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EDITORIAL COMMENT

Cardiac Dysfunction in Multisystem Inflammatory Syndrome in Children

A Call to Action*

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected >25 million people worldwide and led to more than 830,000 deaths. Compared with adults, children are less commonly symptomatic from acute COVID-19 infection. Indeed, only 2% of confirmed cases have occurred in persons <18 years, and the mortality rate in children is 0.5% (1). However, the early comfort that healthy children were largely spared from critical COVID-19-related illness has been shattered in recent months by descriptions of a severe post-infectious syndrome among children exposed to SARS-CoV-2, with clinical features resembling both Kawasaki disease (KD) and toxic shock syndrome. This emerging syndrome has been defined by health organizations worldwide and named multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) by the US Centers for Disease Control and Prevention (CDC). MIS-C prevalence typically surges 3 to 6 weeks after the peak of COVID-19 in a geographic region (2–5). This timing, together with findings of positive serology and negative NTPCR in most affected children suggest that pathogenesis is related to host immune response and hyperinflammation (3–6).

Involvement of the cardiovascular system in MIS-C is common (80% to 85% of cases) and is a primary determinant of illness severity (4–7). Cardiac findings in MIS-C may include left ventricular (LV) dysfunction; coronary artery (CA) dilation or aneurysms; arrhythmias; valvar dysfunction; pericardial effusion; and elevated troponin, brain natriuretic peptide (BNP), or N-terminal BNP (1–6). Case series have reported depressed LV ejection fraction (EF) in approximately 40% to 60% of patients (1–6), with the mechanism of dysfunction incompletely elucidated. To date, the trajectory of recovery of systolic function has been characterized only in small retrospective case series (2–9). However, early reports suggest that LVEF normalizes in most patients within 1 to 2 weeks after initial presentation (7,8).

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In this issue of the *Journal* Matsubara et al. (10) assess cardiac findings by echocardiography in a single-center, retrospective study of patients with MIS-C. The strength of the paper is its comprehensive echocardiographic evaluation of systolic and diastolic parameters of LV and right ventricular function. In this report, the authors compare 28 patients with MIS-C with 20 similar-aged normal control subjects and with 17 patients with classic KD. Of note, 78% of patients with MIS-C were treated with vasopressors and 25% with invasive ventilation. Compared with control subjects and patients with KD, the MIS-C group had lower LVEF and, even more strikingly, reduced measures of global LV systolic strain and strain rate. Most measures of right ventricular systolic function were also worse in patients with MIS-C. Several left atrial and diastolic ventricular deformation parameters, and tissue Doppler measures of LV diastolic function, were lower in patients with MIS-C compared with both control groups. Importantly, abnormalities in myocardial systolic and diastolic

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function were present even in patients with MIS-C with preserved EF; these generally improved over median follow-up of 5 days. Patients with "myocardial injury," defined here as elevated BNP or troponin, had a greater degree of impairment in systolic and diastolic function. These findings emphasize the importance of comprehensive echocardiographic assessment of myocardial function in patients with MIS-C. The findings on longitudinal assessment of LV function and on CA changes should be interpreted with caution, given the small sample size and short follow-up duration.

In previously published MIS-C case series, approximately 50% of hospitalized children have greater than or equal to mild LV systolic dysfunction (1-7). In most cases, ventricular dysfunction is global and associated with presentation in hemodynamic shock. The earliest MIS-C case series focused the sickest children who presented with shock and, not surprisingly, most of these early cases had acute LV dysfunction (2,7,9). Two more recent multicenter series captured larger populations of hospitalized patients with MIS-C. Feldstein et al. (5) collected data from 53 American centers finding that 71 of 186 (38%) of patients had LVEF <55% (33% with EF 30% to 54% and 5% with EF <30%). Dufort et al. (4) reported 95 children with MIS-C, of whom 52% had ventricular dysfunction, although EF was not quantified. In the largest case series published to date (n = 570), the CDC reported cardiac dysfunction in 41% of patients, elevated troponin in 31%, and elevated BNP in 43% (6). These series, particularly the multicenter studies, are limited by lack of standardized, central review of cardiac findings and uniform echocardiographic protocols with standard definitions of LV dysfunction. In some publications even basic measures of LV function, such as EF, were not measured. Multicenter studies with standardized definitions and ideally Core Lab review using comprehensive function protocols, such as those presented by Matsubara et al. (10) are needed to more accurately define the incidence, severity, and natural history of myocardial dysfunction in MIS-C.

The reported recovery of LV systolic function in most cases within 1 to 2 weeks of diagnosis (7,8) suggests that dysfunction may be secondary to cytokine milieu, systemic inflammation, and acute stress. Because MIS-C is a recently recognized syndrome, only short-term follow-up and limited cardiac magnetic resonance imaging, biopsy, and autopsy data are available to inform the understanding of the pathologic mechanisms underlying ventricular dysfunction. The longer-term implications for myocardial health, including risk for of myocardial fibrosis with accompanying diastolic dysfunction, are unknown. A recent study performed comprehensive, serial echocardiograms showing similar findings to Matsubara et al. (10) and cardiac magnetic resonance imaging in 20 hospitalized patients with MIS-C (8). By magnetic resonance imaging, 1 patient had focal myocardial delayed enhancement and 10 patients (50%) had myocardial edema, most commonly global (n = 6) or involving basal septal segments (n = 3).

The lack of significant CA changes reported by Matsubara et al. (10) should be interpreted with caution. The sample size is small and the reported findings differ from those in larger case series. Although the incidence of CA changes varies considerably across studies, all have reported CA abnormalities (incidence: ~9% to 25%) and a small number of large/giant CA aneurysms have been reported (2-6). In the initial CDC series, 9% of patients had CA aneurysms, defined by at least 1 CA segment *z*-score ≥2.5 (5). Similarly, Dufort et al. (4) reported CA aneurysms in 9% of children. The most recent CDC case series (n = 570) reported CA *z*-score ≥2 in nearly 20% of cases (6). This variation could reflect differences in definition or in frequency and quality of CA imaging. In KD, coronary aneurysms can continue to enlarge for weeks after illness onset. However, few data are available on changes in coronary size over time or the pathogenesis of coronary enlargement in MIS-C (i.e., disruption in the integrity of the coronary arterial wall vs. vasodilation from fever and inflammation).

In summary, Matsubara et al. (10) demonstrate that patients with MIS-C have widespread and significant abnormalities in ventricular systolic and diastolic function that may be underestimated using only traditional echocardiographic measures, such as EF. Although MIS-C is thought to be rare compared with COVID-19, occurring in 2 versus 322 per 100,000 individuals age <21 years (3), the severely-ill patients described in the first wave of publications may be the tip of an iceberg. Future MIS-C studies should include long-term surveillance in a large, multicenter cohort representing a spectrum of disease severity to assess how cardiac abnormalities evolve over time. This information is vital to provide prognostic information on cardiac health after MIS-C, to inform longer-term clinical care pathways, and to guide lifestyle recommendations including return to competitive sports.

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REFERENCES

1. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:458–64.

2. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259–69.

3. Lee PY, Day-Lewis M, Henderson LA, et al. Distinct clinical and immunological features of SARS-COV-2-induced multisystem inflammatory syndrome in children. J Clin Invest 2020 Jul 23 [E-pub ahead of print].

4. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York state. N Engl J Med 2020;383:347–58.

5. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334–46.

6. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children — United States, March–July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074–80.

7. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020 May 17 [E-pub ahead of print].

8. Theocharis P, Wong J, Pushparajah K, et al. Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. Eur Hear J Cardiovasc Imaging 2020 Aug 7 [E-pub ahead of print].

9. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607–8.

10. Matsubara D, Kauffman HL, Wang Y, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol 2020;76:1947–61.

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