Myocarditis and heart failure: need for better diagnostic, predictive, and therapeutic tools

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This editorial refers to 'A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis' by A.L.P. Caforio et al., on page 1326

Viral infection of the heart is increasingly recognized as an important cause of both acute and chronic heart failure. Enteroviruses and adenoviruses have been considered the most common pathogens of viral cardiomyopathy (CMP), but parvovirus B19 (PVB19) is increasingly found in endomyocardial biopsies of patients with acute myocarditis or idiopathic dilated cardiomyopathy (ICM).1,2 In addition to direct cytopathic effects of these cardiootropic viruses, there is convincing evidence that autoimmune responses induced by viruses contribute to the heart disease in a significant subset of patients with myocarditis.3

Caforio et al.,4 present a prospective study in 174 consecutive patients with myocarditis included between 1992 and 2005. They identify biventricular dysfunction as the main predictor of death or transplantation. A myocardial biopsy and serum anti-heart autoantibodies (AHA)-driven diagnosis and classification of myocarditis patients are used. As such, viral genome present in biopsies is further identified as a univariate predictor of adverse prognosis. Importance of a thoughtful and generally accepted classification of patients with myocarditis to allow further studies on pathogenesis, prognosis, and treatment of myocarditis is underlined by this study.

Clinically, patients with acute viral myocarditis will spontaneously recover in about three-fourth of cases, whereas the remaining one-fourth will develop progressive heart failure. Cardiac biopsies and autoimmune serology are therefore essential in the diagnostic process of myocarditis evolving to ICM. Recent biopsy series in patients with ICM have revealed that long-term persistence of cardiootropic viruses triggers heart failure at long term: >70% of patients with ICM carry a cardiootropic virus in the heart.5,6 Elimination of the virus after acute myocarditis, either spontaneously or after treatment, results in improvement of cardiac function,6 supporting a causal role of viral infection in ICM. Understanding the pathogenesis of heart failure induced by viral myocarditis is essential to better focus diagnostic tools. Direct cytopathic effects and immune dysregulation induced by the viral myocarditis trigger cardiac dysfunction.7 Cardiootropic viruses are able to degrade cell–cell, cell–matrix, and intracellular elements. These proteases aim to facilitate the entry of the virus into cells, but result in myocyte slippage, injury, and cardiac dilatation.8 Cardiootropic viruses also trigger adverse inflammation, further increasing degradation of the extracellular matrix and myocyte skeleton by increased production of proteases including matrix metalloproteinases,9 evolving in dilated CMP. Thus, future diagnosis and treatment should concentrate on targeting inflammation, proteases, and immune modulation.

As viruses, inadequate inflammation, and autoimmune processes all facilitate cardiac dysfunction during myocarditis, the lonesome use of Dallas criteria in myocarditis is therefore inadequate. Dallas criteria do not classify patients with myocarditis in the perspective of the viral cause, autoimmunity, or inflammation. Dallas criteria myocarditis at biopsy, proposed in 1986, only requires an inflammatory infiltrate with or without associated myocyte necrosis or damage and is analysed by a simple haematoxylin–eosin staining. Sampling error of inflammation, variation in expert reading, in addition to variance with other markers of viral infection, and immune activation in the heart are other arguments against the use of Dallas criteria.10 Also, the present study5 confirms a lack of sensitivity for myocarditis when using the Dallas criteria, as more than half of their patients would not have been unmistakably diagnosed in the absence of immunohistochemistry for leucocytes.

Beside histopathology for leucocytes and viral PCR in cardiac biopsies, detection of autoantibodies (AHA) in blood or HLA staining in cardiac biopsies adds to the diagnostic work-up in myocarditis. In the study of Caforio et al.,4 AHA were present in 56% of patients with myocarditis, which is high compared with other studies, but probably mirrors a group of patients included in the acute phase of inflammation where AHA are more often detected than in the more chronic stage of myocarditis. AHA induce inadequate inflammation in the heart and directly injure
cardiomyocytes by binding to sarcolemma, β-receptors, and contractile proteins such as myosin, actin, and troponin. Another aim of a novel classification would be the prediction of adverse prognosis. The latter was determined by biventricular failure and virus presence at diagnosis in the present study. These findings are concordant with deterioration of cardiac function related to virus persistence. Cardiac dysfunction as a major determinant of adverse prognosis is therefore not surprising. However, understanding the pathogenesis is a major issue to predict the prognosis of viral CMP. Which are the genetic and immunological determinants causing or predicting heart failure induced by virus persistence in the heart? Does virus persistence also play a causal role in the progression of ischaemic, hypertensive, or genetic cardiomyopathies? What about the high prevalence of PVB19 in patients with myocarditis and ICM:1,2 How does PVB19 injure the heart? Finally, patients with myocarditis require an effective treatment. Whether biopsy- and inflammation-driven classification of patients offers sufficient information regarding ideal treatment is not addressed in the current study.4 Previous studies suggest dissociation between Dallas criteria myocarditis and response to immune modulation therapy (reviewed by Baughman10). In the Myocarditis Treatment Trial, no difference in the 1- or 5-year survival or 28-week ejection fraction in patients with Dallas criteria myocarditis treated with immunosuppressive therapy or placebo was demonstrated. However, no cardiac biopsies were taken, and both patients with viral CMP or autoimmune heart disease were treated with immunosuppressive therapy. In addition, positive HLA staining in cardiac biopsies and the presence of AHA in blood in new-onset CMP identify these patients, who show improved cardiac function in response to immunosuppressive therapy. Failure to respond to immunosuppressive therapy, however, is related to virus persistence and a low presence of AHA. Therefore, the presence of Dallas criteria myocarditis does not identify patients who respond to immune modulation therapy. Evidence of viral persistence identifies patients who fail to respond to immunosuppressive therapy and predicts a worse prognosis, as also demonstrated in the present study.

In conclusion, detailed diagnosis of virus presence, inflammation, and autoimmune dysregulation in myocarditis is needed to study a disease that affects young and older people in a dramatic way. A combined effort of clinicians, pathologists, and immunologists must contribute to the development of new criteria of myocarditis, which should include clinical presentation, auto-antibodies, imaging, and cardiac biopsies for detailed study of inflammation, auto-immunity, fibrosis, and virus presence. These new criteria to be developed will help to better classify, treat, and predict the prognosis of a given patient with myocarditis.

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References