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Respiratory Viral Infections in Patients with Cardiovascular Diseases: the Role of Interferon Preparations

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Abstract: Acute respiratory infections significantly contribute to the development and progression of cardiovascular diseases and their complications. The innate immune system, particularly interferons (IFN), serves as the first line of defense against viral pathogens. A deficiency of type I IFN, commonly observed in elderly patients with cardiovascular comorbidities, predisposes to a more severe course of viral infections. Growing vaccine hesitancy has further limited preventive strategies. In this context, antiviral drugs present a valuable alternative, offering advantages such as applicability in broad population groups, including immunocompromised individuals, and expanding therapeutic and preventive options for respiratory viral infections, including COVID-19. However, certain antiviral agents may induce oxidative stress, thereby aggravating its already elevated level during viral infections. To mitigate this effect, combining antiviral therapy with antioxidants appears rational. Recombinant IFN alpha-2b in combination with ascorbic acid and tocopherol provides such a therapeutic opportunity, enhancing both antiviral efficacy and oxidative stress control in patients with cardiovascular diseases at risk of severe respiratory viral infections.

Keywords: *respiratory viral infections, cardiovascular diseases, interferon, antiviral therapy, oxidative stress, antioxidants, COVID-19.*

Introduction

Cardiovascular disease (CVD) is the leading cause of death among adults worldwide [1]. Despite advances in the treatment of patients through primary and secondary prevention, a significant number of them still experience serious cardiovascular complications or death. Adverse cardiovascular outcomes that occur despite adequate preventive treatment are referred to as “residual cardiovascular risk” and are thought to be associated with various inflammatory conditions, including those of infectious origin [2]. The relevance of this problem has increased in connection with the COVID-19 pandemic.

The aim of this study was to analyze data from the current literature on the ways in which respiratory infections affect the cardiovascular system, as well as effective, safe, and widely available methods of prevention and early treatment of such infections, including COVID-19.

Respiratory infections — a risk factor for cardiovascular complications

A number of studies have demonstrated an association between infections, especially those affecting the respiratory system, and an increased risk of cardiovascular and cerebrovascular complications, as well as all-cause mortality [3–5]. The mechanisms by which infections increase the risk of cardiovascular complications are multifactorial and include activation of the immune system, systemic inflammation, hypercoagulation, activation of the sympathetic nervous system, and increased myocardial oxygen demand. The course of a respiratory infection naturally exacerbates hypoxia. These mechanisms interact

with each other, contributing to endothelial dysfunction, rupture of atherosclerotic plaques, myocardial dysfunction, and heart failure. They can both cause CVD and exacerbate existing CVD, leading to adverse outcomes. These findings have prompted research into the use of antimicrobial drugs in patients with CVD to prevent complications. After conducting a systematic review and meta-analysis of 38 clinical studies involving 26,638 people, N.J. Sethi et al. [6] found no evidence of the effectiveness of such intervention for the secondary prevention of coronary heart disease (CHD). Moreover, the authors showed that the use of macrolide and quinolone antibiotics for cardiovascular prevention may increase the risk of all-cause mortality, cardiovascular mortality, sudden cardiac death, and stroke.

Subsequently, researchers' interest in the development of CVD and its complications shifted from the influence of microbes to the action of viruses. It has been established that annual influenza vaccination is associated with a reduction in the incidence of myocardial infarction in patients with stable atherosclerotic CVD, improved prognosis in patients with heart failure, and a reduced risk of CVD in adults aged 65 years and older [7]. In addition, it has been shown that influenza vaccination administered early after myocardial infarction or in patients with high-risk coronary artery disease leads to a reduction in the risk of all-cause mortality and cardiovascular mortality within 12 months [8]. Therefore, influenza vaccination is recommended for all patients with acute coronary syndromes and should be administered primarily during index hospitalization during the influenza season for those who are not yet protected by seasonal vaccination [9].

The COVID-19 pandemic has been a global challenge for the healthcare system. Although the SARS-CoV-2 virus mainly affects the lungs, causing interstitial pneumonia and acute respiratory distress syndrome, a number of patients experience extensive clinical manifestations, such as gastrointestinal symptoms, cardiovascular involvement, and renal dysfunction. The most common cardiovascular diseases were myocarditis and pericarditis, arterial hypertension, arrhythmia, myocardial damage and heart failure, various forms of coronary artery disease, stress cardiomyopathy, ischemic stroke, and blood clotting disorders and dyslipidemia were commonly observed. According to current understanding, the two important pathogenetic mechanisms of cardiovascular damage are direct viral cytotoxicity and indirect hyperimmune responses of the body to SARS-CoV-2 infection [10]. Recently, the negative impact of oxidative stress has been recognized as playing an important role in the development of CVD and its complications.

Oxidative stress is an important pathogenetic mechanism in viral infections

Oxidative stress is defined as an imbalance between oxidants and antioxidants, which can potentially lead to damage to body tissues. If reactive oxygen species (ROS) accumulate and an imbalance occurs, the normal antioxidant system usually attempts to maintain ROS homeostasis by regulating their production and elimination. This is done with the help of internal low-molecular-weight antioxidants (ascorbic acid, glutathione, tocopherols) and enzymes that restore antioxidants (superoxide dismutase, glutathione peroxidase, catalase). However, if ROS are produced in excess and escape the effective control of antioxidant mechanisms, oxidative stress can occur, which damages cell structures and has a significant negative impact on the cardiovascular system [11].

Reactive oxygen species are involved in modulating the inflammatory response, regulating vascular tone, oxidizing low-density lipoprotein cholesterol, and cell growth. Their concentration in the walls of arteries increases in diabetes mellitus, dyslipidemia, arterial hypertension, and smoking, contributing to the development of atherosclerosis. The role of ROS in the development and progression of atherosclerosis also includes endothelial dysfunction and a negative effect on the stability of the fibrous cap of plaques. As a result, the likelihood of atherosclerotic plaque rupture increases, as does the frequency of cardiovascular complications such as myocardial infarction. ROS can also cause a decrease

in the bioavailability of nitric oxide, reducing endothelium-dependent vasodilation and contributing to the development of hypertension. They also have a negative effect on the ryanodine receptor type 2, which is responsible for regulating calcium ion homeostasis in the atria, causing their dysfunction, which may contribute to the development of atrial fibrillation. In the myocardium, ROS trigger signaling cascades associated with inflammation, impaired contractility, interstitial fibrosis, or myocardial hypertrophy, affecting cellular architecture and function and contributing to heart damage. Sources of ROS include mitochondrial dysfunction, nicotinamide adenine dinucleotide phosphate oxidase, xanthine oxidase, nitric oxide oxidase, the endoplasmic reticulum, and other causes, such as xenobiotics, ionizing radiation, air pollution, chemicals, including certain drugs, and viral infection [11].

The influenza virus causes inflammatory reactions through several mechanisms, primarily by increasing the level of intracellular ROS, which disrupt the redox balance in host cells. During the infectious process, ROS are by-products of mitochondrial metabolism, and their increased production leads to oxidative stress, causing cell damage. This imbalance promotes virus replication by weakening the host's immune defense, enhancing virus penetration into cells and its replication within them. In addition, the accumulation of ROS triggers programmed cell death (apoptosis) and stimulates the release of pro-inflammatory cytokines and chemokines, such as interferons, tumor necrosis factor, and interleukins. The resulting “cytokine storm” exacerbates tissue damage, especially in the lungs, leading to severe respiratory symptoms [12]. Increased ROS production contributes to the development of severe inflammatory reactions in patients with COVID-19, often leading to acute respiratory distress syndrome and other complications, including cardiovascular complications [13].

Despite their effectiveness in combating viral replication, some antiviral drugs can paradoxically exacerbate inflammatory reactions, indirectly contributing to oxidative stress [14]. Antiretroviral therapy agents — reverse transcriptase inhibitors (zidovudine and lamivudine) — disrupt mitochondrial function, increasing the production of ROS. Neuraminidase inhibitors, such as oseltamivir, which is mainly used against influenza viruses, can affect cellular signaling pathways, potentially contributing to oxidative stress [15]. Remdesivir, used to treat COVID-19, may increase oxidative stress in liver cells, raising concerns about its potential hepatotoxicity [16]. The following approaches may address these issues: 1) taking antioxidants or using antioxidants in combination with antiviral therapy to counteract oxidative stress; 2) developing less toxic antiviral drugs that maintain efficacy while reducing their impact on cellular antioxidant systems [17]. Antiviral drugs are essential for treating viral infections. However, a deeper understanding of how they affect antioxidant mechanisms is needed. This will help reduce the risk of side effects from therapy, especially in vulnerable populations, such as patients with CVD.

General principles for managing patients with heart damage as a result of COVID-19

Up to 45% of people who have had COVID-19, regardless of hospitalization status, experience a range of persistent post-COVID symptoms for up to 4 months [18]. World Health Organization experts define long COVID, or post-COVID syndrome, as “the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with symptoms persisting for at least 2 months without any other explanation” [19]. Cardiovascular and other chronic diseases are associated with COVID-19 and long COVID as risk factors, comorbidities, and consequences of infection [20]. At the same time, COVID-19 survivors with pre-existing CVD have a significantly higher risk of developing post-COVID syndrome symptoms than survivors without pre-existing CVD [21].

People at risk, such as those with pre-existing CVD, should pay particular attention to basic preventive measures such as wearing masks, frequent hand washing, and social distancing to avoid reinfection. In acute conditions, any patient with symptoms indicating heart damage, such as chest pain, shortness of

breath, or rapid heartbeat, especially those who have recently had COVID-19, should undergo a comprehensive cardiovascular examination. This includes determining the levels of cardiac biomarkers in the blood, such as cardiac troponin, the level of which is crucial for diagnosing myocardial damage. Chronic conditions requiring ongoing cardiological monitoring include persistent or late symptoms occurring after recovery from COVID-19, such as persistent chest discomfort, unexplained fatigue, rapid heartbeat, shortness of breath, arrhythmia, as well as serious disorders such as myocarditis, pericarditis, and postural tachycardia syndrome [22]. These patients are advised to undergo periodic examinations using electrocardiography, echocardiography, and serum biomarker analysis to monitor possible long-term effects on the cardiovascular system. Patients with a history of CVD or new risk factors during COVID-19 or after recovery should be under close medical supervision with regular cardiological examinations to monitor and reduce the risk of exacerbation of existing diseases or the development of new complications in a timely manner [23]. It is extremely important to control common risk factors for CVD, such as hypertension, diabetes mellitus, and hyperlipidemia, and to maintain a healthy lifestyle, including a balanced diet and moderate physical activity. Currently, there is no consensus on the rationale for prolonged preventive anticoagulant therapy for all patients with COVID-19 discharged from the hospital [24]. The question of the advisability and method of correction of chronic inflammation and immune disorders observed in people with long COVID-19 remains unresolved. All of the above demonstrates the need for significant time and resources to manage patients with long-term consequences of acute respiratory viral infections and emphasizes the need for timely and adequate treatment in the acute phase, especially in patients with a history of CVD.

Antiviral therapy for respiratory infections: focus on interferon

The COVID-19 pandemic has served as a powerful stimulus for the development of treatments for this new infectious disease. At the same time, traditional symptomatic therapy (oxygen therapy/artificial ventilation in cases of respiratory failure, antibiotics to prevent secondary bacterial infection, plasma substitute infusion), while various options for special treatment that followed one another did not provide the desired efficacy and safety. Antiviral therapy expands the possibilities for treatment and prevention, providing an alternative solution for those who cannot or do not want to be vaccinated, and is an integral part of the fight against SARS-CoV-2. Antiviral drugs can be divided into categories depending on how they counteract the virus, including virus entry into the host cell, virus replication, protein transport, post-translational processing, and immune response regulation. Drugs that affect the virus's entry into the cell include: monoclonal antibodies — combinations of tixagevimab + cilgavimab, casirivimab + imdevimab, and bamlanivimab + etesevimab, bebtelovimab, sotrovimab, umifenovir, nitazoxanide, and chloroquine. Drugs that prevent the virus from replicating include: nirmatrelvir + ritonavir, remdesivir, molnupiravir, favipiravir, ribavirin, and ritonavir + lopinavir. Drugs that inhibit protein transport and post-translational processing include nitaxanide and ivermectin. Finally, drugs that affect the regulation of the immune response include interferons (IFNs) and anti-inflammatory drugs such as dexamethasone [25]. Most of the drugs listed are not recommended for the treatment of COVID-19, so the search for effective, safe, and widely available therapies for this disease continues.

In the mid-20th century, A. Isaacs and J. Lindenmann [26] first reported on a substance that prevents viruses from replicating in host cells, which was named “interferon.” Since this first description, knowledge about interferons, their regulators, effects, and associated regulatory factors has continued to expand far beyond virology. It is important to note that IFNs and their associated signaling pathways are recognized as factors in the pathogenesis of CVD or even protection against it.

Interferons belong to the class II cytokine family, a group of α-helical cytokines with weak sequence homology but structural similarity. The IFN family consists of three types, differing from each other in

the type of receptor with which they bind: type I IFN (IFN-α and IFN-β), type II IFN (the only representative of IFN-γ) and type III IFN (IFN-λ1, IFN-λ2, IFN-λ3, and IFN-λ4). Almost all cells can produce type I interferons, although the main sources of type I IFN are innate immune cells [27].

Viral infection leads to a continuous battle between the body's defense mechanism, which seeks to destroy infected cells or suppress viral replication, and the replication of the virus itself. In this context, the interferon response plays a crucial role in the innate immune response to pathogen invasion. It is triggered after pathogen-associated molecular patterns are recognized by specific pattern recognition receptors encoded by the body and represents the first line of defense against viruses. This coordinated response leads to the formation of an antiviral state, which includes the transcriptional activation of hundreds of IFN-stimulated genes, with the induction of proteins with antiviral properties [28]. IFN suppresses viral replication and/or induces apoptosis of the infected cell, rendering neighboring cells resistant to viral infection. In addition, IFNs activate the adaptive immune system, causing high-affinity antigen-specific reactions of B and T cells.

Despite the presence of mechanisms in viruses to evade the antiviral activity of the host (direct suppression of IFN induction or inhibition of its signaling pathway), the IFN system is still capable of limiting or preventing infection by most viruses [29]. Various studies have demonstrated that treatment or pretreatment with type I IFN has a protective effect on cells infected with SARS-CoV-2, indicating its potential ability to reduce the severity of COVID-19 [30].

Regulating type I IFN activity within the physiological range may be clinically significant for the prevention and treatment of viral and inflammatory diseases [31]. Optimizing the response to type I IFN is extremely important for the outcome of COVID-19, as the production of a strong IFN response at the onset of SARS-CoV-2 infection plays a crucial role in the development of a protective immune response. However, both insufficient and excessive activation of IFN signaling can have negative effects [32]. Persistently elevated levels of IFN and other pro-inflammatory cytokines may contribute to chronic inflammation and immune dysfunction observed in people with long COVID-19 [33].

Overall, clinical data support the potential use of IFN in the treatment of patients with COVID-19, whereas suppression of IFN signaling contributes to the development of severe forms of COVID-19 [34], and a lack of type I IFN in the blood may indicate a severe form of the disease [33]. SARS-CoV-2 is capable of inhibiting the production of type I IFN, which is the main antiviral agent. This strategic evasion allows the virus to replicate longer, potentially enhancing transmission. IFNs play a critical role in fighting viruses and lead to the release of chemokines that attract neutrophils and macrophages [35]. Infectious cells showed an insufficient response to IFN. It was found that patients have autoantibodies against many proteins that regulate immunity, and the link between antibodies to type I IFN and disease severity and mortality is especially important [36]. Thus, the innate immune response may not be able to destroy infected cells, potentially contributing to viral replication in the early stages of infection. Uncontrolled initial virus replication leads to an overly aggressive response, contributing to the development of cytokine release syndrome (interleukin 1, interleukin 6, and tumor necrosis factor α) — a “cytokine storm” [37]. It is noteworthy that a high incidence of respiratory failure and severe pneumonia has been reported in elderly people and individuals with comorbidities, including diabetes mellitus, obesity, and arterial hypertension, i.e., factors leading to a deficiency in IFN production in response to pathogen infection [38].

When considering the choice of a type I IFN drug for non-specific emergency treatment and prevention of viral infections, the available scientific evidence on the possible effectiveness of the intervention based on the studies conducted should be taken into account. It is clear that the most vulnerable group is patients with CVD, especially the elderly. They have the highest chances of obtaining a significant

positive effect from non-specific prevention and treatment of respiratory viral infections, including COVID-19, by creating an increased concentration of IFN in the blood plasma when using its drug form. For the prevention and treatment of acute respiratory viral infections, including influenza and COVID-19, the recombinant IFN α-2b drug with antioxidants (vitamins C and E) — Viferon® — may be recommended. The drug is available in the form of rectal suppositories, which provide systemic action, as well as in the form of a gel and ointment for external and local use. The availability of various forms and dosages of the drug allows it to be used in various clinical scenarios, including in high-risk patients. It has previously been shown that the use of recombinant IFN α-2b suppositories in combination with vitamins E and C in the treatment of acute respiratory viral infections and influenza in children significantly reduces the duration of catarrhal symptoms, rhinorrhea, intoxication, fever, and the period of viral shedding, and improve immune response indicators, which is accompanied by a decrease in the frequency of complications and recurrent diseases. The use of the drug for the treatment of acute respiratory viral infections and influenza in adults, including complicated forms, also led to a more rapid dynamics of the main clinical symptoms, a statistically significant reduction in the duration of antibiotic therapy and the disease as a whole [39, 40].

Conclusion

Cardiovascular disease is the leading cause of death among adults worldwide. There is a known association between infections, particularly those affecting the respiratory system, and an increased risk of cardiovascular and cerebrovascular complications, as well as all-cause mortality. This explains the importance of vaccination for people with CVD risk factors or existing CVD, but vaccination rates remain low. Preventive and therapeutic measures for respiratory viral infections should take into account their pathogenesis, in particular the role of oxidative stress. Regulating type I IFN activity within the physiological range may be clinically relevant for the prevention and treatment of viral and inflammatory diseases. Despite the fact that viruses have ways of evading the antiviral activity of the host, the IFN system is still capable of limiting or preventing infection by most viruses. The domestic drug recombinant IFN α-2b with antioxidants (vitamins C and E) (Viferon®) has been well studied in the Russian population, is effective against viruses that cause respiratory infections, including COVID-19, is highly safe, as established in studies in adults, children, and pregnant women, and can be considered the drug of choice for the prevention and early treatment of respiratory viral infections in patients with CVD.

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