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## EDITORIAL

# Viral Infections and the Heart

MANZOOR MAHMOOD[1] AND MD HARISUL HOQUE[2]

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**Introduction:**

Viral infections of the heart cause serious clinical problems, either as infectious myocarditis, which usually is a consequence of acute infection or as idiopathic dilated cardiomyopathy, resulting rather from a chronic infection. There is a long list of viruses that have been implicated as causative agents. However, Adenoviruses, Enteroviruses, (coxsackievirus), Herpesviruses (human herpesvirus 6, Epstein–Barr virus), Hepatitis C virus, HIV, Influenza A, Parvovirus B19 and SARS- CoV-2 of corona virus family are common pathogens to name a few.

**Pathophysiology[1]:**

Heart infection begins when virus invades the cardiomyocytes with the participation of a specific receptor. Coxsackievirus uses coxsackie-adenovirus receptor (CAR), which is a junctional protein. In the absence of CAR expression on cardiomyocytes, the viral invasion of these cells is impossible. The decay accelerating factor (DAF, CD55) is a co-receptor for HEV internalization, and αv-type integrins are needed for adenovirus penetration. It can result in a heart failure or death due to the direct cytopathic effect caused by an active replication. Hypothesis for cardiac injury in COVID-19 include ACE-2 mediated direct damage, hypoxia induced myocardial injury, cardiac microvascular damage and systemic inflammatory response syndrome (SIRS).[2]

The first, acute stage of an infection, can end with elimination of the virus from the heart and renovation of damaged tissue. The innate immunity is the first line of defence against virus. This conservative system activates the inflammatory process by tolllike receptors (TLRs), especially TLR-3 and TLR-4, which are located in large quantities in the cells of cardiovascular system.

The second stage of the infection is subacute and lasts weeks to months. It is characterized by more sublimated immune reactions. Signals from the innate immunity system contribute also to the activation of specific T and B lymphocytes, responding to viral antigens. The highest point of antibodies production also occurs in this phase. Antibodies, which are produced to destroy viruses, often react with the structures of human heart and can cause damage of myocardium. The cytotoxic T-cells response is one of the most important mechanisms responsible for the lysis of virus-infected cells as well as for far reaching damage of myocardium. In addition, autoimmune reactions are also observed, when the cytotoxic lymphocytes attack healthy part of the myocardium because of the molecular mimicry.

Myopathy phase is the next stage of an infection, where generally it is impossible to detect the virus in myocardium. In case of the persistent inflammatory response, the heart may develop idiopathic DCM due to the remodeling. Pathogenic role may be played by the antibodies against sarcolemma, beta-receptor, acetylcholine receptor, laminin and cardiac conducting tissue.

**Diagnosis:**

The diagnosis of acute myocarditis is complex and challenging. The use of the Dallascriteria in the diagnosis of myocarditis is associated with poor sensitivity and specificity because of the sampling error related to the often focal distribution of the specific histological lesions in cardiac tissue and the variability in pathological interpretation. To improve histological diagnosis, additional virological evaluation of cardiac tissues is required, with immunohistochemical and polymerase chain reaction (PCR) techniques allowing identification and quantification of viral infection markers. The diagnostic gold standard is endomyocardial biopsy (EMB) with the histological Dallas criteria, in association with new immunohistochemical and PCR analyses of cardiac tissues. Using real-time PCR and reverse transcription PCR assays, parvovirus B19, CoxsackieB virus, human herpesvirus 6 (HHV-6) type B, adeno virus have been detected in 37, 33,11 and 8% of EMB, respectively, from young adults (aged < 35 years) with histologically proven acute myocarditis. Viral co-infections have also been found in 12% of acute myocarditis cases, generally parvovirus B19 plus HHV-6. Moreover, herpes viruses such as the Epstein-Barr virus or cytomegalovirus can also be associated with myocarditis after heart transplantation.[3]

**HIV myocarditis**: Myocarditis was present in 44% of HIV-associated cardiomyopathy cases, 36% of heart transplant recipients, and 25% of participants with idiopathic dilated cardiomyopathy. While myocarditis was acute in 50% of HIV- and heart transplant-associated myocarditis, it was chronic in all those with idiopathic dilated cardiomyopathy. Cardiotropic viral infection was present in all HIV-associated cardiomyopathy and idiopathic dilated cardiomyopathy cases, and in 90% of heart transplant recipients. Multiple viruses were identified in the majority of cases, with HIV-associated cardiomyopathy, heart transplant recipients and idiopathic dilated cardiomyopathy patients having an average of 2.5, 2.2 and 1.1 viruses per individual, respectively.[4]

**Prognosis and Predictors of Severity:**

Grun and co-authors found a relevant long-term mortality in myocarditis patients (19.2% all cause, 15% cardiac, and 9.9% sudden cardiac death [SCD]). The presence of late gadolinium enhancement (LGE) yields a hazard ratio of 8.4 forall-cause mortality and 12.8 for cardiac mortality, independent of clinical symptoms. This is superior to parameters like left ventricular (LV) ejection fraction, LV end-diastolic volume, or New York Heart Association (NYHA) functional class, yielding hazard ratios between 1.0 and 3.2 for all-cause mortality and between 1.0 and 2.2 forcardiac mortality. No patient without LGE experienced SCD, even if the LV was enlarged and impaired. When focusing on the subgroup undergoing follow-up CMR, we found an initial NYHA functional class>I as the best independent predictor for incomplete recovery ($p = 0.03$). Among our population with a wide range of clinical symptoms, biopsy-proven viral myocarditis is associated witha long-term mortality of up to 19.2% in 4.7 years. In addition, the presence of LGE is the best independent predictorof all-cause mortality and of cardiac mortality. Furthermore, initial presentation with heart failure may be a good predictor of incomplete long-term recovery.[5]

In another study Kaþukauskienë and co-workers has shown that two markers-cardiotropic viruses and myocardial inflammation- are prevalent among DCM patients. They are also helpful in identifying subgroups of DCM. An increased number of T-lymphocytes in the myocardium is a predictor of poor mid-term and long- term prognosis.[6]

**Conclusion:**

Myocarditis is a frequent cause of dilated cardiomyopathy with heterogeneous clinical presentations and a wide range of clinical outcomes. After infection by a cardiotropic virus, a maladaptive post-viral response ensues, which can cause myocardial cell dysfunction and compromised contractility. Advances in our diagnostic capabilities using cardiac MRI as well as molecular detection of viruses by endomyocardial biopsy have improved our understanding and ability to characterize the disease. The use of immuno modulatory and antiviral therapy remains largely investigational at this time.[7]

**Manzoor Mahmood[1],** Professor, Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

**Md. Harisul Hoque[2],** Professor and Head, Division of Clinical Cardiology, Heart Failure, Rehabilitation and Preventive Cardiology, Department of Cardiology, BSMMU, Dhaka.

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