Strain Echocardiography and Myocardial Dysfunction in Critically Ill Children With Multisystem Inflammatory Syndrome Unrecognized by Conventional Echocardiography: A Retrospective Cohort Analysis

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OBJECTIVES: Multisystem inflammatory syndrome in children is a newly defined complication of severe acute respiratory syndrome coronavirus 2 infection that can result in cardiogenic shock in the pediatric population. Early detection of cardiac dysfunction is imperative in directing therapy and identifying patients at highest risk for deterioration. This study compares the strengths of conventional and strain echocardiography in identifying cardiac dysfunction in critically ill children with multisystem inflammatory syndrome in children and their association with ICU therapeutic needs and clinical outcomes.

DESIGN: Retrospective, observational cohort study.

SETTING: A large, quaternary care PICU.

PATIENTS: Sixty-five pediatric patients admitted to the PICU with the diagnosis of multisystem inflammatory syndrome in children from March 2020 to March 2021.

INTERVENTIONS: Global longitudinal strain four chamber was measured retrospectively by strain echocardiography and compared with conventional echocardiography. Cardiac dysfunction was defined by left ventricular ejection fraction less than 55% and global longitudinal strain four chamber greater than or equal to −17.2%. Clinical variables examined included cardiac biomarkers, immune therapies, and ICU interventions and outcomes.

MEASUREMENTS AND MAIN RESULTS: Twenty-four patients (37%) had abnormal left ventricular ejection fraction and 56 (86%) had abnormal global longitudinal strain four chamber. Between patients with normal and abnormal left ventricular ejection fraction, we failed to identify a difference in cardiac biomarker levels, vasoactive use, respiratory support needs, or ICU length of stay. Global longitudinal strain four chamber was associated with maximum cardiac biomarker levels. Abnormal global longitudinal strain four chamber was associated with greater odds of any vasoactive use (odds ratio, 5.8; 95% CI, 1.3–25.3; *z*-statistic, 2.3; $p = 0.021$). The number of days of vasoactive infusion was correlated with global longitudinal strain four chamber ($r = 0.400$; 95% CI, 2.4–3.9; $p < 0.001$). Children with abnormal strain had longer ICU length of stay (4.5 d vs 2 d; $p = 0.014$).

CONCLUSIONS: Our findings suggest strain echocardiography can detect abnormalities in cardiac function in multisystem inflammatory syndrome in children patients unrecognized by conventional echocardiography. These abnormalities are associated with increased use of intensive care therapies. Evaluation of these patients with strain echocardiography may better identify those with myocardial dysfunction and need for more intensive therapy.

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KEY WORDS: cardiac dysfunction; multisystem inflammatory syndrome in children; pediatric intensive care unit; strain echocardiography

Multisystem inflammatory syndrome in children (MIS-C) is defined as a constellation of symptoms including: serious illness requiring hospitalization, an age of less than 21 years, fever, laboratory evidence of inflammation, multisystem (> 2) organ involvement, no plausible alternative diagnosis and evidence of infection with severe acute respiratory syndrome coronavirus 2 based on reverse transcriptase-quantitative polymerase chain reaction, antibody testing, or exposure to persons with coronavirus disease 2019 in the past month (1). A subset of children with MIS-C develop acute cardiogenic shock with left ventricular dysfunction and clinical symptoms similar to myocarditis requiring admission to the PICU (2, 3). These patients frequently require critical care interventions including vasoactive infusions and positive pressure ventilation (PPV) as well as steroids, IV immunoglobulins (IVIGs), biologic therapies anticoagulation, and supportive care (1, 4–9).

Identifying early markers of cardiac dysfunction would be helpful to both direct therapy and identify MIS-C patients at highest risk for deterioration. In the absence of endomyocardial biopsies or cardiac MRI, elevation of serum biomarkers N-terminal brain natriuretic peptide (BNP), and troponin-I have been used to diagnose and quantify myocardial injury, as they correlate with the degree of myocardial inflammation (10). Echocardiographic findings during the acute phase of MIS-C have shown abnormalities in systolic function, atrioventricular valve regurgitation, and coronary artery abnormalities (11). Conventional echocardiographic assessment of systolic function uses left ventricular ejection fraction (LVEF); however, it can be limited by loading states (12).

Strain echocardiography (SE) is a validated measure that quantifies displacement of segments of myocardium. It can detect subtle perturbations in left and right ventricular deformation that correlate with stroke volume and other intrinsic measures of cardiac function (12–14). SE evaluation of myocardial function in MIS-C patients found that global strain correlated with biochemical measures of myocardial injury (BNP > 500 pg/mL and troponin-I > 0.3 ng/mL) (10). In non-MIS-C children with myocarditis and sepsis, measures of myocardial strain have been sensitive indicators for systolic dysfunction (13–16).

The association between echocardiographic parameters (SE and LVEF) and ICU severity of illness markers in critically ill children with MIS-C has not been assessed. Our objective was to compare SE and LVEF (as markers of systolic function) in critically ill children with MIS-C and correlate them with biomarker evidence of cardiac dysfunction, ICU therapeutic needs, and clinical outcomes.

METHODS

Clinical Protocol

This was a retrospective study in a large urban academic quaternary care freestanding children's hospital in Washington, DC. The Institutional Review Board at Children's National Hospital approved this study (Protocol 00014477). All pediatric patients (< 21 yr) admitted to the PICU with the diagnosis of MIS-C from March 2020 to March 2021 were reviewed. Confirmation of each diagnosis was done by a multidisciplinary task force and only those patients with confirmed MIS-C were included in our cohort. Demographic information was obtained on each patient including age, gender, race, and ethnicity. Presence of underlying chronic medical conditions, baseline functional status score measured by the Functional Status Scale (FSS) score and initial location of admission (inpatient floor or PICU) were recorded for each patient (17). A multidisciplinary team developed diagnostic and treatment protocols to identify and treat these patients. As a part of the clinical protocol, patients received echocardiograms to diagnose cardiovascular dysfunction and/or acquired alterations in coronary arteries, a panel of inflammatory markers to determine the effect of immunological activation, and laboratory analyses to determine end-organ dysfunction and involvement. The clinical protocol for confirmed cases included supportive care, IVIG, immune modulation, and empiric anticoagulation. Treating clinicians were not blinded to biomarkers or conventional echocardiography findings.

Echocardiography

The first echocardiogram obtained during the index hospitalization for each patient was used for the analyses. The echocardiograms were performed on either a

Phillips (Andover, MA) or GE (Chicago, IL) vendor machine. Standard protocol was followed for each echocardiogram study, and each was read by a pediatric cardiologist. Conventional echocardiographic measurements were made in accordance with American Society of Echocardiography guidelines, including LVEF by modified Simpson's biplane method (18). SE was performed retrospectively on each echocardiogram by an experienced sonographer blinded to clinical parameters and reviewed by an attending pediatric cardiologist. SE was done on the TomTec (Chicago, IL) vendor platform. SE measurements were not available to clinicians at the bedside and therefore did not influence clinical management of the patients. Global longitudinal strain (GLS_{4ch}) was measured on the apical four-chamber view. GLS measurements with SE are feasible in patients with sufficient image quality and have good inter- and intra-observer reproducibility comparable with that of LVEF measurements with conventional echocardiography. SE can be conducted in real-time on standard echocardiography machines or retrospectively with vendor nonspecific post-processing software (19). Patients were excluded if both LVEF and GLS_{4ch} were not able to be measured on the first echocardiogram. We defined preserved or normal LVEF as 55% or greater (20). By convention, GLS_{4ch} is reported as a negative percentage, representing an averaged percent change of individual segments of myocardium. A GLS_{4CH} value more negative than –17.2% is consistent with preserved or normal global longitudinal strain (19, 21). Presence of pericardial effusion was noted on the first echocardiogram and classified as none, trivial, mild, moderate, or significant.

Clinical Variables

The clinical variables included serum biomarkers of cardiac dysfunction and ICU therapies. Serum biomarkers included N-terminal BNP (in pg/mL) and troponin-I (ng/mL) levels. For each biomarker, we reported the level obtained within 24 hours of admission and maximum level during the hospitalization. ICU therapies included vasoactive infusions and PPV. Vasoactive infusions included epinephrine, norepinephrine, vasopressin, and milrinone. Duration of vasoactive infusions in days and maximum Vasoactive-Inotropic Score (VIS) were recorded for each patient (22). PPV included use and days of any noninvasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation (MV). For patients requiring endotracheal intubation and MV, findings of chest radiograph after intubation were reviewed for presence of infiltrates, atelectasis, pleural effusion, and/or pulmonary edema. Other outcomes included ICU and hospital length of stay (LOS) and hospital survival.

Statistics

Statistical analysis was performed with Wizard Pro, Version 1.9.48 (Evan Miller, Boston, MA; https://www.wizardmac.com). Binary and categorial data were expressed as absolute numbers and percentages. Continuous data were summarized by medians and interquartile ranges (25–75th percentiles). chi-square or Mann-Whitney *U* tests were used to compare proportions of binary or continuous outcomes between normal and abnormal LVEF and SE subgroups. Correlations were assessed using Pearson correlation. Odds ratios were calculated to compare strength of associations. A probability value of less than 0.05 was treated as significant in this analysis.

RESULTS

There were 82 children with a confirmed diagnosis of MIS-C admitted to the PICU between March 2020 and March 2021. There were 65 patients with LVEF and GLS_{4ch} measurements on their first echocardiogram (**Fig. 1**). Patients were a median age of 8.5 years (interquartile range [IQR], 4.2–13.4 yr), 36 (55%) were male, 2 (3%) had chronic medical conditions, and only one had an abnormal baseline FSS. There was a predominance of Black (49%) and Hispanic/Latino patients (43%). The majority (n = 46; 71%) were admitted directly to the ICU and 19 (29%) were admitted to non-ICU locations and subsequently transferred to the ICU.

Median time to first echocardiogram was 17 hours (IQR, 8–28 hr) from hospital admission. **Table 1** shows measurements of cardiac function and cardiac biomarkers. Median LVEF for all patients was 58% (IQR, 49.7–62.1%). Abnormal LVEF was seen in 24 of 65 patients (37%) with a median LVEF of 48.1% (IQR, 42.9–50.4%), consistent with mild dysfunction. Only one patient in our cohort had a LVEF consistent with moderate dysfunction (< 40%). Pericardial effusions were found in 19 of 65 patients (29%); however, of these, 17 (89%) were trivial and 2 (11%) were mild. Abnormal strain was seen in 56 of 65 patients (86%).

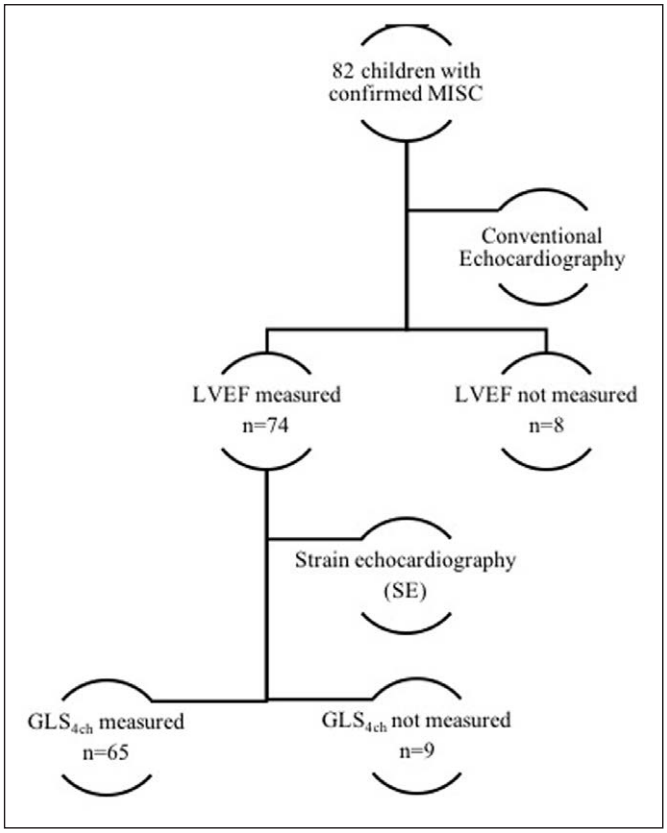

Figure 1. Conventional and strain echocardiography image acquisition in children with multisystem inflammatory syndrome in children (MISC). GLS_{4ch} = global longitudinal strain four chamber, LVEF = left ventricular ejection fraction, SE = strain echocardiography.

Of the 41 patients with normal LVEF, 32 (78%) had abnormal strain. All patients with abnormal LVEF had abnormal strain. There was a significant correlation of GLS_{4ch} with LVEF (r = –0.535; 95% CI, –14.4 to –12.4; $p < 0.001$). All patients had increased maximum BNP concentrations (> 500 pg/mL) with a median value of 18,480 pg/mL and 38 (58%) patients had increased troponin-I levels (> 0.3 ng/mL) with a median value of 0.37 ng/mL. There was no difference in admission or maximum BNP or troponin levels between patients with normal and abnormal LVEF. Admission troponin was higher in those with abnormal strain (0.12 vs 0.03; $p = 0.032$). Both maximum BNP and troponin values were higher in patients with abnormal GLS_{4ch} compared with those with normal GLS_{4ch} (19,910 vs 9,592 pg/mL; $p = 0.042$ and 0.415 vs 0.110 ng/mL; $p = 0.014$).

LVEF was higher in those patients admitted to non-ICU locations compared to those admitted directly to the ICU (61.9% [IQR, 57.3–64.6%] vs 56.1% [IQR, 48.4–61.1%]; $p = 0.005$). There was no difference in strain based on initial location of admission. **Table 2** shows ICU therapies and clinical outcomes for our patients based on LVEF and SE. Of the patients requiring endotracheal intubation, post-intubation films showed pleural effusion in only one of 13 patients, pulmonary edema in eight of 13 patients, and atelectasis in four of 13 patients. At the time of their first echocardiogram, 8 (12%) of our patients were receiving MV and 32 (49%) were receiving vasoactive infusions, with a median VIS of 7.5. Of the 32 patients on vasoactives at the time of the echocardiogram, median LVEF was 56.8% (IQR, 50.4–61.6%) and median strain was –12.4% (IQR, –14.7% to –10%). There were 12 of 32 patients (37%) who had abnormal LVEF, whereas 30 of 32 patients (94%) had abnormal GLS_{4ch}. We did not identify a difference in use or duration of vasoactives, use of PPV, or use or duration of NIPPV or MV between patients with normal and abnormal LVEF. Abnormal GLS_{4ch} was associated with greater odds of any vasoactive use (odds ratio, 5.8; 95% CI, 1.3–25.3; z-statistic, 2.3; $p = 0.021$). The number of days of vasoactive infusion was correlated with GLS_{4ch} (r = 0.400; 95% CI, 2.4–3.9; $p < 0.001$). We did not identify a difference in ICU or hospital LOS between patients with normal or abnormal LVEF. However, patients with abnormal GLS_{4ch} had a longer ICU LOS (4.5 vs 2 d; $p = 0.014$) than those with normal GLS_{4ch}. GLS_{4ch} was correlated with ICU LOS (r = 0.271; 95% CI, 3.8–6.6; $p = 0.029$). All patients survived to hospital discharge.

DISCUSSION

In this single-center retrospective study, we compared cardiac dysfunction in critically ill MIS-C patients assessed by conventional and SE and examined the association of echocardiographic findings with cardiac biomarkers and clinical outcomes. Our findings suggest SE can detect abnormalities in cardiac function that are unrecognized by conventional echocardiography and are associated with increased use of intensive care therapies.

Published case series have reported abnormal LVEFs in 34–80% of MIS-C patients, with median LVEF values ranging from 46% to 60% (1, 8, 10, 11, 23–25). This mild degree of dysfunction is similar to our study, where the median LVEF in our abnormal EF group was 48.1% and all patients was 61.4%. While LVEF is the most commonly used metric to assess for cardiac dysfunction, there are several important

TABLE 1.
Measurements of Cardiac Function and Cardiac Biomarkers by Conventional Echocardiography and Strain Echocardiography

Measurement	All Patients ($n = 65$)	Conventional Echocardiography			Strain Echocardiography		
		Normal LVEF (≥ 55%, $n = 41$)	Abnormal LVEF (< 55%, $n = 24$)	p	Normal GLS_{4ch} (< −17.2%, $n = 9$)	Abnormal GLS_{4ch} (≥ −17.2%, $n = 56$)	p
LVEF (%), median (IQR)	58 (49.7–62.1)	61.4 (58.4–64.0)	48.1 (42.9–50.4)	< 0.001	62.2 (61.4–64.9)	56.6 (49–61.6)	0.003
GLS_{4ch} (%), median (IQR)	−13.5 (−15.9 to −10.7)	−14.5 (−16.7 to −12.6)	−11.0 (−12.6 to −10.0)	< 0.001	−20 (−21.6 to −18.6)	−12.6 (−14.5 to −10.1)	< 0.001
Admission BNP (pg/mL)[a]	4,882 (2,176–14,925)	4,844 (2,121–14,122)	5,341 (3,726–17,886)	0.420	4,777 (1,920–15,401)	6,072 (4,462–14,925)	0.708
Maximum BNP (pg/mL)	18,480 (9,592–31,261)	17,042 (8,436–24,784)	19,225 (12,690–34,000)	0.192	9,592 (7,099–17,042)	19,910 (10,507–32,699)	0.042
Admission troponin (ng/mL)[b]	0.09 (0.02–0.31)	0.05 (0.02–0.31)	0.19 (0.04–0.41)	0.312	0.03 (0.02–0.05)	0.12 (0.02–0.49)	0.032
Maximum troponin (ng/mL)	0.37 (0.12–1.01)	0.33 (0.11–0.71)	0.75 (0.15–3.72)	0.061	0.11 (0.09–0.17)	0.415 (0.2–1.43)	0.014

BNP = brain natriuretic peptide, GLS_{4ch} = global longitudinal strain four chamber, IQR = interquartile range, LVEF = left ventricular ejection fraction.

[a]Admission BNP values were obtained in 56 of 65 patients.

[b]Admission troponin values were obtained in 57 of 65 patients.

cautions for interpreting the results. LVEF is a volume-based measure and is subject to loading conditions and use of vasoactive agents (26). Our finding of median LVEF of 56.8% in patients on vasoactives at the time of echocardiogram suggests potential normalization of LVEF values despite intrinsic cardiac dysfunction.

SE is an angle-independent, direct measurement of myocardial tissue motion and deformation and is relatively independent of loading conditions, allowing it to be a useful measure in clinical scenarios where fluid resuscitation and vasoactive infusions are commonly employed (15, 26). Global longitudinal strain has been studied extensively as a method to detect abnormal myocardial mechanics and has superior prognostic value to LVEF in predicting major adverse cardiac events and mortality (27–32). While we found a higher prevalence of abnormal strain in patients with normal LVEF than other studies, the general observations of systolic dysfunction by SE in MIS-C patients with preserved LVEF are consistent with our results (10, 11, 23, 24, 33). The high prevalence of impaired strain in our cohort (86%) may arise from the clinical status of our patients being in the ICU with physiologic derangements consistent with more disease severity.

Several studies have shown significant correlations of multiple metrics of strain, including global longitudinal strain, with both BNP and troponin-I (10, 24, 33). Although there is sparse histologic data describing the etiology of cardiac dysfunction in MIS-C, myocardial inflammation related to the systemic inflammation has been a proposed mechanism (24). This inflammation has been seen on endocardial biopsy and cardiac MRI in select case reports. However, n-terminal BNP and troponin-I levels have more widespread use (2, 7, 8, 10, 11, 5). While nearly all our patients showed elevation in biomarkers, there was no difference in BNP or troponin-I between patients with normal and abnormal LVEF,

TABLE 2.
ICU Therapies and Outcomes by Measurements of Cardiac Function

ICU Therapies	All Patients ($n = 65$)	Conventional Echocardiography			Strain Echocardiography		
		Normal LVEF (≥ 55%, $n = 41$)	Abnormal LVEF (< 55%, $n = 24$)	p	Normal GLS_{4ch} (< −17.2%, $n = 9$)	Abnormal GLS_{4ch} (≥ −17.2%, $n = 56$)	p
Any vasoactives, *n* (%)	50 (77)	30 (73)	20 (83)	0.348	4 (44)	46 (82)	0.013
Days vasoactives, median (IQR)	3.5 (2–5)	2 (0–4)	3 (2–5)	0.158	2 (2–4)	4 (2–5)	0.099
Maximum Vasotropic-Inotropic Score, median (IQR)	15 (7–25)	17 (7–25)	12 (9.5–23)	0.262	17 (10–40)	14.8 (7–25)	0.577
Any positive pressure ventilation, *n* (%)	36 (55)	22 (51)	14 (67)	0.714	3 (33)	33 (59)	0.152
NIPPV, *n* (%)	28 (43)	16 (39)	12 (50)	0.388	1 (11)	27 (48)	0.037
Days of NIPPV, median (IQR)	2 (2–4)	2 (2–4)	2.5 (2–6)	0.837	2 (2–2)	2 (2–4)	0.714
Mechanical ventilation, *n* (%)	13 (20)	8 (20)	5 (21)	0.898	2 (22)	11 (20)	0.857
Days mechanical ventilation, median (IQR)	5 (4–5)	4.5 (4–5)	5 (5–7)	0.284	4.5 (4–5)	5 (3–7)	0.769
ICU outcomes							
ICU LOS, median (IQR)	4 (2–6)	3 (2–5)	4.5 (3–7)	0.145	2 (2–4)	4.5 (3–7)	0.014
Hospital LOS, median (IQR)	12 (8–14)	11 (8–14)	13 (8–18)	0.288	10 (8–13)	12 (8–15)	0.581
Mortality, *n* (%)	0 (0)	NA	NA	NA	NA	NA	NA

GLS_{4ch} = global longitudinal strain four chamber, IQR = interquartile range, LOS = length of stay, LVEF = left ventricular ejection fraction, NA = not available, NIPPV = noninvasive positive pressure ventilation.

while patients with abnormal strain had maximum levels two- to four-fold as high. These associations were not seen with admission BNP levels, suggesting strain may have utility in early identification of myocardial inflammation in patients with normal LVEF.

We found an association of strain and several ICU outcomes, including intensity of vasoactive use and ICU LOS that were not observed with LVEF. In a study with critically ill septic children, a correlation between higher VIS and worsening left ventricular longitudinal strain was been seen and thought to be the result from poor intrinsic cardiac function leading to increased need for inotropes (13). These findings support strain as a sensitive and clinically relevant indicator of cardiac dysfunction that is associated with severe illness and requirement of cardiovascular and respiratory support. Similar relationships have been seen with strain and various clinical metrics; however, in a population less critically ill as ours (24).

The limitations of this study include its population from a single center, retrospective design, lack of uniformity of timing of echocardiogram with clinical interventions, and 17 of 82 patients (21%) excluded due to inadequate imaging for one of the imaging measures. We also only analyzed only one SE metric of systolic strain (GLS_{4ch}). Additional measurements, including more specific assessment of diastolic dysfunction may yield additional associations with clinical outcomes. There were also variable amounts of volume

resuscitation, PPV support, and vasoactive administration at the time of the imaging studies, which may have had disproportional effects on LVEF and strain.

CONCLUSIONS

Abnormal myocardial strain is common in children with MIS-C admitted to the PICU and may be indicative of myocardial dysfunction in the setting of normal LVEF. Patients with abnormal strain required more intensive therapies. Real-time SE may identify MIS-C patients at risk for more aggressive interventions, while normal strain measurements may identify children with milder symptoms and less aggressive course of disease.

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