Cardiac Magnetic Resonance Findings and Prognosis in Type 1 Myotonic Dystrophy

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Research Article

Keywords: DM1, myotonic, Steinert, heart, CMR, magnetic resonance

Posted Date: January 3rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1217399/v1

Abstract

Purpose

Cardiac involvement is a major determinant of prognosis in type 1 myotonic dystrophy (DM1), but limited information is available about myocardial remodelling and tissue changes. Aim of the study was to investigate cardiac magnetic resonance (CMR) findings and their prognostic significance in DM1.

Methods

We identified all DM1 patients referred from a neurology unit to our CMR laboratory from 2009 to 2020.

Results

Thirty-four patients were included (aged 45±12, 62% males). At CMR, 5(15%) had a left ventricular ejection fraction (LVEF)<50% and 4(12%) a right ventricular ejection fraction (RVEF)<50%. Compared to age- and sex-specific reference values, 12(35%) had a decreased end-diastolic volume index (LVEDVi), 7(21%) a decreased mass index (LVMi), and 29(85%) a reduced LVMi/LVEDVi. Nine (26%) showed mid-wall late gadolinium enhancement (LGE; 5±2% of LVM), and 14(41%) fatty infiltration. In a subset of 13(38%) patients, native T1 in the interventricular septum (1,041±53 ms) approached the upper reference limit (1,089 ms) and the extracellular volume was slightly increased (33±2%, reference<30%). Over 2.5(1.5-4.0) years, 2(6%) patients died for infectious and respiratory complications, 5(15%) underwent device implantation; 4/21(19%) with Holter developed repetitive ventricular ectopic beats (VEBs). Lower RV volumes (p=0.043), higher anteroseptal wall thickness (p=0.024) and LV fatty infiltration (p=0.029) were associated with device implantation, LGE mass was associated with VEBs (p=0.003) and death (p<0.001).

Conclusion

DM1 patients display structural and functional cardiac abnormalities, with variable degrees of cardiac muscle hypotrophy, fibrosis and fatty infiltration. Such changes, as evaluated by CMR, may anticipate the worsening of electrical disturbances.

Introduction

Type 1 myotonic dystrophy (DM1), also known as Steinert disease, is the most common genetic form of muscular dystrophy. The estimated prevalence is 520:100.000, but population screening programmes suggest that the actual prevalence may be up to fivefold greater[1]. Transmission is autosomal dominant and the genetic defect consists of an abnormal expansion of CTG triplet repeats within the 3’ untranslated region (3’-UTR) of the *DMPK* (Dystrophia Myotonica Protein Kinase) gene. Normal subjects

carry 5-34 CTG repeats; 35-49 repeats identify a premutation allele, which is not clinically evident, but may become so in offspring, due to anticipation; more than 50 repeats result in full-penetrance phenotypes [2, 3]. The typical form has juvenile-adult onset and features distal muscles weakness, grip myotonia, ptosis and weakness of oropharyngeal muscles. Respiratory function may be affected and frequently requires non-invasive ventilation. Early-onset cataracts, metabolic and endocrine dysfunctions--most notably diabetes and thyroid disease--gastrointestinal dismotility and cognitive and behavioural impairment, commonly implying scarce disease awareness, have been linked to the disease[4, 5].

Cardiac involvement is another very common feature of DM1. Abnormalities at the electrocardiogram (ECG) or at ECG Holter monitoring are observed in about 80% of patients[6–8]. They often include atrioventricular and intraventricular conduction disturbances, bradyarrhythmias and ventricular or supraventricular tachyarrhythmias. Bradyarrhythmias and ventricular tachyarrhythmias may account for the relatively high incidence (~0.56% per year) of sudden cardiac death (SCD)[9, 10]. PR and QRS elongation and atrial tachyarrhythmias have been shown to anticipate SCD[9–12]. Yet, surface ECG has a limited positive predictive value (~12%) for sudden death[9, 11], so that current strategies for risk stratification need to be improved, in order to guide therapy[13].

Structural heart disease is frequently observed at echocardiography. Left ventricular (LV) hypertrophy and dilation, mitral valve prolapse and regional wall motion abnormalities are among the most common findings, each affecting about 10-20% of patients[14]. LV systolic dysfunction has a similar prevalence (7-14%)[10, 14, 15], while diastolic abnormalities appear to be common even in early disease stages[16–19].

Cardiac magnetic resonance (CMR) allows a non-invasive characterization of myocardial tissue *in vivo* and an accurate estimate of cardiac mass and volumes. Such features make it particularly suitable for studying cardiac involvement in neuromuscular disorders[8, 20]. CMR case series have showed a reduction of mean cardiac mass and volumes in patients with DM1[21–23], previously unnoticed by echocardiographic studies. A normal mass/volume ratio has been reported[22], but most studies did not evaluate ventricular geometry.

At histology, myocardial disease in DM1 is characterized by fibrosis, fatty replacement[24–27] and lymphocytic infiltrates[27], along with an increased variability in fibre size, with coexisting atrophic and hypertrophic myocytes[24, 27]. Such changes promote re-entry phenomena[28–30] and likely also conduction disturbances.

Myocardial tissue abnormalities manifest with late gadolinium enhancement (LGE)[21–23, 31–36], most often mid-wall and septal/inferolateral[21, 23, 31, 34–37], and an expansion of extracellular volume demonstrated through mapping techniques[21, 22, 34, 36, 38]. However, the link between CMR findings and electrical disturbances in DM1 is still controversial[21–23, 33–35, 39, 40] and their prognostic significance is unclear, since follow-up data are lacking. As a result, a dedicated statement by the American Heart Association does not include any specific recommendation about CMR use in DM1[8].

In this study we provide further data about cardiac involvement in DM1, as assessed through CMR, with a particular focus on ventricular geometry and tissue changes, and their prognostic relevance.

Materials And Methods

Patient population

We reviewed electronic health records (EHRs) at Fondazione Toscana Gabriele Monasterio [FTGM], Pisa, Italy) to retrieve all patients (1) with a genetic diagnosis of DM1, (2) referred for cardiological assessment between 2009 and 2020 and (3) with sufficiently detailed clinical information at Neurological Unit AOUP (Azienda Ospedaliera Universitaria Pisana). Patients with a history of myocardial infarction, coronary revascularization or cardiac surgery were excluded as we were interested in studying the cardiomyopathy specifically associated with DM1, which is considered to differ from ischemic heart disesase[41].

Seventy-three patients (43 males, age 48±15 years) with DM1 were identified. One patient was excluded because of the lack of follow-up data, and two because of a prior myocardial infarction. Other 36 patients had not undergone a CMR scan because of a PM/ICD (n=14) or refusal to undergo the examination (n=22). The final study population then included 34 patients with DM1.

All clinical, laboratory, electrocardiographic and echocardiographic data at the time of CMR were recorded. Neuromuscular disability was assessed by the Muscular Impairment Rating Scale (MIRS), a five-point scale evaluating extent and severity of muscular impairment (from score 0 – asymptomatic – to score 5 – severe proximal weakness)[42]. The study complied with the Declaration of Helsinki; all patients gave written informed consent.

Cardiac magnetic resonance

Patients underwent CMR with a 1.5 T scanner (Signa CVi, GE Healthcare, Milwaukee, USA). Biventricular systolic function was assessed by breath-hold steady-state free precession (SSFP) cine imaging in the short-axis (SA) stack (8-mm thickness, no gap). Sequence parameters were: field-of-view: 360-400 mm, repetition/echo time: 3.2/1.6 ms, flip angle: 45-60°, matrix: 224×224, phases: 30. Late gadolinium enhancement (LGE) imaging was performed between 10 and 20 min after contrast agent administration (Gadoteric acid, DOTAREM, 0.2 mmol/kg) using a segmented T1-weighted gradient-echo (GRE) inversion-recovery pulse sequence. In SA orientation, the left ventricle (LV) was encompassed by contiguous 8-mm thick slices (with no inter-slice gap). Inversion time (TI) was individually adapted to suppress the signal of normal remote myocardium (220–320 ms). LGE was also confirmed or excluded in vertical and horizontal long-axis views. Sequence parameters were: field-of-view: 360–400 mm, slice thickness: 8 mm, repetition/echo time: 4.6/1.3 ms, flip angle: 15-20°, matrix: 224×192. Native (pre-contrast) T1 mapping was acquired in 3 short-axis slices (basal, medium and apical) using a modified Look-Locker (MOLLI) sequence (3,3,5 scheme; flip angle: 35°; matrix: 172x172 pixels; partial Fourier=0.75) in a subset of 13 (38%) patients; post-contrast T1 mapping was acquired 15-20 minutes after gadolinium injection in 9 (27%) patients.

All CMR studies were analysed offline on the Advantage Workstation (GE Healthcare, Milwaukee, USA) with dedicated software (MASS 6.1, Medis, Leiden, Netherlands) by one of 4 experienced CMR readers (A.B., G.T., C.G., G.A) blinded to all other patient data. LV and right ventricular (RV) volumes, mass and global function were calculated on SA cine images and indexed on body surface area. The presence and extent of LGE were determined on short-axis images by detecting myocardial areas with signal intensity ≥6 standard deviations above remote, non-enhanced myocardium[43, 44]. Native and post-contrast T1-mapping were analyzed by drawing a region of interest in the septum (segments 2,3,8,9,14). Native T1-mapping was available for a subset of 13 (38%) patients, while both native and post-contrast T1 were available for 9 (27%) of them. In these nine patients, myocardial extracellular volume (ECV) was calculated as (ΔR1myocardium/ΔR1blood)*(1-haematocrit), where ΔR1=(1/T1postcontrast - 1/T1precontrast)[45]. Total LV matrix and cell volumes were calculated from the product of LV myocardial volume (LV mass [LVM] divided by the specific gravity of myocardium [1.05 g/ml]) and ECV or (1-ECV), respectively[46].

Mass/volume (M/V) ratio was calculated as the ratio between LVM index (LVMi) and LV end-diastolic volume index (LVEDVi). The mass/thickness index[47] was calculated as the ratio between the LVM and the maximal end-diastolic thickness (the thickest of the two standard measurements at the anteroseptal and inferolateral basal wall).

CMR findings were compared with reference values from our CMR laboratory[47, 48]. To analyse serial CMR evaluations, we selected the first and the last examination for each patient.

Follow-up

Follow-up data were retrieved in October 2020 from EHRs, patients, cardiologists or general practitioners. All available ECG, Holter recordings and device interrogations performed after CMR examination were searched for evidence of atrioventricular blocks (AVB), intraventricular conduction disturbances (IVCD), atrial fibrillation or flutter (AF/Fl) and repetitive (Lown class 4)[49] ventricular ectopic beats (VEBs). Furthermore, all echocardiographic and CMR reports were checked for the presence of LV systolic dysfunction (LVSD). Overall, AVB, IVCD, AF/Fl, evidence of Lown class 4 VEBs at Holter monitoring and LVSD were considered as separate surrogate endpoints. When available, CMR examinations after the first one were analysed.

Statistical analysis

The R software (version 4.0.2, 2020)[50] with the packages *survival*[51, 52] and *coxphw*[53] was used. Normality was assessed through Shapiro–Wilk test. Categorical variables are reported as count (percentage). Normal continuous variables are presented as mean±sd, while non-normal continuous variables were presented as median (interquartile interval). Paired-samples Wilcoxon or t-tests were used as appropriate to compare continuous variables; chi-square tests were used for proportions. Univariate Cox regression models were fitted to the data; survival curves were compared through the likelihood ratio test. Schoenfeld residuals were tested for each model; when data significantly deviated from proportional hazards, time-dependent weights were applied as proposed by Schemper *et al.*[53, 54]. Accordingly, an

average hazard ratio (AHR) is shown instead of the hazard ratio (HR) in such cases; these are marked by *italic* type in **Tables S1-S2**. We computed 95% confidence intervals (CI) for HR and AHR. A two-tailed p-value of less than 0.05 was considered to indicate statistical significance in all tests.

Results

Baseline population characteristics

Thirty-four patients were enrolled, predominantly males (62%), with a median age of 45 (36-52) years. Neurologic and genetic features of the recruited patients are presented in **Tables S3-S4**. At neurological examination, 8 (24%) patients had minimal neurological signs, 15 (44%) distal weakness (44%), 9 (26%) mild-to-moderate proximal weakness and 2 (6%) proximal muscular involvement.

There were no cases of severe valve disease. At the time of CMR, 13 (38%) patients had an history of atrioventricular block, 30 (88%) an intraventricular conduction disturbance and 4 (12%) an atrial fibrillation or flutter. The main baseline characteristics of our cohort are reported in Table 1.

Table 1

Baseline characteristics of the cohort at the time of CMR, including clinical and electrocardiographic (rest ECG and Holter) findings, and pharmacologic provisions throughout follow-up. (a) One patient by the date of CMR had had evidence of both atrial fibrillation and flutter. ACE - angiotensin-converting enzyme; AF/Fl - atrial fibrillation/flutter; ARB - angiotensin II receptor blockers; AVB - atrioventricular block; CCB - calcium channel blockers; ECG - electrocardiogram; incRBBB - incomplete right bundle branch block; IVCD - intraventricular conduction disturbance; LAFB - left anterior fascicular block; LBBB - left bundle branch block; MCRA - mineralocorticoid receptor antagonist; nsIVCD - nonspecific intraventricular conduction disturbance; RBBB - right bundle branch block; V - verapamil (phenylalkylamine) family.

Variables	**Patients (n=34)**
Clinical findings	
Age at CMR (yr.)	45 ± 12
Gender (m/f)	21/13
BMI (kg/m^2)	26 ± 4
Smoking	7 (21%) active smokers, 8 (24%) ex-smokers
Hypertension	2 (6%)
High Cholesterol	12 (35%)
Diabetes	0 (0%)
Systolic Arterial Pressure (mmHg)	114 ± 13
Diastolic Arterial Pressure (mmHg)	69 ± 8
Mean Arterial Pressure (mmHg)	84 ± 9
Baseline electrocardiographic findings	
Atrioventricular block	13 (38%)
1st degree AVB	12 (35%)
2nd degree Mobitz I	1 (3%)
Intraventricular conduction disturbance	30 (88%)
LAFB	3 (9%)
LBBB	5 (15%)
incRBBB	1 (3%)
RBBB	5 (15%)
nsIVCD	16 (47%)
Atrial fibrillation/flutter	4 (12%)

Variables	Patients (n=34)
Atrial fibrillation[a]	4 (12%)
Atrial flutter[a]	1 (3%)
Pharmacologic therapy	
Thyroxin	5 (15%)
Calcium channel blockers (CCB)	1 (V) (3%)
β-blockers	4 (12%)
ACE-inhibitors/ARB	7 (21%)
Mineralocorticoid receptor antagonist (MCRA)	1 (3%)
Loop diuretics	1 (3%)
Mexiletine	4 (12%)

CMR findings

At CMR, 5 patients (15%) displayed LV systolic dysfunction (LVEF <50%) and 4 (12%) a depressed RV function (RVEF <50%). Baseline CMR findings are reported in Table 2. Compared with age- and sex-specific reference values (Table 3), 12 (35%) patients had a small LV end-diastolic volume index (LVEDVi) and 7 (21%) a small RV end-diastolic volume index (RVEDVi). Both left and right atrial area were frequently below the 5th percentile, following a general trend towards reduced cavity size. A low stroke volume index (SVi) was found in 13 (38%) patients. Seven patients (21%) had a reduced LV mass index (LVMi) and a similar number showed a thin (<5th percentile) inferolateral or anteroseptal wall. Noteworthy, while no patient presented with an LVMi or an ILW above reference, in 6 (18%) subjects the anteroseptal wall thickness was above the 95th percentile. Twenty-nine patients (85%) had a decreased M/V ratio (Figure 1). Other remodelling parameters were frequently altered as well: the mass/thickness ratio was higher than normal in 14 (41%) patients, while the RVEDVi/LVEDVi ratio was altered both above (24%) and below (18%) the extreme percentiles.

Nine patients (26%) presented with mid-wall LGE (mean extent 5±2% of LVM). The distribution of LGE is shown in Figure 2: the inferoseptal and inferolateral segments were more frequently involved. An exemplar case with LGE and biventricular fatty infiltration is shown in Figure 3. Fourteen patients (41%) had some areas of fatty infiltration (n=9 involving the LV, n=13 the RV).

In 13 (38%) patients with appropriate CMR sequences, native T1 in the interventricular septum could be measured: in these subjects, native T1 (1,041±53 ms) approached the upper reference limit (1,089 ms) for our CMR laboratory[48]. The extracellular volume could be measured in 9 patients (27%), and was slightly increased (33±2%, reference values <30%)[48].

Eleven (32%) patients underwent at least another CMR scan (after 1.6 [1.2 - 2.3] years from the baseline scan). Table 4 compares the first and the last examinations. Overall, LVEF increased, though none of the 3 patients with LV systolic dysfunction and serial CMR evaluations achieved a normal LVEF during follow-up. Eight out of eleven patients (73%) had an increase in LVEF. Of these eight patients, four were not on therapy; one was on loop diuretics; one on β-blockers; one on ACE-inhibitors and one on both β-blockers and ACE-inhibitors. Three of them were on thyroid hormone replacement therapy. The anteroseptal wall thickness also increased, while the inferolateral wall thickness did not vary significantly over time. The number of patients with LGE or fatty infiltrations did not change. However, patients with LGE showed a nearly significant expansion of LGE mass, both in absolute terms and relative to cardiac mass.

Table 2

Baseline CMR findings. (a) In those subjects presenting with LGE; (b) in 13 subjects with suitable acquisitions; (c) in the interventricular septum; (d) in 9 subjects with suitable acquisitions. ASW - anteroseptal wall thickness; CI - cardiac index; CO - cardiac output; HR - heart rate; ILW - inferolateral wall thickness; LAA - left atrial area; LAAi - left atrial area index; LGE - late gadolinium enhancement; LV - left ventricle; LVEDV - left ventricular end-diastolic volume; LVEDVi - left ventricular end-diastolic volume index; LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume; LVESVi - left ventricular end-systolic volume index; LVM - left ventricular mass; LVMi - left ventricular mass index; M/V - mass (LVMi) /volume (LVEDVi) ratio; RAA - right atrial area; RAAi - right atrial area index; RV - right ventricle; RVEDV - right ventricular end-diastolic volume; RVEDVi - right ventricular end-diastolic volume index; RVEF - right ventricular ejection fraction; RVESV - right ventricular end-systolic volume; RVESVi - right ventricuolar end-systolic volume index; SV - stroke volume; SVi - stroke volume index; WMA - wall motion abnormalities; WMSI - wall motion score index.

Variables	Patients (n=34)
HR (bpm)	66 ± 12
LVEDVi (ml/m^2)	73 ± 22
LVESVi (ml/m^2)	29 (19-38)
LVEF (%)	60 ± 10
RVEDVi (ml/m^2)	70 ± 18
RVESVi (ml/m^2)	29 ± 9
RVEF (%)	58 ± 7
SVi (ml/m^2)	42 ± 11
CI (l/min/m^2)	2.7 ± 0.5
LAAi (cm^2/m^2)	11 ± 3
RAAi (cm^2/m^2)	10 ± 2
WMSI	1 (1-1.04)
WMA	26%
ASW (mm)	9 ± 2
ILW (mm)	8 (7-8)

Variables	Patients (n=34)
LVMi (g/m^2)	53 ± 10
LV Mass/thickness index	11 ± 2
RVEDVi/LVEDVi	0.99 ± 0.16
M/V (g/ml)	0.72 (0.61-0.86)
Fatty infiltration (patients %)	LV: 9 (26%)
	RV: 13 (38%)
	Total: 14 (41%)
LGE (patients %)	9 (26%)
LGE mass (g)[a]	4 (3 - 5)
LGE mass (%) [a]	5 ± 2
Native T1 (ms)[b,c]	1,041 ± 53
ECV (%)[c,d]	33 ± 2
Total LV matrix volume (ml/m^2)[†]	16 ± 3
Total LV cell volume (ml/m^2)[†]	33 ± 6

Table 3
Comparison of baseline CMR findings with age- and sex-specific reference values from our laboratory[47]. For abbreviations, see Table 4.

Variables	<5th percentile	>95th percentile
LVEDVi	12 (35%)	3 (9%)
LVESVi	6 (18%)	7 (21%)
SVi	13 (38%)	1 (3%)
LVEF	7 (21%)	1 (1%)
RVEDVi	7 (21%)	2 (6%)
RVESVi	1 (3%)	1 (3%)
RVEF	6 (18%)	0 (0%)
LVMi	7 (21%)	0 (0%)
ASW	4 (12%)	6 (18%)
ILW	5 (15%)	0 (0%)
RAAi	10 (29%)	1 (3%)
LAAi	9 (26%)	2 (6%)
LV Mass/thickness index	14 (41%)	0 (0%)
RVEDVi/LVEDVi	8 (24%)	6 (18%)
M/V	29 (85%)	0 (0%)

Table 4
Serial CMR evaluations. Comparison between the first and the last CMR evaluation of n=11 patients for whom both were available. *p<0.05; (a) In patients with LGE. For abbreviations, see Table 4.

Variables	First CMR (n=11)	Last CMR (n=11)	p-value
HR (bpm)	58 ± 10	61 ± 15	0.560
LVEDVi (ml/m^2)	86 ± 22	81 ± 25	0.124
LVESVi (ml/m^2)	37 ± 13	34 ± 15	0.231
LVEF (%)	57 ± 6	60 ± 9	**0.046***
RVEDVi (ml/m^2)	78 (73-87)	74 (65 - 92)	0.068
RVESVi (ml/m^2)	36 ± 9	32 ± 11	0.086
RVEF (%)	56 ± 6	59 ± 6	0.223
SVi (ml/m^2)	48 ± 11	47 ± 12	0.173
CI (l/min/m^2)	2.6 ± 0.5	2.5 ± 0.5	0.336
LAAi (cm^2/m^2)	11 ± 2	11 ± 3	0.605
RAAi (cm^2/m^2)	10 ± 2	10 ± 3	0.495
WMSI	1 (1-1.03)	1 (1-1.06)	0.684
ASW (mm)	9 ± 2	10 ± 2	**0.042***
ILW (mm)	8 (8 - 9)	8 (7 - 8)	0.586
LVMi (g/m^2)	57 ± 9	59 ± 16	0.797
RVEDVi/LVEDVi	0.96 (0.94 - 1.04)	0.98 (0.74-1.01)	0.123
M/V (g/ml)	0.62 (0.56-0.81)	0.61 (0.56-0.82)	0.831
Fatty infiltration (patients %)	LV: 2 (18%)	LV: 2 (18%)	1.000
	RV: 3 (27%)	RV: 3 (27%)	1.000
	Total: 3 (27%)	Total: 3 (27%)	1.000
LGE (patients %)	3 (27%)	3 (27%)	1.000
LGE mass (g)[a]	3 (3 - 3)	5 (5 - 6)	0.094
LGE mass (%)[a]	3 ± 1	6 ± 3	0.118

Follow-up

After a median follow-up of 2.5 years (1.5-4.0) after baseline CMR, 2 (6%) patients died, both for infectious and respiratory complications. Five (15%) had a device implanted - 4 (12%) permanent pacemakers (PM) and 1 (3%) cardioverter/defibrillator (ICD). Three pacemakers were indicated for progression of conduction disturbances, one for bradyarrhythmias including sinoatrial pauses up to 3.5 s; the ICD was implanted because of trifascicular block and family history of sudden cardiac death. No device was used for cardiac resynchronisation therapy. Data on the other endpoints are shown in Table 5. Only one patient developed left ventricular systolic dysfunction (LVSD) during follow-up, while most patients had already developed an intraventricular conduction disturbance (IVCD) before CMR, so that we did not consider these two endpoints for further analyses.

The influence on our endpoints of some major potential confounding factors was tested; results are shown in **Table S1**. Except for an effect of age on all-cause death and of female gender on device implantation, no other significant relationship was noted.

Table 5

Follow-up data. (a) A history of neurologic symptoms could be recollected only for 31 patients; (b) considering the two patients who have developed symptoms during follow-up; (c) data are given after eliminating patients who miss specific follow-up data after CMR; (d) Holter recordings were available for 21 patients, no patient developed Lown class 5 VEBs; (e) as a percentage of the patients who had not developed the event by the time of CMR; (f) including both CMR and echocardiographic examinations (see methods); (g) five patients had a LVEF<50% at CMR, while one more patient had a previous report of LVSD at ultrasound and developed LVSD soon after CMR, although LVEF at CMR was nearly normal (54%). AF/Fl - atrial fibrillation or flutter; AVB - atrioventricular block; IVCD - intraventricular conduction disturbance; LVSD - left ventricular systolic dysfunction; PPM/ICD - permanent pacemaker or cardioverter/defibrillator implantation; VEBs - ventricular ectopic beats.

	Patients (n=34)		
Age at the end of follow-up (yr.)	48 ± 12		
Overall duration of follow-up (yr.)	2.5 (1.5-4.0)		
Neurological symptoms at follow-up[a]	30/31 (97%)		
Onset of neurological symptoms (yr.)[b]	28 (19 -32)		
Events	**Baseline**	**Follow-up[c]**	**New events after CMR[e]**
Atrioventricular block (AVB)	13/34 (38%)	18/34 (53%)	5/21 (24%)
Intraventricular Conduction Disturbance (IVCD)	30/34 (88%)	33/33(100%)	3/3 (100%)
Atrial fibrillation/flutter (AF/Fl)	4/34 (12%)	6/31 (19%)	2/27 (7%)
Lown 4 ventricular ectopic beats (VEBs)[d]	0/21 (0%)	4/21 (19%)	4/21 (19%)
Device implantation (PPM/ICD)	0/34 (0%)	5/34 (15%)	5/34 (15%)
Left ventricular systolic dysfunction (LVSD)[f]	6/34 (18%)[g]	7/25 (28%)	1/19 (5%)
Deaths	-	2/34 (6%)	2/34 (6%)

The association between CMR findings and our endpoints is presented in **Table S2**. No significant predictor was found for the occurrence of atrioventricular blocks (AVB). Lower right ventricular cavity dimensions and an increased anteroseptal wall thickness (ASW) were associated with device (PM/ICD) implantation. A lower mass/thickness ratio was associated with device implantation and the occurrence of atrial fibrillation or flutter. A higher extent of LGE was significantly correlated with the appearance of Lown class 4 VEBs. Likewise, fatty infiltration of the LV, but not of the right ventricle, was associated with need for PM/ICD implantation. A low RV ejection fraction and stroke volume index, a high M/V ratio, LGE and wall motion abnormalities were all univariate predictors of all-cause mortality.

Discussion

In the present study we investigated with CMR the myocardial remodelling and tissue changes occurring in DM1 patients. In particular, we found a reduction of cardiac volumes and mass, together with a reduction of the mass-to-volume ratio and of the mass/thickness ratio, as the most common findings, while LV or RV systolic dysfunction only in a minority of patients. Tissue characterization showed LGE in 26% and fatty infiltration in 41% of patients. During a median follow-up of 2.5 years, 2 (6%) patients died for respiratory complications, 5 (15%) patients underwent device implantation; 4 developed repetitive (Lown class 4) ventricular arrhythmias. Lower RV volumes, higher anteroseptal wall thickness and LV-fatty infiltration were associated with the need for device implantation, while LGE mass was associated with the occurrence of ventricular arrhythmias and death.

CMR studies on DM1 have been highly heterogeneous as to the prevalence and patterns of cardiac involvement[21, 22, 39, 40, 23, 31–37]. To some extent, this is also due to the rarity of the disease and the limited availability of the technique - as compared to echocardiography. Previous reports seem to confirm echocardiographic findings of left ventricular dilation[35], hypertrophy[21, 32, 35], biventricular systolic dysfunction[21–23, 31, 33, 35, 36, 38] and wall motion abnormalities[23, 35, 40]. In addition, CMR could detect a trend towards reduced ventricular volumes [21, 22] and mass[21–23]. Our study provides additional evidence of a reduction of cardiac cavities and mass in DM1 patients.

Such a trend seems to have been overlooked by echocardiography[14, 33, 41]. This is probably due to the higher accuracy of CMR[47,56,57]. Echocardiography is known to overestimate mass[58–60], when compared with CMR. However, it is also known to underestimate volumes[61], but the often poor acoustic window accompanying muscular dystrophies[8] may account for this apparent inconsistency. It has also been supposed that CMR studies may exclude more severely compromised[33,35,39] patients, thereby ignoring some cases of ventricular dilation. Provided that this is the case, then we might have depicted an early stage of the disease before more severe systolic dysfunction ensues.

Various phenomena may be held responsible for small cardiac size and mass in DM1. Above all, a reduction in stroke volume has been noted[22,23] and must be taken into account: this is likely to be the result of the decreased metabolic demands of dystrophic muscles. Indeed, an inverse correlation has been observed between LV end-diastolic volume and MIRS (Muscular Impairment Rating Scale)[23], a disease-specific scale for myotonic dystrophy where higher scores correspond to worse functional status[42].

Primary cardiac disease should be considered as well. At pathology, cardiomyocyte atrophy has been observed in DM1[24, 27, 62], so that cardiac muscle hypotrophy is another likely explanation for a decrease in mass and volume indices, which would parallel the reduced volume of skeletal muscles[63], similarly to ageing in healthy subjects[47,57].

The reduction of mass and volume appears not to be proportional, so that we measured a reduced M/V ratio in 85% of subjects. A low M/V ratio was the single most frequently altered CMR finding in our DM1

cohort, suggesting that it may be specific to the disease. This index had been previously evaluated in one CMR study on DM1 by Turkbey et al.[22], who did not find significant differences from control subjects.

The second most frequently altered geometric parameter was the mass/thickness index, which was low in about 40% of DM1 patients. This can be linked to the anteroseptal wall thickness (ASW) being above reference values in 18% of our patients, while the inferolateral wall was within or below the normal range. The anteroseptal wall is known to be thicker than the inferolateral wall in healthy subjects[47], but the interventricular septum is also a preferential location for LGE[21,23,31,34,35,37] and, seemingly, for fibrosis at pathology[27] in DM1, thus raising questions about the nature of our finding. In facts, despite a short follow-up and a limited sample size, we could demonstrate an increase of ASW over time, which hints at some progressive process.

Left ventricular dysfunction was quite prevalent (≈15%) in our cohort. This is consistent with existing literature[21-23,31,33]. Nonetheless, we observed a significant increase in left ventricular ejection fraction (LVEF) over time, which was evident in 8 out of 11 patients with serial CMR examinations, though none of the three patients with LVSD and serial CMR evaluations normalised their LV function at follow-up. Therapy doesn't seem to justify such changes, since half of the patients who appearently improved their function were not on therapy. The increased accuracy of CMR in determining volumes might partly explain the increase in LVEF, which might be influenced by the reduction in LV end-diastolic volumes. Another potentially confounding factor is the link between DM1 and mitral valve prolapse[64,65]. Further studies are needed to confirm our findings, which might prove relevant to the correct evaluation of systolic function in DM.

Our data confirm that LGE is rather common (≈26%) in DM1[21–23,31–36] and that it is mainly found in the mid-wall layer of septal and inferolateral segments[21,23,31,34–37]. We lacked statistical power to demonstrate an increase of LGE mass over time, but such a trend could be observed. Despite considerable clues exist of a link between myocardial tissue alterations assessed through magnetic resonance imaging and conduction disturbances and arrhythmias[21–23,33–35,39,40], no definitive evidence has been obtained so far. We could add another piece to the puzzle by observing that LGE mass might be linked to ventricular ectopic beats at follow-up.

Frequent fatty infiltration in DM1 was first reported by De Ambroggi et al.[32], with now outdated technology, and then investigated by Vignaux et al.[40], but only as far as the right ventricle was concerned. We could confirm that intramyocardial fat is common in both ventricles of myotonic dystrophy type 1 patients and that it may be encountered in as much as 40% of subjects. Adipose tissue is frequently found in healthy hearts and it has been associated with ageing[66], just as reduced mass and volumes have been. However, it is also a distinctive feature of a number of diseases, where it is likely to play some pathogenetic role[67,68]. The extent and patterns of infiltration which we observed seemed to go beyond what we would normally expect in an otherwise healthy patient. Fatty infiltration of the right ventricle in DM1 has been associated with the induction of ventricular arrhythmias[40], though they were mainly non-sustained. Our study further suggests that there might be a link between fatty infiltration and

arrhythmias, as adipose tissue in the left ventricle seemed to anticipate device implantation and, close to significance, the occurrence of ventricular ectopic beats.

Much of the relevance of our work lies in the inclusion of serial CMR evaluations and the assessment of the prognostic value of CMR in DM1. Indeed, except for one analysis on PR and QRS prolongation over time[22], more generally purposed longitudinal studies and serial CMR evaluations in these patients are currently lacking or have provided insufficient follow-up data[34].

As we have already mentioned, LGE mass and fatty infiltration seem to anticipate device (PM/ICD) implantation and arrhythmias. Cardiac remodeling appears to be related to electrical events as well: a low mass/thickness index and a thick anteroseptal wall seemed to predict PM/ICD implantation. A low mass/thickness index was also linked to the occurrence of atrial fibrillation or flutter. Moreover, a low RV ejection fraction and stroke volume index, a high M/V ratio, LGE and wall motion abnormalities were all univariate predictors of all-cause mortality.

Evidence exists of right cardiac involvement in DM1 both from mechanical[23] and electrical[40] standpoints. Some link with Brugada syndrome, which appears to arise from the right ventricular outflow tract[69], has also been suggested[70–72]. In our cohort, right ventricular volumes seemed to anticipate the need for PPM/ICD implantation.

Several limitations must be acknowledged. While AVB, IVCD, AF/Fl and LVSD are widely accepted predictors of adverse prognosis in DM1[9–12,14,41], the occurrence of ventricular ectopic beats with a Lown class of 4 still needs validation as a surrogate endpoint in these patients. However, it has been previously observed that spontaneous non-sustained ventricular tachycardia (Lown class 4B) predicts the occurrence of sustained episodes[9], which in turn affect prognosis[11]. The choice to group PM and ICD as a single endpoint might be regarded as controversial as well. However, it is currently uncertain whether an ICD or a PM is best suitable for SCD prevention in DM1 [13], resulting in a substantial overlap in their respective indications[73]. In our experience, ICDs are generally employed in more severely diseased patients, where often conduction disturbances and ventricular arrhythmias coexist. Although CMR is offered as part of our routine assessment in DM1 patients, many of them refuse it. Such a low compliance may well be related to the cognitive impairment observed in some of these subjects[4]. Although this is certainly a limitation, we do not suspect any substantial referral bias, as it is established practice in our institution that all DM1 patients who consent will undergo CMR. Although the retrospective observational design and enrolment by chart review are less than ideal methods, they are common devices for dealing with the rarity of DM1[9,74]. Until recently, there has not been a standardised cardiological follow-up protocol for DM1 patients[8]. On one side, this might have favoured uneven examination rates between patients. However, periodical ECG and Holter monitoring has become established routine in our Institute during the last few decades. On the other side, lack of specific recommendations about CMR interpretation in DM1 should have reduced the bias due to clinicians being aware of CMR results during follow-up.

In conclusion, patients with DM1 display several structural and functional cardiac abnormalities, with variable degrees of cardiac muscle hypotrophy, fibrosis and fatty infiltration. Such changes, as evaluated by CMR, may anticipate the worsening of electrical disturbances.

Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Andrea Barison and Marco Leali. The first draft of the manuscript was written by Marco Leali and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

Ethics Approval

This retrospective analysis conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the institutional review board (protocol number: 1437; approval date 25/05/2017).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in Figure 3.

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Figures

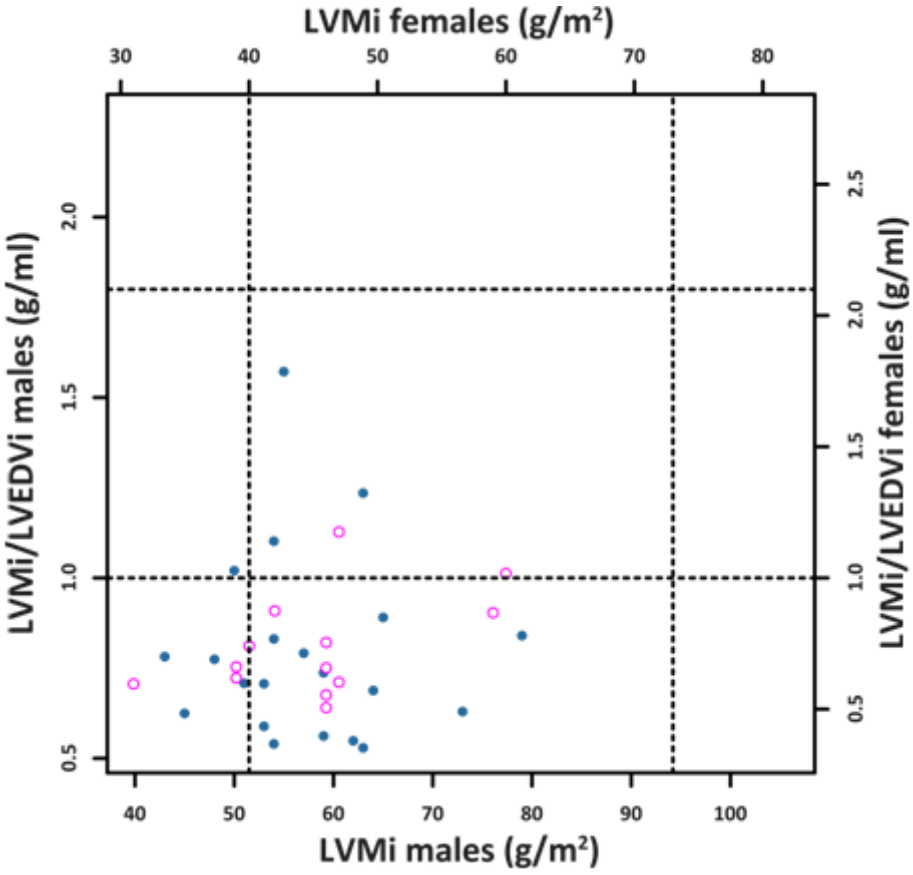

Figure 1

Ventricular remodelling in our DM1 cohort. Overall sex-specific 5th and 95th percentiles for left ventricular mass index and mass/volume ratio are shown. Close dots represent male patients, while open dots represent female patients.

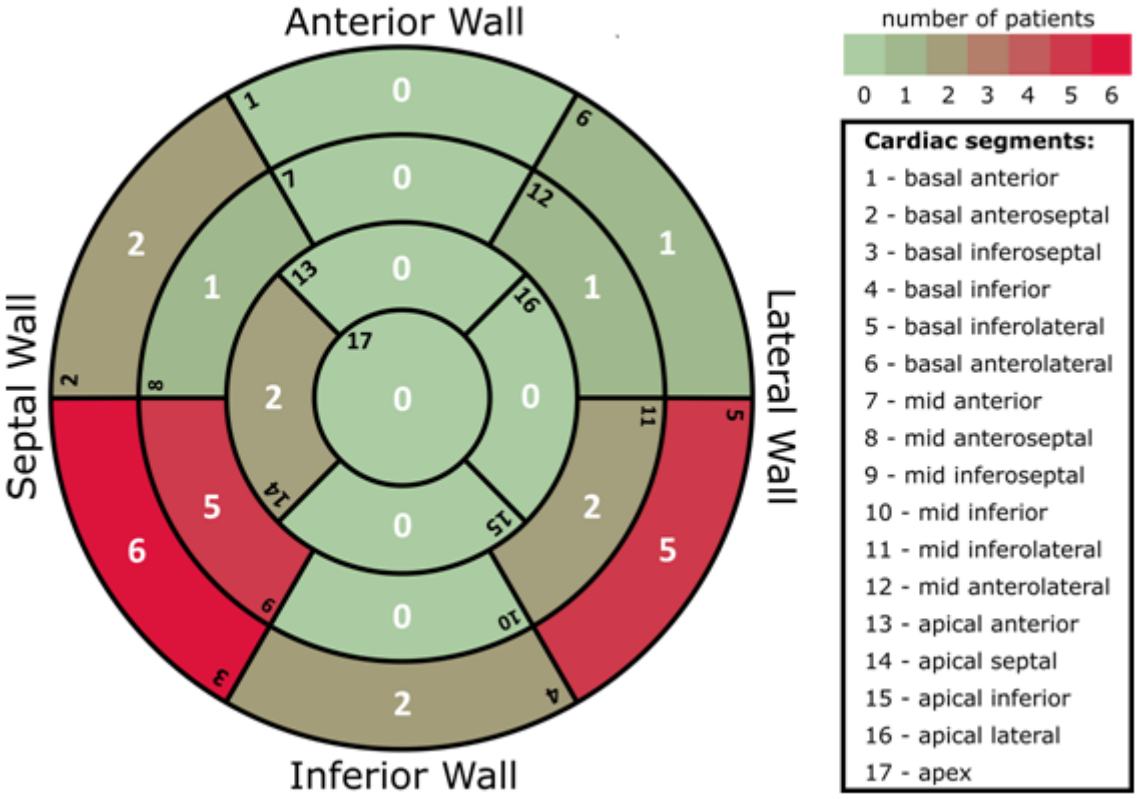

Figure 2

Distribution of late gadolinium enhancement (LGE) in a 17-segment[55] bullseye schematic of the heart. Bigger white numbers represent the number of patients with LGE, smaller black numbers correspond to cardiac segments: a legend of AHA segments has been reported to the right side of the figure.

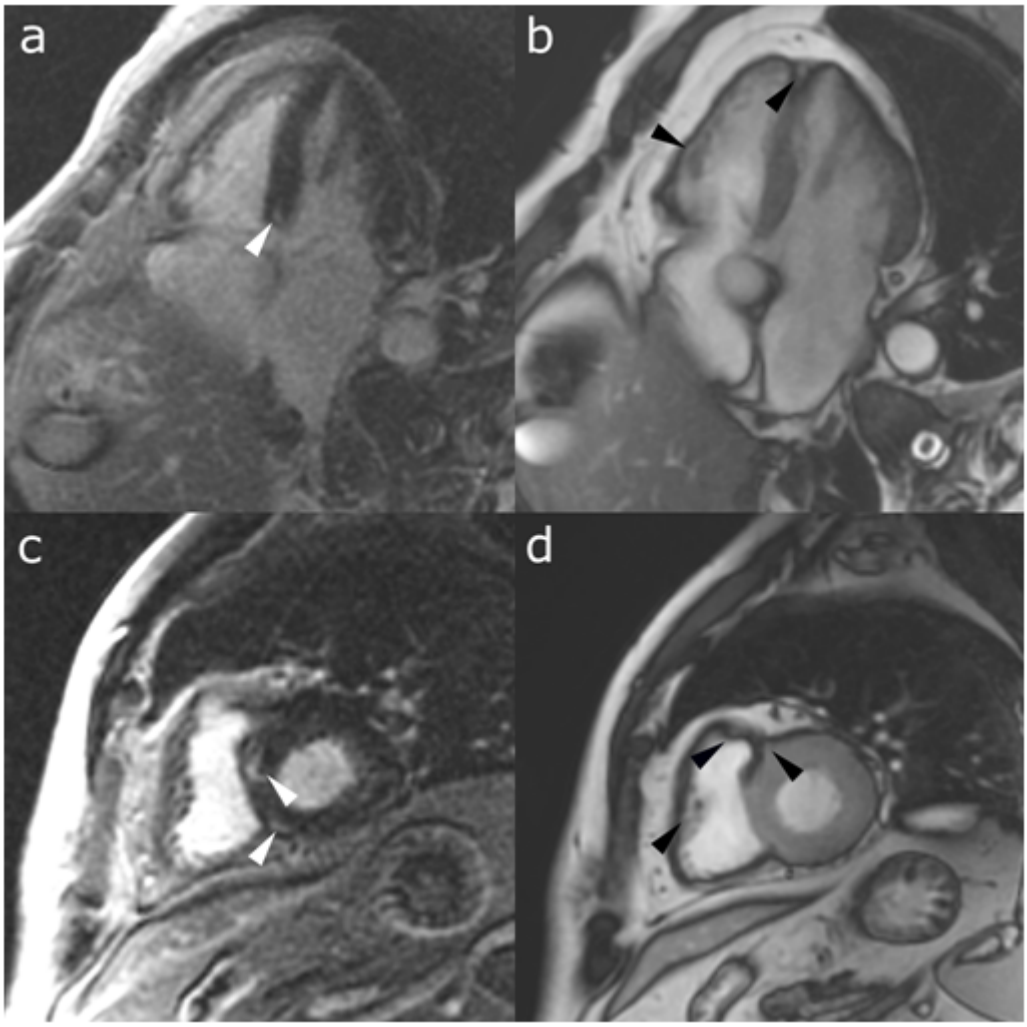

Figure 3

Example of a DM1 patient with septal LGE and biventricular fatty infiltration. (a) and (c) are late enhancement images, (b) and (d) are cine SSFP images. Above are 4-chamber views, below are short axis images. White arrowheads point at LGE areas, black arrowheads point at fatty infiltration areas.

Supplementary Files

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