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EDITORIAL COMMENT

Understanding Myocarditis

From an Early Sketch Toward a More Complete Picture*

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Acute myocarditis represents a rapid-onset inflammatory process of the myocardium. The description of inflammation of the heart was first identified in the mid-1700s by Dr Jean Baptiste Senac in France.[1] Without a clear understanding of what the disease encompassed, the term "myocarditis" was developed in 1837 by Dr Joseph Freidrich Sobernheim.[1] In 1900, Dr Carl Ludwig Alfred Fiedler histologically defined myocarditis.[2] Work in the mid-to-late 1900s examined the role of viruses.[1] The Dallas criteria for diagnosing myocarditis came about in 1986[3] which then supported the use of endomyocardial biopsy (EMB) as the gold standard for diagnosis. In recent years, we have made significant advances in laboratory and imaging tools. Cardiovascular magnetic resonance (CMR) is able to noninvasively detect myocardial inflammation, thereby improving the robustness of the diagnosis.[4] The study of immune mechanisms and modulation of disease has also steadily grown.[5] Despite the advances and the many years between initial identification of an acutely inflamed heart and today, the full picture of what myocarditis entails is incomplete.

The effects of sex and age comprise part of the unknowns, and they are key components to understanding the mechanistic origin of myocarditis. Immune response differences between sexes may impact differences in the manifestation of disease. For example, autoimmune disease more often presents within women than men.[6] Within the heart, hormones such as testosterone and estrogen influence the immune response and myocardial function.[7-9] When one considers that sex is determined by an individual patient's genetic profile, one can better understand that differences in chromosomal complement correspond to male-female differences at a molecular level. Similarly, immune modulation differs through the life course of an individual.[10] Understanding the changing variables related to sex and age may help create individualized risk profiles for patients.

In this issue of *JACC: Advances*, Thevathasan et al.[11] perform a sex- and age-based comparison within a large group of patients with myocarditis, presenting multicenter cohorts from Germany (n = 6,023) and the United States (n = 9,079), with data collected between 2005 and 2021. The German cohorts were diagnosed by EMB or CMR. The U.S. cohort data originated from the National Inpatient Sample.

Examining the different rates of frequency among the collective group of patients, the study found a clear dominance of male presentation within the "young" adult (ages 18-35 years) with 72.9% German and 74.3% U.S. affected male patients and the "medium-aged" adults (ages 35-54 years) with 61% German and 62.4% U.S. male patients affected. Upon examining the group of patients older than 54 years, males and females presented in a more similar frequency (52% German males, 45.8% U.S. males).

The youngest (prepubescent) and oldest (age >54 years) patients had the highest rates of in-hospital mortality, hospital length of stay, and medical complications. Also of note is the fact that the German group had lower rates of mortality compared to the U.S. group. Of interest, over the course of the study, a decrease in the use of EMB was observed in the German cohort. A substudy analysis determined that the youngest age patients had the highest levels of leukocytes and C-reactive protein.

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The authors have leveraged the power of large database and registry data to provide a straightforward yet penetrating message. While simply analyzed and presented, the findings underscore the importance of considering the many variables that contribute to disease presentation and outcomes. The findings were informative, yet only hinted at causal mechanisms behind differences between myocarditis presentation and outcomes in different sexes and age groups. Additional questions arise from the authors' findings, as their work catalyzes the conversation of what additional work needs to be done in order to better understand this disease.

Well-planned preclinical models of myocarditis that represent differences in aging and sex are needed. Additional work in understanding genetic predisposition may yield earlier diagnoses and interventions in patients with undiagnosed cardiomyopathy in whom myocarditis unmasks the predisposition. Bench work to understand differences in patients' immune response to stress and inflammation is ongoing and might give further clues to what appears as differences in pathogenicity. Long-term follow-up of patients with myocarditis may provide information linking "idiopathic" dilated cardiomyopathy to earlier life myocarditis that may be underdiagnosed in larger numbers than previously appreciated.

Sex- and age-based differences are integral to the improved understanding of myocarditis, but the research and clinical teams also need to delve into other influencing factors. In addition to genetic factors and predisposition, variables such as individual molecular profiles, comorbid conditions, environmental exposures and risks, and social determinants of health all impact disease presentation.

More in-depth work examining the presentation and outcomes in patients of diverse ethnic and racial backgrounds is likely forthcoming. These studies must also carefully assess whether some of the ethnic and racial differences are biologic or more related to issues of access to care and other social determinants of health or perhaps under-representation in hospitalizations, research studies, and registries. Ethnic and racial differences in outcomes in heart failure have already been identified, as Black patients have higher incidence of dilated cardiomyopathy and increased mortality.[12] Pediatric patients with myocarditis who are from racial and ethnic minorities have higher rates of mortality.[13]

Additional studies need to include an analysis of transgender patients who take hormonal replacements and may have different risks for myocarditis. There are limited data examining the use of gender-affirming hormone therapy and cardiovascular risk.[14]

The role of EMB should be re-examined. While advanced imaging has helped to obviate the need for EMB in the general clinical diagnosis of acute myocarditis, the role of tissue-level characterization and studies remains important, and there may be areas of high complementarity between CMR and EMB. Poor biopsy yield related to poor sampling might be improved upon by using imaging to help guide EMB location.[15,16] Improved sampling may then yield more informative histological diagnoses and expand viral genomic and proteomic understanding of myocarditis.

There have been recent efforts to comprehensively phenotype patients with heart failure and cardiomyopathy.[17,18] One might consider myocarditis to represent an early stage in the spectrum of cardiomyopathy and possibly heart failure. While detailed phenotyping of myocarditis requires additional work, clearer understanding of the fundamental pathophysiological mechanisms and susceptibilities that are derived may direct more individualized therapies. With enough components, modular data, artificial intelligence, and machine learning algorithms may then ultimately be able to provide improved risk assessments.

The recent COVID-19 pandemic raised awareness of acute systemic viral illness, including myocarditis, on an international level. Because of the global nature of the disease, there were large-scale coordinated efforts to gain insight into the mechanisms of disease. These efforts taught us much about the virus and its mechanism of pathology. The rapidly mobilized systemic process of organizing and coordinating data from multiple international sites, as well as sharing of data, has demonstrated effective means in which the scientific and medical communities may work together to effectively study "myocarditis" as a disease entity.

The work of Thevathasan et al[11] highlights the importance of considering variables such as sex and age in the study of myocarditis, which is a conversation starter for improving the comprehensive phenotyping of myocarditis etiology, presentation, response to therapy, and outcomes. The work is an acknowledgment of differences in immune response between sexes and how the changes in immune response across age may impact the likelihood of developing myocarditis and how this may also impact the severity of disease. Over the course of a few hundred years, the field has steadily expanded its knowledge-base on myocarditis. As we continue to study and catalog the many contributing

variables of disease pathogenesis and presentation, more information and clarity of myocarditis will be forthcoming. Many broad strokes remain to be made in creating a complete picture.

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