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Value of Global Longitudinal Strain for Identification and Monitoring of Left Ventricular Dysfunction in Becker Muscular Dystrophy

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Cardiac involvement is the main cause of death in Becker muscular dystrophy (BMD). Identification of left ventricular (LV) function is crucial, but standard echocardiographic measurements such as LV ejection fraction (LVEF) might not be sensitive enough to detect early myocardial dysfunction. We explored the value of LV global longitudinal strain (GLS) as a more accurate echocardiographic parameter to detect and monitor LV dysfunction in BMD. Furthermore, we studied possible factors associated with LV dysfunction and progression. A total of 40 patients with BMD (age 39.0 ± 13.2 years) and 21 matched controls were included. Clinical variables, pulmonary tests, serum biomarkers, and echocardiograms were collected at baseline and after 2 years. LV systolic function was assessed by LVEF and LV GLS; a significant progression in LV dysfunction was defined as an absolute LV GLS deterioration ≥15%. Responsiveness to cardiac disease progression was determined using standardized response means. Patients showed impaired LVEF and LV GLS compared with controls (p <0.001). Of interest, 31 patients (77.5%) showed impaired LV GLS (defined as greater than −18%), whereas only 24 patients (60%) had reduced LVEF. LV GLS and LVEF correlated with troponin I (ρ = 0.553 and −0.523) and N-terminal pro-b-type natriuretic peptide (ρ = 0.506 and −0.585), but not with skeletal muscle or pulmonary function. At follow-up (2.0 ± 0.5 years, n = 29), LV GLS worsened significantly (−1.3 ± 0.8%, p = 0.002, standardized response mean = 0.70, annually = 0.60%), whereas LVEF remained stable. No risk factors for LV dysfunction progression were identified. In BMD, LV GLS is frequently impaired and shows deterioration over time compared with LVEF. LV GLS could be used as a more sensitive parameter to identify and monitor LV dysfunction. **(Am J Cardiol 2022;162:170−176)**

Becker muscular dystrophy (BMD) is caused by inframe mutations in the DMD gene,[1] resulting in slowly progressive skeletal muscle weakness. As heart failure is the main cause of death,[2] close cardiac monitoring is of great importance. Conventional echocardiographic parameters, such as left ventricular (LV) ejection fraction (EF), are currently used as primary diagnostic tool to monitor LV function in BMD. The possible low sensitivity of LVEF to detect subtle myocardial dysfunction[3] could, however, lead to underestimation of cardiac involvement and delay specific treatments because initiation of medication is suggested only in case of reduced LVEF.[4] Advanced echocardiographic techniques, such as speckle tracking echocardiography (STE), may improve assessment of early myocardial involvement.[3] Global longitudinal strain (GLS), quantified by STE, has been shown to be more sensitive and reproducible compared with LVEF and of significant prognostic value,[3,5] and it could detect early LV dysfunction (with preserved LVEF) in several diseases.[6–9] In this study, we explored the value of LV GLS for detecting and monitoring LV systolic dysfunction compared with LVEF and LV volumes. We studied correlations with serum biomarkers and clinical and functional parameters and tried to identify baseline characteristics associated with a deterioration in LV GLS over time.

Methods

This study consisted of 2 patient populations. The first population consisted of patients with BMD recruited from the Dutch Dystrophinopathy Database[10] in the 4-year

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prospective BMD natural history study that started in 2014 at the Leiden University Medical Center (LUMC). Inclusion criteria were male patients, aged 18 years or older, diagnosed with BMD based on genetic confirmation (inframe mutation), and/or on clinical phenotype (ambulant >16 years). Specific pathogenic variants are described in Supplementary Table 1. The protocol included yearly 1-day visits with measurements of several clinical characteristics, pulmonary and skeletal muscle function tests, and venous blood sampling. Echocardiographic measurements were performed at baseline and at the third follow-up visit (thus with 2 years apart). The study was approved by the medical ethical committee. Written informed consent was obtained from all participants.

The second patient population consisted of retrospectively included patients aged 18 years or older, diagnosed with BMD based on genetic confirmation (inframe mutation) and/or on clinical phenotype (ambulant >16 years), and who had visited the outpatient clinic at the LUMC for regular follow-up. During these annual consultations, patients were seen by a neurologist, physiotherapist, and cardiologist among others. The 2 most recent echocardiograms were selected with, whenever available, approximately 2 years in between. Ethical approval was obtained from the medical ethical committee, and informed consent was waived for these patients. An age- and gender-matched control group with structural normal hearts and no cardiovascular disease or risk factors was selected from the echocardiography database at the cardiology department of the LUMC.

Data on age, body mass index, systolic blood pressure and diastolic blood pressure, cardiac medication use, medical history, and the presence of a cardiac device were recorded. Functional tests included the North Star Ambulatory Assessment (NSAA), 10-meter run/walk test velocity and 6-minute walk test and were performed as previously described.[11,12] Pulmonary function was measured 3 times using a handheld spirometer (Microloop, Carefusion, Hants, United Kingdom). The measurement with correct curves and the highest value was used for the analysis. High sensitivity cardiac troponin I was measured from the blood on the Abbott Architect c module, using the STAT High Sensitive troponin I reagents. N-terminal pro-b-type natriuretic peptide (NT-proBNP) was measured on the Roche Cobas 8000 (E602) using the Elecsys proBNP II reagents.

Commercially available ultrasound systems equipped with M5S transducers (Vivid-7 or E9 systems, General Electric Vingmed, Horten, Norway) were used to acquire 2-dimensional, color, continuous, and pulsed wave Doppler data from parasternal and apical views with the patient in the left lateral decubitus position. Images were stored digitally on hard disks for offline analysis (EchoPac version 202; GE Medical Systems). LV end-diastolic and end-systolic volumes were measured from the apical 2- and 4-chamber views using Simpson's method and the LVEF was derived. LV mass was calculated and defined according to current recommendations and guidelines.[13] Normal LVEF was defined as ≥52%.[13]

LV GLS was measured by 2-dimensional STE with commercially available software (EchoPac version 202; GE Medical Systems). On the apical 3-, 4-, and 2-chamber views, the LV endocardial border was traced, and the software displayed a region of interest automatically encompassing the LV myocardial wall; if needed, the region of interest was adjusted manually. LV GLS was then calculated as the average of longitudinal strain values of each apical view, and a color-coded 17-segment bull's eye plot was provided (Figure 1). As currently recommended, LV GLS was considered as normal if less than −18%,[14] and a substantial deterioration in LV GLS at follow-up was defined as a percentual change of ≥15% from the absolute baseline value, as previously proposed.[15]

Results are presented as mean ± SD if normally distributed or median (interquartile range [IQR]) for non-normally distributed continuous variables. Categorical data are reported as frequency (percentage). Patients with BMD were compared with healthy controls using the independent samples *t* test or Mann-Whitney *U* test. Fisher's exact test was used for the comparison of categorical variables. Correlations were made using Pearson or Spearman's correlation coefficient. Differences between baseline and follow-up were assessed using the paired samples *t* test or Wilcoxon signed-rank test. Linear regression was used to calculate the deterioration in LV GLS per year using the difference

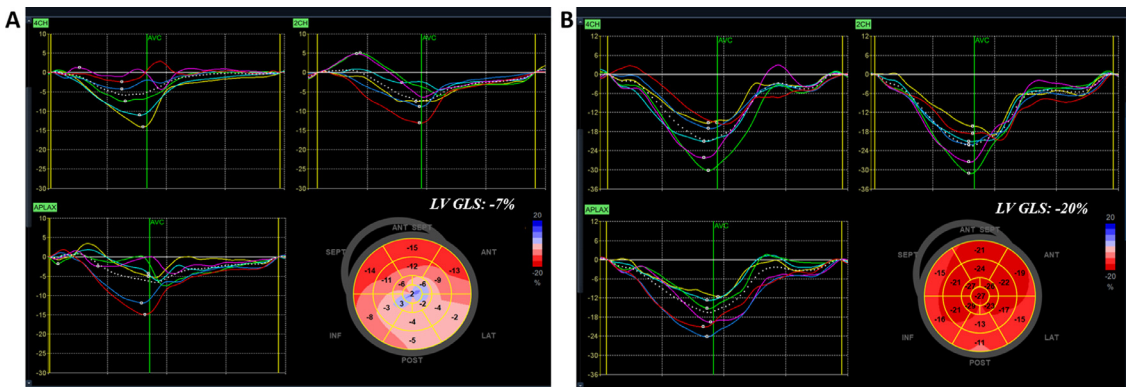

Figure 1. Example of assessment of LV GLS by speckle tracking strain echocardiography in a patient with Becker muscular dystrophy (*A*) versus a healthy subjects (*B*) displayed with color-coded bull's eye plots (dark red as preserved LV GLS, to pink/blue as impaired LV GLS) for LV GLS (panel *A* for a patient with Becker muscular dystrophy; LV GLS = −7% and panel *B* for a healthy control; LV GLS = −20%). Curves of longitudinal strain per segment and averaged in the segments (dotted line for the 3-chamber, 4-chamber, and 2-chamber apical views) are also displayed.

Table 1
Clinical characteristics of the patient population

Variable	Patients with BMD (n = 40*)	Controls (n = 21)	p value
Age (years)	39.0 (13.2)	43.2 (15.7)	0.275
BMI (m^2/kg)	24.3 (4.8)†	23.6 (2.9)	0.444
SBP (mm Hg)	121.6 (17.5)‡	121.5 (13.5)	0.958
DBP (mm Hg)	73.8 (9.4)‡	75.8 (9.2)	0.437
HR (beats/min)	77.0 (15.1)	71.7 (13.4)	0.280
Implantable cardiac device	5 (12.5%)	-	
Pacemaker	1 (2.5%)	-	
Skeletal muscle function tests			
NSAA (points), median + IQR	16.0 (26)†	-	
10-meter run/walk test (m/s), median + IQR	1.0 (2.3)‡	-	
6MWT (m), median + IQR	343 (510)§	-	
Pulmonary function test			
FEV1 (%)	89.3 (18.7)§	-	
FVC (%)	88.5 (20.4)§	-	
NT-proBNP (ng/L)	139.9 (194.7)‖	-	
Troponin-I (ug/L)	0.02 (0.01)¶	-	
Medication			
ACEi/ARB	23 (57.5%)	0	
Beta blockers	10 (25%)	0	
Ca^{2+} channel blocker	2 (5%)	0	
Diuretics	6 (15%)	0	
Oral anticoagulation	6 (15%)	0	
Antiplatelet	1 (2.5%)	0	
Steroids	0		

Data expressed as mean (SD) or frequency (percentage) unless otherwise indicated.
* Applies to all variables unless otherwise stated.
† 4 patients with missing data.
‡ 6 patients with missing data.
§ 5 patients with missing data.
‖ 12 patients with missing data.
¶ 15 patients with missing data.
6MWT = 6-minute walk test; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMD = Becker muscular dystrophy; BMI = body mass index; DBP = DBP = diastolic blood pressure; FEV1 = forced expiratory volume in 1 second percent of predicted value; FVC = forced vital capacity percent of predicted value; HR = heart rate; IQR = interquartile range; NSAA = North Star ambulatory assessment; SBP = systolic blood pressure.

in LV GLS and amount of time in years between baseline and follow-up. To identify potential baseline clinical characteristics and serum biomarkers associated with a substantial deterioration in LV GLS, univariate logistic regression analyses were performed. Standardized response means (SRMs) were calculated as the mean change between follow-up and baseline divided by the SD of the mean change. The SRM can be used to measure outcome measure responsiveness for hypothetical clinical trials.[16] A variable with SRM 0.20 <0.50, 0.50 to 0.80, or ≥0.80 is considered to have small, moderate, or high responsiveness, respectively.[17] SRMs were used to calculate the sample size of a clinical trial using Lehr's formula as described by Morrow et al.[16] In this calculation, we assumed a 50% slower disease progression over 24 months as a result of the hypothetical treatment, a power of 80%, and an α <0.05 in a 1:1 randomization. Statistical analysis was conducted using SPSS version 25.0 (IBM, Armonk, New York). Significance was set at 2-sided p ≤0.05 for all tests.

Results

A total of 36 patients participated in the BMD natural history study. Echocardiograms were not available for 2 patients, and 1 patient was excluded because of poor echocardiographic window. An addition of 7 patients had visited the LUMC outpatient clinic, leading to a total of 40 patients who were included in the baseline analysis. The control group consisted of 21 healthy men. Mean age, body mass index, blood pressure, and heart rate were comparable between the patients and healthy controls (Table 1).

Baseline clinical characteristics of the patients with BMD are listed in Table 1. A total of 8 patients were nonambulant (defined as the inability to walk 10 meters with support of a cane). Functional assessments showed high variability at baseline. Among the patients who could perform the 6-minute walk test (n = 25), the walking distance ranged from 226 meters (equal to a speed of 2.3 km/h) to 654 meters (speed of 6.5 km/h). Forced expiratory volume in 1 second percent of predicted value was below 60% in 3 patients (7.5%). One patient was on nocturnal ventilatory support. A total of 23 patients (57.5%) used at least 1 type of cardiac medication. None of the patients had ever used steroids. The troponin I of 1 patient was excluded in the statistical analysis because of being an extreme outlier (0.727 ng/L) without explanation for this value.

Patients, compared with controls, showed significantly lower LVEF, greater LV volumes, and more impaired LV GLS (Table 2). Importantly, a total of 31 patients (77.5%) had impaired LV GLS, whereas only 24 patients (60%)

Table 2
Baseline echocardiographic characteristics of the patient population

Variable	Patients with BMD (n = 40)	Controls (n = 21)	p value
LV mass (g)	146.7 (51.3)	128.3 (34.7)	0.148
LVEF (%)	46.8 (10.8)	61.3 (7.4)	0.000
LVEDV (ml)	134.4 (53.0)	112.9 (20.2)	0.03
LVESV (ml)	74.3 (43.5)	44.1 (12.6)	0.000
LV GLS (%), median + IQR	-15.9 (-17.7 -12.3)	-19.4 ((-21.1 -18.3)	0.000
Normal EF* & normal GLS†	9 (22.5%)	21 (100%)	0.000
Normal EF* & reduced GLS‡	7 (17.5%)	0	0.044
Reduced EF§ & normal GLS†	0	0	-
Reduced EF§ & reduced GLS‡	24 (60%)	0	0.000

Data expressed as mean (SD) or frequency (percentage) unless otherwise indicated.
*,§ Values of ≥52% and <52% were considered normal and abnormal, respectively.
†,‡ Values of ≤−18% and >−18% were considered normal and abnormal, respectively.
BMD = Becker muscular dystrophy; EF = ejection fraction; IQR = interquartile range; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LV GLS = global longitudinal strain; n/a = not applicable.

Table 3
Follow-up echocardiographic characteristics of patients with Becker muscular dystrophy (n = 29)

Echocardiographic variable	Baseline value	Follow-up value	p value	SRM	SS
LVEF (%)	47.7 (10.8)	47.0 (12.8)	0.455	0.14	3227
LVEDV (ml)	131.5 (42.2)	132.8 (52.5)	0.810	0.04	31659
LVESV (ml)	70.7 (35.1)	73.3 (44.9)	0.491	0.13	3814
LV GLS (%), median + IQR	-16.0 (-17.9 to -13.4)	-14.4 (-16.7 to -11.5)	0.002	0.70	133

Data expressed as mean (SD) unless otherwise stated.
GLS = global longitudinal strain; IQR = interquartile range; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end-systolic volume; ml = milliliter; SRM = standardized response mean; SS = sample size.

showed reduced LVEF. In 7 patients with BMD, LV GLS was reduced, whereas LVEF was preserved versus none in the control group (p = 0.044).

LVEF and LV GLS correlated significantly with each other ($\rho = -0.813$, p <0.001). Both LVEF and LV GLS did not correlate with the NSAA ($\rho = 0.05$ and $\rho = -0.118$), 10-meter run/walk test velocity ($\rho = 0.106$ and $\rho = -0.177$), forced vital capacity ($\rho = 0.016$ and $\rho = -0.075$), and forced expiratory volume in 1 second ($\rho = 0.148$ and $\rho = -0.180$). However, significant correlations were found between LVEF and LV GLS and troponin I ($\rho = -0.523$ and $\rho = -0.553$, p ≤0.006, respectively) and NT-proBNP ($\rho = -0.585$ and $\rho = -0.506$, p ≤0.007, respectively). Example correlations of LV GLS versus variables are shown in Figure 2.

A total of 29 patients with BMD had follow-up echocardiographic measurements available after a mean of 2.0 ± 0.5 years. During this period, LV GLS significantly worsened from a median of −16.0% (IQR −17.9 to 13.4) to −14.4% (IQR −16.7 to 11.5), p = 0.002, mean deterioration −1.3 ± 0.8%), whereas LVEF (47.7 ± 10.8% to 47.0 ± 12.8%, p = 0.455) and LV volumes remained unchanged (Figure 3, Table 3). The calculated annual deterioration of LV GLS was 0.60% ($R^2 = 0.32$, p = 0.001). The SRM of LV GLS was 0.70 (moderate responsiveness), resulting in a hypothetical trial sample size of 133 patients. LVEF showed only a minimal responsiveness to disease progression (SRM 0.14, sample size = 3,227).

In 11 of 29 patients (38%), a substantial deterioration in LV GLS was observed at follow-up. None of the baseline clinical (age, angiotensin-converting enzyme inhibitors, forced vital capacity, NSAA, 10-meter run test) or laboratory (NT-proBNP and troponin I) characteristics were significantly associated with a substantial LV GLS deterioration in univariate logistic regression (Table 4). Therefore, no multivariable regression model was included.

Discussion

We explored the value of LV GLS to identify LV dysfunction and its potential progression in BMD. Our findings suggest that LV GLS is able to detect subtle LV dysfunction in the absence of overt reduction of LVEF. Moreover, LV GLS was more sensitive to demonstrate progression of LV dysfunction over a relatively short period compared with conventional echocardiographic measures (e.g., LVEF).

In our study, the prevalence of reduced LVEF was comparable with previously published cohorts with a similar age, in which 50% to 70% of the patients showed impaired LVEF.[18−20] However, 2 other studies reported reduced LVEF values in only 26% and 21% of the patients.[6,21] This difference may be explained by the use of different cutoff values for reduced LVEF, different imaging techniques, or difference in age, as myocardial involvement has been shown to increase with age.[19,22] Of interest in our study, impaired LV function was found in additional 7 patients (17.5%) when LV function was assessed with a more sensitive tool than LVEF, that is, LV GLS. These results are consistent with a previous small study of patients with BMD. In

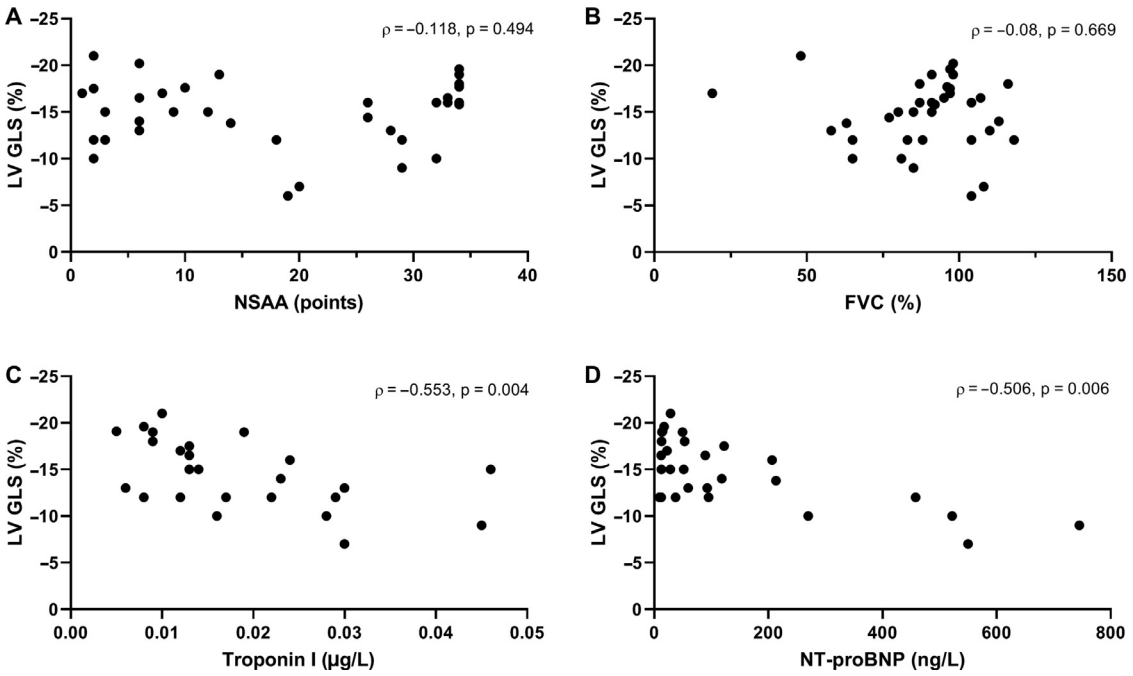

Figure 2. Example correlations of LV GLS and functional, pulmonary, and laboratory variables. LV GLS did not correlate significantly to the NSAA (*A*) and FVC (*B*). Significant correlations were found to both troponin I (*C*) and NT-proBNP (*D*).

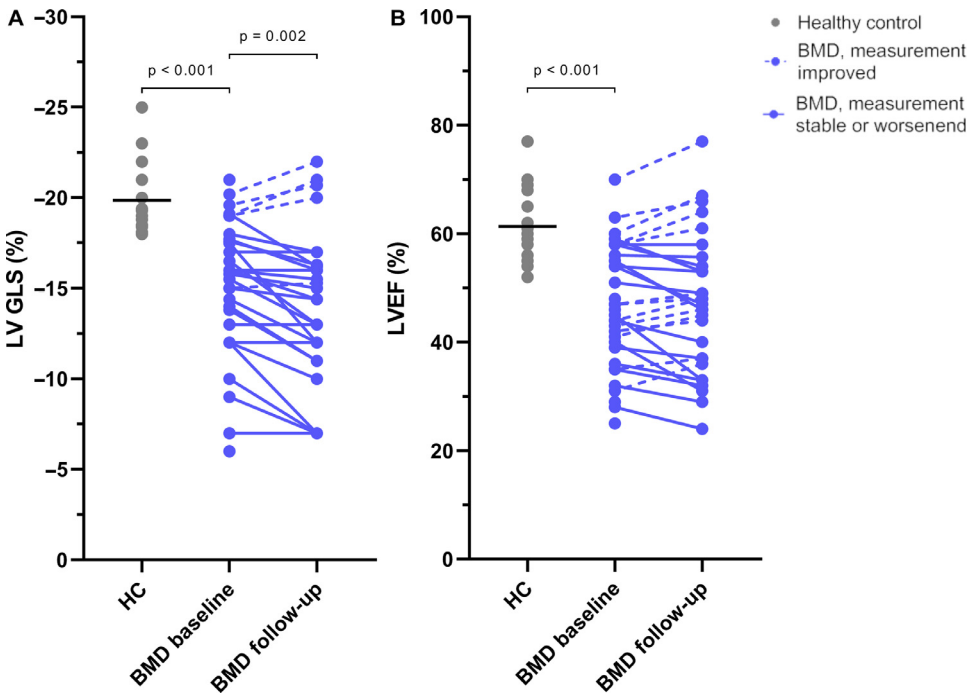

Figure 3. Baseline and follow-up values of LV GLS and LVEF. Baseline values of LV GLS (*A*) and LVEF (*B*) were significantly different (p <0.001) in healthy controls (gray) and patients with BMD (blue). In patients with BMD, only LV GLS worsened significantly (p = 0.002). Continuous lines indicate values that remained stable or worsened at follow-up within 1 patient. Dotted lines indicate measurements that improved. HC = healthy control.

this study, LVEF and LV GLS were measured cross-sectionally in 14 patients with BMD (mean age 18.1 ± 5.9 years) and 1 patient had impaired LV GLS with preserved LVEF.[6] These findings suggest that STE-derived LV GLS can detect subtle changes in LV function, which may reflect earlier disease activity and involvement of the myocardium. Studies have shown that cardiac involvement in neuromuscular diseases may be underdiagnosed unless more sensitive tools, such as cardiac magnetic resonance imaging (cMRI), strain magnetic resonance imaging, or LV GLS, are used than conventional echocardiography.[9,23,24] Implementation of LV GLS as a diagnostic tool may therefore contribute to a timelier initiation of appropriate treatment strategies in BMD.

Table 4
Association between baseline characteristics and substantial deterioration in LV GLS

n = 29 Patients with BMD
Relative LV GLS decline from baseline ≥ 15%: 11
Relative LV GLS decline from baseline < 15%: 18

	Univariate analysis	
Baseline	OR (95% CI)	p value
Age, years	1.012 (0.955−1.072)	0.692
ACEi, yes/no	4.500 (0.752−26.931)	0.099
FVC (%)	0.979 (0.939−1.020)	0.314
NSAA (points)	0.935 (0.867−1.007)	0.077
10 meter run test (m/s)	0.359 (0.127−1.014)	0.053
NT-proBNP (ng/L)	1.004 (0.999−1.009)	0.121
Troponin-I (μl/L)	0.000 (0.000−6.34 × 10^{27})	0.670

ACEi = angiotensin-converting enzyme inhibitor; BMD = Becker muscular dystrophy; GLS = global longitudinal strain; FVC = forced vital capacity; LV = left ventricle; NSAA = North Star Ambulatory Assessment.

Close monitoring of cardiac function over time is of great importance because of the increased risk of heart failure in BMD. Systolic LV function is currently monitored by LVEF and LV volumes. Other imaging techniques, such as cMRI, have been suggested to accurately evaluate cardiac function in BMD,[18,19,21] also providing information on myocardial fibrosis, detected by late-gadolinium enhancement, which has been associated with the development of adverse cardiac events in BMD.[19] However, cMRI may not be suitable to use for repeated evaluations because of the high cost and increased number of patients with implantable cardiac devices. In turn, LV GLS is widely and readily available and has been shown to correlate with the amount of myocardial fibrosis in several cardiovascular diseases.[25,26] To our knowledge, no longitudinal studies investigating cardiac function in BMD exist. We demonstrated that LV GLS could detect progressive impairment in LV systolic function, whereas conventional echocardiographic measurements remained stable. In particular, LV GLS deterioration 0.60% each year. An impaired LV GLS or its significant deterioration over time could prompt physicians to start specific cardioprotective therapy because previous studies have suggested that early treatment with angiotensin-converting enzyme inhibitors (i.e., before the presence of overt myocardial dysfunction) delays deterioration of LV function in Duchenne muscular dystrophy.[27,28]

Although the deterioration in LV GLS over 2 years was substantial in 38% of the patients, we were not able to identify baseline clinical or serum biomarker risk factors related to this progression. This may be due to the limited number of patients in the logistic regression model, or alternatively, because the severity of cardiac disease seems to be independent of skeletal muscle and respiratory function in BMD.[19,22] It is also important to note that most troponin I values in our study were within the reference range despite overt LV dysfunction. However, troponin I levels may not accurately reflect cardiac involvement if myocardial damage has already occurred or is minimal. Although a relation between NT-proBNP and development of cardiomyopathy in BMD has been suggested,[21] both the present study and other previous studies could not confirm these results.[29] NT-proBNP levels are thought to mostly relate to relative acute changes in pressure gradients in the ventricles[30] and may therefore not accurately reflect the myocardial damage if the patient is euvolemic. Thus, the present study emphasizes the importance of regular controls of cardiac function using imaging techniques.

Until now, no clinical trials exist in BMD aimed at restoring or slowing progression of cardiac involvement. The design of clinical trials in BMD is highly complicated because of the slow and variable disease progression. This emphasizes the identification of primary end points that show treatment effect over a limited duration of time in the least number of patients. We show that the responsiveness to disease progression, as measured by the SRM, was higher for LV GLS compared with LVEF. Translated to a sample size for a potential clinical trial, this resulted in approximately 3,100 less patients needed to demonstrate 50% slower cardiac disease progression over 2 years when using LV GLS rather than LVEF as the primary end point. The results of this study therefore provide important insight in the natural history of progression of LV systolic dysfunction and may aid in the design of future clinical trials in BMD and potentially other neuromuscular diseases with cardiac involvement.

Several limitations should be acknowledged. Patients from the outpatient clinic were retrospectively included to increase the number of patients. Potential bias could be present in the analysis with blood serum biomarkers, and to a lesser extent with skeletal muscle function tests, as these were only available in a limited number of patients. We could not calculate the sensitivity and specificity of LV GLS and LVEF because of the unavailability of a reference standard for this assessment (e.g., cMRI). Outcome data were not included in the analysis and the relative prognostic value of LV GLS over LVEF in this population should be investigated in future studies.

In conclusion, development and progression of LV systolic dysfunction in patients with BMD could be measured using LV GLS measured by STE, but not by conventional echocardiographic parameters. Implementation of LV GLS in regular clinical assessments could aid clinicians in defining more accurate treatment strategies for BMD. LV GLS could also potentially serve as a new outcome measure in clinical trials.

Disclosures

Dr. Niks is member of the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD). Dr. Niks worked as investigator in a clinical trial of Givinostat in Becker muscular dystrophy. The remaining authors have no conflicts of interest to declare.

Acknowledgment

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.09.016.

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