Cardiac disease in mucopolysaccharidosis type III

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Abstract
Mucopolysaccharidosis type III (MPS III; Sanfilippo disease) is primarily characterized by neurocognitive decline with limited somatic disease. Only few reports addressed cardiac disease (CD) in MPS III. We investigated the prevalence of CD in a relatively large cohort of patients. In this cross-sectional study, extensive echocardiographic studies were performed in 30 MPS III patients (16 patients <18 years), all without clinical symptoms of CD. Results were compared to data from matched controls. The mean global longitudinal strain on speckle-tracking echocardiography (STE) was impaired in both pediatric and adult patients vs controls (resp. −18.4% vs −20.7%; mean difference 2.25, 95% CI 0.61-3.89, P = 0.009 and −16.9% vs −19.5%; mean difference 2.64, 95% CI 0.78-4.49, P = 0.007), indicating early systolic dysfunction. Left ventricle ejection fraction (LVEF) was normal in pediatric patients and (slightly) impaired in adult patients vs controls (48.7% vs 55.8%, P = 0.002). Tissue Doppler imaging (TDI) showed significantly slower early diastolic velocities (e') compared to controls indicative for diastolic dysfunction. Furthermore, mitral and aortic valve abnormalities were prevalent (43% and 33% of patients, respectively). Finally, 15.6% of the patients had a first-degree atrioventricular block on electrocardiography (ECG). The impaired STE reveals early, subclinical LV dysfunction which is supported by results of TDI. In addition, mild valvular disease and ECG abnormalities are prevalent. The lowered LVEF in adult patients suggests that the LV dysfunction is progressive, and may ultimately lead to clinical myocardial disease when patients live longer due to an effective disease-modifying treatment of which a number of options are now in clinical trials.

KEYWORDS
cardiac disease, longitudinal strain, MPS III, speckle-tracking echocardiography

1 INTRODUCTION

Mucopolysaccharidosis type III (MPS III or Sanfilippo disease) is a rare autosomal recessive lysosomal storage disorder caused by an enzyme deficiency leading to accumulation of the glycosaminoglycan (GAG) heparan sulfate (HS). Four subtypes (A-D) are recognized, depending on the different enzyme deficiencies.1 MPS III is characterized by progressive neurocognitive decline. Accumulation of HS in the central nervous system (CNS) triggers a complex pathophysiological cascade,2 resulting in a characteristic brain disease. MPS III presents around 2 to 4 years of age with a developmental delay followed by disease progression with further deterioration of cognition and loss of previously achieved milestones.3
Typically, somatic disease is limited. Two distinct phenotypes are recognized, a rapidly progressing (RP) phenotype and a slowly progressing (SP) phenotype. Both have the same disease course but the latter evolves more slowly. Patients with a RP phenotype generally die in their second or third decade of life.

MPS III belongs to the group of mucopolysaccharidoses (MPSs), comprising a total of seven different genetic disorders all characterized by accumulation of different types of GAGs. Cardiac disease (CD) is highly prevalent (60%-100% of patients) in several of the MPSs, including MPS type I (Hurler syndrome or the more attenuated Scheie syndrome), II (Hunter syndrome), and VI (Maroteaux-Lamy syndrome). In MPS types I and II, the GAGs dermatan sulfate (DS) and heparan sulfate (HS) accumulate while in MPS VI only DS accumulates. DS is an important component of the GAGs in healthy human heart valves, which may explain the high prevalence of valvular heart disease in these MPSs. CD in MPSs presents predominantly with valvulopathy, mainly involving the mitral and aortic valves. However, cardiomyopathy, arrhythmias, coronary artery disease, aortic root dilatation and conduction abnormalities have all been reported.

While CD was previously not considered to be present in MPS III, several recent studies reported cardiac involvement. In addition, CD may also be related to sudden unexpected death reported in some patients.

As a number of disease-modifying treatment options for MPS III are currently being investigated, probably leading to an increase in life expectancy with preservation of cognitive function in the near future, extensive knowledge on the prevalence and nature of CD in MPS III is important. We aimed to investigate the presence of CD in MPS III patients and performed echocardiography and electrocardiography cross-sectional studies in a relatively large cohort of MPS III patients.

2 | METHODS

2.1 | Patients

This study describes a single-center cross-sectional study enrolling all patients with MPS III, confirmed in all by enzymatic testing, seen at the Dutch reference center for MPS III (Amsterdam UMC, location AMC, the Netherlands) from January 2016 to April 2017. Cardiac screening involved a medical history, physical examination, echocardiography and electrocardiography. The results were compared to previously collected data from healthy controls at our center. Healthy controls were evaluated for a positive family history of structural cardiac abnormalities, a cardiac murmur or because of miscellaneous complaints. All subjects in this control cohort showed no abnormalities at cardiac evaluation. A convenience sample of controls was selected. Patients and healthy controls were matched according to age, gender and body surface area (BSA). BSA was calculated according to the formula of Dubois. Ethical approval was sought from the medical ethical committee of the Amsterdam UMC and waived as cardiac screening is standard of care.

The study was conducted in compliance with ethical standards. No informed consent was obtained as patients were screened as standard of care. This article does not contain any studies with animal subjects performed by any of the authors.

2.2 | Echocardiographic measurements

All patients were studied using the Vivid 9 ultrasound system (GE Medical Systems, Chicago, Illinois) using a standardized protocol which includes two-dimensional (2D) gray scale images (2D-Mode), M-mode echocardiography, tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE). Off-line analyses were done using the EchoPac workstation (GE Medical Systems). Echocardiography and all analyses were done by one pediatric cardiologist (IMK). The average of three measurements was automatically calculated. Assessments were performed in accordance with the guidelines of the American Society of Echocardiography (ASE).

2.3 | 2D-mode

To assess the aortic root diameter, the following parameters were assessed in 2D mode: aortic valve annulus (AVA), sinuses of Valsalva (SoV), and sinotubular junction (STJ). Aortic root dilatation (ARD) at the SoV was defined as an aortic root diameter $z$-score >2 according to reference values for children or above the 95% confidence interval of normal for adults.

To investigate LV dysfunction, the ejection fraction (LVEF) was assessed according to the Simpson method. An abnormal EF in adults was defined as <52% for men and <54% for women. For children an EF <50% was considered abnormal.

The ostium of the coronary arteries was subjectively assessed for epicardial luminal narrowing.

2.3.1 | M-mode and Doppler flow

M-mode echocardiography was performed from parasternal long axis views to assess (a) fractional shortening (FS) as measure for left ventricular (LV) systolic function and (b) LV dimensions to assess left ventricular hypertrophy.
(LVH) which included: interventricular septum thickness at end-diastole and end-systole (IVSd; IVSs), left ventricular internal diameter at end-diastole and end-systole (LVIDd; LVIDs), and left ventricular posterior wall thickness at end-diastole and end-systole (LVPWd; LVPWs).

LVH was defined as a LV mass index (LVMI) (g/m2.7) >95th percentile according to normal values for age and gender.17,21 For assessment of LVH in the pediatric population, LVM was corrected by raising height to an exponential power of 2.7 according to the Devereux formula.22

Valve abnormalities were graded using the guidelines and standards of the ASE.19

2.3.2 | Speckle-tracking echocardiography

To investigate LV dysfunction, myocardial longitudinal strain (LS) by STE was assessed on 2D gray scale images which were acquired in parasternal apical four-chamber view at frame rates between 48 and 77 frames per second.23 STE measures myocardial deformation, and represents shortening. Therefore, LS is a negative value. LS is a marker for early LV dysfunction, even when the EF is not yet impaired.24–27 Longitudinal LV strain measurements were performed based on previous reported protocols to measure end-systolic strain.28 Manual off-line tracing of the endocardial LV border was done during end-systole for the following six segments: apical septum, mid septum, basal septum and apical lateral, mid lateral, basal lateral. Segments were automatically approved or rejected by the program and subsequently needed manual approval. Tracking could be manually corrected when needed. The average strain in each from the six segments equals the mean global longitudinal strain (GLS). In addition, a mean base-to-apex gradient was calculated (average difference between the apical and basal segments). The echocardiographic data were compared to a healthy control group. Intra-observer reproducibility for the offline strain measurements by the same pediatric cardiologist (IMK) has previously proven to be good.28 Other articles also reveal a good reproducibility for the longitudinal LV strain measurements.29

2.3.3 | Electrocardiography

The ECG’s were evaluated by one pediatric cardiologist (IMK). Reference values for pediatric patients were used in the evaluation of the ECG’s.30

2.3.4 | Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 23.0 for windows (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. First, descriptive statistics were used to describe the socio-demographic characteristics of patients and controls. Baseline differences (age, gender, and BSA) between patients and controls were analyzed with Independent-samples *t* tests for continuous data and χ² tests/Fisher’s exact tests for categorical data. Second, to assess differences between MPS III patients and controls, Independent-sample *t* test analyses for continuous data and χ² test analyses for categorical data were used. Post-hoc analyses were performed to assess correlations between the parameters age and phenotype and cardiac findings on echocardiography. Correlations with age were assessed using Pearson’s *r* analyses (parametric). Phenotype (RP/SP) were assessed with Spearman rho’s analyses (nonparametric). A *P* value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients

Thirty-six patients were eligible for inclusion in this study. Three patients could not attend the clinic at our center because the clinical condition prohibited travelling. Of the

| TABLE 1 | Socio-demographic characteristics |
|---------------------|---------------------|---------------------|---------------------|
| MPS III patients | Controls | MPS III patients | Controls |
| *n* = 30 | % | *n* = 30 | % | *P* |
| Age in years; mean (SD) | 15.74 (8.24) | 15.31 (7.81) | 0.839 |
| Male gender | 16 | 53.3 | 11 | 36.7 | 0.194 |
| Adults (>18 years) | 14 | 46.7 | 14 | 46.7 | |
| BSA | 1.72 (0.20) | 1.86 (0.22) | 0.086 |
| Age in years; Mean (SD) | 23.10 (4.70) | 22.33 (4.28) | 0.656 |
| Children | 16 | 53.3 | 16 | 53.3 | |
| BSA | 1.11 (0.29) | 1.15 (0.30) | 0.688 |
| Age in years; mean (SD) | 9.29 (4.16) | 9.17 (3.97) | 0.933 |

*a*Body surface area.
remaining 33 MPS III patients, echocardiographic data could successfully be obtained in 30 patients as in three patients the clinical condition (hyperactivity, restlessness, and aggression) prohibited investigations. The remaining 30 patients were included in this study. Not all echocardiographic data could be obtained due to restlessness of some patients. Sixteen patients were male (53.3%), 17 patients had MPS III type A (56.7%), 6 type III B (20%), and 7 type IIIC (23.2%). Sixteen patients (53.3%) were <18 years of age. The mean age was

TABLE 2  
Echocardiographic outcomes in MPS III patients compared to controls

|                         | MPS III patients | Controls |          |          |
|-------------------------|------------------|----------|----------|----------|
| n                       | Mean (SD)        | n        | Mean (SD) | P        |
| 2D-mode                 |                  |          |          |          |
| HR (bpm)                | 30               | 83 (30.70) | 27       | 76 (13.58) | 0.253   |
| Aortic valve annulus (mm)| 24              | 19.40 (4.46) | 26       | 18.00 (3.25) | 0.220   |
| Aortic SoV (mm)         | 25               | 24.64 (5.58) | 27       | 23.38 (6.28) | 0.450   |
| Aortic STJ (mm)         | 22               | 20.98 (4.75) | 23       | 21.27 (5.19) | 0.847   |
| LV EF (%)               | 26               | 51.17 (4.38) | 22       | 55.56 (5.67) | 0.004   |
| M-mode and Doppler flow |                  |          |          |          |
| FS (%)                  | 28               | 40.68 (5.51) | 28       | 37.94 (4.68) | 0.05    |
| IVSd (mm)               | 27               | 6.70 (1.65) | 28       | 6.18 (1.70) | 0.245   |
| IVSSs (mm)              | 27               | 10.24 (1.93) | 27       | 8.22 (1.76) | <0.001  |
| LVIDd (mm)              | 28               | 42.58 (8.19) | 28       | 44.78 (4.94) | 0.229   |
| LVIDs (mm)              | 27               | 25.72 (5.02) | 28       | 27.90 (3.57) | 0.069   |
| LVPWd (mm)              | 28               | 6.73 (1.31) | 28       | 6.39 (1.71) | 0.399   |
| LVPWs (mm)              | 27               | 12.76 (2.94) | 27       | 11.61 (2.75) | 0.146   |
| LVMI                    | 28               | 48.12 (30.84) | 28       | 40.67 (19.44) | 0.284   |
| Tissue Doppler imaging |                  |          |          |          |
| IVS s’ (cm/s)           | 29               | 6.44 (1.31) | 29       | 8.29 (1.64) | <0.001  |
| IVS e’ (cm/s)           | 29               | 9.84 (2.03) | 29       | 13.96 (2.17) | <0.001  |
| IVS a’ (cm/s)           | 29               | 5.58 (1.75) | 29       | 6.04 (1.27) | 0.257   |
| LW LV s’ (cm/s)         | 29               | 7.16 (1.90) | 29       | 7.32 (2.21) | 0.766   |
| LW LV e’ (cm/s)         | 29               | 12.57 (3.34) | 29       | 17.07 (2.74) | <0.001  |
| LW LV a’ (cm/s)         | 29               | 6.16 (2.62) | 29       | 6.08 (1.29) | 0.882   |
| LW RV s’ (cm/s)         | 29               | 11.56 (2.11) | 23       | 13.12 (2.33) | 0.015   |
| LW RV e’ (cm/s)         | 29               | 13.72 (2.30) | 23       | 15.10 (2.51) | 0.044   |
| LW RV a’ (cm/s)         | 29               | 9.32 (2.98) | 23       | 9.25 (2.36) | 0.933   |
| MV E (m/s)              | 24               | 0.91 (0.17) | 26       | 0.97 (0.14) | 0.228   |
| MVdecT (m/s)            | 24               | 166.52 (32.93) | 26     | 171.73 (37.05) | 0.603   |
| MV A (m/s)              | 24               | 0.60 (0.16) | 26       | 0.48 (0.08) | 0.002   |
| MV E/A ratio            | 24               | 1.60 (0.44) | 26       | 2.09 (0.46) | <0.001  |
| Septal E/e’ ratio       | 24               | 9.42 (2.48) | 26       | 7.20 (1.48) | <0.001  |
| Mitral E/e’ ratio       | 24               | 7.82 (2.57) | 26       | 5.90 (0.98) | 0.002   |

Abbreviations: a’, late diastolic velocity; DecT, deceleration time of early diastolic transmitral flow; e’, early diastolic velocity; EF, ejection fraction; FS, fractional shortening; HR (bpm), heart rate in beats per minute; IVS, interventricular septum; IVSd + IVSSs, interventricular septum thickness at end-diastole and end-systole; LV, Left ventricle; LVIDd + LVIDs, LV internal diameter at end-diastole and end-systole; LVMI, left ventricular mass index; LVPWd + LVPWs, left ventricular posterior wall thickness at end-diastole and end-systole; LW, lateral wall; Mitral E/e’ ratio, ratio of early mitral inflow to mitral annular velocity; MV A, active filling velocity; MV E, passive filling velocity; MV, mitral valve; RV, Right ventricle; s’, early peak systolic velocity; Septal E/e’-ratio, ratio of early septal inflow to septal annular velocity; SoV, diameter at the level of the sinuses of Valsava; STJ, diameter at the level of the sinotubular junction.

Mean values were compared between patients and controls using Independent-sample t tests. P values printed in bold are <0.05.
15.74 ± 8.24 years. Fourteen patients had a RP phenotype (of which 11 were children) and 16 patients had a SP phenotype (of which 11 were adults). The control group was comparable to the patient group with respect to age, gender and BSA (Table 1). None of the patients had clinical signs or symptoms of CD.

### 3.2 | 2D-mode

No significant differences were found in aortic root diameter between MPS III patients and controls (Table 2). The AVA diameter was >2SD from normal in 2/24 patients (8.3%) and normal in all controls. Four out of 24 evaluable patients (4/24; 16.7%) met the criteria for ARD at the SoV, compared to 1/27 of the controls (3.7%). One out of 24 evaluable patients (4.1%) met the criteria for ARD at the STJ compared to 1/23 of the controls (4.3%).

Mean LVEF was lower in patients compared to controls (Table 2). Mean LVEF did not differ significantly between pediatric patients (53.3%) and controls (55.2%). However, the mean LVEF was lower in adult patients compared to controls (48.7% ± 3.56 vs 55.8% ± 6.43; P = 0.002).

### Table 3 Left ventricle longitudinal strain (%)

| I. All ages | MPS III patients | Controls | P | Mean difference [95% CI] |
|-------------|------------------|----------|---|-------------------------|
| GLS         | −17.69 ± 2.84    | −20.12 ± 1.79 | <0.000 | 2.32 [1.20-3.66] |
| Basal Septal| −14.37 ± 3.62    | −17.23 ± 2.17 | 0.001 |
| Mid Septal  | −17.90 ± 3.04    | −20.17 ± 1.58 | 0.001 |
| Apical Septal| −22.70 ± 4.99   | −23.30 ± 3.39 | 0.593 |
| Apical Lateral| −21.23 ± 5.14  | −21.31 ± 5.29 | 0.955 |
| Mid Lateral | −16.50 ± 4.99    | −20.43 ± 2.40 | <0.000 |
| Basal lateral| −14.31 ± 4.26   | −18.60 ± 4.52 | 0.001 |
| Base-to-apex gradient | 7.81 ± 5.59 | 4.36 ± 5.90 | 0.031 |

| II. Pediatric | MPS III patients | Controls | P | Mean difference [95% CI] |
|---------------|------------------|----------|---|-------------------------|
| GLS           | −18.41 ± 2.83    | −20.66 ± 1.42 | 0.009 | 2.25 [0.61-3.89] |
| Basal Septal  | −16.13 ± 2.92    | −17.56 ± 2.03 | 0.116 |
| Mid Septal    | −19.13 ± 2.85    | −20.69 ± 1.20 | 0.057 |
| Apical Septal | −23.82 ± 5.60    | −23.19 ± 3.56 | 0.709 |
| Apical Lateral| −22.63 ± 5.24    | −21.33 ± 6.56 | 0.548 |
| Mid Lateral   | −16.00 ± 4.99    | −21.13 ± 2.39 | 0.001 |
| Basal lateral | −14.29 ± 3.60    | −19.38 ± 5.45 | 0.009 |
| Base-to-apex gradient | 7.86 ± 5.97 | 3.70 ± 7.48 | 0.111 |

| III. Adults   | MPS III patients | Controls | P | Mean difference [95% CI] |
|---------------|------------------|----------|---|-------------------------|
| GLS           | −16.86 ± 2.71    | −19.49 ± 2.00 | 0.007 | 2.64 [0.78-4.49] |
| Basal Septal  | −12.36 ± 3.37    | −16.86 ± 2.35 | <0.000 |
| Mid Septal    | −16.50 ± 2.71    | −19.57 ± 1.78 | 0.002 |
| Apical Septal | −21.44 ± 4.02    | −23.43 ± 3.30 | 0.166 |
| Apical Lateral| −19.64 ± 4.70    | −21.29 ± 3.71 | 0.314 |
| Mid Lateral   | −17.07 ± 5.11    | −19.64 ± 2.24 | 0.102 |
| Basal lateral | −14.33 ± 5.09    | −17.71 ± 3.12 | 0.049 |
| Base-to-apex gradient | 7.76 ± 5.37 | 5.07 ± 3.70 | 0.146 |

GLS + individual segments presented in means ± SD. P values printed in bold are <0.05.

I. Means for all patients and controls.
II. Means for pediatric patients and controls.
III. Means for adult patients and controls.
No epicardial luminal narrowing was observed in the left coronary artery (26 evaluable patients) and the right coronary artery (18 evaluable patients).

3.2.1 | M-mode and Doppler flow

There was no significant difference in LVMI between patients and controls. Only the IVSs was significantly thicker in MPS III patients compared to controls. Four out of the 28 evaluable patients (14%) met the criteria for LVH compared to none of the controls.

Mitral valve abnormalities were seen in 13/30 patients (43%) and comprised of thickened leaflets (37%) and insufficiency (10%). Of the pediatric patients, 5/16 (31%) had mitral valve abnormalities compared to 8/14 adults (57%). Aortic valve abnormalities were seen in 10/30 patients (33%) and comprised of insufficiency (28%), and thickened leaflets (17%). Of the pediatric patients, 6/16 (38%) had aortic valve abnormalities compared to 4/14 adults (29%). No valvular abnormalities were observed in the controls.

3.2.2 | Tissue Doppler imaging

The MV E/A ratio was significantly lower in patients compared to controls, indicative of LV diastolic dysfunction. In addition, a significant lower e' value in the IVS and LV lateral wall was found resulting in respectively an increased septal and mitral E/e' ratio in patients compared to controls, also indicative of LV diastolic dysfunction (Table 2).

3.3 | Speckle-tracking echocardiography

The longitudinal strain represents myocardial shortening and is therefore a negative value. The results of the global

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**FIGURE 1** Two-dimensional (2D) speckle-tracking echocardiography (STE) for left ventricular longitudinal strain (LS) in a healthy control subject (A) and a patient with MPS III (B). The peak systolic strain (%) is measured in six individual segments (eg, yellow basal septum, light blue mid septum, green apical septum, red basal lateral, dark blue mid lateral, purple apical lateral). The right-sided figures show the mean global LS (GLS), represented as the dotted line, which is the mean of the six individual segments. The mean GLS in the patient (B; −17%) is significantly less negative compared to the control (A; −23.7%)
longitudinal strain (GLS) and segmental strain in patients and controls are presented in Table 3. First, the Kolmogorov-Smirnov test confirmed that all data was normally divided. Patients and controls were compared using an Independent-samples t test.

The mean GLS was significantly less negative (thus less myocardial deformation) in patients compared to controls (Table 3), and 10/30 patients (33.3%) had an impaired mean GLS (<2SD of the mean of controls). As assessing the individual strain segments, the two apical segments did not differ from controls, but all other segments (mid and basal) were significantly less negative in patients compared to controls, leading to a significantly greater base-to-apex gradient in MPS III patients compared to controls (Table 3). Mean GLS in pediatric and in adult patients were less negative compared to controls (Table 3). No significant difference in mean GLS was found between different phenotypes (RP vs SP) and different genotypes (MPS IIIA, IIB, and IIIC).

An example of a normal STE in one of the controls (A) and an impaired STE in one of our patients (B) is shown in Figure 1.

### 3.3.1 Correlation of CD with age and phenotype

The following echocardiographic measurements were selected for the post-hoc correlation analyses based on significant differences that were found between patients and controls; GLS and LVEF (systolic function), MV E/A ratio, septal and mitral E/e' ratios (diastolic function), and the presence of valvular abnormalities. LVMI (LVH) and aortic root diameters were also included in the post-hoc analyses as hypertrophy and ARD are reported abnormalities in MPS patients. As cardiac dimensions increase with age, the measurements IVSs, LVMI, and aortic root diameters were not included in the correlation analyses with age.

### 3.3.2 Age

There was a negative correlation between age and (a) LVEF \( r = -0.504; \ P = 0.009 \) and (b) mitral E/e' ratio \( r = -0.469; \ P = 0.021 \); younger patients had a greater LVEF and mitral E/e' ratio. There was no association between age and the other echocardiographic measurements.

### 3.3.3 Phenotype

There was a negative correlation between phenotype (RP vs SP) and the septal E/e' ratio \( r = -0.44; \ P = 0.032 \) and mitral E/e' ratio \( r = -0.54; \ P = 0.007 \). Patients with a RP phenotype had greater E/e' ratios. There were no other associations detected.

### 3.3.4 Electrocardiography

An ECG was successfully obtained from 32/33 MPS III patients. An increased PR-interval (first degree AV block) was found in 5/32 patients (15.6%). Two patients had a shortened PR-interval. Two patients showed ventricular extrasystoles (VES). There were no other arrhythmias detected. The abnormal ECG's can be found in the Appendix S1, Supporting Information.

### 4 DISCUSSION

Our study shows a number of important cardiac abnormalities in MPS III patients.

First, subclinical systolic dysfunction is prevalent in MPS III patients. The LV strain assessed by STE in pediatric and adult MPS III patients shows signs of early LV dysfunction. In addition, the mean GLS in pediatric patients differs significantly from pediatric controls in the absence of LVEF abnormalities, suggesting that STE may be an early marker for LV dysfunction in MPS III. STE has proven to be a good marker for early LV dysfunction in Duchenne muscular dystrophy and in various hypertrophic myopathies, whereas LVEF is impaired in case of substantial LV dysfunction. Strikingly, strain in the apical segments did not differ between patients and controls, a phenomenon known as apical sparing, which led to an increased base-to-apex gradient in MPS III patients. This has previously been reported in Primary Hyperoxaluria Type 1, cardiac amyloidosis and Fabry disease. The causes and consequences of apical sparing are, however, not known. No difference in mean GLS between RP and SP patients was found, indicating that SP patients may develop CD despite their more attenuated phenotype.

Second, the results of TDI also reveal LV (diastolic) dysfunction. Although the lower MV E/A ratio might be affected by mitral valve abnormalities (causing a small MV gradient) and thus incorrectly be labeled as diastolic dysfunction, the increased E/e' ratios in patients compared to controls also suggest the presence diastolic dysfunction.

Third, valvular abnormalities were observed in the majority of the patients. In all cases the affected valves were the mitral and aortic valve. This is in line with previous studies in MPS III and other MPSs. Both the aortic valve and the mitral valve mainly showed an insufficiency.

In our cohort, there was no significantly higher incidence of ARD at the SoV compared to controls. In contrast, two recent publication reported a higher incidence of ARD in MPS patients, respectively in 39.1% and 35%. However, Poswar et al did not include any MPS III patients in their study, and Bolourchi et al reported the same mean ARD at the SoV in 6 MPS III patients as we report in our patients.
This might be due to the use of different reference values as Bolourchi et al and Poswar et al used a z-score equation which was based on reference values for healthy children whereas we used specific pediatric, adolescent and adult reference values.

Age was negatively correlated with the E/e' ratios, indicative for a worse LV diastolic dysfunction in younger patients. This is most likely due to the fact that most of the young patients had a RP phenotype while the older patients predominantly had a SP phenotype.

Furthermore, coronary artery disease, which has previously been reported in two MPS III patients, was not detected in this study. However, this could only be assessed by subjective reporting of the epicardial lumen. Superior quantitative assessment by CT angiography would require general anesthesia, which is not standard of care in MPS III in our center and therefore could not be performed within the scope of this study.

Finally, a first-degree AV block was seen in 15.6% of the patients compared to a reported prevalence of 0.5% to 5% in healthy adults. Additional investigations (eg, Holter ECG) were not possible due to restlessness of the patients.

We propose several explanations for the observed CD in MPS III. First, in the MPSs with highly prevalent and often severe CD (MPS I, II, and VI) DS is the accumulating GAG (in MPS I and II in combination with HS). DS entails 20% of the normal cardiac valves, probably explaining the high prevalence of valvular disease in these patients. Recent studies showed that DS also accumulates in MPS III, albeit to a much lesser extent than HS, potentially contributing to the valvular abnormalities observed in MPS III.

Second, the first-degree AV block seen in our patients might be explained by HS storage material in the cardiac conducting system, which was recently reported in a MPS III patient.

Third, a previous study examining an endomyocardial biopsy in a MPS IIIA patient showed ballooned cardiomyocytes with storage vacuoles containing GAG's. This might be the cause of the early left ventricular dysfunction reported by us.

Although none of the patients appeared to have significant signs or symptoms of CD, one patient had moderate to severe aortic valve insufficiency with a moderate dilated LV and LVH. The lack of symptoms in this patient may have been masked by a more advanced disease phase obstructing exercise and leading to relatively less demands of the cardiovascular system.

We believe that our study adds important new information to the existing scarce literature. We used a relatively large sample size compared to other studies. Furthermore, we used a control group allowing comparison with controls based on BSA, gender and age. In addition, our study includes STE analyses, which provides insight on early LV function in MPS III. Finally, all assessments were done at the same center, on the same machine by one pediatric cardiologist.

Our study has some limitations. First, our cohort of patients only included patients capable of travelling to the hospital and remaining calm during the cardiac investigations. Therefore, six of the more severely affected patients in the final stages of the disease could not be included in this study. Since MPS III is a progressive disease, presumably the cardiac abnormalities will also increase in severity with age. Therefore, our study might underestimate the severity of CD. Furthermore, as this is a cross-sectional study, we cannot assess the course of the reported CD.

Disease-modifying treatment in MPS III, of which several options are currently in clinical trial, primarily aims to halt disease progression in the CNS. However, somatic disease, including CD, may become a clinically very relevant problem with increased life expectancy. Follow-up of patients should therefore include assessment of the cardiovascular system. Preliminary data suggest that several of the now investigated treatment options may also lead to (partial) correction of somatic disease (NCT02716246: https://www.abeonatherapeutics.com/), but it remains yet unclear if this sufficiently targets the cardiovascular system.

We conclude that CD is prevalent in MPS III, affecting the myocardium, the mitral and aortic valves, and the conduction system. However, in the relatively young cohort studied, and with older patients generally being immobile, this had not yet resulted in clinical disease. Our findings are important in view of imminent disease-modifying treatment, including gene and enzyme replacement therapy, and we demonstrate that cardiac assessment needs to be included in the follow-up of these patients.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.
AUTHOR CONTRIBUTIONS

R. de B.-B., I.K., S.N. and F.W. were involved in conception and design of this study, in analyses and interpretation of the data. S.N. drafted the article. R. de B.-B., I.K., and F.W. critically revising the article. All authors are in agreement with submission of this draft to JIMD. F.W. is the guarantor for this article.

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**SUPPORTING INFORMATION**

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

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