REVIEW

Cardiovascular Complications In Viral Respiratory Infections

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Abstract: Viral respiratory infections (VRI) represent one of the most prevalent types of infectious diseases. The most common viruses include influenza, respiratory syncytial virus (RSV), coronaviruses, and other emerging viruses, like the metapneumovirus. While primarily affecting the respiratory system, they present cardiovascular tropism to some extent and lead to several complications such as thrombotic complications, myocarditis, pericarditis, and arrhythmic events. In the current review, we will present the pathophysiology of each complication, risk stratification, and prevention measures.

Keywords: *viral respiratory infections, cardiovascular complications.*

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INTRODUCTION

Viral respiratory infections (VRI) may occur at any age, with peak seasonal incidence specific to the virus type (e.g., influenza in the winter and enteroviruses in the summer and autumn). The clinical manifestations of these infections are heterogeneous and may involve the upper and lower respiratory tract, comprising rhinosinusitis, pharyngitis, the common cold, laryngotracheitis, bronchitis, bronchiolitis, and eventually pneumonia [1]. According to the host's background, such as comorbidities or immunity, VRI may lead to extrapulmonary manifestations with predominant involvement of the cardiovascular, renal, gastrointestinal, and central nervous systems [2]. In this mini-review, we will focus on the cardiovascular involvement of these infections. Viral respiratory diseases may not only exacerbate the already existing cardiac pathology such as heart failure and coronary artery disease, but can also trigger the onset of viral-related cardiac events and conditions such as myocarditis, pericarditis, pulmonary embolism, myocardial ischemia, or arrhythmic events [1].

PATHOPHYSIOLOGY OF THROMBOTIC COMPLICATIONS

The thrombotic complications of VRI include venous thromboembolism and arterial thrombotic events (myocardial infarction). In a recent study, among patients hospitalized with viral pneumonia from 2002 to 2014, the combined incidence of arterial and venous thrombosis was 5.0% with higher mortality rates [3].

Venous thromboembolism (VTE) is known to be a common respiratory and cardiovascular complication in hospitalized patients with viral infections [4]. Different theories have described the interplay between viral infections, the coagulation

pathway, and the hemostasis system. Most of these theories are based on endothelial inflammation and injury caused by uncontrolled viral replication. Coagulopathy is linked to various viral diseases, including SARS-CoV-2, and H1N1 influenza A virus. It is known to induce natural anticoagulant dysregulation, resulting in platelet dysfunction and higher D-dimer levels. For example, VTE was found in 15% of individuals with COVID-19 in a recent extensive meta-analysis of 44 trials focusing on severe complications and death in 14,866 hospitalized individuals with COVID-19 [4]. Another review showed that the pooled prevalence of VTE among ICU COVID-19 patients receiving prophylactic or therapeutic anticoagulation across all studies was 31%, suggesting that there is a high prevalence of thromboprophylaxis failure among COVID-19 patients [5].

Regarding arterial thrombosis related to VRI, it seems that approximately 53% more cases of acute myocardial infarction were reported in winter than during the summer [6]. This seasonality is not fully explained, but the increased incidence of upper respiratory tract infections is considered to play a role due to their multifaceted impact on blood rheology and therefore the functioning of the cardiovascular system [7]. There are several pathophysiological links between VRI and the triggering or worsening of myocardial ischemia, including (i) inflammation; (ii) prothrombotic imbalance (the impairment of fibrinolysis and anticoagulant function of the endothelium); (iii) hypercoagulability; and (iv) increased metabolic demands of the myocardium [8]. Systemic inflammatory processes triggered by VRI include the release of pro-inflammatory cytokines which are key mediators of atherosclerosis and may directly impact plaque rupture through local inflammation [9]. Furthermore, infections induce hemodynamic and pro-coagulant effects which predispose to ischemia and thrombosis [8].

It appears that the incidence of acute myocardial infarction is elevated in the clinical context of influenza and, to a lesser extent, after infection with noninfluenza respiratory viruses [10]. A systematic review and meta-analysis showed that influenza vaccines can reduce major adverse cardiovascular events by 13% in individuals with a history of cardiovascular disease, which supports international guidelines that advocate for influenza immunization in individuals older than 65 years of age to protect against ischemic coronary events [11].

Another cardiotropic virus is SARS-CoV-2. Among patients recovered from recent COVID-19, in magnetic resonance imaging (MRI), cardiac involvement was found in 78% of subjects, while myocardial inflammation was present in 60% of enrollees [12]. COVID-19 is related to an increased risk for ischemic complications. The risk of myocardial infarction (type 1 myocardial infarction as well as type 2 myocardial infarction) is five times higher and the risk of stroke is ten times higher during the first two weeks after diagnosis and persists for at least one month [13].

VIRAL MYOCARDITIS AND POST-INFLAMMATORY CARDIOMYOPATHY

Myocarditis is histologically defined by the presence of an inflammatory infiltrate in the myocardium in conjunction with degenerative and/or necrotic changes of adjacent cardiomyocytes not typical of ischemic damage [14]

Clinical presentation of viral myocarditis is heterogeneous and varies from asymptomatic to fulminant life-threatening conditions such as cardiogenic shock, ventricular arrhythmias, or even sudden cardiac death. In between, a broad spectrum of symptoms can occur, from chest pain

(ischemic-like or pleuritic-like), dyspnea, fatigue and less specific palpitations or syncope [12].

Respiratory viruses are established to be the most common triggers of myocarditis, and the most frequently identified ones are adenoviruses, enteroviruses, influenza viruses, and coronaviruses [15]. Adenoviruses and enteroviruses are cardiotropic viruses, responsible for direct damage to myocardial tissue. Viral invasion into cardiomyocytes occurs via the transmembrane receptor and is followed by viral replication, leading to the destruction of the cytoskeleton, cytolysis, and eventually an immune cell reaction. Persistent viral activity following the acute phase of the disease can result in progressive cardiac dysfunction with a poor prognosis (dilated cardiomyopathy) [16]. In this context, entero- or adenoviral genomes were detected in 26% of patients with idiopathic left ventricular dysfunction and in 13% of patients with idiopathic dilated cardiomyopathy [17]. Influenza A and B viruses, together with the Coronaviridae family, are classified as cardiotoxic agents, provoking myocarditis indirectly through activation of the immune system responses, leading to augmented cytokine release and cytokine-mediated myocardial damage (so-called "cytokine storm")[18].

PERICARDIAL DISEASE

Acute pericarditis is an inflammatory disease characterized by infiltrates of immune cells into the pericardium. Pericarditis may also present alongside other pericardial syndromes, including pericardial effusion, cardiac tamponade or constrictive pericarditis [19]. Diagnostic evaluation typically includes an electrocardiogram, chest x-ray and echocardiogram with additional laboratory tests to identify underlying causes.

In developed countries, viral etiology is the most common in both acute pericarditis and pericardial disease as a whole. Among respiratory viruses, enteroviruses, adenoviruses, and influenza viruses are the most prevalent in patients with pericarditis, being identified in 25%, 19%, and 6% of patients, respectively [20].

Acute pericarditis is frequently associated with varying degrees of myocarditis, leading to a condition known as “myopericarditis”. In clinical practice, pericarditis and myocarditis coexist, as they are both caused by similar etiological factors, primarily cardiotropic viruses. These include enteroviral infections in 15% of cases and influenza, parainfluenza, or adenoviral infections in 10% of cases each [21].

ARRHYTHMIAS

Supraventricular and ventricular arrhythmias can be triggered by direct mechanisms, such as cardiomyocyte invasion in acute myocarditis, which often complicates VRI, or by indirect mechanisms, including the excessive release of pro-inflammatory cytokines. These inflammatory responses, particularly when combined with coexistent complications such as acute myocardial ischemia or viral myocarditis (with giant-cell myocarditis being a common example), can further promote arrhythmic episodes by disrupting the heart's electrical stability [22].

A few studies have outlined the link between VRI and arrhythmias. A significant correlation between active influenza disease and the incidence of ventricular arrhythmias requiring shock or ATP treatment in patients with implantable cardioverter-defibrillators could be observed [23]. Additionally, among adult patients hospitalized due to respiratory syncytial virus infection, 8% developed a new arrhythmia, further emphasizing the arrhythmogenic potential of viral infections in individuals [24].

Risk assessment

The degree of disease severity is closely related to age, male sex, obesity, and possibly smoking, and the presence of chronic major comorbidities such as diabetes or hypertension [25].

First of all, it seems that the incidence of acute respiratory infection, particularly pneumonia, is higher in patients with increased cardiovascular risk, defined as diagnosed hypertension or a QRISK2 10-year risk score of more than 10% [25]. Cardiovascular risk is derived from associations identified in univariable analysis (manifestations of atherosclerosis-angina, peripheral vascular disease, and previous myocardial infarction, hypertension, hyperlipidemia, diabetes, chronic heart disease among first-degree relatives and smoking status). Furthermore, not surprisingly, patients with chronic cardiovascular disease or with increased cardiovascular risk are particularly vulnerable to developing cardiovascular complications after an acute respiratory infection because they are more susceptible to the additional stress induced by infection and inflammation [25].

Another major risk factor that contributes to a severe VRI with cardiovascular complications is immunodeficiency. Patients with human immunodeficiency virus and those who have undergone solid organ transplantation or allogeneic stem cell transplantation are particularly at risk [26].

Prevention

The primary strategy for preventing complicated VRI remains vaccination. Vaccines against viral infections such as influenza, SARS-CoV-2, and respiratory syncytial virus are important preventive healthcare measures in the general population and in patients with cardiovascular diseases [27]. Numerous studies have demonstrated the importance of vaccination in the prevention of severe VRI. As an example, influenza vaccination showed a potential benefit for primary and secondary prevention of cardiovascular diseases across all ages, lowering MACEs by 25% [27].

Furthermore, it appears that preventive cardiovascular treatments, particularly among individuals with high cardiovascular risk, could reduce acute respiratory infection-related complications [25].

Concerning anticoagulation, the decision of prophylactic anticoagulation should be individualized according to risk factors such as immobility or severity of illness. If deep venous thrombotic events still occur, proper dosing of anticoagulation in therapeutic doses should be a priority [28].

Antiviral treatment such as Remdesivir for COVID-19, Oseltamivir for influenza, or Ribavirin for respiratory syncytial virus may reduce the severity of disease, but it has not been demonstrated to reduce cardiovascular complications in particular [29,30].

CONCLUSIONS

To conclude, cardiac disease and high cardiovascular risk patients have been associated with an increased risk of cardiovascular complications such as thrombotic, immune-mediated, or arrhythmic events following acute VRI and seem to be reduced in patients who are vaccinated.

Author Contributions:

A.M.M. and C.C.D conceived the original draft preparation. A.U and M.C. were responsible for conception and design of the review. A.M.M. and C.C.D. were responsible for the data acquisition and for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All

authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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