Letter to Editor for AHA Scientific Statement:
Diagnosis and Management of Myocarditis in Children

The Endomyocardial Biopsy: An Archaic Method for Advanced Medicine?

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We were pleased to read the recent American Heart Association Scientific Statement regarding the diagnosis and management of myocarditis in children by Law et al. (1) Given the invasive and low-sensitivity nature of endomyocardial biopsy (EMB), the advances of non-invasive techniques including cardiac magnetic resonance (CMR) to aide in disease diagnosis and management of various pathological conditions is becoming an area of continual focus and research. More recently, Blanco-Domínguez et al. identified novel microRNA that can distinguish myocarditis from myocardial infarction with area under the ROC curve of 0.927(95% CI, 0.879 - 0.975). (2) These findings further challenge the role of the EMB as a "gold standard".

The most recent 2021 international position statement on EMB highlights indications for EMB in conditions such as myocarditis but also notes the dismal diagnostic yield (1.39%) for detecting clinically silent rejection following heart transplantation. (3) With the advent of non-invasive tests, such as CMR, microRNA and cell-free-DNA (cf-DNA), when should EMB be considered, if at all?

The success of non-invasive tests such as cf-DNA in materno-fetal medicine, oncology, and transplant nephrology to identify genetic abnormalities, disease progression and rejection has limited the role of invasive procedures in their respective fields. (4) With their noted success, will cf-DNA eventually replace surveillance EMBs following heart transplantation? Will CMR and microRNA replace EMBs for diagnosis of myocarditis?

The EMB is becoming archaic. While there may always be a need, multi-disciplinary teams may ultimately decide what invasive and non-invasive tests are needed for each individualized patient. (5) The increased use of non-invasive tests such including CMR, microRNA and cf-DNA is evident, and with time, these methods will only improve, eventually replacing the EMB.

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Letter to Editor: Cardiac Magnetic Resonance Imaging for Emerging SARS-CoV-2 and mRNA COVID-19 Vaccine Associated Myocarditis.

Bibhuti Das, MD

The American Heart Association (AHA) scientific statement by Law et al., "Diagnosis and Management of Myocarditis in Children," is an essential step based on emerging shreds of evidence on myocardial inflammation.[1] This statement highlights a paradigm shift in the diagnosis of myocarditis by cardiac magnetic resonance imaging (CMR). Confirming the diagnosis of myocarditis in children by CMR is very timely. It will be helpful to tackle the resurgence of myocarditis cases during the COVID-19 pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The cardiac involvement with COVID-19 portends worse clinical outcomes. Several mechanisms have been postulated to elucidate the pathogenesis by which SARS-CoV-2 induces myocardial injury: 1) myocardial injury is directly induced by SARS-CoV-2 infection, and 2) myocardial injury is an indirect result of multiple factors such as systemic inflammatory response, hypoxia, apoptosis, and cytokine storm. Should SARS-CoV-2 be considered cardiotropic, and is it necessary to test for this virus with other common viral agents for diagnosing viral myocarditis in the future?

The role of CMR in acute myocarditis is not questionable, but the timing is. CMR studies performed at variable time points after the acute phase of myocarditis can result in different findings. Generalized myocardial edema can be homogeneous throughout the myocardium in the initial stage to the point that CMR may not easily detect it on qualitative analysis. Although diffuse changes could still be identified as an increased global signal intensity ratio normalized against reference regions in the skeletal muscle, coexisting skeletal muscle inflammation may lead to false-negative results.[2] Furthermore, young children with acute myocarditis can be clinically unstable. Is CMR necessary to confirm acute myocarditis with a higher risk of sedation or intubation required for imaging in younger children? Does confirmation of the myocarditis diagnosis by CMR in a child with suspected myocarditis will change the management?

We need uniform CMR criteria to diagnose a specific etiology, which can be helpful as myocardial biopsy findings are similar in all types of myocarditis except few exceptions like acute fulminant, hypersensitivity, or giant cell myocarditis. Moreover, the recent rise in cases of myocarditis associated with mRNA COVID-19 vaccine[3-5] both in the US and Europe led the US Food and Drug Administration and European Medicine Agency to warn about the risk of myocarditis and pericarditis after mRNA COVID-19 vaccine administration. Although the available limited data have reported that mRNA vaccine-associated myocarditis patients recover entirely from clinical symptoms and have normalization of inflammatory markers and troponin within a short period, there is substantial evidence of myocardial inflammation by CMR. The changing pattern of myocarditis in children emphasizes the need for more in-depth information on CMR findings to diagnose and manage myocarditis in children.

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Response by Lal, Law, and Godown to Letters Regarding Article, "Diagnosis and Management of Myocarditis in Children"

In Response:
We appreciate the interest generated by our recent publication, "Diagnosis and Management of Myocarditis in Children" (1). Both Alam et al. and Das raise important questions related to the role of biopsy and cardiac magnetic resonance imaging (CMR) in diagnosing myocarditis.

We agree with Alam et al. that the role of endomyocardial biopsy (EMB) in the diagnosis of myocarditis has evolved in the current era with a clear trend towards increasing use of CMR and decreased use of EMB. However, it is premature to consider EMB "archaic". In challenging cases that do not follow the expected clinical course, EMB is a crucial tool that can be helpful to make a diagnosis of giant cell or hypersensitivity myocarditis, potentially altering clinical management. Viral PCR from the tissue can also support the diagnosis as well as isolate an infectious cause. These findings offer the opportunity to advance our understanding of emerging cardiac diseases through translational science, a point that is particularly relevant in the current era of SARS-CoV-2. While we applaud advances in other modalities such as CMR, micro-RNA and cell free DNA, we would argue that these modalities remain complementary and are not ready for prime time to relegate the EMB archaic.

Our colleague Das raises many important questions related to the role of CMR in the SARS-CoV-2 era. We agree that despite significant advancements related to CMR, there remain challenges with timing, differentiation of causes, ability to assess and reproduce the Lake Louise criteria across centers in children. This statement was an attempt to update academic centers and community hospitals with current advancements in CMR in the context of other diagnostic modalities. As to whether Coronavirus, previously not considered a top viral pathogen associated with myocarditis, will remain an important cause in the future remains an open question.

We contend that the changing pattern of myocarditis in children emphasizes the need for more in-depth information, not just with EMB and CMR, but in the entire clinical spectrum. We surmise that myocarditis in children is different from adults, and as illustrated in this correspondence, it is important for us to collaborate to acquire the data that can answer some of these questions. In the meantime, medical decision making about the best approach to assess patients should be made on a case by case, or center by center basis, and should consider CMR capabilities, catheterization lab experience and a center's treatment algorithm based on the findings from these and other more elaborate tests. As highlighted in our statement, most of the advances related to myocarditis focus on diagnosis, but we believe that these advances can be leveraged to improve management and treatment in the next era.

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