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MINI-REVIEW

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Viral Myocarditis

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Viral myocarditis is associated with the development of dilated cardiomyopathy (DCM), left ventricular dysfunction, and heart failure. This review addresses the mechanisms of viral myocarditis and its treatment.

INTRODUCTION

Viral infection is considered to be the predominant etiology of myocarditis (viral myocarditis). Viral myocarditis is associated with the development of dilated cardiomyopathy (DCM), left ventricular dysfunction, and heart failure [1,2]. Besides viral myocarditis, other infectious etiologies of myocarditis include bacterial, fungi, or protozoa, which can also induce cardiac dysfunction.

Viral myocarditis occurs after viral respiratory infection and viral pneumonia. Based on the different virus epidemics in different seasons and regions, the viruses associated with viral myocarditis are also different, which is made evident by the coronavirus disease 19 (COVID-19) pandemic from 2020. There are many data showing the occurrence of myocarditis after the COVID-19 pandemic, especially in severe forms. Patients hospitalized with severe COVID-19 have a significantly higher rate of cardiovascular complications, including acute heart failure, arrhythmias, cardiogenic shock, myocardial ischemia or infarction, and myocarditis [3,4]. During the influenza pandemic, in at least 10% of patients suffering from viral infection, the virus replication took place in the heart. This results in a focal infiltration of inflammatory cells, usually mononuclear cells, accompanied by interstitial edema and cardiac necrosis [5].

Due to the advances in and utility of Polymerase chain reaction (PCR) technology in endomyocardial biopsy (EMB), numerous viruses have been tested and associated with viral myocarditis in EMB. The common viruses associated with myocarditis include adenoviruses and enteroviruses (such as coxsackie A viruses or coxsackie B viruses and echoviruses); parvovirus B19 (B19V); human herpesvirus 6 (HHV6); Epstein–Barr virus and human cytomegalovirus; human immunodeficiency virus (HIV); hepatitis C virus (HCV); influenza A virus and influenza B virus; coronavirus including Middle East respiratory syndrome coronavirus (MERS-CoV); as well as severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 [1,2,6,7].

Viral myocarditis symptoms include dyspnea, chest pain, fatigue, palpitations, arrhythmia, heart failure, cardiac shock, and sudden cardiac arrest. Accurate diagnosis and appropriate treatment are important for the prognosis of the patients.

MECHANISM OF CARDIAC INJURY FROM VIRAL MYOCARDITIS

After viral respiratory infection or viral pneumonia,

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Abbreviations: DCM, dilated cardiomyopathy; PCR, Polymerase chain reaction; EMB, endomyocardial biopsy; HHP6, human herpesvirus 6; SARS-CoV, severe acute respiratory syndrome coronavirus; TNF, tumor necrosis factor; IFN-γ, interferon; TRIM, tripartite motif; FM, fulminant myocarditis.

Keywords: influenza virus, lung infection, viral myocarditis

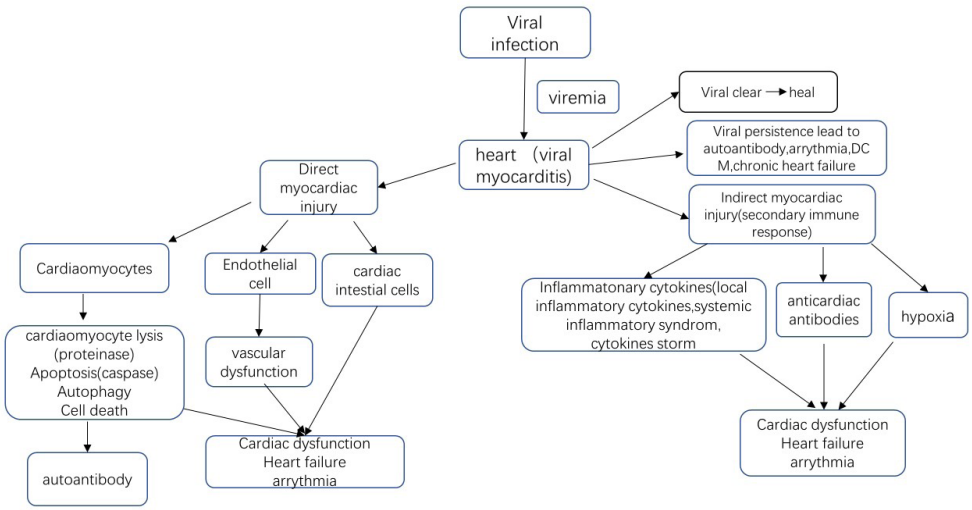

Figure 1. **Mechanism of viral myocarditis after viral respiratory infection**. Virus infection cardiac myocyte, endothelial cell, cardiac intestial cells lead to cardiac dysfunction or heart failure in acute phage and DCM in chronic phage, inflammatory cytokines, or anticardiac antibody lead to cardiac dysfunction, heart failure or arrythmia.

the virus can cause viremia and systemic infection, leading to the infection of heart cells. The sequence of viral myocarditis includes acute, subacute, and chronic. Acute phase 1 involves viral entry into myocytes and activation of innate immunity; subacute phase 2 involves viral replication and activation of acquired immune responses; and chronic phase 3 is either resolution with recovery or development of dilated cardiomyopathy [2]. Several days after the initial infection, persistent viral replication leads to myocyte necrosis and triggers the host's immune system. High levels of cytokines, particularly tumor necrosis factor (TNF), interleukin (IL) IL-1a, IL-1b, IL-2, and interferon (IFN-γ), are produced. Virus replication within the cardiomyocyte causes cell lysis. In phase 2, both cellular and humoral responses contribute to autoimmune-mediated injury. In phase 3, some individuals experience complete resolution of myocardial injury as viral titers decrease. However, in other patients, the viral genomic material persists, contributing to chronic inflammation and dilated cardiomyopathy [2] (Figure 1).

DIRECT INJURY

The virus can infect and be observed in cardiomyocytes, cardiac interstitial cells, endothelial cells, and inflammatory cell infiltration [7-9]. The virus that infects cardiomyocytes induces direct myocardial injury, including cytoskeletal disruption, cardiomyocyte necrosis, cardiomyocyte lysis, apoptosis or autophagy [10]. The loss of functional cardiomyocytes can directly affect cardiac function or induce secondary cardiac remodeling, leading to dilated cardiomyopathy in the long term. The persistence of virus RNA can be observed in cardiomyocytes in the chronic phase of infection [10].

Other viruses can cause myocarditis with the infection of cardiac endothelial cells, such as parvovirus B19, which infects the cardiac endothelium. Parvovirus B19 genomes have been found in the endothelial cells of venules, small arteries, and arterioles in patients with fulminant myocarditis [11]. The virus exerts its pathogenic effects by the activation of cytokines (IL-6 and TNF) and the induction of cardiac endothelial cells apoptosis, leading to endothelial dysfunction and microvascular dysfunction. Although the parvovirus does not directly infect cardiomyocytes, endothelial cell infection can lead to ventricular dysfunction and eventual cardiomyopathy and heart failure [2].

INDIRECT INJURY

Viruses indirectly trigger myocarditis by activating the immune system. Swirski showed the potential immune mechanisms in viral myocarditis. A virus, such as coxsackievirus, specifically infects cardiomyocytes, for example, through coxsackievirus and adenovirus receptor (CXADR). This leads to death of the cardiomyocytes and the release of damage-associated molecular patterns (DAMPs), which alert the innate immune system, giving rise to the recruitment and activation of phagocytes such as monocytes and dendritic cells (DCs). Swirski and Nahrendorf note that phagocytes ingest dead and dying cardiomyocytes and migrate to the draining lymph nodes. In the draining lymph nodes, DCs present viral antigens to naive B cells and T cells, generating a population of effector lymphocytes [12]. They also note that molecular mimicry between viral antigens and cardiac antigens,

as well as exposure of cardiac neoantigens and epitope spreading, lead to an autoimmune response that propagates inflammation even after the virus is cleared [12].

Human interferons are antiviral proteins produced by human cells, especially Type 1 IFN, IFN-α, IFN-β. It is reported that tripartite motif (TRIM) TRIM18 could control pathogenesis of viral myocarditis by employing protein phosphatase 1A (PPM1A) to dephosphorylate (TANK binding kinase 1) TBK1 for regulating type I interferon production [13]. Recently, TRIM29 has been shown to enhance (protein kinase RNA-like endoplasmic reticulum kinase) PERK-mediated ER stress immune responses, thereby promoting viral myocarditis induced by cardiotropic RNA viruses [14].

The virus's indirect injury in viral myocarditis include inflammatory cytokines or autoimmunity.

INFLAMMATORY CYTOKINES

After viral infection of the heart, macrophages, mast, and T cells can produce inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, TNF-alpha, neutrophils, and monocytes, which produce additional mediators such as IL-12 [15]. Cardiomyocytes, fibroblasts, and endothelial cells are also sources of cytokines, chemokines, and growth factors. The mast cell-derived tumor necrosis factor (TNF), which activates endothelial cells; cardiomyocyte-derived IL-6, which activates neutrophils via the expression of intercellular adhesion molecule 1 (ICAM1); T cell-derived IL-17, which stimulates cardiac fibroblasts; fibroblast-derived granulocyte-macrophage colony-stimulating factor (GM-CSF), which induces the production and recruitment of myeloid cells; and macrophage-derived transforming growth factor-β (TGFβ), vascular endothelial growth factor (VEGF), and IL-10 promote collagen production, neoangiogenesis, and resolution of inflammation [12]. High levels of cytokines, particularly tumor necrosis factor (TNF), IL-1a, IL-1b, IL-2, and IFN-γ, together with antibodies to viral and cardiac proteins, can further potentiate cardiac damage and compromise systolic function through the derangement of the contractile apparatus and/or interstitial cells and matrix proteins [2].

Inflammatory cytokines, such as IL-1, IL-6, and TNF-alpha, exert important arrhythmogenic effects via several mechanisms, including direct cardiac activities and indirect systemic changes. Direct effects include cardiac remodeling, characterized by structural and electrical changes. Lazzerini et al. note that cytokines can also induce (over weeks or months) structural remodeling by activating the myofibroblast-driven synthesis of the extracellular matrix responsible for cardiac fibrosis [16,17]. In patients hospitalized due to COVID-19, it was found that new-onset atrial fibrillation or atrial flutter was associated with inflammatory markers, including IL-6. The incidence of in-hospital atrial fibrillation (AF)/atrial flutter (AFL) was higher in the $\text{Influenza}_{\text{Primary}}$ than the $\text{COVID-19}_{\text{Primary}}$ cohort, but the incidence of new-onset AF/AFL was similar. The levels of inflammatory markers were not significantly different in AF/AFL patients in the $\text{Influenza}_{\text{Primary}}$ cohort; however, they had increased markers of cardiac injury (troponin) [18].

A cytokine storm in viral myocarditis can cause fulminant myocarditis (FM), which can result in severe heart failure. The core mechanism underlying the development of FM is the occurrence of an inflammatory cytokine storm [19].

HEART-SPECIFIC AUTOANTIBODIES

Anticardiac antibodies include Anti-actin, Anti-Ach, Anti-AH, Anti-β1, Anti-sinus node, Anti-AV node, Anti-Purkinje, Anti-desmin, Anti-myosin, and Anti-Troponin I, among others [15]. Antigenic mimicry between microbes and cardiac proteins causes autoimmunity in myocarditis. Autoimmunity to cardiac antigens leads to heart failure [20].

The mechanisms of autoantibodies in the pathophysiology of myocarditis are as follows: (i) various autoantibodies can produce inadequate inflammation in the heart and directly injure cardiomyocytes; (ii) the transfer of human lymphocytes from patients with proven heart-reactive autoantibodies into severe combined immunodeficient mice leads to autoantibody production, myocardial inflammation, and impaired cardiac function; (iii) active immunization with cardiac autoantigens leads to autoantibody production, heart-specific inflammation, and cardiac dysfunction; and (iv) the direct transfer of autoantibodies against cTnI and β-adrenoreceptor into rodents results in cardiac dilatation and dysfunction [1].

PERSISTENT VIRUSES EXIST IN VIRAL MYOCARDITIS

Cardiomyocytes can be clear from the virus or some viruses can persist. The most common viruses associated with inflammatory cardiomyopathy include primary cardiotropic viruses that can be cleared from the heart, including adenoviruses and enteroviruses (such as coxsackie A viruses or coxsackie B viruses, and echoviruses). Vasculotropic viruses that are likely to have lifelong persistence, including parvovirus B19 (B19V). Lymphotropic viruses with lifelong persistence that belong to the Herpesviridae family include the human herpesvirus 6 (HHV6), Epstein–Barr virus, and human cytomegalovirus [7]. Viral persistence is strongly dependent on the function of the host's immune system [6].

Enterovirus (EV), adenovirus (ADV), parvovirus

B19 (PVB19), and HHV6 persistence detected in the myocardium of patients with LV dysfunction was associated with a progressive impairment of left ventricular ejection fraction (LVEF), whereas spontaneous viral elimination was associated with a significant improvement in left ventricular (LV) [21]. The myocardial persistence of various viruses, often presenting as multiple infections, may play a role in the pathogenesis of DCM [22].

ARRYTHMIA IN VIRAL MYOCARDITIS

Viral myocarditis leading to arrhythmia can result in atrial fibrillation, ventricular arrhythmias, supraventricular tachycardia, atrioventricular block, ventricular fibrillation, ventricular tachycardia, atrial tachycardia, sinus node dysfunction, etc. Lee et al. note that three of the most common proposed viral mechanisms of arrhythmogenesis include direct invasion of myocytes leading to immune-mediated damage, infection of the vascular endothelium, and alteration of cardiac ion channels [23].

Inflammatory cytokines, particularly TNF, IL-1, and IL-6, can directly and indirectly promote cardiac arrhythmias. Inflammatory cytokines lead to a prolonged action potential duration or corrected time of Q wave to T wave on electrocardiogram (QT) (QTc) interval, enhanced ectopic firing, and slowed or heterogeneous propagation of electric impulses throughout the working and conducting myocardium. In turn, this triggers re-entry-driven tachyarrhythmias and bradyarrhythmias, as well as conduction disturbances [17].

Cardiomyocyte-immune cell interactions also promote and maintain atrial fibrillation. Dynamic interactions between cardiac cells and immune cells create a proinflammatory substrate for the promotion and maintenance of atrial fibrillation. Cardiomyocyte Ca2+ handles abnormalities, including ryanodine receptor 2 (RYR2) channel remodeling, delayed afterdepolarizations, and triggered action potentials and ectopic activity, as well as re-entry-promoting effective refractory period (ERP) shortening and fibrotic structural remodeling, thereby inducing the principal mechanisms responsible for atrial fibrillation [24].

CARDIAC DYSFUNCTION IN VIRAL MYOCARDITIS

The viral mechanisms of cardiac dysfunction include direct infection of myocytes leading to myocytes, endothelial or interstitial cell death, cytokines, autoantibodies, and viral persistence.

Like the virus directly infecting myocytes, inflammation cytokines also induce cardiac dysfunction. Hang et al. show that pro-inflammatory cytokines, like IL-1 and tumor necrosis factor-alpha (TNF-α), have a negative ionotropic effect and directly decrease myocardial contraction strength and velocity [19]. A severe cytokine storm can directly inhibit mitochondrial function. The degradation of sarcomeric proteins like troponin and dystrophin will directly damage the normal structure of the sarcomere and fracture the myocardial filament. The breakdown of the myofilament results in an inability to transduce the contraction strength of the heart, diminishing its ability to efficiently pump enough blood into circulation. The activation of different cell death pathways, including apoptosis, necrosis, pyroptosis, and necroptosis, results in decreased viability. Importantly, the loss of terminally differentiated cardiomyocytes will significantly reduce the heart's contraction ability. In addition, the increased cell death in the myocardium will further trigger inflammatory responses and exposure of self-antigens, worsening the condition [19].

Reddy et al. show that viral persistence in the myocardium is associated with progressive cardiac dysfunction [20]. A time course analysis of long-term consequences associated with biopsy-proven myocarditis and idiopathic DCM suggests that virus clearance correlates with LVEF improvement [6,22].

DIAGNOSIS OF VIRAL MYOCARDITIS

1. Serum cardiac biomarkers, specifically troponin I and troponin T, can be elevated in cases of myocarditis, which helps to confirm the diagnosis, but they lack sensitivity. Natriuretic peptides (NPs) and troponin elevation strongly and independently predict in-hospital death, including in patients without cardiovascular disease [25].

2. Electrocardiogram findings are neither sensitive nor specific for the diagnosis of myocarditis; for patients with suspected myocarditis, virus serology has no relevance for the diagnosis of myocardial infection [26].

3. Cardiovascular magnetic resonance (CMR) is particularly useful in facilitating a guided approach by virtue of its utility in distinguishing between a diseased and normal myocardium. In addition, the presence of late gadolinium enhancement (LGE) is the best independent predictor of all-cause mortality and of cardiac mortality [27]. In patients with biopsy-proven viral myocarditis, the presence of midwall LGE in the (antero-) septal segments is associated with a higher rate of mortality (including sudden cardiac death (SCD)) compared with absent LGE or other LGE patterns, underlining the prognostic benefit of a distinct LGE analysis in these patients [28].

4. EMB and polymerase chain reaction (PCR). EMB is the gold diagnostic method for viral myocarditis according to the Dallas criteria.

5. Other tests: In patients with suspected myocarditis, myocardial edema but no irreversible injury correlates with the presence of the viral genome in peripheral blood.

The combined assessment of edema and virus serology may be very efficient for diagnostic and therapeutic decision-making [29]. Blanco-Domínguez et al. show that after identifying a novel microRNA in mice and humans with myocarditis, they found that the human homologue (hsa-miR- Chr8:96) could be used to distinguish patients with myocarditis from those with myocardial infarction [30].

TREATMENT OF VIRAL MYOCARDITIS

1. Immunosuppressive therapy: Immune suppression with prednisolone, administered at 3 months after the onset of acute myocarditis, is effective in significantly bringing about improvement and cure in persistent left ventricular failure [31].

2. Immunomodulatory therapy: Intravenous immunoglobulin IgG subtype and polyvalent intravenous immunoglobulins IgG, IgA, and IgM can frequently resolve inflammation [32]. However, Robinson et al. proved that IVIG favored but did not significantly improve survival in child and adult viral myocarditis, and that the evidence for treatment with IVIG for presumed viral myocarditis is uncertain [33].

3. Antiviral therapy: Antiviral treatment has been an effective form of treatment for viral myocarditis in recent years. In a pilot study of 22 patients with persistent or progressive LV dysfunction, a 6-month treatment course with IFN-β effectively cleared the enterovirus or adenovirus from the hearts of 100% of patients, with a resultant improvement in LV function in 68% of these patients [34]. The phase II BICC trial investigated the effects of immunomodulation with IFNβ therapy on viral clearance in patients with inflammatory cardiomyopathy and myocardial viral persistence (adenoviruses, enteroviruses, or B19V). Immunomodulatory IFN-β-1b treatment is a well-tolerated and safe treatment option, leading to effective virus clearance or reduction in the virus load in patients with chronic viral cardiomyopathy. Favorable clinical effects assess the quality of life, NYHA functional class, and patient global assessment [34]. Schultheiss et al. and Kuhl et al. show that IFNβ improve enterovirus-positive myocarditis or adenovirus-positive myocarditis viral clearance and survival [35,36]. For the influenza virus epidemic season and area, Oseltamivir is an effective anti-flu virus treatment. Early diagnosis and antiviral treatment are critical to prevent the disease's life-threatening complications [37].

4. Supportive care: Both CQ10 and trimetazidine decreased inflammatory and oxidative stress biomarker levels compared with baseline measurements. However, combination therapy with CQ10 and trimetazidine showed a significantly more powerful effect not only on markers of inflammation and oxidative stress, but also on left ventricular systolic function and troponin, compared with either treatment alone [38,39].

5. Other treatments, such as anti-IL-17 monoclonal antibodies (secukinumab) or stem cell treatment, are currently being researched. PERK inhibitor GSK2656157 mitigated viral myocarditis by disrupting the TRIM29-PERK connection, thereby bolstering cardiac function, enhancing cardiac antiviral responses [14]. IL-37 alleviates Coxsackievirus B3-induced viral myocarditis via inhibiting NLRP3 inflammasome-mediated pyroptosis [40].

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