INTRODUCTION

The multi-inflammatory syndrome in children (MIS-C) associated with COVID-19 infection (also variably mentioned as Pediatric Inflammatory Multisystem Syndrome temporally associated with COVID-19) is a novel clinical entity first reported in Italy.[1] The disease is characterized by fever, gastrointestinal symptoms, hemodynamic instability, and elevated acute-phase reactants. The cardiovascular involvement is significant with evidence of left ventricular systolic and diastolic dysfunction as well as coronary dilatation.[2] However, a number of children do not have overt cardiovascular dysfunction on echocardiographic assessment despite characteristic clinical features.[3] Investigations in a small subset of such children had documented elevated NT pro-BNP levels often in excess of 10,000 pg/mL (personal communication with Dr Kartik Surya). This suggests that the children have cardiac abnormality not detected on standard echocardiographic assessment. The clinical picture of this condition has been shown to overlap with Kawasaki disease (KD) and early work in KD has shown an association with reduced peak left atrial longitudinal strain (PALS) even in the absence of coronary artery abnormalities.[4] Similar data have been reported in one series of children with MIS-C.[2] We hence performed left atrial (LA) longitudinal deformation imaging in six children with MIS-C and noted that the PALS was reduced compared to normal in published literature in all six children.

METHODS

Six-consecutive patients who satisfied the clinical criteria for MIS-C underwent a detailed echocardiogram. All echocardiograms were performed by the same cardiologist. The echocardiograms were performed in an Epiq Elite ultrasound machine (Philips Medical Systems, Andover, MA, USA) using a X5-1 matrix transducer or a S 9-3 single crystal transducer based on the child’s age and...
weight. The studies were electrocardiographically (ECG) gated. The coronary artery dimensions were measured in the para-sternal short-axis view using the S9-3 transducer in all patients [Figure 1a and b]. The coronary artery values were normalized for body surface area using published z-score values. The left ventricle (LV) ejection fraction was calculated by M-mode echocardiography, two-dimensional echocardiographic, and apical four-chamber (A4C) and two-chamber (A2C) views by the biplane Simpson’s disc summation method and, whenever feasible, the Global Longitudinal Strain (GLS) was calculated based on composite analysis of the A4C, A2C and apical three chamber (A3C) views by the Autostrain LV package (TomTec Systems, Munich, Germany) provided by the vendor on the machine [Figure 2]. The diastolic function was assessed by calculating the mitral valve lateral annulus e’ velocity on tissue Doppler imaging as well as the mitral valve E velocity by pulse-wave Doppler in the mitral inflow. The LA volume was calculated by biplane Simpson’s disc summation method when good quality LA images were obtained in both the views. When the atrial imaging on the A2C view was unsatisfactory, only the A4C view was used. An indexed volume >20 ml/m² was considered as LA enlargement. An ECG gated A4C view was obtained for five consecutive beats. This was then exported for offline analysis. LA longitudinal deformation analysis [Figure 3a and b as well as Video 1] was performed offline by a dedicated software (AutoStrain LA, TomTec Systems, Munich, Germany).

RESULTS

The clinical and echocardiographic details of all the children are tabulated in Table 1. All children satisfied the clinical criteria for MIS-C.

There was clinical, echocardiographic, or laboratory evidence of cardiovascular compromise in 4 of 6 children with a low ejection fraction in 2. None of the children had abnormal diastolic function on conventional parameters (Lat e’ and E/Lat e’). However, three children had enlarged LA based on the indexed LA volume. All six children had PALS below 30% suggesting abnormal LA longitudinal deformation.

The children were treated with immune-modulatory medications (intravenous methylprednisolone and/or intravenous immunoglobulin [IVIG]). One child (patient 5) required a second dose of IVIG before fever settled. All other children became afebrile with the first line therapy and were discharged home on anti-platelet dose of aspirin after acute-phase reactants normalized and they remained afebrile for 48 hours.

DISCUSSION

LV diastolic dysfunction precedes LV systolic dysfunction in all forms of myocarditis. The PALS which is an assessment of the LA reservoir function has been shown to be reduced in adults with diastolic dysfunction. It has been shown to be reduced in children with LA dilatation from varied causes. The parameter was studied in children with KD and was shown to be superior to Lat e/e’ in differentiating acute KD from controls.

The initial reports from Europe and North America have shown that the coronary artery dilatation in MIS-C is less spectacular than KD with a very low incidence of giant aneurysms. The first series from our country reported a very low incidence of cardiac abnormalities in all our patients, there were no aneurysms and the coronary artery z-scores seldom exceeded +2.5. Coronary artery prominence and peri-vascular echogenicity have been reported more widely. However, both these findings are subjective and have very high inter-operator variability.

The incidence of ventricular dysfunction is higher in children with MIS-C than classical KD suggesting more extensive myocardial involvement. This was noted in our series with more than 50% of children presenting with ventricular dysfunction or other evidence of hemodynamic instability. The first report of comprehensive echocardiographic assessment of children with MIS-C from North America reported that...
reduced PALS was the single strongest echocardiographic index in children with MIS-C. Although the PALS was reduced in children with MIS-C who did not have other features suggesting myocardial injury, the PALS was lower in children with additional evidence of myocardial injury. This is similar to the values seen in our series as well. Patient 2 had a disproportionately low GLS and PALS compared to the ejection fraction. This patient had a hyper-acute presentation with high grade fever and hypotension on day 3 of illness which may account for impaired deformation even before mechanical dysfunction was more evident. Patient 5 also had a heart rate much higher than the physiological range. Although imaging at a good frame rate was obtained, the fidelity of the deformation parameters at such high heart rates is not well understood.

PALS appears to be an attractive option as the analysis is not angle dependent and is not affected by LV myocardial abnormalities which can potentially alter TDI values. Most commercially available echocardiogram equipment and pediatric probes achieve sufficient frame rates to ensure accuracy of the analysis and a standard A4C view can be obtained by most operators with echocardiographic training. It should be emphasized that MIS-C (similar to KD) remains a clinical diagnosis with echocardiography providing additional diagnostic utility. The need for advanced functional assessment like PALS, which are not widely available at present, should not result in a delay in institution of immune-modulatory therapy.

A major limitation of our study is the absence of age-matched controls. There are no published normative data for LA strain among Indian children. However, the PALS of each of our children was lower than the published values in both East Asian and Caucasian population. We also did not have follow-up data on our children to look for normalization of LA deformation after recovery of illness. LA deformation analysis has not been incorporated into routine clinical practice among adults and further studies will need to be performed in normal children and those with congenital and acquired heart diseases before the modality can be recommended for regular practice.

In conclusion, PALS appears to be a promising addition to the echocardiographic evaluation of children with MIS-C based on our preliminary experience. However, further studies including comparisons with age-matched controls should be performed before this can be recommended as a diagnostic feature of the condition. Sequential cardiac imaging and PALS in these children will provide

Table 1: Clinical and echocardiographic parameters in the 6 children included in the study

| Parameter               | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Age (in y)              | 9 years   | 12 years  | 12 years  | 7 years   | 4 months  | 7 months  |
| BSA (in m²)             | 1.18      | 1.72      | 1.57      | 0.79      | 0.3       | 0.36      |
| Clinical evidence of hemodynamic compromise | Yes | Yes | No | No | Yes | No |
| LVFS (M-mode)           | 23.7%     | 25.6%     | 29.9%     | 37.8%     | N/A       | 31.5%     |
| LVEF (M-mode)           | 49%       | 54.5%     | 56.1%     | 68%       | N/A       | 61.6%     |
| LVEF (2D)               | 51%       | 52.4%     | 56.4%     | 60%       | 58.9%     | 60%       |
| GLS                     | -17.2%    | -11%      | N/A       | -22%      | N/A       | -21.6%    |
| Lat e' (in cm/s)        | 10.9      | 18.6      | 14.8      | 16        | N/A       | 13        |
| E/Lat e'               | 8.7       | 5.1       | 7.7       | 7.5       | N/A       | 8.8       |
| LMCA z-score            | 2.35      | 0.15      | 0.48      | 2.07      | 1.86      | 2.03      |
| LAD z-score             | 2.28      | 1.39      | 0.44      | 2.35      | 2.41      | 1.9       |
| RCA z-score             | -0.24     | 0.37      | -1        | 1.7       | 2.08      | 1         |
| HR                      | 79        | 127       | 113       | 111       | 214       | 90        |
| Frame rate (fps)        | 50        | 55        | 92        | 76        | 77        | 82        |
| PALS                    | 26.3%     | 12.7%     | 21.2%     | 27.8%     | 16.6%     | 29.8%     |

BSA – body surface area, fps – frames per second, GLS – Global longitudinal strain, HR – heart rate, LAD – left anterior descending artery, LAVI – left atrial volume indexed to body surface area, LMCA – left main coronary artery, LVEF – left ventricle ejection fraction, LVFS – left ventricle fractional shortening, RCA – right coronary artery, PALS – peak atrial longitudinal strain
information on the persistence of myocardial damage in this cohort and improve our understanding of the natural history of this condition.

**Acknowledgments**

The authors would like to thank Philips Medical Systems India Ltd. for providing a limited period complimentary access to the Autostrain LA package for offline analysis.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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