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EDITORIAL COMMENT

Light at the End of the Myocarditis Tunnel*

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Myocarditis is in need of a systems change. In this issue of *JACC: Heart Failure*, Patriki et al. (1) take a much needed step toward a transformative approach to this poorly understood disease. Acute myocarditis is a clinical problem that is estimated to have an annual incidence of approximately 1.5 million people worldwide. Moreover, U.S. registry data have found myocarditis to be the third leading cause (6%) of cardiovascular death among young athletes, after hypertrophic cardiomyopathy (36%) and coronary artery anomalies (17%). An Israeli study based on 162 autopsies of patients under 40 years of age dying unexpectedly reported that 16% had evidence of myocarditis (2). Approximately 1% to 5% of patients who test positive for acute viral infection may exhibit a form of myocarditis (3). Yet, the true incidence of myocarditis is unknown and likely underestimated due to variable and nonspecific clinical presentations and the low sensitivity of diagnostic methods (4).

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The etiologies of myocarditis are generally, but not uniformly, classified into an autoimmune syndrome in the setting of systemic disease, drug reactions, and infection, the latter presumed to be the most common cause. The diagnosis of myocarditis has been difficult to establish because patients may be asymptomatic or, conversely, manifest malignant arrhythmias, cardiogenic shock, or death. The differential diagnostic process that leads ultimately to acute myocarditis is most frequently one of exclusion. Typically, an adult patient is admitted with chest pain, elevated troponin, and abnormal electrocardiographic findings, but is subsequently shown to have no evidence of epicardial coronary artery stenosis, usually by coronary arteriography (admittedly, the level of clinical suspicion for myocarditis in children is much higher, so that the diagnostic algorithm is different in this population). Adult patients may be labeled as having a myocardial infarction with no obstructive coronary atherosclerosis or MINOCA. Etiologic considerations include acute myocarditis, Takotsubo cardiomyopathy, coronary artery spasm, hypertrophic cardiomyopathy, or pericarditis; imaging, particularly cardiac magnetic resonance (CMR) imaging, has been very helpful in sorting out the diagnostic possibilities.

As early as 1991, CMR was recognized as an important diagnostic tool to use in patients suspected of myocarditis and, by 2009, the Lake Louise Criteria were published and widely adopted. Since then, there have been scores of publications detailing and perfecting the technologic aspects of CMR to diagnose myocarditis (4). However, as compelling as these data have become, it is important to recognize that most of the studies were single-center reports with small sample sizes and variable inclusion criteria and patient populations. Furthermore, CMR studies were performed at widely variable time points after symptom onset, often after therapy had commenced, and typically did not include myocardial biopsy for confirmation. Nevertheless, MR-weighted imaging and 2 different contrast-enhanced techniques, the early gadolinium enhancement and late gadolinium enhancement, can diagnose acute myocarditis in the presence of at least 2 of the following 3 findings on the respective sequences: 1) myocardial edema detected by T2-weighted imaging; 2) myocardial hyperemia detected by early gadolinium enhancement; and 3) myocardial damage with a nonischemic pattern detected by late gadolinium enhancement.

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TABLE 1 Topics of Uncertainty in Myocarditis

Overall incidence of myocarditis
Optimal diagnostic criteria for myocarditis
When and in whom should magnetic resonance imaging be done?
Role of endomyocardial biopsy
Role of molecular diagnostic techniques
Role of immunohistochemistry criteria
Role of pathogen-specific viral biomarkers
Genetic susceptibility to the autoimmune process of myocarditis
Management of presumed viral myocarditis
How often does myocarditis lead to cardiomyopathy?
Contribution of myocarditis to sudden cardiac death
Appropriate monitoring and risk stratification of established myocarditis

The definitive diagnosis of myocarditis still requires the results of an endomyocardial biopsy (EMB), which is performed infrequently, although much more often in Europe than in the United States. Indeed, consensus documents have provided conflicting guidance as to which patients should undergo a biopsy; none of the recommendations are supported by high-grade evidence (5-7). Some studies have demonstrated that the use of EMB changed management in 20% to 25% of patients who had biopsy was recommended, and helped to guide prognosis in 25% of patients who had myocarditis was not suspected. In general, the most recent consensus statement suggested that EMB should be performed in settings in which histological information will uniquely impact prognosis or guide treatment (5). This reasoning uncovers yet another dilemma with myocarditis: what is the clinical relevance of diagnosing acute viral myocarditis when there is no consensus about effective treatment options?

The precise pathophysiology of myocarditis is incompletely understood and studies of pathophysiology are largely limited to animal models; lymphocytic viral myocarditis is perhaps the most studied type. There have been some recent intriguing clinical data regarding genetic susceptibility to myocarditis, as well as to the interaction of genes and environmental exposures in causing pathological cardiac inflammation (2). Likewise, many promising avenues of therapeutic intervention, pursued in animal model systems, have yet to be studied in humans. Human studies are hampered by the relative infrequency of a viral myocarditis diagnosis, the highly variable time point at which patients present after the initiation of their illness, and the near impossibility, to date, in establishing the actual onset of cardiac inflammation (3).

It is into this staggering sum of unknowns (**Table 1**) that the investigators from the University Hospital in Zurich marched forth (1). They changed their 2015 criteria for CMR imaging from performing the study only in patients assessed to have a "high likelihood of myocarditis" to undertaking CMR in all patients with chest pain and elevated troponin, and in whom coronary disease was excluded, irrespective of the clinical likelihood of myocarditis. As a result, the percentage of CMRs judged to be positive for myocarditis doubled, from 5% in 2015 to 13% in 2016. They identified twice as many patients with symptomatic myocarditis in whom appropriate management could be administered. At the same time, the imaging-related diagnosis of other cardiac disorders did not change substantially, suggesting that their results could not be attributed to a change in imaging technique or image interpretation.

System change is defined as a transformation in organizational culture, policies, and procedures within or across organizations that enhance needed services by a target population—in this case, the unknown number of people with myocarditis. The Zurich research is the beginning of the system change required to fully understand myocarditis. The tool of CMR was applied to a new population with unexpected results and, if confirmed, will likely change our view of the disease. Next steps could include studies of CMR imaging in college students or military recruits seeking medical attention for a severe upper respiratory infection—but not chest pain—to determine how often a diagnostic CMR for myocarditis occurs in the setting of viral infection. Or, to perform CMR on all patients admitted with new onset atrial fibrillation, or ventricular dysfunction, or unexplained palpitations. We may also be able to assess the sensitivity and specificity of clinical and laboratory criteria for myocarditis, determine methods to assess prognosis and activity of disease, assess genetic susceptibility to disease and to the course of disease, and design studies of therapeutic strategies. Alternatively, perhaps it is time for an update of the Dallas criteria, a consensus determination of the pathologic criteria to diagnose myocarditis by EMB, originally developed in the mid-1980s! New recommendations are needed to incorporate emerging techniques in immunohistochemistry and molecular diagnostics, which are often not routinely performed even when an EMB is undertaken.

Finally, and arguably most important, an enhanced ability to identify the full spectrum of patients with myocardial inflammation may lead to a greater pathophysiological understanding of the thousands of patients with dilated cardiomyopathy. The increasing recognition that many patients with dilated cardiomyopathy have inherited genetic

mutations does not discount the possibility that a trigger for their observed ventricular dysfunction may be inflammation. Patriki et al. (1) should be congratulated on allowing a new look at myocarditis, one that is sorely needed.

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