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ORIGINAL RESEARCH ARTICLE

# Cardiac involvement in a cross-sectional cohort of myotonic dystrophies and other skeletal myopathies

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## Abstract

**Aims** Cardiac involvement in myopathies that primarily affect the skeletal muscle is variable and may be subtle, necessitating sensitive diagnostic approaches. Here, we describe the prevalence of cardiac abnormalities in a cohort of patients with skeletal muscle disease presenting at a tertiary care neuromuscular centre.

**Methods and results** We systematically investigated patients with skeletal myopathies and comprehensively analysed their cardiac phenotype including 24 h electrocardiogram, echocardiography with strain analyses, contrast-enhanced cardiac magnetic resonance imaging, and, if at increased risk of coronary artery disease, computed tomography coronary angiography. We prospectively screened 91 patients with diverse skeletal myopathies and enrolled 73 patients. The most pronounced cardiac involvement was present in patients with dystrophic myopathies (cardiac abnormalities in 59% of patients). We analysed myotonic dystrophies ($n$ = 29) in more detail and found prolonged QRS (99.4 ± 15.6 vs. 91.5 ± 10.3 ms; $P$ = 0.027) and QTc times (441.1 ± 28.1 vs. 413.0 ± 23.3 ms; $P < 0.001$) and increased left atrial size (27.28 ± 3.9 vs. 25.0 ± 3.2 mm/m$^2$; $P$ = 0.021) when compared with healthy controls. Left ventricular systolic function was reduced (ejection fraction < 55%) in 31% of myotonic dystrophies, while only 4% had an ejection fraction < 50%. Apical peak systolic longitudinal strain was slightly reduced ($P$ = 0.023).

**Conclusions** Screening for cardiac involvement in the skeletal muscle disease seems prudent particularly in patients with dystrophic myopathies. In the subset of myotonic dystrophy patients, QRS and QTc times as well as myocardial strain may be useful parameters. Their potential for predicting cardiac adverse events needs further evaluation.

**Keywords** Myotonic dystrophy; Skeletal muscle disease; Cardiac involvement; Conduction defect; Strain; Cardiac magnetic resonance

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## Introduction

Skeletal muscle disorders can be caused by a variety of mechanisms. Hereditary myopathies are typically the result of mutations in structural or functional myocyte proteins. Moreover, skeletal muscle can be involved in inflammatory processes or affected as a consequence of primarily neuronal disease.

Although skeletal and cardiac muscles show many similarities, being both striated and sharing a number of their functional proteins, there are numerous differences on a structural, functional, and proteomic level. In contrast to skeletal myocytes, cardiomyocytes are connected via intercalated discs, making the myocardium a functional syncytium; they show a different branch-like fibre arrangement and have a different depolarization behaviour. To account for the heart's

unique demands, many proteins occurring in the myocardium have specific cardiac isoforms that are distinctly expressed in cardiomyocytes, for example, MYH6, TNNI3, or CDH2.[1] Besides such myocardium-specific proteins, many proteins are expressed in both the skeletal muscle and myocardium, including proteins compromised in certain hereditary myopathies, such as dystrophin, sarcoglycans, or emerin.[2] Therefore, hereditary muscle diseases can affect the skeletal muscle and the heart to a variable degree.

Cardiac involvement in skeletal myopathies may range from the development of dilated cardiomyopathy and heart failure to rhythm disorders and sudden cardiac death. In some myopathies, the cardiac phenotype has been well characterized (e.g. in dystrophinopathies[3]); in others however, there is only anecdotal evidence, mostly due to the rarity of the diseases.

Further, cardiovascular disease including ischaemic heart disease, heart failure, and atrial fibrillation has a high prevalence and is the leading cause of death in the general population. Thus, it is often hard to discriminate potential cardiac involvement in myopathy from underlying cardiac co-morbidity in both the clinical and research settings, where concomitant cardiovascular disease may bias studies that aim to characterize cardiac involvement in skeletal muscle diseases. This is further complicated by the fact that in skeletal myopathies, cardiac troponin T (cTnT) is often elevated, not necessarily reflecting cardiac involvement.[4,5]

Therefore, we meticulously assessed the prevalence of cardiac involvement while accounting for underlying cardiovascular risk and co-morbidity in a cohort of diverse skeletal muscle diseases in a tertiary care neuromuscular centre.

# Methods

Patients older than 18 years presenting at a tertiary care neuromuscular centre (neuromuscular outpatient clinic of the Department of Neurology, Medical University of Graz) between June 2014 and June 2016 with an established diagnosis of a genetic or acquired neuromuscular disease were prospectively enrolled. Some patients had undergone skeletal muscle biopsy during their diagnostic workup. No myocardial biopsies were performed. Patients with history or signs of previous myocardial infarction or significant (>50% stenosis) coronary artery disease were excluded. At baseline, patients underwent a comprehensive cardiac examination including blood sampling, electrocardiogram (ECG), 24 h ECG, 24 h ambulatory blood pressure monitoring, echocardiography including strain analyses, and cardiac magnetic resonance (cMR) with late gadolinium enhancement (LGE). Patients gave written informed consent. The study conformed with the Declaration of Helsinki, was approved by the ethics committee of the Medical University in Graz, Austria (26-282 ex 13/14), and complied with all pertaining legal regulations.

## Cardiac characterization

Cardiac markers [high-sensitivity cTnT, creatine kinase, and N-terminal-pro-brain natriuretic peptide (NT-proBNP)] were determined on a Cobas automated analyser (Roche Diagnostics, Mannheim, Germany). cTnI was determined by Abbott ARCHITECT STAT Troponin-I high sensitive assay.

Patients underwent 12-lead, 24 h ECG and 24 h ambulatory blood pressure measurements.

A standard transthoracic echocardiography study was performed. Left atrial volume (LAV) was determined with the biplane method.[6] Diastolic function was assessed according to current guidelines.[7] In the presence of tricuspid regurgitation, systolic pulmonary artery pressure (sPAP) was assessed via tricuspid systolic gradient and estimated right atrial pressure. Global longitudinal systolic strain (GLS) was measured from tissue Doppler images as previously described.[8]

Patients without contraindications for magnetic resonance underwent 1.5-T ECG-gated cMR (Siemens, Erlangen, Germany) with LGE. cMR protocol was performed according to current guidelines including functional analysis and LGE.[9]

Patients with increased cardiovascular risk and no contraindications underwent cardiac computed tomography (CT) with CT coronary angiography (CTA) (Somatom 64 Multislice, Siemens, Erlangen, Germany).

## Statistical analysis

Myotonic dystrophy was the most frequent diagnosis, and these patients were additionally compared with healthy controls derived from a previous cohort[10] matched for gender and age. Left ventricular (LV) mass, end-diastolic volume (EDV), and LA size were indexed to body surface area [LV index (LVMi), EDV index (EDVi), LAV index (LAVi)]. Values are presented as mean ± SD, median [inter-quartile range (IQR)] or relative and absolute frequencies. The groups were compared using *t*-test or Mann–Whitney *U*-test as appropriate. Binary variables were compared using Fisher's exact test. A $P$-value $< 0.05$ was considered statistically significant.

# Results

## Patients

Ninety-one patients agreed to participate and underwent baseline examinations. cMR imaging was performed in 80 patients, and 36 patients underwent CTA imaging. Nine patients were excluded because an initially suspected myopathy was not confirmed or remained questionable. Nine patients were excluded because of concomitant cardiac disease not related

to skeletal myopathy, leaving a total of 73 patients for analysis (*Figure* 1).

The majority of patients ($n$ = 31) suffered from myotonic dystrophy types 1 and 2 (DM1 and DM2, respectively). Other diagnoses were less frequent and included Duchenne and Becker muscular dystrophy (DMD and BMD, respectively), facioscapulohumeral muscular dystrophy (FSHD), limb-girdle muscular dystrophy (LGMD), X-linked myopathy with postural muscular atrophy (XMPMA), non-dystrophic myotonias, inflammatory myopathies, and primarily neuronal muscle diseases. Demographics and cardiac parameters of the cohort are shown in *Table* 1.

## Evidence of cardiac involvement in the combined cohort

### *Imaging*

Cardiac involvement was most frequent in patients suffering from dystrophic myopathies, especially in XMPMA (*Figure* 2). Out of the whole cohort, LV systolic function was impaired [ejection fraction (EF) $<$ 55%] in 22% (15/68) of patients, and non-ischaemic LGE was present in 16.2% (11/67). Patients with XMPMA ($n$ = 5) and dystrophinopathies ($n$ = 4) tended to have lower EFs (56.2 ± 11.9% and 54.1 ± 8.4%). XMPMA patients also exhibited the most impaired GLS (−14 ± 4.2%). LGE was most pronounced in a patient with BMD, who had LGE in all myocardial segments. Also, four out of five XMPMA patients; two out of 20 DM2 patients; and single cases of FSHD, hereditary IBM, and a DMD mutation carrier showed LGE of a non-ischaemic pattern.

No patient had LV dilation as assessed by LV-EDVi; and only one patient with DM2, who also suffered from arterial hypertension, showed mild myocardial hypertrophy. Applying established cut-offs (>34 mL/m$^2$),[6] a relatively large proportion of 47.8% (33/69) had increased LAVi. Septal E/e', a marker for diastolic LV function, which correlates with LV filling pressures, was increased (>15) in four patients.

**Figure 1** Flow chart of patient inclusion and exclusion. MI, myocardial infarction; CAD, coronary artery disease; FSHD, facioscapulohumeral muscular dystrophy; XMPMA, X-linked myopathy with postural muscle atrophy; LGMD, limb-girdle muscular dystrophy.

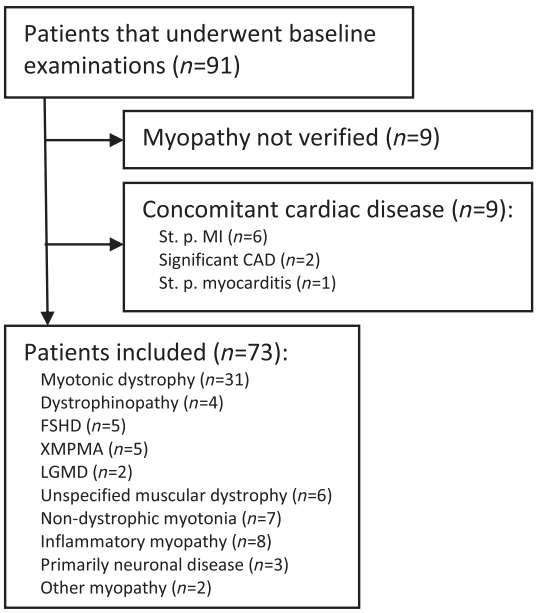
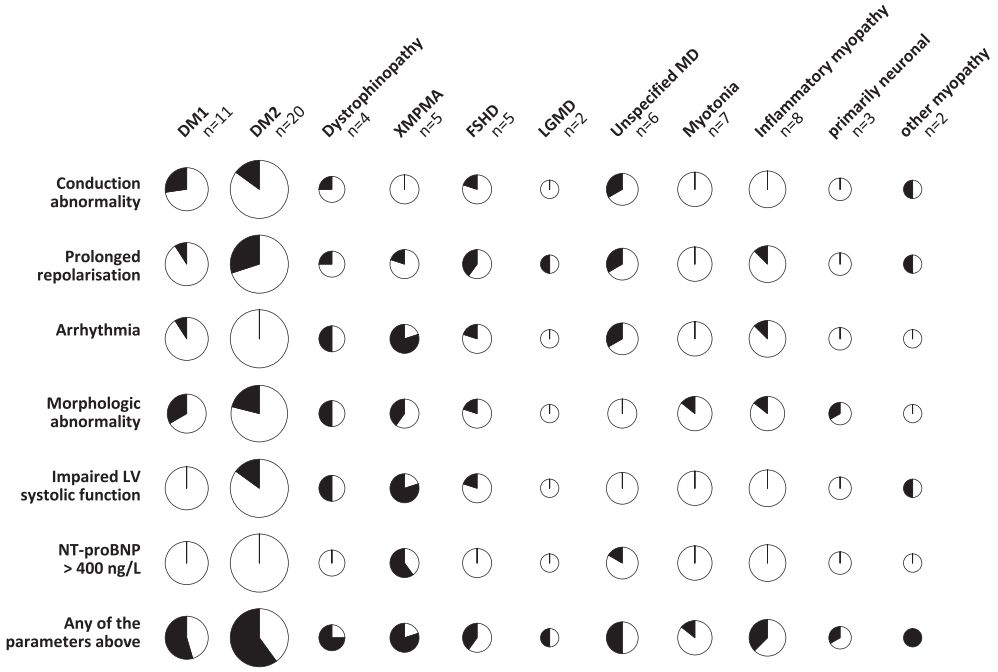



**Table 1** Patient characteristics of the study cohort ($n$ = 73)

| | |
|---|---|
| Age (years) | 46.0 ± 14.0 |
| Female sex | 49.3% (36) |
| BMI (kg/m$^2$) | 26.1 ± 5.8 |
| Hypertension (ABPM) | 52.1% (38) |
| Framingham risk (%) | 5.1 [1.0–20.6] |
| NT-proBNP (ng/L) | 59.0 [29.0–455.0] |
| NT-proBNP > 125 ng/L | 26.0% (19) |
| NT-proBNP > 400 ng/L | 5.5% (4) |
| CK (U/L) | 341.0 [177.0–3730.0] |
| CK > 170 (male) > 145 (female) U/L | 78.1% (57) |
| cTnT (ng/L) | 24.0 [11.0–247.0] |
| cTnI (ng/L) | 3.6 [2.4–22.1] |
| Myoglobin (μg/l) | 91.2 [47.9–377.2] |
| eGFR (mL/min/1.73 m$^2$) | 111.0 ± 27.5 |
| Sinus rhythm | 97.3% (71) |
| PQ time (ms) | 153.0 ± 23.0 |
| PQ > 200 ms | 2.8% (2) |
| QRS time (ms) | 96.0 ± 18.0 |
| QTc interval (ms) | 435.8 ± 32.1 |
| QTc > 450 (male) > 470 (female) ms | 21.9% (16) |
| LBBB or pacemaker | 5.5% (4) |
| Lown 0 | 15.1% (11) |
| 1 | 39.7% (29) |
| 2 | 1.4% (1) |
| 3 | 28.8% (21) |
| 4a | 8.2% (6) |
| 4b | 4.1% (3) |
| VPB ≤30/h | 93.0% (66) |
| >30/h | 7.0% (5) |
| APB ≤30/h | 94.4% (67) |
| >30/h | 5.6% (4) |
| EF (%) | 59.9 ± 6.8 |
| EF < 50% | 7.4% (5) |
| EF < 55% | 22.1% (15) |
| EDVi (mL/m$^2$) | 73.0 ± 11.4 |
| EDVi normal | 100.0% (67) |
| LVMi (g/m$^2$) | 53.5 ± 11.4 |
| LVMi > 85(male) > 81 (female) g/m$^2$ | 1.5% (1) |
| LGE | 14.9% (10) |
| E/e' > 15 | 5.5% (4) |
| LAVi > 34 mL/m$^2$ | 47.8% (33) |
| GLS (%) | −18.4 ± 2.9 |

Continuous variables presented as mean ± SD or median [IQR], categorical variables as percentage ($n$).
APB and VPB, atrial/ventricular premature beats in 24 h ECG; ABPM, ambulatory blood pressure monitoring; BMI, body mass index; CK, creatine kinase; EDVi, left ventricular end-diastolic volume index; EF, ejection fraction from cMR; GLS, global longitudinal systolic strain; HR, heart rate; LAVi, left atrial volume index; LGE, late gadolinium enhancement; LVMi, left ventricular mass index.

**Figure 2** Cardiac involvement in myopathies. Area of pie reflects patient number. For values, see *Table* S1. Conduction abnormality (AV block, LBBB, or RBBB), prolonged repolarization (increased QTc), ventricular arrhythmia (repetitive VPBs Lown 4a and 4b, or frequent VPBs > 30/h), abnormal cardiac morphology (LGE, increased EDVi, or increased LVMi), and impaired LV systolic function (EF < 55%).




Right ventricular dilation was absent in our cohort, and RV systolic dysfunction (tricuspid annular plane systolic excursion < 17 mm) was rarely present ($n$ = 3). Estimated sPAP was elevated in four patients.

### *Rhythm monitoring*

ECG analysis revealed atrial fibrillation in one patient (XMPMA). Bundle branch block morphology was present in eight patients [three left bundle branch block (LBBB; two DM1 and one BMD) and five right bundle branch block (RBBB)]. First-degree atrioventricular (AV) block was present in two patients; and a higher-degree AV block necessitated a pacemaker implant in one patient (unspecified muscular dystrophy). QTc was prolonged in 18.9% (14/74) of patients, especially in DM2 (6/20) and other dystrophic myopathies.

Patients' 24 h ECGs were classified according to Lown (Table S3)[11]: 0 (15.5%, 11/71), I (40.8%, 29/71), II (1.4%, 1/71), IIIa (29.6%, 21/71), IVa (8.5%, 6/71), and IVb (4.2%, 3/71); none was Lown V. Patients in category IV were mostly patients suffering from dystrophic myopathies. Five patients had more than a maximum of 30 ventricular premature beats (VPBs) per hour (two XMPMA, one BMD, one DM1, and one FSHD).

### *Biomarkers*

NT-proBNP was elevated >125 ng/L[12] in 26 patients (19%), but only four patients had NT-proBNP values > 400 ng/L (three XMPMA and one unspecified progressive muscular dystrophy).

As previously reported, patients had a high prevalence of raised cTnT but not cTnI.[5] XMPMA patients had significantly higher cTnT levels than had patients with other dystrophic myopathies. Within this subgroup of dystrophic myopathies, a cTnT cut-off of 128 ng/L yielded a sensitivity of 100% and specificity of 97.9% to detect XMPMA in receiver operating characteristic analysis. Similarly, cTnT aids in distinguishing between myotonic dystrophies and non-dystrophic myotonias. Within patients with any myotonia, a 14 ng/L cut-off had a sensitivity of 71.0% and specificity of 100% to detect myotonic dystrophy (*Figure* S1).

### *Symptoms*

While a large proportion of the cohort did not have heart failure symptoms, some reported dyspnoea during physical activity, corresponding to New York Heart Association (NYHA) class II in 27% and NYHA III in 3%. No patient complained of dyspnoea at rest (NYHA IV). Detailed numbers can be found in Table S2. These numbers must be interpreted cautiously, as patients are variably handicapped by skeletal muscle degeneration and weakness, limiting possible physical activity. At least one previous syncope was reported by 10%, and any palpitations were reported by 29% of patients.

**Table 2** Comparison between patients with myotonic dystrophies (DMs) and healthy controls

| | DM1 ($n$ = 11) | DM1—controls ($n$ = 11) | $P$ | DM2 ($n$ = 18) | DM2—controls ($n$ = 18) | $P$ | All DM ($n$ = 29) | All controls ($n$ = 29) | $P$ |
|---|---|---|---|---|---|---|---|---|---|
| Age | 36.8 ± 9.2 | 38.3 ± 11.8 | 0.751 | 53.2 ± 12.4 | 47.2 ± 10.1 | 0.124 | 47.0 ± 13.7 | 43.8 ± 11.5 | 0.349 |
| Female sex | 6 (54.5%) | 6 (54.5%) | — | 12 (66.7%) | 12 (66.7%) | — | 18 (62%) | 18 (62%) | — |
| Body mass index (kg/m$^2$) | 24.8 ± 3.8 | 25.5 ± 3.1 | 0.616 | 26.5 ± 7.3 | 25.2 ± 4.4 | 0.540 | 25.8 ± 6.1 | 25.3 ± 3.9 | 0.721 |
| NT-proBNP (ng/L) | 59 [19–98] | 53 [42–82] | 0.847 | 110 [50–170] | 43 [36–93] | **0.008** | 74 [44–155] | 49 [36–88] | 0.068 |
| LVMi (g/m$^2$) | 47.1 ± 12.3 | 49.4 ± 8.9 | 0.656 | 55.2 ± 11.4 | 45.2 ± 9.3 | **0.013** | 52.9 ± 12.1 | 46.8 ± 9.2 | 0.79 |
| EDVi (mL/m$^2$) | 72.0 ± 12.1 | 77.0 ± 10.2 | 0.359 | 75.5 ± 16.6 | 74.3 ± 10.2 | 0.823 | 74.3 ± 15.0 | 75.4 ± 10.1 | 0.764 |
| EF (%) | 55.7 ± 6.6 | 61.5 ± 3.3 | **0.031** | 59.3 ± 5.3 | 59.0 ± 4.2 | 0.864 | 58.1 ± 5.9 | 60.0 ± 4.0 | 0.193 |
| EF < 50% | 1 (11.1%) | 0 (0%) | 1.000 | 0 (0%) | 0 (0%) | — | 1 (3.8%) | 0 (0%) | 1.000 |
| EF < 55% | 4 (44.4%) | 0 (0%) | 0.082 | 4 (23.5%) | 2 (14.3%) | 0.664 | 8 (30.8%) | 2 (8.7%) | 0.080 |
| GLS (%) | −19.1 ± 2.3 | −19.2 ± 2.8 | 0.988 | −19.3 ± 1.9 | −21.0 ± 2.3 | **0.021** | −19.23 ± 2.00 | −20.24 ± 2.63 | 0.116 |
| E/e′ | 9.9 ± 1.5 | 9.3 ± 3.6 | 0.625 | 10.7 ± 3.3 | 9.0 ± 3.0 | 0.118 | 10.41 ± 2.77 | 9.14 ± 3.17 | 0.109 |
| LA diameter (mm) | 47.1 ± 6.7 | 45.5 ± 5.5 | 0.564 | 51.0 ± 6.7 | 46.7 ± 5.5 | **0.042** | 49.5 ± 6.9 | 46.2 ± 5.4 | 0.050 |
| LA diameter index (mm/m$^2$) | 25.5 ± 2.4 | 24.4 ± 3.5 | 0.396 | 28.3 ± 4.3 | 25.4 ± 3.0 | **0.025** | 27.28 ± 3.9 | 25.0 ± 3.2 | **0.021** |
| PQ time (ms) | 168.2 ± 26.2 | 145.2 ± 19.0 | **0.029** | 158.4 ± 23.9 | 154.2 ± 19.0 | 0.562 | 162.1 ± 24.8 | 150.8 ± 19.2 | 0.056 |
| QRS time (ms) | 107.3 ± 16.7 | 91.3 ± 8.0 | **0.010** | 94.6 ± 13.1 | 91.6 ± 11.7 | 0.473 | 99.4 ± 15.6 | 91.5 ± 10.3 | **0.027** |
| QTc interval (ms) | 434.8 ± 26.8 | 408.7 ± 28.7 | **0.039** | 444.9 ± 29.0 | 415.6 ± 19.7 | **0.001** | 441.1 ± 28.1 | 413.0 ± 23.3 | **<0.001** |
| QTc prolonged | 1 (9.1%) | 0 (0%) | 1.000 | 5 (27.8%) | 0 (0%) | **0.045** | 6 (20.7%) | 0 (0%) | **0.023** |
| VPB (24 h) | 4 [0.5–10.0] | 7 [0–24.5] | 0.606 | 3 [1–7] | 1.5 [0–10.5] | 0.245 | 3.5 [1–8.0] | 4 [0–13.5] | 0.586 |
| APB (24 h) | 2 [1–3.5] | 5 [2–12.5] | 0.056 | 13 [4–31] | 8 [4–18.5] | 0.423 | 4 [1–22.5] | 7 [2.5–15.5] | 0.521 |

*P*-values from Student's *t*-test, Mann–Whitney *U*-test, or Fisher's exact test as appropriate. *P*-values < 0.05 in bold. For abbreviations, see *Table* 1.


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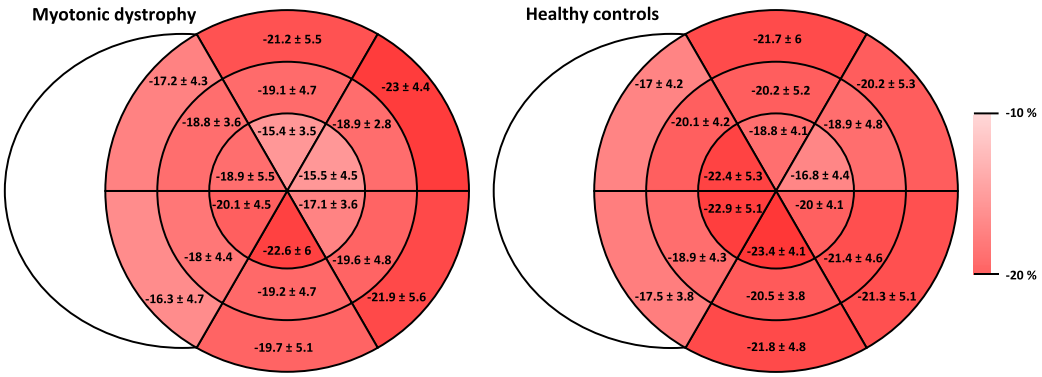
**Figure 3** Bullseye plots for longitudinal strain in myotonic dystrophy and controls. Peak systolic longitudinal strain from echocardiography (mean ± SD) of patients with myotonic dystrophy (left, *n* = 28) and healthy controls (right, *n* = 27). The table shows differences in strain on a basal, mid, and apical level (*P*-value from *t*-test). Global longitudinal systolic strain (GLS) was −19.2 ± 2.0 in myotonic dystrophy and −20.2 ± 2.6 in controls (*P* = 0.116).




| Peak systolic longitudinal strain (%) | Myotonic dystrophy | Healthy controls | p |
|---|---|---|---|
| Basal | -19.96 ± 2.37 | -19.01 ± 3.23 | 0.941 |
| Mid | -18.88 ± 2.48 | -19.42 ± 3.38 | 0.498 |
| Apical | -18.44 ± 3.49 | -20.65 ± 3.51 | 0.023 |

### Cardiac involvement in myotonic dystrophies

The majority of our patients suffered from DM1 and DM2, which allowed a more in-depth analysis and an additional comparison with an age and sex matched cohort of healthy volunteers. Only patients with proven myotonic dystrophies (*n* = 29, 11 DM1 and 18 DM2) were included (*Table* 2); one patient with additional spinobulbar muscular atrophy and one without genetic proof were excluded from this analysis.

Patients had significantly higher LA diameter indices (27.28 ± 3.9 vs. 25.0 ± 3.2 mm/m$^2$; *P* = 0.021), QRS times (99.4 ± 15.6 vs. 91.5 ± 10.3 ms; *P* = 0.027), and QTc intervals (441.1 ± 28.1 vs. 413.0 ± 23.3 ms; *P* < 0.001) than controls. LGE was present in two DM2 patients. While one patient with DM1 had reduced EF (EF = 46%), overall, DM patients did not significantly differ in systolic function as assessed by EF and GLS when compared with controls. However, a detailed analysis of regional myocardial strain revealed slightly decreased peak systolic longitudinal strain in patients with myotonic dystrophies at apical myocardial regions (−18.44 ± 3.49 vs. −20.65 ± 3.51%; *P* = 0.023; *Figure* 3).

In subgroup analyses (*Table* 2), DM1 patients (*n* = 11) had significantly lower EF and longer PQ intervals, QRS times, and QTc intervals than their matched controls. DM2 patients (*n* = 18) had significantly higher LV mass and LA diameter indices and longer QTc intervals. These changes were accompanied by higher NT-proBNP levels, slightly reduced GLS, and a non-significant trend towards increased E/e' ratios on tissue Doppler imaging in DM2 patients.

## Discussion

Clinicians face the intricate issue of potential myocardial involvement in patients with skeletal muscle disease. Different myopathies feature different cardiac abnormalities with varying frequencies, ranging from a normal cardiac phenotype, subtle functional impairment, or rhythm disorders to increased incidence of sudden cardiac death or pronounced cardiomyopathy and heart failure.[13] Even within one entity, the cardiac phenotype can be highly variable. Common limitations of studies characterizing cardiac involvement in these patients are a small sample size owing to the rarity of skeletal muscle diseases and a lack of accounting for underlying cardiovascular disease that has a high prevalence in the general population. Thus, we carefully and prospectively assessed a cohort of patients with different myopathies reflecting the disease spectrum of a tertiary neuromuscular care centre using state-of-the-art imaging modalities, laboratory examinations, and comprehensive rhythm and blood pressure monitoring. Our protocol thereby allowed the exclusion of patients with underlying cardiovascular disease and hence assessed the prevalence of genuine cardiac involvement.

### Myotonic dystrophies

DM is a multisystem disorder involving not only the skeletal muscle but also endocrine, central nervous, ophthalmic, and other systems. Cardiac involvement is variable and mainly characterized by conduction defects and arrhythmias,[13]

where the biggest concern is an increased risk of sudden cardiac death,[14–16] which has been linked to severe ECG abnormalities.[17] Although ECG findings were unremarkable in many patients using established cut-offs, depolarization (QRS time and BBB) and repolarization (QTc interval) were significantly longer than in healthy controls. Importantly, prolonged QTc has been shown to be associated with poorer prognosis in the general population.[18,19]. Previous studies also reported on longer PQ invervals,[20] which was not as pronounced in our patients, although DM1 patients had longer PQ intervals than controls and one DM2 patient had AV block I.

LAVs were larger in DM patients than in controls, especially in DM2 patients. In these patients, LV mass was also increased. The blood biomarker NT-proBNP, which reflects diastolic wall stress and filling pressures, was also higher in these patients supporting our imaging findings. Of all DM patients, only one (4%) had a reduced EF below 50%. Using the same cut-off, previous studies found a slightly higher prevalence of impaired systolic LV function between 9% and 19%.[21,22] However, when we tested an EF cut-off of 55%, 31% were below, which is a larger proportion than the previously reported 12% to 18%.[23,24] These deviating numbers between studies are likely a result of differences in patient selection and methodology (echocardiography vs. magnetic resonance imaging). Nevertheless, in direct comparison with a matched healthy cohort, only DM1 patients had significantly reduced LV function if assessed by LV EF. We also used strain imaging of myocardial deformation to assess LV systolic function. In contrast to LV EF, which is the mere ratio of LV systolic over diastolic volumes and thus a surrogate for LV contractility, strain imaging assesses myocardial mechanics more directly and allows an objective analysis of regional wall motion patterns.[25] GLS was similar to or slightly higher than in previous reports using different methodology.[26,27] Particularly in apical wall regions of the LV, we detected slightly decreased myocardial strain in DM patients, which did not significantly affect global longitudinal systolic strain (GLS) or LV EF, similar to previous findings.[28]

Non-ischaemic LGE is a cMR marker of regional interstitial fibrosis. In our DM cohort, only two patients (6.5%) had non-ischaemic LGE, which is lower than in previous studies that reported a prevalence of myocardial fibrosis in myotonic dystrophy between 14% and 40%.[24,27]

Interestingly, cTnT was often elevated in patients with myotonic dystrophies, in contrast to patients with non-dystrophic myotonias. This marker could thus support a clinical suspicion in patients with typical findings of myotonia before genetic workup. However, one should keep in mind that cTnT elevation does not always reflect cardiac involvement and elevated cTnT levels may be related to skeletal muscle sources.[5] The seven patients with non-dystrophic myotonias, apart from one patient with borderline EF, all had normal cardiac examinations.

## Other myopathies

Patients with certain dystrophic myopathies had most pronounced cardiac involvement, namely, XMPMA and dystrophinopathies. XMPMA is known to be associated with spongiform cardiomyopathy featuring hypertrophy in an apical distribution, myocardial fibrosis, and reduced systolic function.[10] Of the five patients included, three had LGE, EF was reduced in two, GLS was reduced in four, and one had atrial fibrillation. Two patients were in Lown category IV.

Patients with dystrophinopathies develop a well-studied dilated cardiomyopathy in the course of their disease.[3] Of the patients with proven DMD or BMD in our cohort, one patient with BMD had the most pronounced cardiac involvement. He had LGE in all myocardial segments, reduced EF, LBBB, and a maximum of 42 VPB/h and several couplets and triplets in 24 h ECG recordings.

Cardiac involvement in other dystrophic myopathies is less studied owing to the rarity of diseases. In our four patients with FSHD, one had RBBB, a common finding in FSHD,[29] and prolonged QTc interval; two had suspected sinoatrial block II. Two young patients with LGMD 2A did not show any cardiac abnormalities.

Several patients suffered from a progressive muscular dystrophy, where a specific diagnosis had not been possible. Also in these patients, some had cardiac abnormalities, such as AV blocks IIa and III, RBBB, repetitive VPBs, or raised NT-proBNP.

Our cohort also comprised eight patients with inflammatory muscle diseases. In this group, one 67-year-old patient with sporadic IBM had one episode of supraventricular tachycardia in her 24 h ECG, one patient had prolonged QTc, and another had mildly reduced EF; otherwise, no cardiac abnormalities were found.

Three patients had a primarily neuronal disease with consecutive muscle wasting. As expected, they showed no evidence of cardiac disease.

## Therapeutic options

As reliable data on therapeutic options to improve cardiovascular outcome in skeletal muscle diseases are currently lacking, management recommendations may only be deduced from studies and guidelines on cardiomyopathies[30,31] and heart failure[12] with the caveat that hard evidence in these patient subsets is limited. A proportion of patients will not have signs of cardiac involvement. In those, follow-up intervals shall be scheduled at the discretion of the treating physician. Signs of subclinical disease (e.g. reduction of myocardial strain and ECG abnormalities) should inform on surveillance intervals and potential further diagnostic workup (e.g. rhythm monitoring). If significant QTc prolongation is present, drugs that further prolong QTc intervals should be avoided or used with caution. For patients suffering from heart failure, we suggest

following the respective management guidelines.[12] Although rare in our cohort, hypertrophic or dilated cardiomyopathies are seen in certain skeletal muscle diseases.[30] More data on potential therapies are available specifically for cardiomyopathy found in dystrophinopathies (please see e.g. Kamdar and Garry[3]). Careful assessment of the risk for sudden cardiac death may reveal patients that will benefit from implantation of an implantable cardioverter defibrillator.[32]

### Limitations and strengths

Small patient numbers due to the rarity of skeletal myopathies are a limitation of this study (and other studies investigating rare diseases) and necessitated pooled presentation of myopathy clusters. While our report on infrequent myopathies can only be descriptive, our cohort comprised enough patients with myotonic dystrophies to allow statistical analyses in comparison with a matched healthy control cohort. Further studies are needed to confirm our findings in different cohorts.

The prospective enrolment, modern diagnostic testing by both neurologists and cardiologists, a matched control cohort for DM patients, and sensitive and extensive diagnostic modalities with ability to exclude patients with ischaemic cardiac disease are strengths of this study.

## Conclusions

The prevalence of genuine cardiac involvement varies substantially between different myopathies. In addition, its severity is highly variable within disease entities. Cardiac abnormalities are prevalent especially in patients with dystrophic myopathies, whereas in non-dystrophic myotonia or inflammatory muscle disease, cardiac involvement is rare. In patients with myotonic dystrophies, apical myocardial strain is slightly reduced and QRS and QTc times are increased.

Our findings emphasize the necessity of cardiologic screening examinations especially in patients with dystrophic myopathies. In myotonic dystrophies, ECG parameters, such as QRS and QTc times, deserve special attention; further studies are needed to evaluate their prognostic significance and assess the value of myocardial strain imaging in these patients.

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## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Cardiac involvement in myopathy.
**Table S2.** Reported symptoms.
**Table S3.** Lown Classification.
**Figure S1.** High-sensitivity cardiac Troponin T (cTnT) concentrations in patients with myotonic dystrophies and non-dystrophic myotonias (A) and patients with XMPMA and other dystrophic myopathies (B).
**Table S4.** List of diagnoses for individual patients.

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