The Heart Under Viral Attack: From Infection and Vaccination to Myocardial Injury

Tokmachev R.E. [†*], Antakova L.N. [†], Pulver A.Yu. [†], Belousova E.Yu. [†], Shkatova Ya.S. [†], Tokmachev E.V.[†]., Annenkova A.V. [†], Gusev I.N. [†], Sheshnikova E.I. [†], Pulver N.A. [†‡]

[†]N. N. Burdenko Voronezh State Medical University, Address: 10, Studentskaya str., 394036, Voronezh, Russian Federation;
[‡]Voronezh State Technical University, 84, 20 letiya Oktyabrya str., 394006, Voronezh, Russian Federation.

Abstract:
Chronic heart failure remains a major global burden, with respiratory viral infections frequently precipitating hospitalisation and mortality. Viral myocarditis has emerged as a significant contributor to cardiac dysfunction, driven by both direct cytopathic effects and immune-mediated pathways. This review synthesises contemporary experimental and clinical evidence on the molecular mechanisms by which cardiotropic viruses—including Coxsackievirus B, herpesviruses (HHV 6, EBV, CMV), parvovirus B19, influenza viruses and SARS CoV 2—damage the myocardium, with particular emphasis on the roles of Toll like receptors, viral proteases and the pro inflammatory cytokines TNF α, IL 6 and IL 1β. These cytokines exert negative inotropic actions, promote cardiomyocyte apoptosis and disrupt extracellular matrix homeostasis, thereby contributing to adverse ventricular remodelling and heart failure progression. The review also examines the veterinary legacy of coronavirus vaccine development, which has been largely overlooked in human cardiology. For over half a century, veterinary medicine has confronted coronaviruses as devastating livestock pathogens, accumulating extensive knowledge of vaccine platforms, viral mutation and immune escape mechanisms that proved instrumental in expediting the creation of mRNA vaccines against COVID 19. Importantly, the review appraises the cardiac safety profile of these vaccines, concluding that the incidence of vaccine associated myocarditis—predominantly observed in young males after the second dose—is substantially lower than the risk of myocarditis following natural SARS CoV 2 infection. Although rare, post vaccination cardiac complications warrant ongoing surveillance and mechanistic research. Overall, this comprehensive overview underscores the convergence of infectious disease, immunology and vaccinology in shaping our understanding of virus related heart disease, while highlighting the translational value of veterinary research. Future investigations should focus on identifying individual susceptibility factors and developing targeted strategies to mitigate both viral and vaccine induced myocardial injury, thereby improving outcomes for patients with or at risk of heart failure.

Keywords: Cardiotropic viruses; chronic heart failure; coronaviruses; COVID-19 vaccines; Coxsackievirus B; cytokines; herpesviruses; IL-1β; IL-6; influenza viruses; inflammation; mRNA vaccines; myocardial injury; myocarditis; parvovirus B19; SARS-CoV-2; TNF-α; veterinary vaccines; viral myocarditis/
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1. Introduction

Chronic heart failure remains a leading cause of hospitalisation and mortality worldwide, with respiratory viral infections serving as major triggers for decompensation. These indicators are largely driven by the exacerbation of heart failure resulting from respiratory infections and other intercurrent illnesses. Analysis of numerous studies suggests that a 5–7% absolute increase in viral disease activity is directly associated with a 24% or greater rise in hospitalisation rates for heart failure.

Inflammation detected in patients with chronic heart failure may, on one hand, result from increased expression of pro-inflammatory cytokines as mediators of protective actions on cardiac cells and rapid adaptation to stress, and on the other hand, from the toxic effects of these cytokines on myocardial cells and systemic circulation.

Viral myocarditis is an increasingly recognised cause of heart failure. Many viruses affect the heart either through direct viral processes, such as host cell lysis or cleavage of proteins by viral proteases, or via indirect mechanisms linked to the host immune response [1]. Although the immune response is essential for combating the virus, it frequently causes substantial cardiac injury and may sometimes be more destructive than the virus itself [2].

[*]Corresponding Author: R.E. Tokmachev.

The aim of this review is to synthesise current experimental and clinical data on the mechanisms of direct and indirect myocardial damage caused by various viruses, and to evaluate the role of vaccination—including the veterinary experience in developing coronavirus vaccines—in cardiovascular events. The literature search was conducted using PubMed, MEDLINE, and the Russian Science Citation Index databases, covering the period from 1996 to August 2024.

2. Principal Cardiotropic Viruses and Their Mechanisms of Action

Myocardial injury is caused by numerous viruses. The most extensively studied are enteroviruses, herpesviruses, parvoviruses, influenza viruses and coronaviruses [1]. Despite the specific action of each virus on cardiomyocytes, common mechanisms exist. Most viruses that cause myocarditis directly damage cardiomyocytes, thereby promoting an immune-mediated response. This immune-mediated injury may result from excessive cytokine production or the development of autoimmune myocarditis [2].

2.1. Enteroviruses

The most frequent cause of myocardial damage is Coxsackievirus B (CVB), a serotype of RNA-containing enteroviruses. The most extensively studied are six serotypes of this virus—CVB1 through CVB6. Viral entry occurs through binding to DAF (decay-accelerating factor) and CAR (coxsackievirus and adenovirus receptor) proteins present on the membrane of nucleated cells, as well as on erythrocytes and platelets [3]. Following viral entry, the released RNA molecule initiates a cascade of events within the cell, leading to the production of mature viral progeny and ultimately to cell death [3].

The initial step involves the synthesis of viral proteins required for replication, capsid formation and cell lysis—that is, translation of viral RNA by the cellular translational machinery. Notably, viral proteins also cleave host factors to enhance viral proliferation and inactivate immune responses [4]. For example, CVB proteases can cleave the key antiviral signalling protein MAVS (mitochondrial antiviral signalling protein), which suppresses type I interferon production [4]. CVB proteins disrupt calcium channel function and endoplasmic reticulum activity, leading to enhanced virion release and reduced cytokine secretion for immune cell activation [4].

The immune response to CVB infection begins with recognition of CVB RNA by Toll-like receptors 3 (TLR3), 7 (TLR7) and 8 (TLR8) [3]. These receptors then activate signalling adapter molecules such as TRIF and MyD88, which ultimately promote transcription of pro-inflammatory cytokines [3]. Early cytokines include interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) [4]. In addition, cytokines activate innate immune cells such as NK cells and macrophages, followed by recruitment of T cells for specific antiviral responses [3]. This response is essential for limiting direct viral damage; however, immune cells may also cause indirect cardiac injury by inadvertently attacking healthy cells [3]. Furthermore, CVB may promote autoimmune-mediated cardiac injury, possibly by inducing immune reactivity to cardiac myosin [4].

2.2. Herpesviruses

Another family of viruses associated with cardiac involvement is the herpesviruses. The most frequent causes of viral myocarditis in this group are human herpesvirus 6 (HHV-6), Epstein–Barr virus (EBV) and cytomegalovirus (CMV) [5]. Herpesviruses are DNA viruses that typically establish latent infections. According to the review by Badrinath S. and co-authors, HHV-6 is detected in 10–22% of patients with cardiac dysfunction [5]. Numerous fatal cases of myocarditis caused by HHV-6 infection have been reported [5].

HHV-6 is known to damage endothelial cells and stimulate pro-inflammatory cytokine production. This promotes recruitment of immune cells into the myocardium and the development of inflammation [5]. Another mechanism by which HHV-6 contributes to heart failure is its capacity to induce immunosuppression [5]. The authors note that EBV and HHV-6 are reactivated in patients with SARS-CoV-2, which may contribute to the myocardial injury observed after severe COVID-19 infection [5].

2.3. Parvovirus B19

Parvovirus B19 is one of the most frequently detected viruses in endomyocardial biopsies of patients with myocarditis and dilated cardiomyopathy [4]. Unlike enteroviruses and herpesviruses, parvovirus B19 predominantly affects endothelial cells of the microvasculature rather than cardiomyocytes themselves. This leads to endothelial dysfunction, myocardial ischaemia and apoptosis. In 2024, an outbreak of paediatric myocarditis associated with parvovirus B19 was reported in Italy: 65 clinically suspected cases, of which 32 were linked to B19V [6]. Since March 2024, the European Centre for Disease Prevention and Control has reported an increase in B19V infections in 14 European countries [7].

2.4. Influenza Viruses

Influenza viruses have long been associated with myocarditis. Seasonal fluctuations in influenza incidence have been observed to correlate with fluctuations in heart failure-related hospitalisations, and influenza vaccination has been shown to reduce hospitalisations for cardiovascular causes [8]. A 2023 systematic review and meta-analysis demonstrated that the cumulative incidence of

cardiovascular complications in hospitalised patients with laboratory-confirmed influenza ranges from 1.51% to 17.47% [8].

2.5. Coronaviruses

Coronaviruses, including SARS-CoV-2, can also cause myocarditis. Myocarditis is considered a major contributor to the high mortality associated with coronavirus infection [9].

Coronaviruses utilise angiotensin-converting enzyme 2 (ACE2) as a receptor for cell entry [9]. Since cardiomyocytes broadly express ACE2, direct infection of cardiac tissue by SARS-CoV-2 is plausible. A 2024 systematic review notes that the disease is caused by both direct and indirect effects of SARS-CoV-2 infection on cardiomyocytes and other cells [9]. Clinical manifestations range from mild (fatigue, dyspnoea) to severe (cardiogenic shock) [9]. Autopsy findings suggest that myocarditis in COVID-19 is more often a consequence of the inflammatory response than of direct viral invasion [9].

2.5.1. The Veterinary Experience in Coronavirus Vaccine Development

It is important to note that long before the COVID-19 pandemic, veterinary medicine had accumulated considerable experience in combating coronavirus infections. In livestock farming, coronaviruses represent an extremely dangerous group of pathogens, causing diseases with high mortality and substantial economic losses. Veterinary science has confronted coronaviruses that, by human medical standards, would be comparable to the most devastating plagues—infectious bronchitis of poultry, transmissible gastroenteritis of swine, canine coronavirus enteritis, and bovine coronavirus [10].

Veterinary practice has a lengthy history of developing vaccines against coronaviruses. Vaccine development for animals began as early as the 1980s. For example, in 1983, a vaccine against canine coronavirus was introduced but was withdrawn from the market within two months due to serious adverse reactions, including neurological disorders and fatalities in over 300 dogs [11]. This and similar cases demonstrated that creating a safe and effective vaccine against coronaviruses posed substantial challenges.

In Russia, in March 2021, the world's first COVID-19 vaccine for animals was registered—"Carnivac-Cov," developed by the Federal Centre for Animal Health, subordinate to the Federal Service for Veterinary and Phytosanitary Surveillance (Rosselkhoznadzor). The veterinary company Zoetis also developed an experimental COVID-19 vaccine for animals.

A critical aspect of the veterinary approach is that upon detection of particularly dangerous coronavirus infections in livestock, especially among mink and poultry, total culling of the entire population is often employed as the only means of halting transmission and preventing viral mutation with potential cross-species transmission to humans. This stringent but effective method, used in veterinary practice for over half a century, is not applicable in human medicine. This is precisely why the development of safe vaccines for humans became a critical necessity.

3. Immune-Mediated Mechanisms of Myocardial Injury

Accumulating evidence indicates that cytokines play an important role in the pathogenesis of chronic heart failure. In many forms of left ventricular dysfunction, rapid myocardial expression of pro-inflammatory cytokines is observed; through specific receptors, these cytokines mediate various processes including gene expression, cell growth and apoptosis [12]. Cytokines exert negative inotropic effects, stimulate protein synthesis, increase capillary permeability, promote the progression of myocardial hypertrophy and participate in left ventricular remodelling. Myocardial cytokine expression contributes to depressed contractile function and adverse left ventricular remodelling [12]. In patients with chronic heart failure, cytokine concentrations are elevated not only in the myocardium but also in the plasma [12].

3.1. Tumour Necrosis Factor-α (TNF-α)

TNF-α is expressed by both immune and non-immune cells, and its systemic expression increases following infection with various cardiotropic viruses [13]. The molecular mechanisms of TNF-α-mediated cardiac dysfunction are relatively well understood. TNF-α functions through activation of one of its two receptors, TNFRSF1A and TNFRSF2A [13]. Activation of TNFR1 in cardiomyocytes promotes apoptotic signalling, while TNFR2 signalling leads to the production of pro-apoptotic factors such as caspase-8, caspase-9 and caspase-3 [13]. TNF-α can also promote apoptosis by activating neutral sphingomyelinase (NSMASE), an enzyme that generates the lipid mediators sphingosine and ceramide, which in turn participate in cardiomyocyte apoptosis [13].

TNF-α reduces collagen expression by fibroblasts and disrupts the regulation of key factors required for maintaining the extracellular matrix, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [13]. This disruption of the extracellular matrix contributes to left ventricular dilation and cardiac dysfunction, which is significant given that cardiac hypertrophy is a key step in the pathogenesis of heart failure.

Mechanistically, TNF-α reduces contractility through a variety of mechanisms. The negative inotropic effect of TNF-α is partly attributable to activation of neutral sphingomyelinase signalling, as sphingosine blocks the ryanodine receptor required for calcium release during contraction [13]. TNF-α

also promotes activation of nitric oxide synthase (NOS), which exerts a negative inotropic effect [13]. The negative inotropic effects of TNF-α may also partially result from inhibition of β-adrenergic receptors [13]. β-adrenergic signalling is the primary pathway through which cardiac output increases during stress, and TNF-α has been shown to blunt β-adrenergic responses in the heart.

In transgenic mice, the rate of progression of left ventricular dilatation correlates with the intensity of myocardial TNF-α overexpression [12]. Clinical studies have demonstrated positive immunoreactivity to TNF-α in right atrial tissue from patients with heart failure.

3.2. Interleukin-6 (IL-6)

Another important cytokine induced by cardiotropic viruses is IL-6 [13]. It is a pleiotropic cytokine that can exert either pro-inflammatory or anti-inflammatory properties depending on cell type and signalling pathway. It directly regulates the activity of various immune cells, including macrophages, NK cells, T cells and B cells [13].

IL-6 can adversely affect the heart through several mechanisms. First, it reduces myocardial contractility by increasing NOS expression in cardiomyocytes. Second, it modulates MMP activity, indicating a role for IL-6 in extracellular matrix remodelling [13]. IL-6 may contribute to autoimmune disease by stimulating the production of T-helper 17 (Th17) cells [13].

In murine models of chronic myocarditis induced by Coxsackievirus B3, sustained IL-6 overexpression has been observed during the chronic phase of the disease [4]. Elevated IL-6 levels have been identified in both the circulation and the heart of patients with chronic heart failure. In myocarditis, cardiomyopathy, transplant rejection and other conditions, circulating IL-6 levels correlate with the severity of left ventricular dysfunction and serve as strong predictors of subsequent clinical outcomes. Continuous and excessive IL-6 production contributes to myocardial injury by disrupting both cytokine networks and viral clearance in viral myocarditis.

It is important to note that IL-1β and IL-6 act synergistically with TNF-α, and myocardial dysfunction is maximal when all three cytokines are present in combination [14].

3.3. Interleukin-1β (IL-1β)

Another pro-inflammatory cytokine activated during viral infection is IL-1β [13]. IL-1β is expressed primarily in monocytes and macrophages [13]. It is initially produced as an inactive precursor, which is activated and released following proteolytic cleavage by caspase-1 of the inflammasome complex [13]. IL-1β exerts negative effects on the myocardium through several mechanisms. Like TNF-α and IL-6, IL-1β exerts a negative inotropic effect [13]. Other mechanisms by which IL-1β reduces contractility include suppression of β-adrenergic signalling, blockade of L-type calcium channels, stimulation of NOS expression and alteration of phospholamban and sarcoplasmic/endoplasmic reticulum calcium ATPase activity [13].

Release of IL-1β leads to extensive inflammation, cardiomyocyte death, progressive loss of viable contractile tissue and ultimately heart failure [13]. There is compelling evidence linking the NLRP3 inflammasome and IL-1 cytokines to the pathogenesis of cardiovascular disease [13].

IL-1β has also been shown to stimulate cardiomyocyte apoptosis in vitro. Treatment of cardiomyocytes with IL-1β leads to increased caspase-3 expression and enhanced cytochrome c release from mitochondria. Both of these processes support caspase-dependent apoptosis. IL-1β treatment has also been shown to increase expression of factors involved in caspase-independent apoptosis, such as endonuclease G. Other mechanisms through which IL-1β adversely affects the heart include cardiomyocyte hypertrophy and extracellular matrix remodelling. The pro-hypertrophic effect of IL-1β has been demonstrated in vitro and may result from induction of a fetal gene expression programme typically associated with hypertrophic growth. IL-1β has been shown to alter extracellular matrix remodelling through multiple mechanisms. It reduces fibroblast proliferation in vitro and has been shown to decrease collagen synthesis while increasing expression of multiple MMPs in cardiac fibroblasts.

In endomyocardial biopsy specimens from patients with myocarditis, IL-1β, IL-6, IL-8 and TNF-α genes were expressed in 100% of cases [4]. In acute myocarditis induced by Coxsackievirus B3, significant activation of various cytokines (IL-1β, IL-6, IL-10, IFN-γ and TNF-α) was observed in the acute phase, with persistent overexpression of IL-6, IL-10 and IFN-γ in the chronic phase [4].

4. Vaccines and the Heart: Potential Risks and Mechanisms

4.1. Historical Context – Post-Vaccination Myocarditis

Post-vaccination myocarditis is not a new phenomenon. Cases of myocarditis were observed following smallpox vaccination, particularly after administration of second-generation vaccines. In subsequent decades, rare cases of myocarditis were reported following influenza, measles, rubella and mumps vaccination. However, the incidence of these complications was extremely low, and they did not attract significant scientific attention until the COVID-19 pandemic.

4.2. mRNA Vaccines Against COVID-19: Epidemiology of Myocarditis and Pericarditis

With the commencement of mass vaccination using mRNA vaccines (BNT162b2, Pfizer-BioNTech and mRNA-1273, Moderna), cases of myocarditis and

pericarditis were reported, predominantly in young males [15]. A meta-analysis including 15 studies with a total of over 39.6 million vaccine doses demonstrated that the pooled incidence of myopericarditis among adolescents aged 12–17 years was 43.5 per million doses for both vaccines (BNT162b2 and mRNA-1273) and 41.8 per million for BNT162b2 alone [15]. Among males, the incidence was 66.0 per million doses compared with 10.1 per million in females [15]. Following the second dose, the incidence reached 60.4 per million doses compared with 16.6 per million after the first dose [15].

A 2025 systematic review and meta-analysis demonstrated that the highest attributable risk of myocarditis or pericarditis was observed after the second dose in males aged 12–17 years—10.18 per 100,000 doses for BNT162b2 and 20.02 per 100,000 doses for mRNA-1273 in young males aged 18–24 years [16].

Another meta-analysis demonstrated that the risk of myopericarditis following COVID-19 infection (1583.9 per million infections) was approximately 42 times higher than following vaccination (37.6 per million doses) [15]. The highest risk following vaccination was observed in the 16–19 year age group (39.5 cases), among males (43.1 cases) and after the second dose (47.7 cases) [15].

A study conducted within the prospective multicentre MYKKE registry demonstrated that the course of COVID-19 vaccine-associated myocarditis in paediatric patients (median age 16.3 years) was mild and differed from non-vaccine-associated myocarditis. However, a significant proportion of patients had residual symptoms and diagnostic abnormalities at follow-up [17].

4.3. Proposed Mechanisms of Post-Vaccination Myocarditis

The mechanisms underlying the development of myocarditis following mRNA vaccination are under active investigation. A 2023 study demonstrated that the pathogenesis involves cytokinopathy with aberrant cytotoxic lymphocyte and profibrotic myeloid responses [18]. Comparative pathological studies of vaccine-associated myocarditis and viral myocarditis suggest that COVID-19 vaccine-associated myocarditis is primarily driven by uncontrolled cytokine-mediated inflammation with possible genetic components in the interleukin-6 signalling pathway [19].

Several possible pathways for the development of post-vaccination myocarditis have been proposed: direct effects of mRNA or lipid nanoparticles on cardiomyocytes and endothelial cells; immunogenicity of the spike protein and its cross-reactivity with cardiac tissues; and hyperstimulation of innate immunity with excessive production of interferons and other pro-inflammatory cytokines [18, 19]. The predominance of cases in young males may be related to higher androgen levels, which modulate immune responses [20,21].

4.4. Comparative Risk: COVID-19 Infection versus Vaccination

Numerous studies demonstrate that the risk of myocarditis following COVID-19 infection substantially exceeds the risk following vaccination. As noted above, the risk of myopericarditis following COVID-19 infection is approximately 42 times higher than following vaccination [15]. This critical ratio allows for an assessment of the benefit–risk balance of vaccination.

It should also be noted that myocarditis in COVID-19 infection often has a more severe course, with higher risks of developing dilated cardiomyopathy, heart failure and fatal outcomes. In contrast, post-vaccination myocarditis is overwhelmingly mild with rapid resolution of symptoms.

5. Diagnosis and Management of Virus-Associated Cardiac Disease

Diagnosis of viral cardiac involvement is based on a combination of clinical, laboratory and instrumental methods. Key biomarkers include troponins I and T, as well as creatine kinase-MB. Elevation of these markers indicates cardiomyocyte injury. Inflammatory response is assessed by C-reactive protein levels, erythrocyte sedimentation rate and pro-inflammatory cytokine concentrations.

Echocardiography is the primary imaging modality, allowing assessment of global and segmental myocardial contractility, cardiac chamber dimensions and the presence of pericardial effusion. Cardiac magnetic resonance imaging with gadolinium contrast is the gold standard for diagnosing myocarditis, enabling visualisation of areas of myocardial inflammation and fibrosis.

Endomyocardial biopsy remains the most informative but invasive method, not only confirming the diagnosis but also enabling identification of the viral agent through polymerase chain reaction.

Treatment of virus-associated cardiac disease includes antiviral therapy, which is effective only against certain viruses (e.g., herpesviruses). Immunomodulatory therapy, including corticosteroids and intravenous immunoglobulins, is employed in severe forms of myocarditis with a pronounced inflammatory response. Supportive therapy for heart failure during infection follows standard guidelines, including ACE inhibitors, beta-blockers, mineralocorticoid receptor antagonists and diuretics.

6. Conclusion

This review summarises current data on the mechanisms of myocardial injury caused by various viruses and vaccine-associated cardiac involvement. It has been shown that viral myocarditis develops both through direct cytopathic effects of viruses and

through immune-mediated mechanisms, including hyperproduction of pro-inflammatory cytokines, activation of apoptosis and autoimmune reactions.

Particular attention has been devoted to coronaviruses, including SARS-CoV-2, and the veterinary experience in combating coronavirus infections. Veterinary medicine has, for over half a century, confronted coronaviruses as extremely dangerous pathogens causing widespread disease and mortality in animals. The accumulated experience in developing vaccines against animal coronaviruses, studying their mutational variability and immune responses has provided a crucial foundation for the rapid development of vaccines against COVID-19 for humans.

Analysis of post-vaccination complications demonstrates that myocarditis and pericarditis following mRNA vaccination are rare complications, the incidence of which is substantially lower than the risk of developing myocarditis following COVID-19 infection. The highest risk is observed in young males after the second vaccine dose; however, the course of the disease is overwhelmingly favourable.

Future research directions include the study of novel antiviral targets, the development of personalised vaccination approaches accounting for individual risk factors, and in-depth investigation of the molecular mechanisms determining differential susceptibility to viral cardiac injury and post-vaccination complications across different age and sex groups.

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