Arrhythmias in Viral Myocarditis and Pericarditis

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KEYWORDS

• Ventricular arrhythmia • Viral myocarditis • Acute pericarditis • CMR

KEY POINTS

- Viral myocarditis is common and frequently unrecognized.
- Arrhythmia is common in acute viral myocarditis. The finding of ventricular arrhythmia (especially ventricular fibrillation [VF]) should prompt investigation to confirm the substrate.
- Cardiovascular magnetic resonance (CMR) is a powerful tool for the diagnosis and follow-up of acute myocarditis and also acute pericarditis; a normal CMR scan confers a good prognosis.
- Acute pericarditis in isolation does not seem to be frequently associated with ventricular arrhythmia but is often present as a perimyocarditis with an incumbent burden of arrhythmia related to the myocardial component.
- Management of arrhythmia in this setting is fundamentally usual management of the underlying arrhythmia and associated hemodynamic/clinical impact.

INTRODUCTION

Acute viral myocarditis and acute pericarditis are typically self-limiting conditions that run a benign course and that may not even involve symptoms that lead to medical assessment. However, ventricular arrhythmia is a frequent occurrence in viral myocarditis; this may be in the form of premature ventricular contractions but may also be far more malignant as sustained ventricular tachycardia (VT) or unheralded VF. Myocarditis is thought to account for a large proportion of sudden cardiac deaths in young people without prior structural heart disease.[1–3] Identification of acute myocarditis either with or without pericarditis is therefore of importance. However, there are many potential hindrances to this. Furthermore, even when the diagnosis is made, therapeutic interventions remain limited and nonspecific. Identifying those at greatest risk of life-threatening arrhythmia is critical to reducing the mortality resulting from this condition.[4] This review summarizes current understanding of this challenging area.

VIRAL MYOCARDITIS

Although there are many potential triggers, in economically developed countries, viruses are the most common cause of myocarditis (inflammation of the heart muscle).[5] The most frequently identified viruses in this setting are adenovirus,[6] parvovirus B19,[7] human herpes virus 6, and enterovirus.

The true incidence of viral myocarditis remains uncertain, largely as a result of its commonly asymptomatic course. Even when symptomatic, viral myocarditis frequently remains unrecognized

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or unconfirmed. Myocarditis has been postulated in 1% to 40% of cases of sudden unexpected death, but the true incidence is poorly characterized. Myocarditis was identified as the cause of death in 40% of cases in a study of Air Force recruits who had sudden cardiac death.[8]

There are 3 phases to viral myocarditis.[9] The first phase consists of active viral replication within the myocardium causing direct lysis of cardiac myocytes and activation of the innate immune response. The consequent myocardial damage may be asymptomatic or may include symptoms anywhere along a spectrum to fulminant cardiogenic shock. Most patients recover fully from this initial acute phase. In some, persistent disease activity is thought to trigger an adaptive autoimmune response to viral and myocardial proteins. Again, in the majority, the pathogenic stimulus is cleared and the immune response diminished. But in some, as a consequence of the harmful inflammatory effect of this response on the myocardium, in this second phase of the disease process, often heart failure manifests. Furthermore, this autoimmune response seems to be the predominant driver of cellular injury, which may then lead to ventricular arrhythmia. The pivotal role of the autoimmune component is highlighted by experimental data that show that the severity of disease is modified by the major histocompatibility complex class 2 genes by modulation of the autoimmune element of myocarditis.[10]

Although left ventricular (LV) size and ejection fraction usually remain normal during acute viral myocarditis, a dilated cardiomyopathy phenotype may develop as a result of persistent myocarditis,[11,12] and this represents the third phase of the disease process. Diagnostic and therapeutic strategies are best directed according to the particular phase of the disease process. Arrhythmia in dilated cardiomyopathy is specifically considered elsewhere in this issue by John and colleagues.

The contribution of viral myocarditis to the development of dilated cardiomyopathy has been inferred by the common isolation of viral genomic material in the myocardium of affected individuals.[6,13] In addition, progressive myocardial dysfunction has been linked to viral persistence, in contrast to improvement of ventricular function wherein the virus is cleared.[14] The etiologic role of viruses is further supported by improvement in ventricular function after therapy with immunomodulators. However, with increased appreciation and understanding of the genetic basis of dilated cardiomyopathy,[15,16] the etiologic mechanisms may in cases be more complex. It is well recognized that the vast majority of the population is infected by cardiotropic viruses at one time or another, yet only a small minority of infected individuals (1%–5%) go on to develop histologically proven myocarditis.[17] It may be that in several cases, an episode of viral myocarditis is the trigger that unmasks a genetic predisposition to dilated cardiomyopathy. However, most of those who are infected with a virus that could cause myocarditis do not go on to develop clinically overt disease and of those who do, only a minority develop an overt cardiomyopathy. In a genome-wide association study, Bezzina and colleagues[18] identified a polymorphism adjacent to the gene encoding a viral receptor implicated in both dilated cardiomyopathy and modulation of the cardiac conduction system, which they found to be more frequently expressed in patients with VF than in controls.

Investigations in Viral Myocarditis

Electrocardiographic (ECG) findings in acute myocarditis are most often nonspecific.[19] Sinus tachycardia is a typical finding. ST-segment elevation potentially mimicking acute myocardial infarction is frequently present. Arrhythmia or bundle branch block may be evident on the ECG. With regard to cardiac enzymes, the superior sensitivity of cardiac troponins over creatine kinase MB has been established,[20] and this is likely even more pronounced with high-sensitivity assays. Likewise, high-sensitivity C-reactive protein (CRP) assays also have good capability to detect acute viral myocarditis.[21]

Confirming a viral cause beyond a history of viral prodromal symptoms requires the detection of an appropriate virus, viral genome, or antibody on serology or in relevant tissue or fluid. Paired sera collected at least a fortnight apart may implicate a viral substrate, but more definitive evidence by direct identification of the virus from biopsy tissue by polymerase chain reaction (PCR) or in situ hybridization is desirable, but not routine.

The Role of Imaging

Echocardiography remains the cornerstone of cardiac imaging. However, CMR has unique capability that makes it a powerful and an increasingly first-line investigation in the diagnosis and assessment of myocarditis. CMR uses the response of hydrogen protons to radiofrequency excitation and consequently is sensitive to regions of increased water content. Specific sequences, notably, short tau inversion recovery (STIR) T2 sequences, have been developed to identify regions of myocardial (**Fig. 1**) and pericardial inflammation or edema. In acute myocarditis, in which there is cell lysis and necrosis in addition to inflammation, regions of myocardial damage are further identified by the administration of gadolinium-based extracellular contrast agents,