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Objectives: This study aimed to evaluate the predicting value of quantitative and qualitative dyssynchrony parameters as assessed by two-dimensional speckle tracking echocardiography (STE) on outcome in children with dilated cardiomyopathy (DCM). Furthermore, the reproducibility of these parameters was investigated.

Background: In previous studies in adults with heart failure, several dyssynchrony parameters have been shown to be a valuable predictor of clinical outcome.

Methods: This multicenter, prospective study included 75 children with DCM and 75 healthy age-matched controls. Using STE, quantitative (time to global peak strain and parameters describing intraventricular time differences) and qualitative dyssynchrony parameters (pattern analysis) of the apical four-chamber, three-chamber, two-chamber views, and the short axis of the left ventricle were assessed. Cox regression was used to identify risk factors for the primary endpoints of death or heart transplantation. Inter-observer and intra-observer variability were described.

Results: During a median of 21 months follow-up, 10 patients (13%) reached an endpoint. Although quantitative dyssynchrony measures were higher in patients as compared to controls, the inter-observer and intra-observer variability were high. Pattern analysis showed mainly reduced strain, instead of dyssynchronous patterns.

Conclusions: In this study, quantitative dyssynchrony parameters were not reproducible, precluding their use in children. Qualitative pattern analysis showed predominantly reduced strain, suggesting that in children with DCM dyssynchrony may be a minor problem.

KEYWORDS
dilated cardiomyopathy, myocardial strain

1 | INTRODUCTION

In children, dilated cardiomyopathy (DCM) is a severe cardiac disorder with a poor prognosis. The 1- and 5-year transplant-free survival is around 70% and 50%, respectively.[1] In children with DCM, follow-up of left ventricular (LV) function is predominantly performed by echocardiography. The most frequently used parameters are fractional shortening (FS) and left ventricular ejection fraction (LVEF). However, when geometric assumptions do not apply or if increased dyssynchrony is present, these parameters are less reliable.[2] Speckle tracking echocardiography (STE) can avoid these problems and has been shown to be a reliable measure of regional and global LV systolic function.[3–5] In addition, global peak strain has been associated with the risk of death and heart transplantation in both children and adults with DCM.[5–7]

STE can also be used to calculate parameters describing dyssynchrony. The presence of dyssynchrony in adults is related to adverse outcome and has been used to predict the effectiveness of cardiac resynchronization therapy (CRT).[8,9] However, it has been shown that reproducibility of quantitative dyssynchrony parameters in healthy children is poor.[10] In addition to quantitative dyssynchrony measures, it has been demonstrated that qualitative pattern analysis better predicts CRT response.[11,12] Carasso et al.[11] defined five different abnormal strain patterns and showed that the presence of some patterns was predictive for cardiac resynchronization therapy (CRT) response Risum et al.[12] showed that the presence of classical-pattern dyssynchrony (CPD) was associated with CRT response. Only one study described the presence of CPD in children with DCM.[13] In a previous study, we concluded that global peak strain is predictive for heart transplantation or death in a large nationwide cohort of DCM patients.[5] In the present study, we further analyzed these patients and evaluated whether dyssynchrony parameters are predictive as well and whether they are reproducible measurements. So the aim of this study was to assess whether strain-derived dyssynchrony parameters in children with dilated cardiomyopathy can be used in a reproducible way and whether they contribute to the prediction of adverse events as death or heart transplantation.

2 | METHODS

2.1 | Patient selection

The patient cohort of this study has been described previously and included 75 children <18 years who had dilated cardiomyopathy.[5] Follow-up data were collected through January 2015. Primary endpoints were death and heart transplantation. We selected age- and sex-matched controls from an earlier described cohort of healthy children.[10] In patients and controls, STE was performed according to the same protocol. The study was approved by the institutional review boards of all centers, and patients and/or parents gave written informed consent.

2.2 | Electrocardiography

QRS duration was derived from an electrocardiogram made on the same day as the echocardiogram. QRS duration was calculated and labeled as above or below 98th percentile, according to reference values.[14]

2.3 | Echocardiography

A complete two-dimensional echocardiographic study was performed in a uniform way using Vivid 7 or Vivid 9 ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway). To minimize inter-observer variability, all centers were instructed about the echocardiography protocol before start of the study. Offline analysis was performed by one observer (SdB) supervised by an experienced pediatric cardiologist (ADJTH) who was involved in previous studies on speckle tracking strain echocardiography. All children were at rest and in sinus rhythm during examination. M-mode of the parasternal long-axis was used to measure LVEDD and LV end-systolic dimension (LVESD), and subsequently, FS was calculated. LVEF was calculated from the apical four-chamber and two-chamber views using Simpson's biplane method.[2] End-systole was defined as the moment of aortic valve closure, measured in a Doppler flow image of the LV outflow tract. Two-dimensional grayscale images of the apical four-chamber, three-chamber, two-chamber, and parasternal short-axis views at the level of the papillary muscle were stored for offline speckle tracking analysis using EchoPAC Software version 12.0.1 (GE Vingmed Ultrasound AS).

2.4 | Two-dimensional speckle tracking strain imaging, quantitative analysis

LV systolic performance was evaluated using speckle tracking strain analyses performed in grayscale images of the apical four-chamber view (longitudinal analysis) and the LV parasternal short-axis view (radial and circumferential analyses) as previously described.[10] Images were obtained with optimized sector width and frame rate (preferably 60–90 frames/second). In these images, manual endocardial border tracing at end-systole was used to set the region of interest. The region of interest was automatically divided into six segments. In the four-chamber view, this included the basal, mid, and apical segments of the LV lateral wall and the interventricular septum; in the three-chamber view, this included the basal, mid, and apical segments of the LV posterior and anteroseptal wall; in the two-chamber view, this included the basal, mid, and apical segments of the LV inferior and anterior wall. The short-axis image was divided into a septal, anteroseptal, anterior, lateral, posterior, and inferior segment to evaluate both radial strain and circumferential strain. In each segment tracking, quality was automatically evaluated, and this resulted in automatic rejection or acceptation of the segment. Although an observer could override this automatic decision based on visual evaluation, this was used very conservatively. Peak strain was defined as the highest strain value at any time point in the cardiac cycle. For all six segments of the four-chamber, three-chamber, and two-chamber views, peak longitudinal strain was registered. Likewise in the short-axis view, peak radial strain and circumferential strain were registered for each of the six segments. Time to peak strain was assessed for each segment using the beginning of the QRS complex as a reference point. Individual

peak strain values were combined in several models. For longitudinal strain, these models included the four-chamber (six segments), the four-chamber and two-chamber (12 segments), and the four-chamber, three-chamber, and two-chamber (18 segments) model. For radial strain and circumferential strain, the models included the six segments of the short-axis view.

Additionally, parameters describing intraventricular time differences were calculated, including the standard deviation of the time to peak strain of all segments in one model (eg, SDt-6) and the difference in time to peak strain between two specified segments. For longitudinal strain, the difference in time to peak strain between the basal septal and lateral segments was calculated (S-L delay). For circumferential strain and radial strain, the difference in time to peak strain between the anteroseptal and posterior segment was calculated (AS-P delay).

2.5 | Qualitative analysis: pattern recognition of strain curves of four-chamber, three-chamber, and two-chamber

The strain curves of the apical four-chamber, three-chamber, and two-chamber views were analyzed using the qualitative methods as described by Carasso et al. and Risum et al.[11,12] In short, the strain patterns of each segment of the four-chamber and two-chamber were scored as (1) normal, (2) mildly reduced shortening, (3) severely reduced shortening, (4) holosystolic stretching, (5) delayed systolic shortening, or (6) pseudodyssynchrony.[11]

Furthermore, the presence or absence of classical-pattern dyssynchrony (CPD) was scored in the four-chamber, three-chamber, and two-chamber views. CPD was present if basal or midventricular segments showing early stretching and late contraction opposed by basal or midventricular segments showing early contraction and late stretching.[12]

2.6 | Intra-observer and inter-observer variability

Intra-observer and inter-observer variability for quantitative analyses were assessed using 20 randomly selected patients. Using the same cardiac cycle, the first observer (SdB) traced the endocardial border again and registered strain parameters, after an interval >3 months. A second observer (AtH), who was blinded to the results of the first observer, traced the endocardial border and registered the strain parameters on the same image and cardiac cycle as the first observer did.

2.7 | Statistical analysis

Continuous variables are reported as mean (±SD) if normally distributed, or as median with interquartile range (IQR) if non-normally distributed. Differences in demographic and echocardiographic parameters between patients and controls were tested using independent sample *t* test or chi-square test if normally distributed, and using Mann-Whitney U test if non-normally distributed. Univariable Cox regression was used to identify risk factors for death and heart transplantation. Intra-observer and inter-observer variability were calculated using the intraclass correlation coefficient (ICC) and coefficient of variation (CV). All statistical analyses were performed using IBM SPSS Statistics 21 (Armonk, NY, USA); $P<.05$ was considered as statistical significant.

3 | RESULTS

3.1 | Patient characteristics

We included 75 DCM patients on a mean age of 7.4 years, range 0–17.9 years (Table 1). The underlying diagnosis included idiopathic DCM (N=37), myocarditis (N=10), neuromuscular disease (N=4), familial CMP (N=6), anthracyclines induced (N=5), and other diagnoses (N=13).The mean QRS duration was 86±18 msec; 25% of the patients had QRS duration >98th percentile for sex and age. Only two patients had QRS duration >120 milliseconds. During a median of 21 months (IQR 15.5–31.2 months) follow-up, 10 patients (13%) reached a primary endpoint; eight underwent heart transplantation and two died.

3.2 | Intraventricular time differences

The SD of the time to peak strain calculated in each model was considerably higher, and the delay between two specified segments (S-L delay and AS-P delay) was significantly longer in patients as compared to controls (Table 2).

3.3 | Pattern recognition in the four-chamber and two-chamber views, according to Carasso et al.[11]

The distribution of patterns differed significantly between adults in the study of Carasso et al. and the children in our study (Figure 1).

TABLE 1 Baseline characteristics of the study population

	DCM n=75
Male, n %)	42 (56)
Age (yr)	7.4±6.4
Time since DCM diagnosis (yr), median (IQR)	1.0 (0.1–4.0)
Medication used, n (%)	
Diuretics	53 (71)
β-Blockers	44 (59)
ACEi	64 (85)
LVEDD z-score	+5.1±3.0
LVESD z-score	+8.1±4.1
Fractional shortening (%)	17.5±6.5
LVEF (%)	33±11
QRS duration (msec)	86 ± 18
QTc (msec)	446±35
Heart rate (bpm)	104±34

All parameters are reported as mean±SD, unless otherwise indicated.
DCM=dilated cardiomyopathy; ACEi=angiotensin-converting enzyme inhibitor; LVEDD=left ventricular end-diastolic dimension; LVEF=left ventricular ejection fraction; LVESD=left ventricular end-systolic dimension.

TABLE 2 Quantitative dyssynchrony parameters in DCM patients as compared to healthy controls

	DCM (N=75)	Controls (N=75)	*P*-value
Intraventricular time differences			
Longitudinal model			
S-L-delay	65 (21-117)	19 (12-47)	<.001
Longitudinal SDt-6	45 (37-79)	30 (24-37)	<.001
Longitudinal SDt-12	46 (36-82)	31 (26-37)	<.001
Longitudinal SDt-18	52 (34-83)	30 (24-36)	<.001
Radial			
AS-P delay	34 (13-87)	24 (12-52)	.033
SdT-6	34 (10-80)	16 (9-25)	<.001
Circumferential			
AS-P delay	130 (72-234)	30 (12-65)	<.001
SDt-6	106 (64-130)	27 (16-37)	<.001

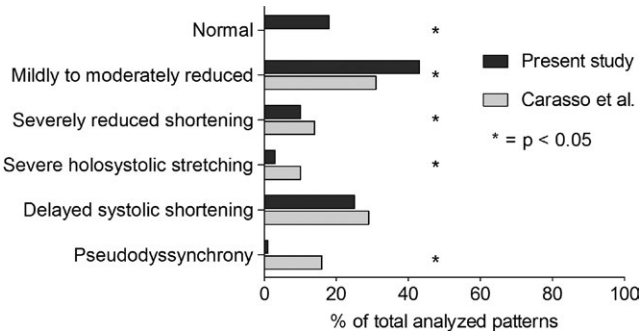

FIGURE 1 Distribution of strain patterns. Numbers are given as percentage of the total number of segments analyzed of the four-chamber and two-chamber views, which is 800 in the present study and 902 in the study of Carasso et al

TABLE 3 Pattern distribution between patients with an endpoint (n=65) and those without (n=10)

	No endpoint n=65		Endpoint n=10		*P*-value
Total number of segments analyzed	690	(100)	110	(100)	
Normal	129	(19)	13	(12)	.08
Mildly to moderately reduced	295	(43)	49	(45)	.73
Severely reduced shortening	61	(9)	21	(19)	**.001**
Severe holosystolic stretching	21	(3)	4	(4)	.74
Delayed systolic shortening	180	(26)	22	(20)	.17
Pseudodyssynchrony	4	(1)	1	(2)	.68

Values are reported as number and percentage [n, (%)] *P*-values indicate the difference between patients with no endpoint (N=65) and patients with an endpoint (N=10) by using the chi-square test. Bold value indicates statistical significance.

Remarkably, we identified 18% of the segments as a normal pattern, whereas in adults, the presence of normal patterns was not described. In children, holosystolic stretching was rare, and we found almost no pseudodyssynchrony. The presence of delayed systolic shortening did not differ between children and adults.

In patients with an endpoint, we found more severely reduced patterns compared to those without an endpoint (19% vs 9%, *P*=.001, Table 3). The presence of all other patterns was comparable.

3.4 | Classical-pattern dyssynchrony in the longitudinal four-chamber, three-chamber, and two-chamber views

CPD was found in five patients (7%), one patient had CPD in the four-chamber view, three patients in the three-chamber view, and one patient in the two-chamber view (Figure 2). In two of those, CPD manifested not as described by Risum et al.,[12] that is, having early terminated septal or anteroseptal shortening and early stretch of the opposing wall, but those had early terminated shortening of a lateral wall segment and early stretch and late shortening in an opposing septal segment.

There was no relationship between the presence of CPD and the risk of death or heart transplantation; none of the patients with CPD had a primary endpoint. We found no relationship between CPD and QRS duration >98th percentile (*P*=.8).

3.5 | Inter- and intra-observer variability

The inter-observer and intra-observer variability of intraventricular time difference parameters were high; the ICCs varied from 0 to 0.82, while most parameters had an ICC <0.50. Only the ICC of the radial intraventricular time differences showed higher values, however, the CV was still 68%–130%.(Table 4 and Table 5).

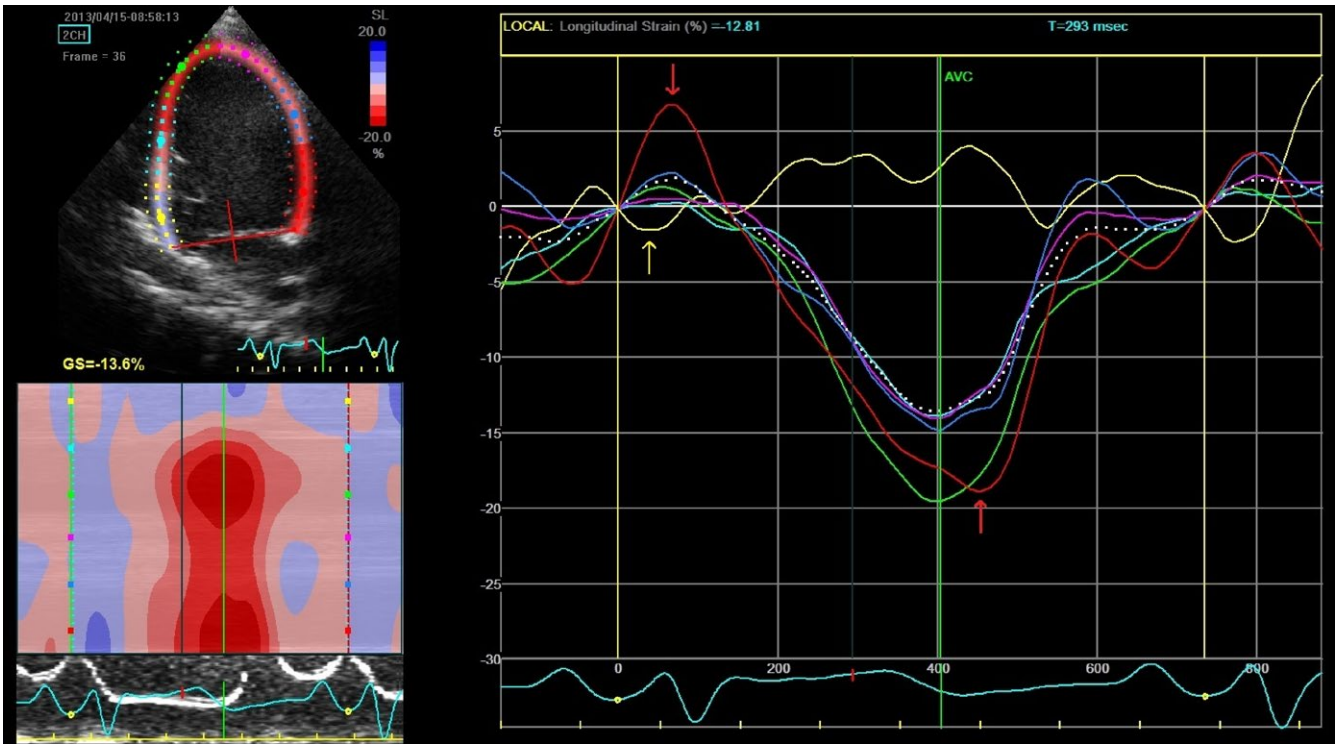

FIGURE 2 Showing classical-pattern dyssynchrony in a two-chamber view of a patient. The septal wall segment shows early terminated contraction (yellow arrow), and an opposite lateral wall segment shows early stretch and late contraction (red arrows)

TABLE 4 Intra-observer variability of quantitative dyssynchrony parameters

Variable	ICC	Bias	Bland-Altman analysis 95% limits of agreement	CV
Longitudinal				
S-L delay	−0.24	9.6	−354.1–373.3	177.5
SDt-6	0.46	21.1	−69.7–111.9	57.1
SDt-12	0.49	18.7	−53.2–90.7	50.6
SDt-128	0.53	5.0	−66.1–76.1	45.5
Radial				
AS-P delay	0.82	28.2	−127.2–183.6	78.1
SDt-6	0.73	18.8	−79.7–117.4	68.1
Circumferential				
AS-P delay	0.30	6.9	−248.6–262.5	81.1
SDt-6	0.63	1.4	−95.2–98.0	38.6

TABLE 5 Inter-observer variability of quantitative dyssynchrony parameters

Variable	ICC	Bias	Bland-Altman analysis 95% limits of agreement	CV
Longitudinal				
S-L delay	0.06	−34.9	−305.1–235.2	148.2
SDt-6	0.23	−5	−85.0–75.0	65.4
SDt-12	0.27	−5.4	−66.2–55.3	55.7
SDt-18	0.50	−11.7	−57.3–33.9	38.0
Radial				
AS-P delay	0.37	28.3	−172.3–228.8	130.2
SDt-6	0.64	2.6	−81.5–86.8	78.6
Circumferential				
AS-P delay	0.14	−9.9	−315.4–295.5	100.0
SDt-6	0.36	−6.2	−125.7–113.4	55.0

4 | DISCUSSION

In the present study, we found higher quantitative dyssynchrony measures in DCM children. However, its reproducibility was very poor. In addition, qualitative dyssynchrony analysis showed predominantly reduced strain; dyssynchrony patterns in children were less common in contrast to previously described findings in adults.

4.1 | Quantitative and qualitative measures of dyssynchrony

Dyssynchrony has been described in children with DCM in several small studies, mainly using Doppler tissue imaging.[15–18] Only one small study used STE and analyzed quantitative dyssynchrony measures. They reported mechanical dyssynchrony in 76% of the children. However, they defined mechanical dyssynchrony according to the

96th percentile of the quantitative dyssynchrony results found in their control population, but reported conflicting results for reproducibility, that is, moderate-to-poor reproducibility for SDt-12 and SL-delay and good reproducibility for radial SDt-6 and AS-P delay.[19] Nonetheless, in the present study, we measured time to peak and intraventricular time differences in a large group of children and found poor reproducibility for all quantitative dyssynchrony parameters. Although, dyssynchrony may be present in children with DCM, the poor reproducibility of quantitative measures precludes its use for definition, risk stratification, and patient follow-up.

In addition to quantitative dyssynchrony measures, we analyzed qualitative strain patterns according to earlier described methods.[11,12] In adults, these methods have been very sensitive to distinguish between CRT responders and nonresponders. In patients with QRS duration >130 msec, the combination of (1) the absence of holosystolic stretching and (2) the presence of pseudodyssynchrony or delayed systolic shortening was 100% sensitive and 94% specific for the response to CRT.[11] We showed that the distribution of patterns differed significantly between children and adults. In our group, holosystolic stretching and pseudodyssynchrony were both rare; only delayed systolic shortening was present in the same amount as in adults.

We analyzed the distribution of the patterns in relation to death and heart transplantation and found that only the presence of severely reduced strain patterns was associated with an endpoint. This is in agreement with our finding that reduced strain can be used as a predictor for death or heart transplantation.[5] In that study, lower mean global longitudinal peak strain of the four-chamber was significantly associated with a higher risk of death or heart transplantation; LVEF and SF were not significantly associated with outcome.

Furthermore, the presence of dyssynchronous patterns was not associated with an endpoint, suggesting that dyssynchrony may not play a critical role in children who are at risk of an endpoint.

The classical-pattern dyssynchrony has been described in adults with LBBB.[12] In these adults, the presence of CPD has been predictive for the response to CRT. In children, we found a CPD prevalence of only 7% and no relation between the presence of CPD and QRS duration. Our results are in line with the results of Forsha et al.[13] who described a CPD prevalence of 12% in children. These low prevalences in contrast to adults may be explained by the low prevalence of LBBB in children. Furthermore, in most children, cardiomyopathy is due to global dysfunction caused by infection, hereditary factors etc., while many adults with cardiomyopathy have a more regionally located dysfunction caused by ischemic factors. In adults with QRS complexes <130 msec, CRT has no favorable effect on outcome and may even be harmful.[20] Therefore, the role of CRT in children with DCM may be limited.

4.2 | Reproducibility of intraventricular time differences

The poor ICC of intraventricular time differences in the present study is in accordance with described poor reproducibility in healthy children.[10] This may hamper its use in clinical practice.

4.3 | Limitations

In children, speckle tracking strain analysis may be challenging, partly due to movement artefacts and partly due to higher HR which may limit the number of frames per heart cycle. However, previous studies have shown the high feasibility of speckle tracking strain analysis in children,[10] and even in neonates.[21] In this study, the echocardiographic studies were performed in seven different hospitals. This might have increased the variability in dyssynchrony parameters. However, all studies were analyzed by the same observer in a core laboratory. Furthermore, inter- and intra-observer variability for dyssynchrony parameters have previously been shown to be high in a healthy pediatric population studied in one hospital.[10]

Although we found a high variability in quantitative dyssynchrony parameters, no answer can be given to the value of CRT in these patients as this procedure was not being performed in any of our patients.

5 | CONCLUSION

Although we find higher quantitative dyssynchrony measures in our patients as compared to healthy controls, the poor reproducibility makes them less appropriate as a long-term follow-up tool. Strain pattern analysis showed mainly reduced strain in children with adverse outcome, while dyssynchrony seemed not a major problem in these children.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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