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Comprehensive left ventricular myocardial deformation assessment in children with Kawasaki disease

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Abstract

Objective: Children with Kawasaki disease (KD) with persistent coronary artery aneurysms (CAAs) can develop chronic vasculopathy and subsequent myocardial ischemia. Early detection of this process is challenging. Myocardial deformation analysis can detect early alterations in myocardial performance. We aim to determine whether there are differences in myocardial deformation between KD patients with and without CAAs.

Design: This is a cross-sectional study of 123 echocardiograms performed on 103 children with KD. Myocardial deformation was measured with two-dimensional speckle tracking (2DSTE). The echocardiograms were divided into groups according to the KD phase in which they were performed: acute, subacute, and convalescent/chronic. The convalescent/chronic phase group was then divided based on the presence or absence of CAAs. Left ventricular (LV) global longitudinal strain (GLS), global longitudinal strain rate (GLSSR), global circumferential strain (GCS), global circumferential systolic strain rate (GCSSR), peak torsion, and torsion rate were measured.

Results: The numbers of echocardiograms analyzed in each of the KD phase groups were: 31 acute, 25 subacute, and 67 convalescent/chronic. Myocardial deformation was within normal limits in all groups. However, GLSSR, GCSSR, peak torsion, and torsion rate were lower in the convalescent/chronic phase group than in the acute phase group (mean, −1.37 ± 0.24 vs −1.55 ± 0.21 1/s; −1.63 ± 0.27 vs −1.84 ± 0.35 1/s; 2.49 ± 1.13 vs 3.41 ± 2.60 °/cm, and 21.97 ± 8.36 vs 26.69 ± 10.86 °/cm/s; $P < .05$ for all). The convalescent/chronic phase subgroup with CAAs had lower GLSSR and GCSSR than the subgroup without CAAs (mean, −1.23 ± 0.22 vs −1.42 ± 0.22 1/s; −1.46 ± 0.25 vs −1.68 ± 0.26 1/s, $P < .05$ for both).

Conclusions: Children in the convalescent/chronic phase of KD have a subtle decrease in strain rate when compared to the acute phase, although within the normal range. This decrease is more pronounced in children with CAAs than those without CAAs. Longitudinal studies are needed to discern whether low-normal strain rate predicts decreased myocardial function in the long term.

KEYWORDS
coronary artery aneurysms, Kawasaki disease, myocardial deformation

1 | INTRODUCTION

Kawasaki disease (KD) is an acute vasculitis of unknown etiology. It is the leading cause of acquired heart disease in children in developed countries.[1] Morbidity and mortality are directly related to the severity of coronary artery involvement, with giant aneurysms having the highest risk for thrombosis and stenosis.[1,2] Treatment of acute KD with intravenous immunoglobulin (IVIG) has decreased the risk of coronary artery aneurysm (CAA) formation from 29% to less than 5%.[3] However, some children treated after the 10th day of illness and some children unresponsive to initial IVIG therapy have persistent coronary artery involvement.[4,5]

The clinical course of KD includes three phases. The acute phase lasts 1 to 2 weeks and is characterized by fever, conjunctival injection, rash, erythema of the mucosa, erythema, and swelling of the hands and feet, and cervical lymphadenopathy. The subacute phase begins approximately 2 weeks after fever onset and lasts 4 weeks. During this time, the patient is afebrile and may develop desquamation of the fingers and toes. The convalescent phase begins after the resolution of the clinical signs of illness and lasts for 6 to 8 weeks.[6] Cardiovascular involvement evolves through these phases. During the acute phase, children can develop myocarditis, valvular regurgitation, and pericardial effusion. CAAs usually develop during the subacute phase and carry a risk for sudden death.[6,7] Approximately 50% of children with CAAs experience spontaneous resolution in 1 to 2 years. Despite resolution of CAAs, there is evidence of persistent endothelial dysfunction in these patients.[8]

Two-dimensional speckle tracking echocardiography (2DSTE) measures myocardial deformation and allows the detection of early alterations in cardiac function before standard measurements of ventricular systolic function.[9] Previous studies using 2DSTE have demonstrated decreased left ventricular (LV) longitudinal myocardial deformation during the acute phase of KD that is independent of coronary artery involvement and most likely related to myocarditis.[10-14] These alterations improve with IVIG. There are limited data regarding myocardial deformation in children with persistent CAAs in the convalescent/chronic phase. The purpose of this study was to determine whether there are differences in myocardial deformation between KD patients with persistent CAAs and those without CAAs.

2 | METHODS

This is a cross-sectional study of echocardiograms performed in children diagnosed with KD between August 2013 and May 2015 at Texas Children's Hospital, Houston, Texas. Inclusion criteria were: (a) patient age less than 18 years at the time of the echocardiogram; (b) diagnosis of complete or incomplete KD per the American Heart Association guidelines[1]; and (c) performance of echocardiograms as part of routine evaluation. Exclusion criteria were: (a) structural heart disease; (b) recurrent KD; or (c) inadequate or suboptimal imaging for myocardial deformation analysis. Two-dimensional images were considered inadequate for myocardial deformation analysis if: (a) they were obtained with an ultrasound machine not compatible with the speckle-tracking software utilized; (b) one or more of the LV myocardium segments were not visible; or (c) the frame rate to heart rate ratio was lower than 0.7 frames/s/bpm.[15] A total of 123 echocardiograms performed on 103 children met inclusion criteria. Echocardiograms were divided into three groups according to the KD phase in which they were performed.[1,6,16] No patient had more than one echocardiogram included in any given KD phase group. The phases were defined as follow: acute phase, from day 1 of illness through day 14 of illness; subacute phase, from day 15 of illness through day 42; and convalescent/chronic phase, from day 43 of illness and onward. Day 1 of illness was defined as the first day of fever as documented in the admission note. To further evaluate the effect of persistent CAAs on myocardial deformation, the echocardiograms from the convalescent/chronic phase group were divided into two subgroups based on the presence or absence of CAAs at the time of the study. The Institutional Review Board approved this study.

2.1 | Clinical and laboratory data

The following clinical data were collected for each patient: gender; days of fever at initial presentation; days from onset of fever to first IVIG dose; treatment resistance, defined as persistent fever more than 36 hours after initial IVIG dose; administration of intravenous steroids; and laboratory studies at presentation, including white blood cell count, hemoglobin, platelet count, albumin, aspartate transaminase, alanine transaminase, erythrocyte sedimentation rate, and C-reactive protein. In addition, patient age, body surface area, and days between illness onset and performance of echocardiogram were collected at the time of each echocardiogram.

2.2 | Conventional echocardiographic data

All studies included conventional M-mode, two-dimensional, and Doppler echocardiographic examinations with a commercial ultrasound imaging system (Vivid 9, General Electric Medical Systems, Milwaukee, WI, USA). All conventional echocardiographic parameters were obtained from reports created by experienced pediatric echocardiography readers using a standardized imaging protocol according to published guidelines.[17] These parameters included: LV shortening fraction, LV ejection fraction, presence or absence of coronary artery dilation, presence or absence of CAAs, presence of pericardial effusion, and qualitative assessment of mitral regurgitation severity. Coronary artery dilation was defined as proximal coronary artery luminal diameter *Z*-score >2 but <2.5, and CAA was defined as proximal coronary artery luminal diameter *Z*-score ≥ 2.5.[1,16]

2.3 | Myocardial deformation analysis

A research sonographer with extensive experience with 2DSTE performed offline myocardial deformation analysis using EchoPAC (version 11.0.0, General Electric Healthcare, Milwaukee, WI, USA).[18,19] This observer was blinded to the KD phase and coronary

artery status at the time of the echocardiograms. The myocardial deformation parameters measured included: LV global longitudinal strain (GLS), global longitudinal systolic strain rate (GLSSR), global circumferential strain (GCS), global circumferential systolic strain rate (GCSSR), peak torsion, and torsion rate. Apical 4-, 3-, and 2-chamber views were used to measure LV global longitudinal myocardial deformation. Short-axis views at the base, papillary muscles, and apex were used to measure LV global circumferential myocardial deformation and torsion. Myocardial deformation analysis was performed according to published echocardiographic protocols.[20,21] Published normal values of myocardial deformation parameters in children were used as reference ranges.[20,22]

2.4 | Statistical analysis

IBM SPSS Statistics for Macintosh, Version 22 (IBM Corp, Armonk, NY) was used to perform all statistical analyses. KD-phase groups were analyzed for differences in clinical, laboratory, and echocardiographic parameters. Continuous variables were expressed as mean ± standard deviation and compared using analysis of variance. Categorical variables were expressed as a percent and analyzed using chi-square analysis. The convalescent/chronic phase subgroups based on the presence or absence of CAAs were compared using *t* test for continuous variables and chi-square analysis for categorical variables. A *P*-value ≤ .05 was considered statistically significant.

3 | RESULTS

The acute, subacute, and convalescent/chronic KD phase groups included 31, 25, and 67 echocardiograms, respectively. Table 1 shows the clinical characteristics of the various KD phase groups. The echocardiograms in the convalescent/chronic phase group were from older children than the echocardiograms in the other groups. The laboratory results at the time of KD presentation were similar for all three KD phase groups. There were no differences in the incidence of treatment resistance or use of IV steroids between the groups. Of note, 14 of the 31 echocardiograms in the acute phase group were performed more than 24 hours after treatment with IVIG.

3.1 | Conventional echocardiographic data

Conventional echocardiographic data are shown in Table 2. The acute phase group had significantly increased incidence of coronary artery dilation when compared to the convalescent/chronic phase group, but showed no difference when compared to the subacute phase group. The convalescent/chronic phase group had a higher incidence of CAAs when compared to the acute phase group. There was no statistically significant difference in the incidence of CAAs between the convalescent/chronic as compared to the subacute phase group. All other conventional echocardiographic parameters demonstrated no statistically significant differences between

TABLE 1 Clinical characteristics of the KD phase groups

	Acute (31)	Subacute (25)	Convalescent/Chronic (67)
Age at time of echocardiogram (years)	2.4 ± 1.6†	2.7 ± 2.1‡	4 ± 2.8†,‡
BSA at time of echocardiogram (m^2)	0.6 ± 0.2†	0.6 ± 0.2	0.7 ± 0.3†
Male gender	20 (64%)	13 (52%)	41 (61%)
Days of fever at diagnosis (days)	6 ± 2	7 ± 4	8 ± 6
Treatment resistance	11(35%)	8 (32%)	15 (22%)
Treatment with intravenous steroids	13 (42%)	14 (56%)	29 (43%)
Laboratory values at presentation:			
White blood cell count, (10^9/L)	14 ± 6	16 ± 6	15 ± 7
Hemoglobin, (g/dL)	10.4 ± 2.4	11.1 ± 5.6	10.3 ± 4.1
Platelet count, (10^9/L)	371 ± 145	370 ± 168	367 ± 185
Albumin, (g/dL)	3.5 ± 0.8	3.4 ± 0.6	3.4 ± 1
Aspartate transaminase, (U/L)	53 ± 39	56 ± 30	63 ± 53
Alanine transaminase, (U/L)	58 ± 62	61 ± 63	69 ± 86
Erythrocyte sedimentation rate, (mm/h)	67 ± 43	74 ± 28	64 ± 34
C-reactive protein, (mg/L)	16 ± 18	16 ± 17	14 ± 13

Continuous variables are expressed as mean ± standard deviation, categorical variables as number of subjects with percent of sample in parentheses.
†Indicates $P < .05$ for acute vs convalescent/chronic.
‡Indicates $P < .05$ for subacute vs convalescent/chronic. BSA: Body surface area.

TABLE 2 Conventional echocardiography assessment of the KD phase groups

	Acute (31)	Subacute (25)	Convalescent/Chronic (67)
LV end-diastolic dimension (mm)	31.52 ± 4.7	31.21 ± 5.1	33.11 ± 6.4
LV end-systolic dimension (mm)	20 ± 3.6	19.61 ± 3.9	20.36 ± 4.8
LV shortening fraction (%)	40 ± 4	37 ± 5	39 ± 8
LV ejection fraction (%)	60 ± 6	59 ± 5	58 ± 8
Coronary artery dilation	13 (41%)†	6 (24%)	12 (18%)†
Coronary artery aneurysm	2 (6%)†	4 (16%)	16 (24%)†
Mitral regurgitation	1	0	1
Pericardial effusion	2	1	0

Continuous variables are expressed as mean ± standard deviation, categorical variables as number of subjects with respective percentage between parentheses.
†Indicates $P < .05$ for acute vs convalescent/chronic.

groups. Mitral regurgitation and pericardial effusion were rare in this patient cohort.

3.2 | Myocardial deformation data

Myocardial deformation analysis data are shown in Figure 1. While all groups had normal LV myocardial deformation when compared to published reference values,[20,22] there were subtle but significant differences between the groups. Specifically, the convalescent/chronic phase group had significantly lower LV GLSSR (Figure 1B), GCSSR (Figure 1D), peak torsion (Figure 1E), and torsion rate (Figure 1F) than the acute phase group. The convalescent/chronic phase group also had significantly lower LV GCSSR than the subacute phase group (Figure 1D).

3.3 | Subanalysis of echocardiograms from the convalescent/chronic phase of KD

Sixteen out of 67 (24%) echocardiograms performed during the convalescent/chronic phase of KD revealed the presence of CAAs. Table 3 shows the clinical characteristics of the subgroups with and without CAAs. The children in the subgroup with CAAs had higher BSA and experienced treatment resistance more frequently than the children in the subgroup without CAAs. Figure 2 shows myocardial deformation parameters for these subgroups. The subgroup with CAAs had significantly lower LV GLSSR (Figure 2B) and GCSSR (Figure 2D) when compared to the subgroup without CAAs.

4 | DISCUSSION

To our knowledge, this is the first comprehensive cross-sectional analysis of LV myocardial deformation using 2DSTE during different phases of KD. Using published normal reference ranges, we determined that the three KD phase groups examined in this study had normal LV myocardial deformation. Comparison between the groups demonstrated decreased myocardial deformation in the convalescent/chronic phase group when compared to the other KD phase groups. Subanalysis of the convalescent/chronic phase group revealed a subtle but significant decrease in myocardial deformation in children with persistent CAAs when compared to children without CAAs.

We found a higher incidence of CAAs in the convalescent/chronic phase group as compared to the acute phase group. This finding is consistent with the known natural history of KD.[1] The lack of a statistically significant difference between the incidence of CAAs in the convalescent/chronic phase group as compared to the subacute phase group is likely a result of small sample size in the subacute phase, and because of increased utilization of echocardiography for follow-up of patients with CAAs (relative to patients without CAAs) in our institution.

Multiple studies have reported depressed LV longitudinal strain in the acute phase of KD with improvement in this parameter after the administration of IVIG.[10-13] The depressed LV longitudinal strain during the acute phase appears to correlate with inflammation and signs of carditis, including mitral regurgitation and pericardial effusion.[12] In this study, the patients included in the acute phase group had a low occurrence of mild mitral regurgitation and pericardial effusion, and normal myocardial deformation parameters. All the KD phase groups had comparable laboratory results at the time of presentation, suggesting a similar degree of inflammation.

With the broad use of IVIG, the incidence of CAAs in KD has decreased dramatically from 29% to 5%.[9] However, the occurrence of severe coronary artery events, including thrombosis, stenosis, myocardial infarction, and death, remains significantly higher in children that develop giant CAAs vs those with small to moderate CAAs (48% vs 1%, respectively).[23] The vasculopathy of KD includes three distinct processes. Self-limited necrotizing arteritis occurs in the first 2 weeks after fever onset. Subacute/chronic vasculitis and luminal myofibroblastic proliferation follow the necrotizing arteritis and can continue for months to years after the initial presentation.[9] These vascular changes eventually lead to apparent normalization

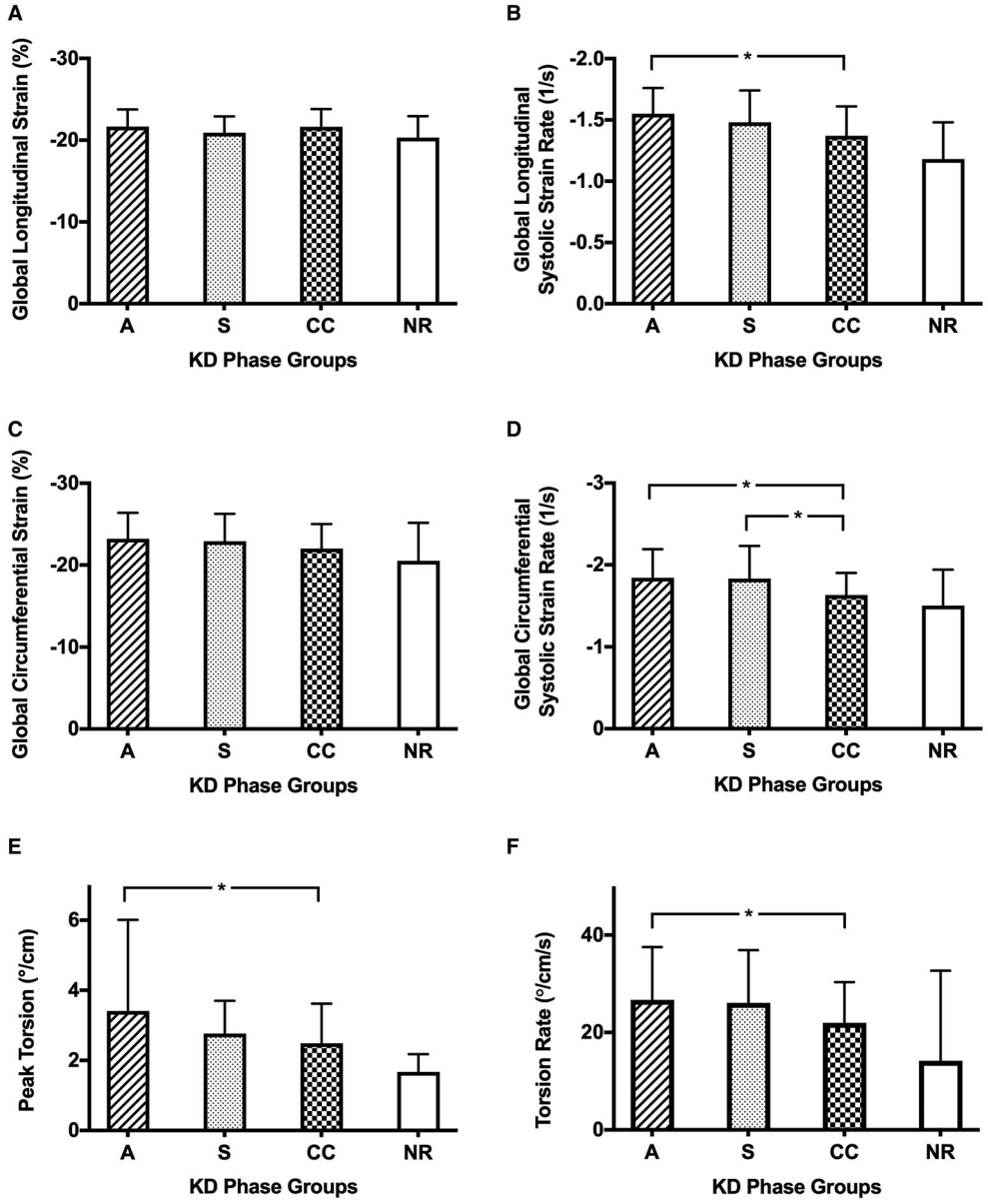

FIGURE 1 Comparison of left ventricular myocardial deformation parameters between the acute (A), subacute (S), and convalescent/chronic (CC) KD phase groups, $^*P < .05$. The corresponding normal published reference values (NR) are shown for visual comparison. The normal reference values were not included in the statistical analyses. (A) Global longitudinal strain. (B) Global longitudinal systolic strain rate. (C) Global circumferential strain. (D) Global circumferential systolic strain rate. (E) Peak torsion. (F) Torsion rate

of the vessel lumen. However, the affected coronary arteries have functional and structural abnormalities and may develop arterial stenosis.[24,25] In consequence, long-term monitoring of myocardial function in KD patients with a history of CAAs is key to early detection of compromised myocardial perfusion.

Dedeoglu et al[26] compared a cohort of 30 children at least 6 months after the onset of KD to healthy controls and found decreased longitudinal strain in the LV basal and apical segments in the children with previous KD. However, they found no difference in longitudinal strain between the children with and without persistent CAAs. Our analysis included additional myocardial deformation indices not evaluated by Dedeoglu et al, which revealed statistically significant differences in GLSSR and GCSSR between children with CAAs and children without CAAs during the convalescent/chronic phase of KD. Unfortunately, the available data do not allow us to evaluate the clinical implications of these differences.

Systolic strain rate quantifies the velocity of myocardial deformation. The assessment of systolic strain rate may be a useful indicator of myocardial contractility in the long-term evaluation in children with KD, as it is independent of heart rate.[27,28] Longitudinal studies of children with a history of KD are needed to determine if GLSSR and GCSSR become abnormal in the follow-up of patients with persistent CAAs.

TABLE 3 Clinical characteristics of the convalescent/chronic KD phase subgroups by coronary artery aneurysm status

	Absent (51)	Present (16)
Age (years)	3.5 ± 2.4	5.4 ± 3.6
Male gender	19 (37%)	7 (44%)
Body surface area (m^2)	0.6 ± 0.2	0.9 ± 0.5†
Treatment resistance	7 (14%)	8 (50%)†
Treatment with intravenous steroids	19 (37%)	10 (63%)†

Continuous variables are expressed as mean ± standard deviation, categorical variables as number of subjects with respective percentage in parentheses.
†Indicates $P < .05$ for absent vs present.

Patients with a remote history of KD and CAAs have alterations in myocardial perfusion that are undetectable by standard echocardiography. Bratis et al[29] reported abnormalities in myocardial perfusion reserve as measured by cardiac magnetic resonance imaging in children 5 years after KD presentation who had coronary artery involvement. All the myocardial segments had decreased perfusion regardless of the status of the coronary arteries at the time of the study and despite normal LV ejection fraction. Yu et al[24] studied adolescents and young adults with a history of KD and coronary involvement using three-dimensional STE and found that patients with persistent CAAs have decreased LV global longitudinal strain, regardless of the presence or absence of myocardial perfusion abnormalities with exercise. Therefore, the use of standard

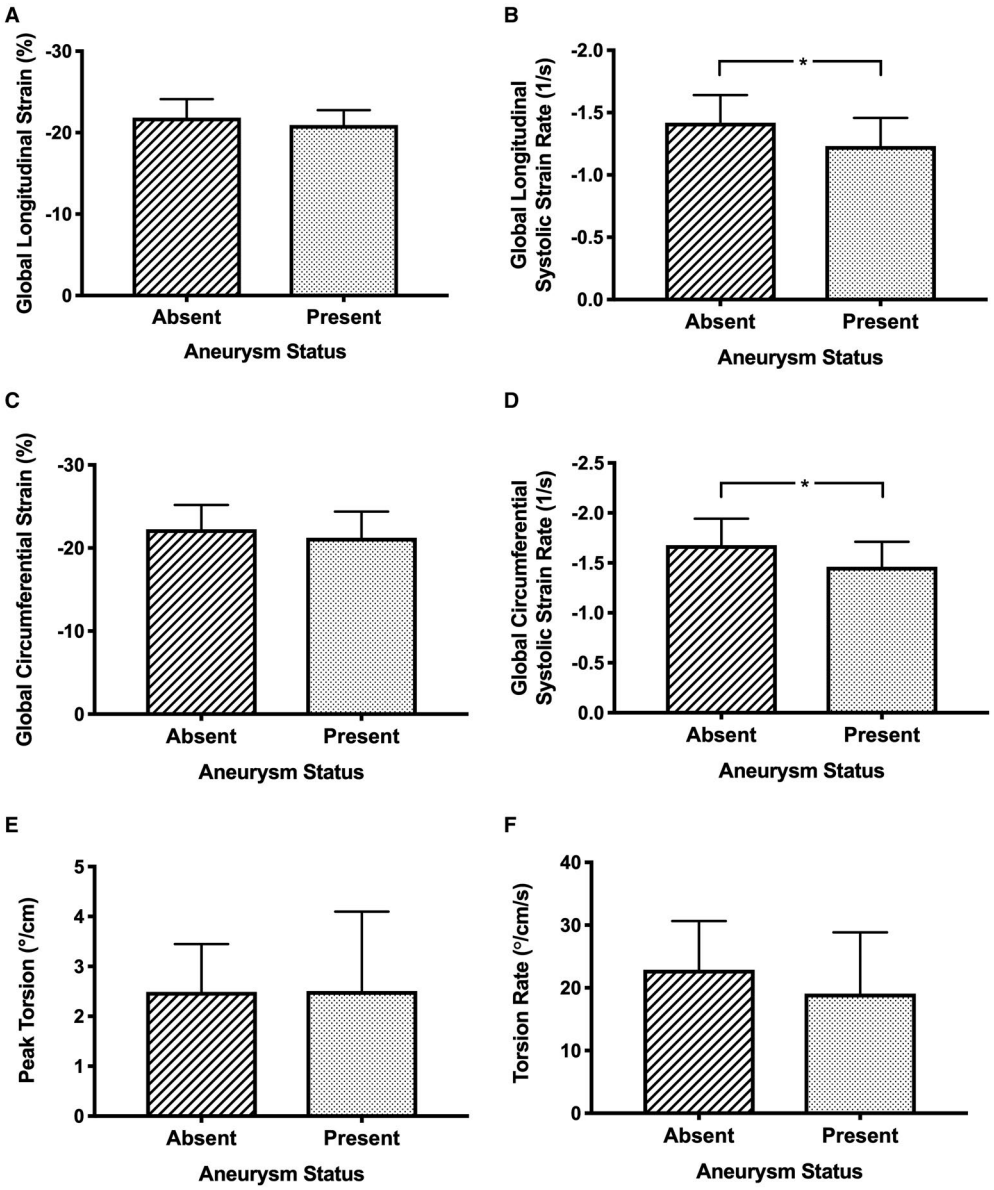

FIGURE 2 Comparison of left ventricular myocardial deformation parameters of convalescent/chronic children grouped by coronary artery aneurysm status at the time of echocardiogram, *$P < .05$. (A) Global longitudinal strain. (B) Global longitudinal systolic strain rate. (C) Global circumferential strain. (D) Global circumferential systolic strain rate. (E) Peak torsion. (F) Torsion rate

echocardiography in the follow-up of patients with KD and CAAs is not sufficient.

Longitudinal myocardial deformation is the most vulnerable component of myocardial mechanics and is primarily determined by the subendocardial fibers.[9] Circumferential myocardial deformation and torsion assess primarily the mid-myocardial and epicardial fibers, which are affected by transmural myocardial disease.[30] KD is a multivessel disease with the potential to cause myocardial ischemia. Hence, assessing global LV longitudinal and circumferential deformation using multiple imaging planes seems appropriate in this population.

The reproducibility of 2DSTE and availability of normative data in children facilitates the use of this technology in clinical practice.[21,22] New equipment and software have decreased the variability in strain measurements among vendors in the last few years.[31] In this study, children in the convalescent/chronic phase were older than children in the acute and subacute phases. Levy et al[22] performed a meta-analysis of LV myocardial deformation and showed that in the pediatric population, age and BSA are not significant determinants of variations of LV myocardial deformation.

4.1 | Limitations

This was a cross-sectional study, and thus longitudinal data from the same patients across the different phases of KD was not available. The echocardiograms were part of routine clinical practice. Therefore, studies that did not include adequate images for myocardial deformation analysis were excluded. The number of patients with CAAs was small, hence assessment of myocardial deformation based on aneurysm size was not possible. Angiographic data regarding the presence or absence of stenotic coronary lesions were not included in this study. The number of echocardiograms included in each group was small, which limits the detection of small differences in myocardial deformation, and limits the scope of our conclusions.

5 | CONCLUSIONS

We performed a comprehensive cross-sectional analysis of LV myocardial deformation using 2DSTE in children with KD. Children in the convalescent/chronic phase of KD have normal LV myocardial deformation. However, when compared to children in the acute and subacute phases of KD, children in the convalescent/chronic phase have a subtle decrease in longitudinal and circumferential systolic strain rate that is more pronounced in the subgroup with persistent CAAs. While the study presented here is unable to determine the clinical impact of the finding of decreased in strain rate, this finding is worth noting, as the impact of chronic coronary involvement on myocardial function in children with KD is not fully understood. Longitudinal studies are needed to discern if children with CAAs go on to develop abnormal myocardial deformation in the long term.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Aura A. Sanchez participated in project design, clinical data collection, evaluation of the quality of the echocardiographic images, drafting the article, critical revision, and approval of the final article.
Sara K. Sexson Tejtel participated in project design, statistical analysis, critical revision, and approval of the final article.
Myriam E. Almeida-Jones participated in project design, clinical data collection, evaluation of the quality of the echocardiographic images, critical revision, and approval of the final article.
Douglas K. Feagin Jr participated in the evaluation of the quality of the echocardiographic images, speckle tracking analysis, critical revision, and approval of the final article.
wCarolyn A. Altman participated in project design, critical revision, and approval of the final article.
Ricardo H. Pignatelli participated in project design, evaluation of the quality of the echocardiographic images, critical revision, and approval of the final article.

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