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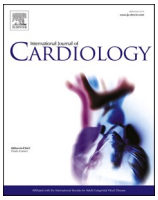

Short communication

Left ventricular strain-volume loops and myocardial fibrosis in pediatric patients with Duchenne muscular dystrophy

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ABSTRACT

Background: The left ventricular strain–volume loop (SVL) combines changes in global longitudinal strain (GLS) and LV volume across a cardiac cycle, providing insight into cardiac dynamics. This study explored the association between left ventricular SVL and presence of fibrosis, assessed with late gadolinium enhancement, in patients with Duchenne muscular dystrophy (DMD).

Methods and results: 34 pediatric patients with DMD were included. Feature tracking analysis was used to assess endocardial GLS and volumetric measurements to construct the SVL. Mean age at the time of assessment was 14 ± 3 and 11 ± 2 years old ($p < 0.01$) in the group with ($n = 18$) versus without fibrosis ($n = 16$), respectively. Left ventricular ejection fraction was not significantly different between groups (fibrosis: 56.4 ± 3.8% versus without fibrosis: 54.0 ± 6.3%, $p = 0.18$). After adjusting for age, the late diastolic slope of the SVL was significantly associated with presence of fibrosis (OR 0.39 [95% CI 0.18–0.85]; area under the receiver operating characteristic curve: 0.83 [95% CI 0.70–0.97]) No significant association was observed for peak strain and fibrosis (OR 1.15 [95% CI 0.86–1.546]).

Conclusion: A lower late diastolic slope of the left ventricular SVL, related to the interplay between longitudinal deformation and volume changes late in diastole, is associated with presence of myocardial fibrosis in pediatric patients with DMD.

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder affecting up to 1:5000 live male births [1]. Patients present with progressive muscle weakness leading to loss of ambulation around the age of 12 years. Additional cardiac complications occur, such as heart failure, and eventually death, the latter mostly occurring in the second or third decade of life [2–4]. Cardiac dysfunction and fibrosis occur due to progressive cardiomyocyte damage [2], leading to primary dilated cardiomyopathy that will be present in 90% of DMD patients around the age of 18 years [2,5]. Periodic imaging is necessary to evaluate cardiac function for the early detection of abnormalities, allowing timely treatment, currently mainly aimed to delay the progression of cardiac dysfunction [6].

Currently, cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) is used to assess cardiac function and fibrosis, requiring intravenous access and additional scanning duration. Interestingly, less invasive alternatives, such as global systolic peak strain, may also detect systolic dysfunction in patients with fibrosis, before any changes occur in left ventricular ejection fraction (LVEF) [7]. Since fibrosis is likely to alter diastolic function [8], an integrated evaluation of both systolic and diastolic function may be valuable in early detection of cardiac dysfunction. Recent work showed that combining strain and volume in the strain-volume loop (SVL) may

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provide additional information to traditional measures of cardiac function (e.g. LVEF, peak strain) to discriminate between pathologies, detect cardiac remodeling, and is associated with long-term survival [9–12]. Therefore, the aim of this study was to explore the association and discriminative value of LV-SVL characteristics in DMD with the presence of fibrosis. We hypothesized that lower slopes and higher uncoupling of the LV-SVL, are associated with LV fibrosis, reflecting altered cardiac mechanics.

2. Methods

2.1. Study design and population

DMD patients aged ≤18 years with CMR imaging with LGE series between June 2017 and November 2021 were included at the Radboud University Medical Center, Nijmegen, The Netherlands as described in detail elsewhere [13]. Exclusion criteria were structural congenital heart defects and low quality CMR exams. The study was approved by the local institutional review board and was performed according to the local code of research conduct and data protection rules.

2.2. CMR acquisition

CMR imaging was part of usual care and performed on a Siemens Avanto 1.5 T scanner system (Siemens, Erlangen, Germany) according to a standardized protocol without sedation. Images were electrocardiogram-triggered and acquired during breath-hold. Biventricular dimensions and function were assessed from short-axis views. Left atrial volume was calculated using the biplane area-length method. Volumetric data were indexed to body surface area (BSA, Dubois & Dubois). The contrast agent 'Dotarem' (Guerbet, France) was administered (0.3 mL/kg) intravenously. LGE series were acquired approximately 15–30 min thereafter. LGE was assessed by a cardiovascular radiologist (W.E.) as previously described [13].

2.3. Strain-volume loop

Offline CMR-FT analyses were performed using QStrain (Medis Medical Imaging, Leiden, The Netherlands) assessing endocardial GLS and volume per frame, derived from two-, three-, and four-chamber views. All analyses were performed by one researcher (T.K.) and supervised by a cardiovascular radiologist (W.E.). SVL was constructed using in-house developed software (MATLAB, The MathWorks Inc., version 2019a, Massachusetts, USA) as described elsewhere (Fig. 2) [14]. The SVL was assessed using systolic and diastolic characteristics as described in Fig. 1, i.e., early systolic slope (ES slope), systolic slope (S Slope), end-systolic longitudinal strain (Peak strain), early diastolic slope (ED slope), late diastolic slope (LD slope), and average difference of longitudinal strain (uncoupling) in systole compared to diastole (i.e. average of systolic – diastolic strain).

2.4. Statistical analysis

Statistical analyses were performed using R version 4.0.4 [15]. Normality was checked using histograms and Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation (SD) or median [interquartile range] and categorical variables as number and proportion (n(%)). Characteristics were compared using a *t*-test or non-parametric equivalent. Proportions were tested using chi-squared tests or Fisher's exact tests. Intra-observer variability was assessed using an intraclass correlation coefficient (ICC) using a two-way mixed model for absolute agreement. Logistic regression was used to assess the association of SVL characteristics and presence of fibrosis. Variables were selected based on univariable logistic regression ($P < 0.1$) and adjusted for age in multivariable analysis. Assumptions were checked using Box-Tidwell tests and variance inflation factors (multicollinearity). To explore the discriminative value, Receiver Operating Characteristic (ROC) curves were used to assess the performance of SVL characteristics in a multivariable model. Optimal cut-off was determined using the Youden-index. $P < 0.05$ was considered significant.

3. Results

Thirty-four patients were included for final analysis. Based on LGE images, 18 (52%) patients had fibrosis and 16 (48%) showed no fibrosis. Mean age at the time of CMR was 14.1 ± 2.7 and 11.9 ± 2.0 years ($p = 0.009$) in the group with versus without fibrosis, respectively. *Z*-scores for height and weight were not significantly different between groups. No difference between groups in LVEF and left atrial volume was observed (Table 1).

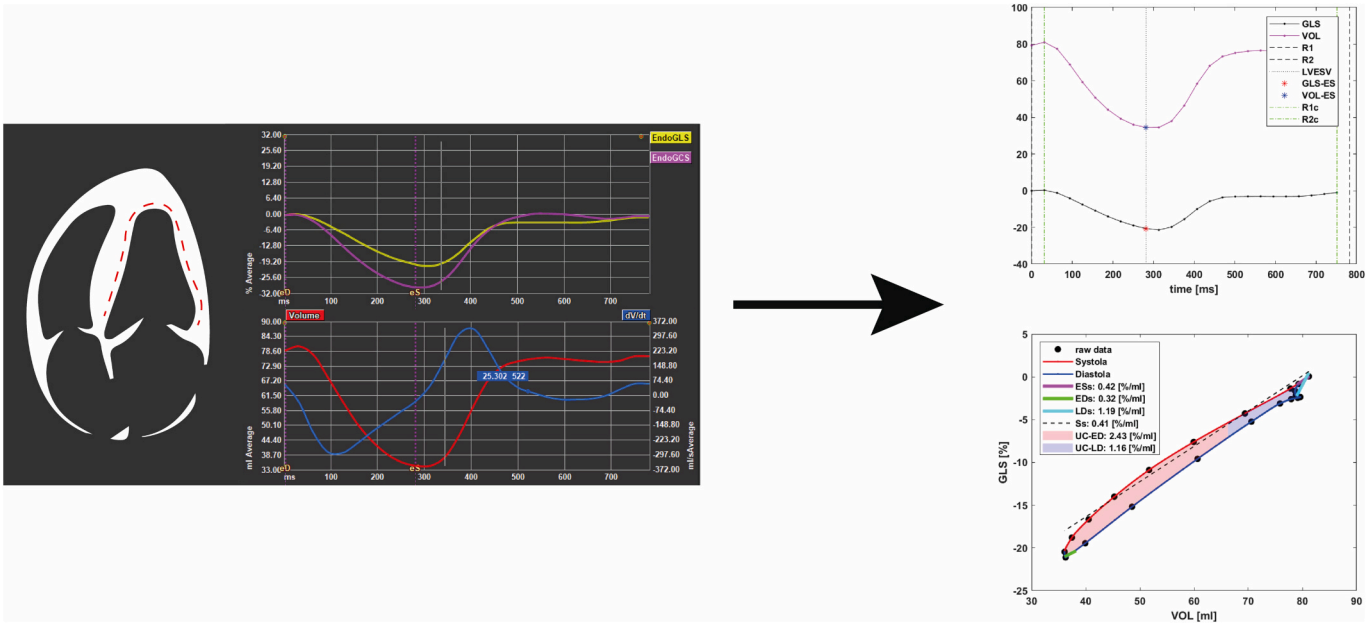

Fig. 2. Representation of the acquisition of strain and volumetric data and the resulting strain-volume loop based on this data.

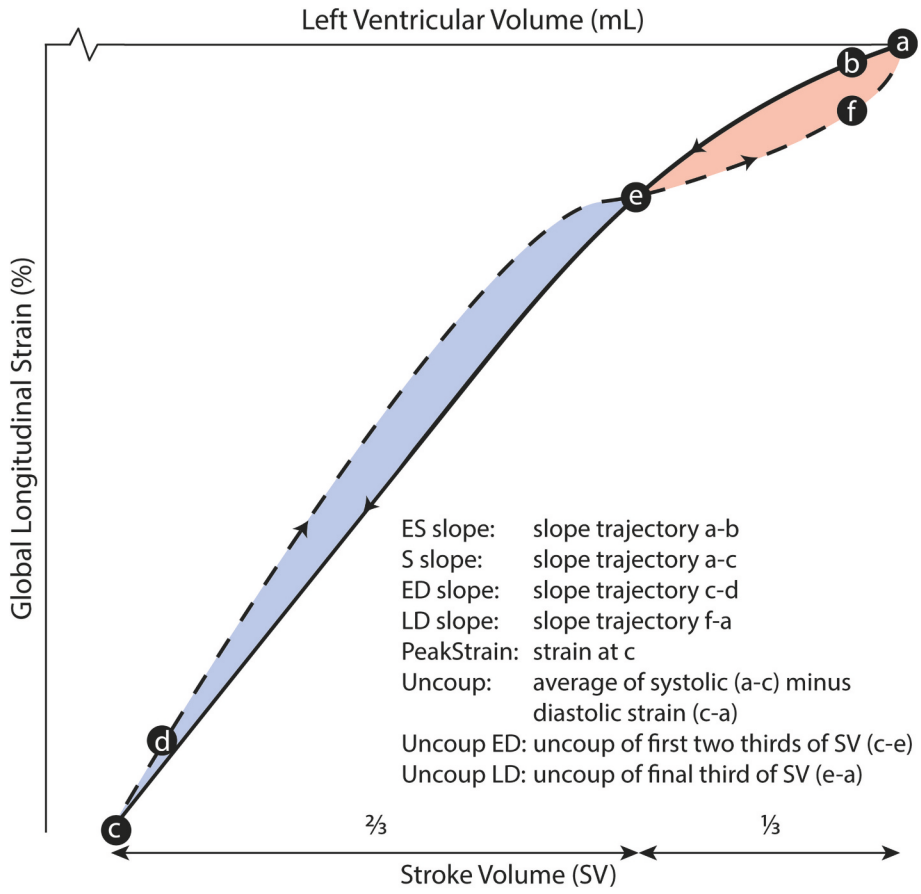

Fig. 1. A schematic overview of the strain-volume loop and derived characteristics. Solid line: systolic strain-volume relation; dashed line; diastolic strain-volume relation. a: end diastolic volume; b: after ejecting 5% of stroke volume; c: end systolic volume d: filling at 5% of stroke volume; e: filling at two thirds of stroke volume; f: filling at 95% of stroke volume; ES: early systolic; S: systolic; ED: early diastolic; LD: late diastolic; Uncoup: uncoupling.

Intraobserver variability. ICC was as follows: ES slope 0.84 (95% confidence interval [CI] 0.44–0.95), S slope 0.98 (95% CI 0.93–0.99), Peak strain 0.89 (95% CI 0.72–0.96), ED slope 0.93 (95% CI 0.84–0.97), LD slope 0.86 (95% CI 0.69–0.94), Uncoupling 0.97 (95% CI 0.92–0.99), Uncoupling ED 0.97 (95% CI 0.92–0.99), Uncoupling LD 0.96 (95% CI 0.89–0.99).

Strain-Volume Loop and Fibrosis. For systolic characteristics of the SVL, only S slope was associated with the presence of fibrosis (odds ratio (OR) 0.32 [95% CI 0.12–0.84]) in univariable analysis. Additionally, for diastolic characteristics, LD slope was associated with the presence of myocardial fibrosis (OR 0.35 [95% CI 0.17–0.73]). After adjusting for age at time of CMR, LD slope remained significantly associated with fibrosis (adjusted OR 0.39 [95% CI 0.18–0.85]) per 0.1 unit increase in LD-slope (range 0.09–0.9) (Table 2). The area under the curve (AUC) of the ROC-plot for LD slope, adjusted for age, was 0.83 (95% CI 0.70–0.97). The optimal cut-off for LD slope in a univariable model was 0.32 based on the Youden-index with a sensitivity of 61% and specificity of 100%. Resulting in this cohort in a positive predictive value of 100% and a negative predictive value of 70%.

4. Discussion

This explorative study revealed that, after adjusting for age, a lower late diastolic slope of the SVL was associated with increased odds for myocardial fibrosis in pediatric patients with DMD. The LD slope of the SVL revealed an AUC of 0.83 in this population. Interestingly, no differences in other diastolic parameters were observed. Additionally, LVEF and peak strain were not associated with presence of fibrosis in this cohort [13]. Taken together, SVL might provide additional insight over traditional measures pertaining to the presence of fibrosis in pediatric patients with DMD. Although this study is predominantly explorative, new parameters might provide non-invasive alternatives, i.e., without intravenous access, to monitor disease progression and cardiac fibrosis when conventional parameters, such as LVEF, are not yet affected.

The observation that SVL characteristics are different between patients with DMD with versus without fibrosis is in line with research demonstrating differences of SVL characteristics between different pathologies and presence of cardiac remodeling [9,16]. To our knowledge, limited previous work examined the relation between SVL characteristics and myocardial fibrosis. Based on a conference abstract, Pagourelias et al. suggested that the systolic slope and uncoupling of the SVL may be related to presence of fibrosis in hypertrophic cardiomyopathy (HCM) [11]. However, this previous study did not analyze diastolic slopes of the SVL, and further details were missing. The different SVL characteristics assessed, combined with a different location of fibrosis in HCM (i.e. mid myocardial and mainly septal) [17] versus DMD (i.e. subepicardial and posterobasal), hampers thorough comparison of the results. Given the relation between cardiac volumetric changes with respect to BSA in pediatric patients, we also explored adjusting LD-slope for BSA in logistic regression analysis. These results (adjusted OR 0.36 [95%CI 0.16–0.84]) reinforce our initial observation. Further research should consider indexing volumetric values for BSA to provide better understanding of the interplay.

The absence of an association for systolic characteristics may indicate that in the presence of fibrosis in DMD, diastolic abnormalities in SVL precede changes in systolic function. Although additional studies with follow-up measurements and healthy controls are required, our

Table 1
Characteristics of the study population.

	Overall (*N* = 34)	No Fibrosis (*N* = 16)	Fibrosis (*N* = 18)	*P-value*
Age, years	13.1 ± 2.6	11.9 ± 2.0	14.1 ± 2.7	0.009
Weight, kg	52 [42–76]	45 [39–58]	62 [50–82]	0.067
Weight, z-score	0.88 ± 1.27	0.73 ± 1.29	1.01 ± 1.27	0.530
Height, cm	150 [138–166]	143 ± 15	158 ± 16	0.008
Height, z-score	−0.63 ± 1.41	−0.87 ± 1.39	−0.41 ± 1.43	0.340
BMI, z score	1.21 ± 1.17	1.27 ± 1.02	1.17 ± 1.32	0.810
Heart rate, bpm	98 ± 16	101 ± 18	95 ± 15	0.357
SBP, mmHg	108 ± 13	106 ± 14	109 ± 11	0.468
Missing, n (%)	1 (2.9%)	0 (0%)	1 (5.6%)	
DBP, mmHg	63 ± 8	63 ± 10	63 ± 7	0.916
Missing, n (%)	1 (2.9%)	0 (0%)	1 (5.6%)	
Duration glucocorticoids treatment, years	6.5 ± 3.6	5.1 ± 2.7	7.8 ± 3.9	0.027
Missing, n (%)	1 (2.9%)	0 (0%)	1 (5.6%)	
ACE-inhibitor, n(%)	6 (17.6%)	3 (18.8%)	3 (16.7%)	1.000
CMR measurements				
LAVI, ml/m^2	33.4 ± 11.3	32.8 ± 10.5	33.8 ± 12.2	0.805
Left atrial peak strain, %	36.7 ± 8.8	36.4 ± 6.5	37.1 ± 10.6	0.814
LVEDV indexed, ml/m^2	66.8 ± 11.3	64.4 ± 10.1	68.9 ± 12.2	0.253
LVESV indexed, ml/m^2	55.1 ± 5.3	28.3 ± 6.1	31.7 ± 6.9	0.144
LVEF, %	55.1 ± 5.3	56.4 ± 3.8	54.0 ± 6.3	0.181
IVSd. mm	6.0 ± 1.3	5.8 ± 1.0	6.2 ± 1.5	0.290
PWd, mm	5.0 [5.0–6.0]	5.0 [5.0–5.3]	6.0 [5.0–6.0]	0.070
LV diastolic longitudinal strain rate, s^{-1}	1.6 ± 0.4	1.7 ± 0.4	1.5 ± 0.3	0.140
RVEDV indexed, ml/m^2	58.4 ± 10.0	58.5 ± 10.0	58.4 ± 10.3	0.969
RSESV indexed, ml/m^2	24.5 ± 5.9	24.3 ± 6.6	24.7 ± 5.3	0.822
RVEF, %	58.1 ± 6.8	58.9 ± 6.4	57.3 ± 7.2	0.499

Data reported as mean ± SD, median [interquartile range], or n (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; CMR, cardiovascular magnetic resonance; LAVI, left atrial volume index; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVEF, left ventricular ejection fraction; IVSd, interventricular septum thickness; PWd, posterior wall thickness; RVEDV, right ventricular end diastolic volume; RVESV, right ventricular end systolic volume; RVEF, right ventricular ejection fraction. *Z*-scores calculated using reference data from Centers for Disease Control and Prevention.

Table 2
Odds ratios and 95% confidence intervals for the logistic regression assessing the association SVL characteristics and presence of fibrosis.

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P-value*	*OR (95% CI)*	*P-value*
ES slope*	0.96 (0.69–1.34)	0.708		
S slope*	0.32 (0.12–0.84)	0.020	0.46 (0.15–1.37)	0.161
Peak strain	1.15 (0.86–1.56)	0.344		
ED slope*	0.81 (0.63–1.04)	0.105		
LD slope*	0.35 (0.17–0.73)	0.005	0.39 (0.18–0.85)	0.018
Uncoupling	0.88 (0.49–1.56)	0.657		
Uncoupling ED	1.00 (0.61–1.62)	0.986		
Uncoupling LD	0.62 (0.32–1.22)	0.165		

Odds ratios were adjusted for age when $p < 0.1$ in univariable analysis. All ORs are per unit increase for the corresponding variable, except for those marked with *, per 0.1 unit increase. ES, early systolic; S, systolic; ED, early diastolic; LD, late diastolic.

observations suggest that measures of systolic function seem comparable, even in the presence of myocardial fibrosis. Our findings regarding diastolic characteristics may relate to changes in diastolic function. Diastolic function assessment is commonly divided into early diastolic relaxation and late diastolic myocardial stiffness [18]. The lower LD-slope in those with fibrosis, suggests that less longitudinal deformation is observed relative to the final 5% of LV filling. Less longitudinal deformation, despite ventricular filling, may be related to alterations in myocardial stiffness. However, this remains speculative since no indices of myocardial stiffness were available [19].

Limitations. The small cohort size possibly affected the ability to detect the association between other SVL characteristics and fibrosis. Due to the small cohort limited number of confounders could be considered in multivariable analysis and our cohort could not be split for validation of the discriminative capacity. This is therefore likely an overestimation. Finally, since LGE might not detect diffuse fibrosis and tissue characterization (e.g., T1/T2-mapping) was not performed [20], structural and possibly functional alterations might already be present in our fibrosis group and not truly represent a group without structural alterations.

Conclusion

This study observed an association of the late diastolic slope of the strain-volume loop and LV myocardial fibrosis in pediatric patients with Duchenne muscular dystrophy, whilst no other analyzed indices of diastolic function were different between groups. Diastolic characteristics of the SVL might be a marker for fibrosis with possibly high specificity. Our exploratory analysis supports performance of larger prospective studies to further investigate this observation and compare findings with conventional parameters.

Author contributions

All authors were involved in the conception, design, analysis, and interpretation of the results. TK, WE, and DT drafted the manuscript. All authors reviewed the results, revised it, approved the final version, and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

None to declare.

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