

# Myocarditis

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# Invited Editorial

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## MYOCARDITIS: THE LAST FRONTIER IN ADVANCED HEART DISEASE

The incidence of congestive heart failure (CHF) is increasing dramatically and CHF is now the most common diagnosis-related group for patients over 65 years of age admitted to hospital. Determining the etiology of heart failure is critical, as this defines the patient's natural history and treatment options. Despite a full evaluation of patients with new-onset or progressive heart failure utilizing traditional techniques, including endomyocardial biopsy (EMB), approximately 50% of patients are deemed "idiopathic" in origin. A "virus" is suspected as the cause of most cases of nonischemic cardiomyopathy and, if true, viral myocarditis diagnosis and treatment represent a remarkable opportunity to alter the observed increase in cardiac dysfunction and heart failure. In this issue of *Dialogues in Cardiovascular Medicine*, the world's experts in myocarditis address our current understanding of the pathophysiology and treatment of this disorder.

Dr Cooper addresses nonviral causes of myocarditis, including giant cell myocarditis, sarcoidosis, and hypersensitivity eosinophilic myocarditis. While the etiology of each of these nonviral disorders is unclear, the pathophysiology, as currently defined (immune, inflammatory, and allergic), does allow appropriate management. Each of these disorders is relatively rare and accounts for only a small portion of those patients in the idiopathic cardiomyopathy category.

Viral or postviral autoimmune myocarditis is much more likely to be responsible for a large proportion of those patients with heart dysfunction of unknown etiology. Kühl identifies mechanisms by which cardiotropic viruses or postviral autoimmune processes may damage the heart, including the site of viral infection. Endothelial infection and secondary dysfunction may cause vasospasm or vascular occlusion, resulting in chest ●●●

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pain or myocardial infarction. Interstitial invasion could result in diastolic or systolic dysfunction. Myocardial invasion results in cardiac dysfunction through several mechanisms, including direct viral damage to the myocyte, innate and adaptive immune response, and cytokine production, all of which cause direct or secondary myocardial deterioration. Therefore, the effect of a virus on the heart may be dependent on its predilection for endothelial, interstitial, or myocardial invasion and the nature of the immune response.

The diagnosis of myocarditis is difficult as the signs, symptoms, electrocardiographic changes, biomarkers, echocardiograms, and other noninvasive studies are nonspecific. **Mahrholdt** and **Sechtem** specifically address the value of EMB vs cardiac magnetic resonance imaging in establishing a diagnosis. The authors have identified the limitations of the Dallas criteria for diagnosing myocarditis by heart biopsy: focal myocardial inflammation; interobserver variability in the histopathologic interpretation of biopsy results; lack of correlation between myocardial invasion with cardiotropic viruses and myocardial inflammation; and poor correlation of Dallas criteria myocarditis with treatment outcomes. Nonetheless, EMB is the only technique capable of definitively diagnosing myocardial inflammation and its etiology.

The authors identify what they currently consider a “complete” EMB should include: obtaining six samples from both right and left ventricles from each patient; and a pathology analysis that includes histology, immunopathology, and DNA and RNA studies for nested polymerase chain reaction (PCR) and reverse transcriptase PCR evaluation of viral genomes.

Magnetic resonance imaging is noninvasive, does not expose the patient to radiation, and is associated with limited risk. Newer techniques and use of gadolinium contrast have allowed investigators to identify focal areas of myocardial inflammation during the acute process or scar tissue in the recovery phase. Both are of value in diagnosing myocarditis. In addition, magnetic resonance imaging may identify extra cardiac disease processes, which may help establish other diagnoses. It is likely that a thorough EMB, in addition to cardiac magnetic resonance imaging (CMR) to establish a diagnosis and define the area to be biopsied, will result in a higher yield of areas of myocardial inflammation. However, CMR may be less sensitive for diffuse forms of myocardial inflammation.

Treatment of myocarditis, and presumably prevention of the advancement of heart disease, is highly dependent on understanding the pathophysiology of the underlying disorder. **Cooper**, **Schultheiss**, and **Kühl** review what is known about current treatment options. Standard therapy includes: lifestyle alterations and avoidance of exercise in the short term; consideration of  $\beta$ -blocker and angiotensin-converting enzyme inhibitor use; 



appropriate use of pacemakers for heart block; implantable cardioverter-defibrillators for malignant arrhythmias; as well as ventricular assist device support and transplant for patients with refractory symptoms. It seems clear from the data thus far available that patients with fulminant myocarditis should be supported without immunosuppressive therapy, while patients with giant cell myocarditis and acute necrotizing eosinophilic myocarditis need high-dose immunosuppressive therapy, perhaps long-term.

Patients with sarcoidosis and hypersensitivity or eosinophilic-related myocarditis also appear to respond to immunosuppressive agents. What is less clear is the appropriate therapies for patients with viral infection or the postviral immune cardiac response. Utilizing the PCR methodologies noted above, viral pathogens have been detected in EMBs of patients with cardiomyopathy and/or heart failure. It is yet to be determined whether or not these viral pathogens are in the endothelium, interstitium, or myocardium and whether or not localization provides additional diagnostic information beyond that of their presence in heart tissue. Increasingly, it appears that patients with viral persistence have a worse prognosis than those with spontaneous viral clearance or those who have no evidence of viral infection. It is also becoming increasingly clear that patients who do not have viral persistence, but have anticardiac antibodies may be more responsive to immunoadsorption or immunosuppressive therapies.

Over the next several years, the authors and further investigations will define the degree to which myocarditis is responsible for the large number of patients who have heart muscle dysfunction of unknown etiology. We finally have, in our grasp, molecular and genetic techniques that significantly enhance our ability to diagnose myocarditis and its viral or immune causes. The recently released guidelines of indications for EMB<sup>1</sup> will allow investigators to identify differences in the clinical subsets being investigated. With these clinicopathologic descriptions and techniques defining the presence and etiology of myocarditis, treatment trials may be possible. With our current enhanced techniques and worldwide attention being paid to myocarditis, idiopathic cardiomyopathy, the last frontier in advanced heart disease, will be conquered.

## REFERENCE

**1. Cooper LT, Baughman KL, Feldman AM, et al.**

*The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology.*

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