



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# The Electrocardiogram in Multisystem Inflammatory Syndrome in Children: Mind Your Ps and Qs



Since its first description in Wuhan province in December 2019, coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has disrupted the health and economic welfare of millions of people around the world. Children were initially thought to be spared from severe disease.<sup>1-3</sup> However, in spring 2020, initial reports from Italy and the UK described a new multisystem inflammatory syndrome in children (MIS-C), with features of cardiovascular involvement and Kawasaki syndrome.<sup>4-6</sup> As of December 2020, almost 1300 cases of MIS-C and 23 deaths from this syndrome had been reported to the US Centers for Disease Control and Prevention.<sup>3</sup> MIS-C seems to crest about 1 month after the peak for positive SARS-CoV-2 testing in a region, and many children have antibodies to SARS-CoV-2 at presentation, suggesting that MIS-C is caused by a postinfectious inflammatory response.<sup>7-10</sup>

Children with MIS-C typically present with fever, hypotension, multiorgan involvement, and markedly elevated inflammatory markers. The great majority of those affected have cardiovascular complications, which may include shock, ventricular dysfunction, coronary artery dilation and aneurysms, or arrhythmias.<sup>7,8,10-12</sup> Whereas acute cardiovascular involvement is frequent, its causes and long-term sequelae remain active areas of investigation. Potential pathophysiologic mechanisms include dysregulated inflammation, direct viral cardiomyocyte toxicity, and microvascular dysfunction, which in turn may cause not only shock and myocardial dysfunction, but also abnormalities of the cardiac electrical conduction (including bradyarrhythmias, tachyarrhythmias, and electrocardiogram [ECG] changes).<sup>7,8,10-14</sup>

In this volume of *The Journal*, Regan et al describe a review of ECGs obtained during hospital admission and follow-up of patients with MIS-C.<sup>15</sup> They found ECG abnormalities during the illness in the majority of patients (n = 42 [67%]). Findings included interval prolongations, decreased amplitude, and T-wave inversion. Most of those abnormalities were seen during hospital admission, improved before hospital discharge, and normalized at outpatient follow-up. All intervals, including PR, QRS, and QTc, were prolonged in patients with MIS-C during hospitalization. Depending upon the interval type (ie, PR, QRS, or QTc), 6%-11% of patients had conduction or repolarization delays for age at time of admission, 7%-17% during hospitalization, 2%-12% at time of discharge, and 2%-3% at the time of follow-up. PR prolonga-

tion was the most frequently encountered conduction delay (n = 16 [25%]) and the last one to normalize, with first-degree atrioventricular block (AVB) in 12% of patients at time of discharge (vs 2%-3% with QRS or QTc prolongation at discharge). The authors also described an abnormal PR:heart rate slope, defined as a paradoxical lengthening of the PR interval at increasing heart rates in patients with a  $\geq 5$  bpm difference in heart rate on  $\geq 2$  ECGs. This finding supports conduction system involvement, beyond the expected PR prolongation due solely to changes in autonomic states.

Two pediatric series have reported conduction abnormalities in 19%-20% of patients with MIS-C.<sup>13,14</sup> One series described first-degree AVB with no progression to higher grade AVB whereas the other reported progression to second- or third-degree AVB in 75% of patients with first-degree AVB.<sup>13,14</sup> The first series describing first-degree AVB found no significant difference in cardiac enzymes, inflammatory markers, and ventricular dysfunction between patients with and without AVB, similar to findings of Regan et al.<sup>14,15</sup> The other series reported that all patients with AVB required admission to the intensive care unit (unrelated to conduction abnormalities) and had echocardiographic evidence of ventricular dysfunction.<sup>13</sup> In all series, the conduction abnormalities peaked during hospitalization, at a median of 6 days after onset of symptoms.<sup>13,14</sup> Although the etiology of AVB in MIS-C remains unclear, we hypothesize that it could be caused by inflammation and edema of the conduction tissue. Conduction abnormalities, including complete heart block, have also been described in viral myocarditis unrelated to coronavirus disease-2019, which is characterized by an inflammatory infiltrate of the myocardium on histopathology.<sup>16</sup>

The hypothesis that conduction disturbances in MIS-C result from diffuse myocardial inflammation and edema is supported by findings of decreased voltages and T-wave changes. The authors have described a sequence of ECG changes, including low QRS amplitude on admission, followed by precordial T-wave flattening and inversion, which normalized before discharge.<sup>15</sup> These dynamic ECG changes have been observed in a variety of conditions often associated with transient ventricular dysfunction, including pericarditis, myocarditis, acute coronary syndrome, myocardial contusion, and Takotsubo or stress cardiomyopathy.<sup>17-21</sup> Despite their frequency, little is known about the pathogenesis of those ECG findings, sometimes referred to as Wellen's

See related article, p 27

AVB	Atrioventricular block
ECG	Electrocardiogram
MIS-C	Multisystem inflammatory syndrome in children
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Funded by The McCance Foundation. J.N. is a member of the Editorial Board of *The Journal of Pediatrics*. The authors declare no conflicts of interest.

0022-3476/\$ - see front matter. © 2021 Elsevier Inc. All rights reserved.  
<https://doi.org/10.1016/j.jpeds.2021.01.061>

phenomenon. A case series described myocardial edema on cardiac magnetic resonance imaging associated with transient T wave inversion in the anterior precordial leads, supporting edema and inflammation as an underlying mechanism.<sup>17,18</sup> Similar mechanisms may be responsible for ECG changes in patients with MIS-C. Prior series have described elevated brain natriuretic peptide in 78-100% patients, elevated troponin in 50-95%, ventricular dysfunction in 35-100%, and coronary artery dilation/aneurysm in 14-48%.<sup>8,10-12</sup> A study using cardiac magnetic resonance imaging in 20 patients 11-29 days after MIS-C diagnosis found abnormal strain in all patients and myocardial edema in half of the patients.<sup>22</sup> Similar to ECG changes described in this manuscript, the finding of myocardial edema did not correlate with ventricular function (ejection fraction and strain). More recently, a study using functional echocardiographic assessment with deformation measures (global longitudinal strain, left atrial strain) showed that all patients with MIS-C had evidence of diastolic dysfunction, with decreased strain measurements compared with normal subjects, suggesting that myocardial involvement may be more frequent than initially thought.<sup>23</sup>

In summary, using serial ECGs in a single-center series, Regan et al provide a comprehensive study of ECG abnormalities during hospitalization for MIS-C, with findings of changes in ECG voltages, T-wave polarity, and conduction times. These frequent and transient ECG changes during the course of illness may reflect systemic inflammation and myocardial involvement during hospitalization for MIS-C, even in patients with preserved systolic function on echocardiogram. This emphasizes the importance of rigorous cardiology follow-up of all children who have had MIS-C, including those without ventricular dysfunction or coronary dilation during the acute phase. Multimodality cardiac testing will help us elucidate the pathophysiologic changes, their importance for long-term cardiac health, and risk of sudden cardiac death with return to play. ■

**Audrey Dionne, MD**  
**Jane W. Newburger, MD, MPH**  
 Department of Cardiology  
 Boston Children's Hospital  
 Department of Pediatrics  
 Harvard Medical School  
 Boston, MA

Reprint requests: Jane W. Newburger, MD, MPH, Harvard Medical School, Department of Cardiology, Children's Hospital, 300 Longwood Ave, Boston, MA 02115 E-mail: [jane.newburger@cardio.chboston.org](mailto:jane.newburger@cardio.chboston.org)

## References

- Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of Covid-19 in children in early January 2020 in Wuhan, China. *N Engl J Med* 2020;382:1370-1.
- Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* 2020;26:502-5.
- Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. Accessed January 4, 2021. [www.cdc.gov/mis-c/cases/index.html](http://www.cdc.gov/mis-c/cases/index.html)
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;395:1607-8.
- Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771-8.
- Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Distributed via the CDC Health Alert Network. <https://emergency.cdc.gov/>.
- Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020;324:259-69.
- Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med* 2020;383:347-58.
- Levin M. Childhood multisystem inflammatory syndrome – a new challenge in the pandemic. *N Engl J Med* 2020;383:393-5.
- Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020;383:334-46.
- Alsaied T, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. *Circulation* 2020;143:78-88.
- Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. *Eur J Pediatr* 2021;180:307-22.
- Dionne A, Mah DY, Son MBF, Lee PY, Henderson L, Baker AL, et al. Atrioventricular block in children with multisystem inflammatory syndrome. *Pediatrics* 2020;146:e202009704.
- Choi NH, Fremed M, Starc T, Weller R, Cheung E, Ferris A, et al. MIS-C and cardiac conduction abnormalities. *Pediatrics* 2020;146:e202009738.
- Regan W, O'Byrne L, Stewart K, Miller O, Pushparajah K, Theocharis P, et al. Electrocardiographic changes in children with multisystem inflammation associated with COVID-19. *J Pediatr* 2021;234:27-32.
- Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, et al. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987;1:3-14.
- Migliore F, Zorzi A, Perazzolo M, Basso C, Corbetti F, De Lazzari M, et al. Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction. *Heart Rhythm* 2011;8:1629-34.
- Tada H. Unraveling the riddle of transient T-wave inversion (Wellens' ECG pattern): T2-weighted magnetic resonance imaging identifies myocardial edema. *Heart Rhythm* 2011;8:1635-6.
- Agatsuma H, Hirai M, Hirayama H, Suzuki A, Takanaka C, Yabe S, et al. Transient giant negative T wave in acute anterior myocardial infarction predicts R wave recovery and preservation of left ventricular function. *Heart* 1996;75:229-34.
- Catanzaro JN, Meraj PM, Zheng S, Suzuki A, Takanaka C, Yabe S, et al. Electrocardiographic T-wave changes underlying acute cardiac and cerebral events. *Am J Emerg Med* 2008;26:716-20.
- Prasas A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008;155:408-17.
- Theocharis P, Wong J, Pushparajah, Mathur SK, Simpson JM, Pascall E, et al. Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. *Eur Heart J Cardiovasc Imaging* 2020;7:jeaa212.
- Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiogram findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. *J Am Coll Cardiol* 2020;76:1947-61.