5†

BMI indicates body mass index; BP, blood pressure measured just before the scan; CMR, cardiovascular magnetic resonance; DM2, myotonic dystrophy type 2; LGE, late gadolinium enhancement; LV-EDV, left-ventricular enddiastolic volume; LV-EF, left ventricular ejection fraction; MRC, Medical Research Council Scale for Muscle Strength; MTG, myocardial triglycerides; and NRS, numeric rating scale.

Patients with positive LGE showed a higher frequency of myotonia and severe conduction disturbances than those with negative LGE. Significant differences were found between healthy subjects and the patient group (*) as well as between LGE-positive and LGE-negative patients (†).

‡Muscular strength inversely correlates with the use of nonsteroidal anti-inflammatory drugs ($r=-0.38$, $P=0.04$).

versus 25.0±2%, $P=0.004$). Apart from that, no significant differences were found between patients showing positive and negative LGE. A detailed comparison of LGE-positive and LGE-negative patients is presented in Tables 1 and 3.

Fat/water-separated imaging of 28 patients was available. It was also performed in 15 healthy subjects. Small myocardial fat deposits were identified in the apical portion of the interventricular septum in 6 patients (21%, all women; Figure 5). No myocardial fibrosis was detectable in

this region. Only one patient showed both fatty infiltration and focal fibrosis, but in different regions. The additional presence of diabetes mellitus did not reach statistical significance (with versus without diabetes mellitus: 25% versus 20%, $P=0.86$). In healthy subjects, no myocardial fat deposit was detected.

H-MRS data of 25 subjects were utilizable. The MTG fraction ranged from 0.014% to 2.36% with a mean of 0.48%. Examples of spectra of a patient with and without focal fibrosis

Table 2. Findings in Patients With DM2 in Regard to the Presence of Diabetes Mellitus

	No Diabetes Mellitus (n=20)	Type 2 Diabetes Mellitus (n=7)	P Value
Female, n	16/20	4/7	0.40
Age, y	52±11	60±6	0.07
BMI, kg/m ²	23.9±3.3	28.3±5.1	0.07
Content of MTG, % (minimum-maximum)	0.43±0.5 (0.04–2.36)	0.71±0.5 (0.01–1.36)	0.14
Apical fat, n	4/19	1/7	0.82
Myocardial fibrosis, n	3/20	3/7	0.29
Positive Groh criterion, n	3/17	2/4	0.36

No significant differences were found in the presence of myocardial fibrosis detected by late gadolinium enhancement, apical fat detected by fat/water-separated imaging, or positive Groh criteria in ECG as well as the content of myocardial triglycerides (MTG). BMI indicates body mass index; and DM2, myotonic dystrophy type 2.

are illustrated in Figure 6. The relation between this ratio, body mass index, and the presence of diabetes mellitus is presented by Figure 7. A correlation of the MTG content to the body mass index was not existent ($r=0.01$, $P=0.9$). There was no significant difference of MTG content between patients with and without diabetes mellitus ($0.71\pm0.5\%$, range 0.01–1.36% versus $0.43\pm0.48\%$, range 0.04–2.36%; $P=0.14$) and the mild correlation did not reach the level of significance ($r=0.32$, $P=0.1$).

Conduction Abnormalities

ECGs were available in 25 patients and Holter-ECGs (31±18 hours) in 20 patients. From one of the LGE-positive patients, no ECG was available. Both, LGE and ECG data were available in 21 subjects. The QRS duration was significantly longer in patients with positive LGE compared with those with negative LGE (Holter-ECG: 101 ± 6 ms versus 78 ± 10 ms, $P=0.002$ and 12-lead ECG: 106 ± 12 ms versus 88 ± 9 ms, $P=0.003$). Using the Groh criteria, 6 patients were classified as indicative of conduction disease. Sixty percent of the LGE-positive patients with 12-lead ECG fulfilled at least one of the Groh criterion (LGE-positive versus LGE-negative patients: 60% versus 12.5%, $P=0.034$). The presence of LGE correlated positively with the presence of positive Groh criteria ($r=0.48$, $P=0.03$). Furthermore, 50% of the patients with myocardial fat accumulation were positive for Groh criteria (fat-positive versus fat-negative patients: 50% versus 23%, $P=0.152$).

Discussion

In our DM2 population, we were able to identify myocardial injury despite preserved ejection fraction. Focal fibrosis and focal fat accumulation were detectable in 22% and 21% of the patients, respectively. The findings occurred in different patients. Interestingly, also an increased ECV adjacent to the focal fibrosis was present indicating a progressive process. In patients with DM2, structural myocardial differences were detectable not only in comparison with healthy age- and sex-matched volunteers but also in comparison with DM2 patients without focal fibrosis. The structural abnormalities seem to have a relation to conduction abnormalities as identified using the Groh criteria.³⁰ To the best of our knowledge, this is the first study identifying subclinical myocardial injuries in terms of myocardial fibrosis and myocardial fat accumulation in genetically confirmed DM2 and preserved ejection fraction applying CMR.

The skeletal muscle of patients with DM2 is primarily characterized by nuclei and fiber changes as well as mild fibrosis and fatty infiltration.^{4,31} Our noninvasively detected myocardial findings are in line with this. The pattern of the focal fibrosis was nonischemic and always located inferolateral basal subepicardial. None of the healthy subjects had focal myocardial fibrosis. The nonischemic pattern of the focal myocardial fibrosis was also depicted in other muscular dystrophies. Subepicardial LGE in the inferolateral

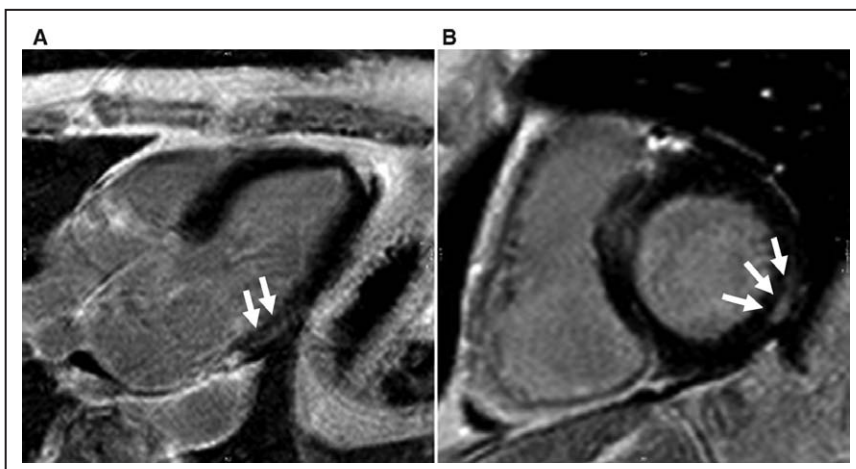


Figure 3. Myocardial fibrosis in a patient with myotonic dystrophy type 2 detected by late gadolinium enhancement imaging. Basal inferolateral fibrosis (arrows) with nonischemic pattern in (A) 4-chamber view and (B) short-axis slice.

Table 3. Global Native and Postcontrast T1 Values (Mean±SD, [minimum/maximum]) of LGE-Positive, LGE-Negative, and Healthy Subjects

T1 Values, ms	LGE-Positive (n=6)	LGE-Negative (n=21)	Healthy (n=17)
Native			
Basal	1048±38 (1011/1121)	1023±24 (981/1081)	1006±24*† (963/1048)
Medial	1030±58 (963/1118)	1007±29 (944/1059)	992±28 (950/1049)
Apical	1045±58 (953/1094)	1007±45 (915/1102)	964±34*† (891/1007)
Postcontrast			
Basal	462±28 (431/505)	456±32 (406/500)	451±27 (408/491)
Medial	468±31 (426/519)	444±35 (377/495)	435±26* (373/468)
Apical	432±40 (372/485)	426±41 (351/483)	495±101 (373/673)

Significant differences were found between healthy and LGE-positive patients (*) as well as healthy and LGE-negative patients (†).

wall is also described in 2 patients with Becker and limb-girdle muscular dystrophy, respectively.³² Both the patients had no cardiac symptoms but reduced LV ejection fraction.³² In Duchenne and Becker dystrophy, nonischemic myocardial fibrosis predominantly involving the lateral wall was shown.³³ But also these patients already had a reduced LV ejection fraction.³³ A recent study investigated 80 patients with DM1.³⁴ There, in 13% of all patients, myocardial fibrosis was detected applying LGE imaging, although one fourth of the study cohort presented LV systolic dysfunction. In DM2, only 1 case report exists postulating focal myocardial fibrosis in a 68-year-old woman.³⁵

Cardiac manifestations in patients with myotonic dystrophies are known to have a prognostic impact.^{10,12} Unspecific cardiac complaints were reported in 2% to 8%, conduction abnormalities in 17% to 20% leading to pacemaker, or defibrillator implantation in 6% to 12%.^{3,10,12} of the patients. Cardiac arrhythmias may evolve from myocardial remodeling.^{13,36} Histology of DM2 cases with sudden death showed

myocardial fibrosis and focal fatty degeneration.¹³ In addition, severe ECG abnormalities were an independent risk factor for sudden death in DM1.³⁰ On the basis of the Groh criteria, in our study, 60% of the LGE-positive subjects showed such ECG abnormalities. Similarly, half of the patients with myocardial fat revealed positive Groh criteria but this relation was not statistically significant. However, 40% of all patients with cardiac injury as detected by CMR had no ECG abnormalities.

Because LGE was positive in the basal inferolateral segment, increased ECV reflects the focal fibrosis in this region. But interestingly, not only these regions had an increased ECV but also the adjacent medial inferolateral segments without focal fibrosis detected by LGE. This finding indicates that not only the presence of focal fibrosis but also a diffuse progressive process in other myocardial regions can be assessed in this genetic disease.

In a previous study, a mixed population of patients with DM1 and DM2 were surveyed by CMR, including postcontrast T1 mapping and LGE.³⁷ In contrast to our results, there was no evidence of focal fibrosis but they found shorter

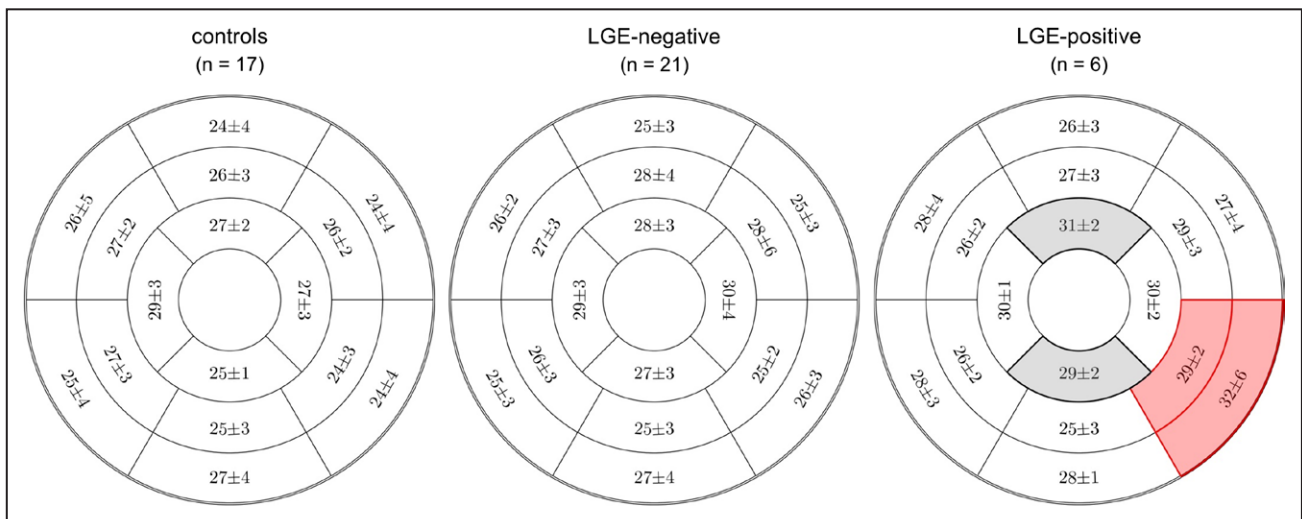


Figure 4. Extracellular volume (ECV) bull's eye plots. Detailed ECV values of the control group (left), patients without focal fibrosis (late gadolinium enhancement [LGE] negative, middle) and with positive LGE (right). Significant differences were found between LGE-positive and LGE-negative patients (red, basal inferolateral: $P=0.046$ and medial inferolateral: $P<0.01$) and between LGE-positive patients and controls (red and gray, basal inferolateral: $P=0.02$, medial inferolateral: $P=0.03$, apical anterior: $P<0.01$, and apical inferior: $P=0.01$). No significant differences were found between controls and LGE-negative patients.

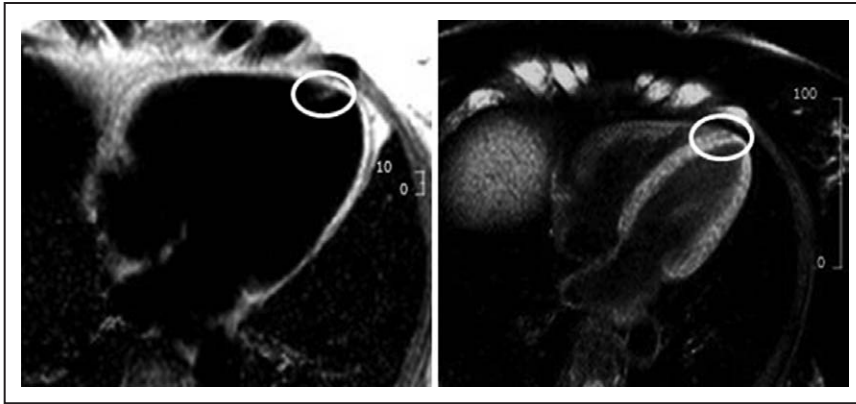


Figure 5. Fat/water separated imaging. Myocardial fat accumulation detected in the apical portion of the interventricular septum (circles) is presented bright in the fat-separated image (**left**) and hypointense in the water-separated image (**right**).

postcontrast T1 times in patients compared with control subjects. The authors hypothesized that the shorter postcontrast T1 times may reflect an interaction of myocardial diffuse fibrosis, fatty infiltration, and edema/inflammation.

The T2 values of our patients were slightly higher compared with the control group. This may be indicative for an inflammatory process, as increased T2 times have also been shown in myocarditis³⁸ and lupus erythematosus.³⁹ However, even the T2 values of the patient group were within the normal range.²¹

As previously described, besides fibrous changes, focal fatty infiltrations were identified not only in the skeletal muscle but also in the myocardium in histological studies.^{4,13} Applying dedicated techniques, we could detect myocardial fat accumulation in one fifth of our patients with DM2. It was always located in the apical part of the interventricular septum. None of our healthy volunteers revealed these alterations.

Furthermore, in DM2 metabolic changes are well known.⁴⁰ We applied H-MRS to record subtle changes. H-MRS may provide even more information about the

subclinical status by quantifying MTG, which can trigger pathological signals for apoptosis.⁴¹ However, in this study, there were no significant differences in comparison with our recently published volunteer group.²⁶ The H-MRS data showed a high standard deviation, and currently we are not able to state if this is disease specific or method related. H-MRS is established in our group in a research setting. The baseline data of this study are in line with previously published ones.²⁶ Both the range of values and the detected mild relationship to the presence of diabetes mellitus are concordant to previous investigations in healthy and insulin-resistant subjects.⁴²

As known from previous studies, fat infiltration in terms of elevated MTG and diffuse and focal fibrosis of the myocardium are described in type 2 diabetes mellitus.⁴²⁻⁴⁴ But there are no studies in diabetics showing focal intramyocardial fat. In our population, focal fibrosis and focal fat were present in patients with and without diabetes mellitus. One may assume that focal fibrosis in patients with DM2 is caused by diabetes mellitus. But as described, the observed pattern of the focal fibrosis is also well known in other muscular diseases.^{32,33}

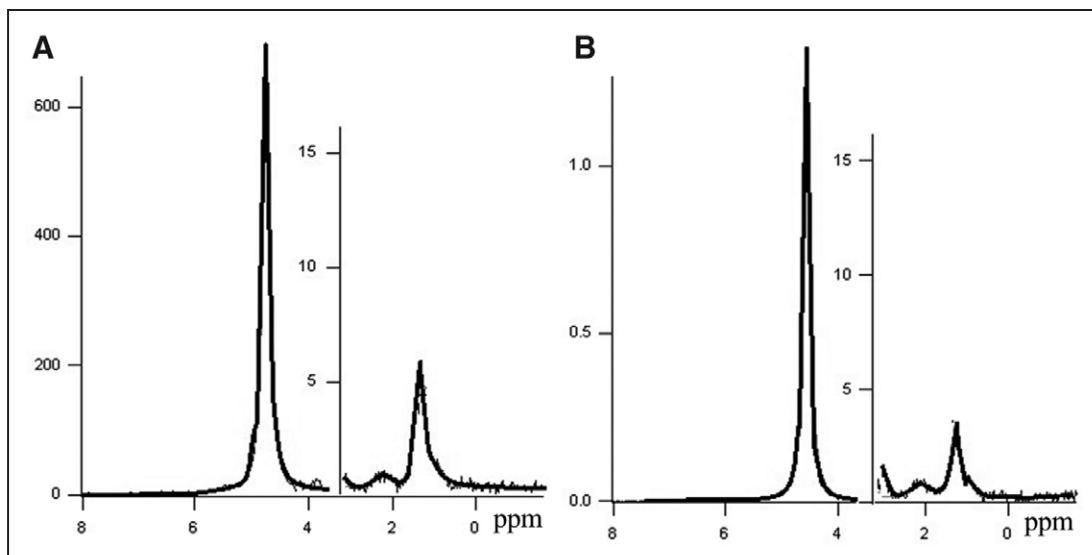


Figure 6. ¹H magnetic resonance spectroscopy: nonsuppressed and water-suppressed spectra. **A**, Spectra of a late gadolinium enhancement (LGE)-positive patient with a myocardial triglycerides (MTG) content of 1.36%. **B**, Spectra of an LGE-negative patient with an MTG content of 0.41%.

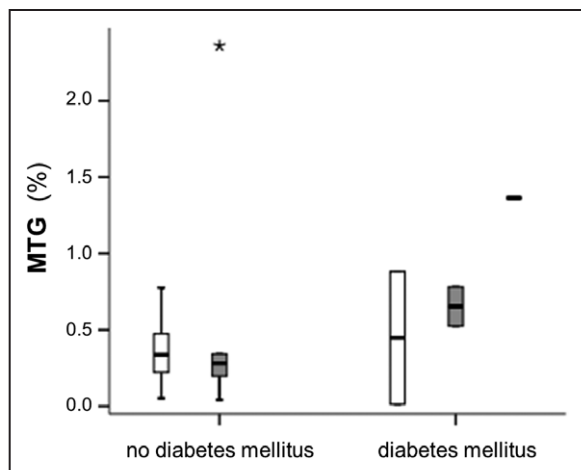


Figure 7. Content of myocardial triglycerides (MTG) of patients in relation to presence of diabetes mellitus and weight category. White: normal weight (body mass index [BMI], 18 to ≤ 25), gray: overweight (BMI, >25 to ≤ 30), and black stripe: obesity (BMI, >30).

The only case report published including a patient with DM2 showed focal fibrosis in the absence of diabetes mellitus.³⁵ Furthermore, no significant differences were found between patients with and without diabetes mellitus with regard to our findings. Hence, we assume that the disease-related diabetes mellitus in our patients with DM2 could not be the only reason for the detected myocardial injury.

Patients with muscular dystrophy get an increasing attention within cardiology. This is reflected, for example, by a more aggressive device management to prevent fatal events.⁴⁵ We assume that our findings may help to detect myocardial injury before the development of heart failure and arrhythmias in patients with DM2 and might guide their management in the future.

Limitations

The sample size seems small; but to the best of our knowledge, this is the largest prospective study in patients with this rare disease. The statistical analysis was not corrected for multiple comparisons. The relation between conduction abnormalities and myocardial alterations could be only evaluated in a subgroup of 21 patients because of missing 6 ECGs. The incidence of a slightly increased diastolic blood pressure compared with controls and the prevalence of DM2-related diabetes mellitus differed in the groups with and without focal fibrosis. But the blood pressure regulation does not necessarily indicate a significant arterial hypertension because it was taken at the beginning of the scan. Both diabetes mellitus and arterial hypertension may potentially be confounding factors to our observations. In our group, however, the myocardial changes in DM2 reached no statistical significance related to diabetes mellitus and blood pressure.

Conclusions

In patients with DM2, subclinical myocardial injury characterized by fibrosis and fat was already detectable in preserved LV ejection fraction. Focal myocardial fibrosis was related to ECG abnormalities. Quantitative mapping techniques and fat

imaging led to a detection of myocardial injury beyond focal fibrosis. Longitudinal trials with a larger sample size will help to define the impact of our findings on long-term prognosis and on therapeutic decision-making.

Acknowledgments

We acknowledge the technicians Kerstin Kretschel, Evelyn Polzin, and Denise Kleindienst for assisting in acquiring the CMR data, the study nurses Elke Nickel-Szczeczek and Annette Köhler-Rhode for assisting in the organization of the CMR scans, and Serkan Doganguezel as well as Anna-Katharina Müller (both member of the Working Group on CMR, Berlin) for interobserver reading. We thank Florian Schubert (head of the working group in vivo MR spectroscopy at Physikalisch-Technische Bundesanstalt Berlin) for his support of the evaluation of the ^1H magnetic resonance spectroscopy data. We also thank the volunteers for participating in this research.

Sources of Funding

Dr Schulz-Menger, medical faculty of the Humboldt University Berlin, was financially supported by research funds of the Charité.

Disclosures

Dr Dieringer is an employee in Siemens Healthcare, Germany (that was not the case in the beginning of this research). Dr Schulz-Menger is a president of Society for Cardiovascular Magnetic Resonance (SCMR), Board of Trustees of International Society for Magnetic Resonance in Medicine (ISMRM), Advisor Bayer Healthcare, Germany.

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CLINICAL PERSPECTIVE

Myotonic dystrophy type 2 is a genetic disorder that affects not only skeletal musculature but is also characterized by different metabolic alterations, including hyperlipidemia, hypothyroidism, and type 2 diabetes mellitus. Arrhythmias occur in up to a third of the patients but are currently difficult to predict. Using cardiovascular magnetic resonance, we have shown that myocardial structural alterations, such as fibrosis and fat deposits, are detectable even in patients with preserved left ventricular ejection fraction. The subtle myocardial abnormalities seem to be associated with conduction abnormalities. Therefore, application of cardiovascular magnetic resonance in this mainly young population should be considered for personalized, therapeutic decision-making. Large-scale multicenter trials should be conducted in specific neuromuscular diseases to evaluate myocardial abnormalities that may be predictive of cardiac risk and to evaluate therapeutic interventions that could alter the course of the disease.

Cardiac Involvement in Myotonic Dystrophy Type 2 Patients With Preserved Ejection Fraction: Detection by Cardiovascular Magnetic Resonance

Luisa Schmacht, Julius Traber, Ulrike Grieben, Wolfgang Utz, Matthias A. Dieringer, Peter Kellman, Edyta Blaszczyk, Florian von Knobelsdorff-Brenkenhoff, Simone Spuler and Jeanette Schulz-Menger

Circ Cardiovasc Imaging. 2016;9:

doi: 10.1161/CIRCIMAGING.115.004615

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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