REVIEW

Risk Impact of SARS-CoV-2 Coronavirus and Spike Protein on Cardiac Tissue: A Comprehensive Review

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Summary

The global COVID-19 pandemic, caused by SARS-CoV-2, has led to significant morbidity and mortality, with a profound impact on cardiovascular health. This review investigates the mechanisms of SARS-CoV-2's interaction with cardiac tissue, particularly emphasizing the role of the Spike protein and ACE2 receptor in facilitating viral entry and subsequent cardiac complications. We dissect the structural features of the virus, its interactions with host cell receptors, and the resulting pathophysiological changes in the heart. Highlighting SARS-CoV-2's broad organ tropism, especially its effects on cardiomyocytes *via* ACE2 and TMPRSS2, the review addresses how these interactions exacerbate cardiovascular issues in patients with pre-existing conditions such as diabetes and hypertension. Additionally, we assess both direct and indirect mechanisms of virus-induced cardiac damage, including myocarditis, arrhythmias, and long-term complications such as 'long COVID'. This review underscores the complexity of SARS-CoV-2's impact on the heart, emphasizing the need for ongoing research to fully understand its long-term effects on cardiovascular health.

Key words

COVID-19 • Heart • ACE2 • Spike protein • Cardiomyocytes • Myocarditis • Long COVID

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Introduction

As the 21st century began, global public health faced numerous challenges; however, the emergence of the COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had an unprecedented and profound impact worldwide. Since the first reported cases in 2019, this virus has rapidly spread on a global scale, leading to significant loss of life, strain on healthcare systems, and considerable socio-economic consequences [1]. To date, the SARS-CoV-2 virus has been responsible for over 7 million deaths worldwide (April 2024, https://covid19.who.int/). Focusing on the causes of death among individuals with SARS-CoV-2 infection, respiratory failure due to severe pneumonia is the immediate and most common cause of mortality in COVID-19 patients [2,3]. In addition, cardiovascular complications, including acute heart failure, arrhythmias, and thromboembolic events, play a crucial role in increasing morbidity and mortality, especially in patients with pre-existing cardiovascular diseases or those who develop severe systemic inflammatory responses leading to a cytokine storm [4].

Throughout the pandemic, research has been concentrated on understanding the mechanisms by which the virus affects the human body, including its interactions with various receptors, cells, tissues, and organs. These interactions are primarily influenced by the virus's ability to invade cells through receptors and

replicate within them, thereby causing tissue damage. As a result, numerous individuals infected with SARS-CoV-2 have suffered from both acute and chronic health complications [5], including the onset or worsening of various cardiovascular conditions such as myocarditis [6]. Apart from the direct effects of the virus on cardiac tissue, serious impacts on the heart are also observed indirectly through systemic inflammatory responses and other pathophysiological mechanisms. Cardiac tissue is particularly vulnerable to both direct and indirect damage by viruses. Understanding how SARS-CoV-2 affects cardiac tissue is critical not only for the treatment and management of patients with acute infection but also for comprehending the long-term effects of SARS-CoV-2 infection on the cardiovascular system.

The aim of this review is to provide an analysis of the impact of the SARS-CoV-2 virus and its Spike protein on cardiac tissue. We will focus on the mechanisms by which the virus penetrates cardiac cells, the potential effects on heart function and the clinical manifestations of cardiovascular involvement in the context of COVID-19.

Structural overview of SARS-CoV-2

SARS-CoV-2, an enveloped virus characterized by a positive-sense, single-stranded RNA genome, belongs to the *Coronaviridae* family within the *Nidovirales* order, classified as a β-coronavirus. This virus exhibits a pleomorphic structure with varying particle diameters, typically between 60 to 100 nanometers, and possesses one of the most extensive RNA genomes (about 30 kilobases) among viruses [7,8]. This expansive genome is organized into two large, overlapping open reading frames, ORF1a and ORF1b, intricately processed to 16 nonstructural proteins essential for viral replication and host cell manipulation. Additionally, the genome encodes four key structural proteins: Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins, pivotal for the virus's entry into host cells and its subsequent propagation. The presence of nine auxiliary proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, and ORF10) further underscores the genetic complexity of SARS-CoV-2, enabling a diverse range of interactions with host cellular mechanisms [9].

The Spike (S) protein of SARS-CoV-2 is crucial for the virus's ability to enter host cells. It features a homotrimeric structure, appearing as a crown-like halo around the virion, essential for attachment and fusion with host cell membranes. The interaction of the SARS-CoV-2 Spike protein with host cells primarily involves the ACE2 receptor, with additional receptors such as neuropilin-1 also facilitating viral entry. The Spike protein is divided into S1 and S2 subunits; the S1 facilitates receptor recognition and binding, while the S2 mediates the fusion of viral and host cell membranes – a pivotal step for viral entry [10,11]. Proteolytic cleavage of the Spike protein by furin-like proteases into S1 and S2, which remain connected *via* non-covalent bonds, initiates crucial structural changes facilitating viral entry [12,13]. This cleavage triggers structural transformations, with the S1 subunit dissociating to allow the S2 subunit to undergo a conformational shift and form an α-helical trimer that engages the host cell membrane. Concurrently, an analogous α-helical trimer, linked to the viral envelope, reconfigures to mirror the trimer now attached to the host membrane. This dynamic interaction between the two α-helical trimers culminates in the creation of an α-helical hexamer or a six-helix bundle, crucially narrowing the gap between the viral and host membranes to facilitate membrane fusion [14]. The orchestration of these molecular events underlines the Spike protein's critical function in SARS-CoV-2's ability to effectively invade host cells [11,13,15].

The Nucleocapsid (N) protein of SARS-CoV-2 is pivotal in the viral life cycle, encapsulating the RNA genome into a ribonucleoprotein (RNP) complex, thereby shielding it from enzymatic destruction by host defenses. This protective mechanism is crucial for the virus's replication and assembly processes within the host cell [16]. Beyond its protective role, the N protein also plays a significant part in manipulating the host's immune response, such as inhibiting interferon production, enhancing the virus's ability to persist and replicate [17].

The Envelope (E) protein plays a critical role in the SARS-CoV-2 life cycle, significantly influencing viral assembly, release, and pathogenicity [18]. Although only a small portion of the E protein is incorporated into the virions, the majority of this protein is localized within the Golgi apparatus and the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), where it facilitates crucial steps in viral assembly and egress [19]. The E protein is capable of homo-oligomerization, assembling into homopentameric helices to form viroporins, which are channels selective for cations, notably allowing the passage of Ca^{2+} ions [20].

Similarly, the Membrane (M) protein is

fundamental to the assembly and release of SARS-CoV-2, harboring a trans-Golgi network localization signal that aids in its function [21]. The M protein exhibits a mild affinity for the N protein, but this interaction significantly strengthens in the presence of both the N protein and RNA, facilitating viral assembly. Additionally, the M protein interacts with the E protein on the membranes of virus-like particles, playing a critical role in mediating the release of the virion, thereby completing the cycle of viral replication and dissemination [22,23].

The role of ACE2 in SARS-CoV-2 infection and cardiovascular complications

The renin-angiotensin system (RAS) plays a vital role in regulating blood pressure and fluid balance, significantly impacting cardiovascular health. ACE2 (Angiotensin-Converting Enzyme 2), the first identified human homolog of ACE, serves as a crucial counter-regulatory enzyme within the RAS by converting angiotensin I (Ang I) and angiotensin II (Ang II) into angiotensin 1-9 (Ang 1-9) and angiotensin 1-7 (Ang 1-7), respectively [24]. Additionally, ACE can catalyze the conversion of Ang 1-9 into Ang 1-7. These conversions are critical, as Ang 1-7, particularly, mediates vasodilatory, anti-inflammatory, and antifibrotic effects, thereby mitigating the pro-inflammatory and pro-fibrotic actions of Ang II and reducing the risk of hypertension, atherosclerosis, myocardial remodeling, heart failure, and diabetes-related cardiovascular complications [24]. The interaction of SARS-CoV-2 with ACE2 may disrupt this balance, posing an increased risk of cardiovascular complications where RAS modulation is a contributing factor.

The complex interplay between SARS-CoV-2 and the ACE2 receptor is a critical mechanism facilitating viral entry into host cells. ACE2 receptors are widely distributed across various body systems, including pulmonary, gastrointestinal, renal, and cardiac tissues, making these areas vulnerable to SARS-CoV-2-induced damage. However, the relationship between ACE2 expression levels and susceptibility to the virus is intricate. Studies, such as those by Zhou *et al.*, highlight a paradox where the lungs, despite their relatively lower ACE2 expression compared to the kidneys and intestines, endure significant damage from the virus, suggesting that factors beyond ACE2 expression influence tissue vulnerability to SARS-CoV-2 [25].

The viral entry process involves not only the ACE2 receptor but also requires co-factors like the transmembrane serine protease 2 (TMPRSS2) and cathepsins B and L, essential for effective cellular invasion [26,27]. TMPRSS2 is particularly critical as it primes the spike protein for binding to ACE2, thus enhancing viral entry. This dynamic is affected by sex-based differences in COVID-19 outcomes [28], likely due to genetic and hormonal factors influencing ACE2 and TMPRSS2 expression. For instance, estrogen is known to shift the ACE/ACE2 balance toward pathways that mitigate severe disease manifestations, potentially explaining the observed gender disparities in COVID-19 severity [29]. Additionally, despite its location on the X chromosome, ACE2 does not undergo X inactivation in males, suggesting that the second X chromosome in females with second ACE2 gene may provide some protection against more virulent COVID-19 forms [29]. Furthermore, TMPRSS2's expression, which is regulated by testosterone, is higher in males and may contribute to the more severe COVID-19 outcomes observed in this group [29].

The expression of ACE2 and other receptors in heart cells

As mentioned above, the entry of SARS-CoV-2 into host cells, including cardiac cells, is facilitated by the ACE2 receptor, a mechanism well-documented in the literature [30-33]. The widespread expression of ACE2 across various tissues accounts for the virus's broad organ tropism. Notably, ACE2 expression is particularly high in the intestines and the nasal airway epithelial cells, as well as in the kidneys [34,35]. Interestingly, ACE2 expression levels in the heart surpass those in the lungs - the primary target of the virus – highlighting the heart's vulnerability to SARS-CoV-2 infection [34-36].

Research shows that 6.6 % of cardiomyocytes and 12.5 % of cardiovascular progenitor cells express ACE2, representing a considerably high proportion compared to cells in other tissues [35]. These cells also express the TMPRSS2 protein, making the heart a high-risk organ for SARS-CoV-2 infection [35,37]. Pericytes, too, display a high percentage of ACE2 on their surface, highlighting their significance as key targets for SARS-CoV-2 infection in the heart [34,38]. Chen *et al.* suggest that the virus’s interaction with pericytes may lead to capillary dysfunction in endothelial cells, potentially resulting in microvascular dysfunction [34]. High levels of ACE2 expression are also seen in fibroblasts and

adipocytes, explaining the increased risk and severity of COVID-19 outcomes in obese individuals [38,39]. Significant differences in ACE2 expression across heart compartments have been observed, with ACE2-positive cells being substantially more prevalent in ventricles compared to atria [38,40], indicating an increased vulnerability of ventricular cells to SARS-CoV-2 infection [37,38,41].

Elevated myocardial ACE2 expression is noted in patients with heart failure, suggesting that these individuals may experience severe disease progression when infected with COVID-19 [34,42]. Similarly, increased expressions of myocardial ACE2, glycosylated ACE2, and TMPRSS2 have been observed in diabetes mellitus (DM) patients. This correlates with a higher localization of SARS-CoV-2 in cardiomyocytes, explaining the worsened clinical outcomes of COVID-19 in DM patients [43,44].

Endothelial dysfunction is a significant pathological feature in COVID-19, potentially driven by both indirect viral effects, such as reduced nitric oxide bioavailability and oxidative stress, and direct viral infection of endothelial cells. Despite low or absent ACE2 expression in endothelial cells across various organs, the presence of alternative receptors and ACE2-independent pathways could facilitate SARS-CoV-2 interactions with endothelial cells [45], suggesting a complex engagement of the virus with the vascular system.

Recent research has not only reaffirmed the role of the ACE2 receptor in SARS-CoV-2 entry but has also identified additional receptors and co-receptors involved in the infection process. These include neuropilin-1 (NRP-1), CD147 or basigin, CD209L or L-SIGN, asialoglycoprotein receptor 1 (ASGR1), KREMEN1, heparan sulfate proteoglycans such as syndecan and glypican, receptor tyrosine kinase AXL, high-density lipoprotein type 1 scavenger receptor (SR-B1), and GRP78, a glucose-regulated protein 78 [46]. Neuropilin-1, in particular, is noted as a potential independent receptor for SARS-CoV-2 entry, adding complexity to the understanding of viral pathogenesis [47]. Recent findings, including those by Eberhardt *et al.* [48], indicate that SARS-CoV-2 is capable of infecting and replicating in macrophages within the coronary vasculature of patients with COVID-19. Autopsy findings have revealed that SARS-CoV-2 infects NRP-1+ macrophages within human coronary tissue. A hyperinflammatory response orchestrated by SARS-CoV-2-infected plaque macrophages and foam cells may serve as a mechanistic link between the infection of atherosclerotic coronary vessels and acute cardiovascular complications of COVID-19 [48].

In addition to ACE2, the transmembrane serine protease (TMPRSS2) plays a significant role in SARS-CoV-2 infection. TMPRSS2 catalyzes the cleavage of peptide bonds in proteins, crucially priming the virus's Spike protein for entry into host cells. Hoffmann *et al.* demonstrated that TMPRSS2 inhibitors could effectively block SARS-CoV-2 infection in experimental settings [49]. Observations in COVID-19 patients have shown increased TMPRSS2 expression across various cardiac cells, indicating a potential vulnerability of the heart to SARS-CoV-2 [50-53]. Although TMPRSS2 expression in cardiomyocytes is typically less than 1 %, its combination with ACE2 enhances the heart's susceptibility to infection [35]. In diabetes mellitus (DM) patients, notable TMPRSS2 expression in cardiomyocytes correlates with heightened sensitivity to COVID-19 and associated cardiac injury [43].

Despite the low overall abundance of TMPRSS2 [40,54], other proteins and auxiliary proteases also facilitate interactions with SARS-CoV-2. Interferon-inducible transmembrane (IFITM) proteins, which generally inhibit virus fusion with host cell membranes, have shown unique interactions with SARS-CoV-2, potentially enhancing viral fusion with ACE2 in early endosomes [55]. High expression of IFITM3 has been noted in pericytes, implicating the IFITM3 pathway in the myocardial impacts of SARS-CoV-2 [54]. Furthermore, Chen *et al.* documented the co-expression of ADAM17 and CTSL (cathepsin L) with ACE2 in pericytes and fibroblasts, particularly pronounced in male patients [44]. The co-expression of other auxiliary proteases and molecules such as AGT (angiotensinogen), CALM3 (calmodulin 3), NRP1 (neuropilin1), ITGA5 (integrin, subunit alpha 5), LMAN, and PCSK5 enhances the virus's entry and replication capabilities within host cells [40,54]. CD147 (BSG) and CD209 were identified as other potential COVID-19 receptors, which are co-expressed with ACE2 in endocardial cells, cardiomyocytes and vascular endothelial cells of heart and thus make the heart to be more vulnerable to COVID-19 infection [56]. The interaction of SARS-CoV-2 with certain proteins, such as those involved in the coagulation cascade, may also contribute to the dysregulation of these proteins, offering a potential explanation for the observed coagulation disorders in COVID-19 patients [57].

The significant roles of ACE2, TMPRSS2, and other receptors in SARS-CoV-2 infection mean that

polymorphisms and genetic variations in their coding genes can influence the virus's ability to infect cells, the susceptibility of individuals to COVID-19, the severity of infection, and treatment responses. This has been confirmed and summarized in various reviews and meta-analyses, where several SNPs and mutations were identified primarily in ACE2 and TMPRSS2 [58-61]. Carrying certain variants of ACE2 or TMPRSS2 may also be associated with various neurological symptoms in COVID-19 patients [62], elevated heart rates [63] or with higher risk of hypertension, especially in obese men who smoke, who face a greater risk of severe COVID-19 [64]. Polymorphisms in other genes such as ApoE (apolipoprotein E), HLA (human leukocyte antigen), and IFITM3 have also been linked to increased susceptibility and/or severity of COVID-19 [59,61]. Variations in SNP frequencies between African, Asian, and European individuals could explain disparities in COVID-19 outcomes among these groups and contribute to understanding the COVID-19 African paradox [58].

Gene expression alterations in cardiac tissues due to SARS-CoV-2

The entry of SARS-CoV-2 into cardiomyocytes *via* the ACE2 receptor initiates viral replication and a cytopathic effect that substantially alters the expression of host cell genes [30,52,65]. This infection results in the downregulation of transcriptional pathways that are crucial for mitochondrial function, oxidative phosphorylation, and mRNA-related biological processes, such as mRNA splicing, transport, and chromosome condensation, suggesting a disruption in transcription processes in COVID-19 heart tissues [30,66]. Downregulation also affects genes coding for tissue skeleton-associated proteins, such as those involved in collagen fibril organization or elastin fiber assembly, and proteins associated with myocardial development, including those involved in sarcomere organization and muscle cell differentiation, indicating potential structural impacts on the heart [66]. Conversely, most of the upregulated genes are associated with the immune response of the heart tissue to SARS-CoV-2 infection [66-68]. This includes genes involved in apoptosis, reactive oxygen stress, energy metabolism, angiogenesis, neutrophil aggregation, cell adhesion, and both innate and chronic inflammatory responses, such as interleukins or tumor necrosis factor-α [30-32,66,68,69]. In patients who fatally succumbed to COVID-19, there was a notable increase in the expression of genes encoding myeloperoxidase (MPO), a marker for neutrophil extracellular traps; CD61, a marker of platelet activation; and CD31, an indicator of angiogenic activity [39]. Bräuninger *et al.* highlighted that the genes upregulated in SARS-CoV-2 infected cardiac tissues predominantly originate from endothelial cells and are linked to pro-inflammatory pathways, while the downregulated genes are primarily related to cardiomyocytes and concern structural integrity [67].

Above mentioned suggests a complex interplay between SARS-CoV-2 infection and cardiac gene expression, potentially leading to both functional and structural changes in the heart. The alteration in gene expression profiles reflects the broad impact of the virus on cardiac health, contributing to the diverse cardiovascular complications observed in COVID-19 patients.

Cardiac tropism and vulnerability to SARS-CoV-2 infection

Since the onset of the COVID-19 pandemic, numerous reports have highlighted cardiac complications concurrent with respiratory symptoms [70]. Research has demonstrated the presence of SARS-CoV-2 viral RNA in the heart, aorta, and other organs, suggesting the virus's broad tissue tropism [2,71-73]. Preexisting cardiovascular diseases significantly increase the risk of myocardial inflammation and injury following infection, elevating mortality rates among COVID-19 patients [74]. Furthermore, the majority of COVID-19 fatalities have occurred in patients with comorbid conditions such as hypertension, diabetes mellitus, and obesity, which are known to exacerbate the severity of the disease and increase the likelihood of intensive care hospitalization [75-77]. Additional risk factors, including smoking, ischemic heart disease, and bacterial pneumonia, also contribute to higher mortality rates in these patients [78]. Interestingly, SARS-CoV-2 has been shown to reactivate latent infections like enterovirus in individuals with cardiovascular conditions, worsening their prognosis [79]. Notably, severe COVID-19 symptoms and significant pathological findings have been observed in patients with and without preexisting health conditions, including neonates born to infected mothers [80-82].

In several cases, the presence of the sense strand of SARS-CoV-2 RNA not only confirmed the presence of the virus but also indicated its active replication within cardiac cells [39,83]. Factors such as the timing of

autopsies, the patient's immune system state, viral load, and detection methods may influence these findings [71,84]. Alba *et al.* found that a shorter duration between diagnosis and biopsy was associated with a higher incidence of organs testing positive for hematogenous dissemination [71]. In accordance with this, Schurink *et al.* reported that in the later stages of COVID-19, only sporadic findings of SARS-CoV-2 infected cells were observed, suggesting that inflammation characterized by neutrophil aggregation and the formation of neutrophil extracellular traps could be indicative of a maladaptive immune response [37].

Mechanisms of cardiac injury and dysfunction in SARS-CoV-2 Infection

Numerous mechanisms contribute to cardiovascular complications in COVID-19 patients. Primarily, direct myocardial injury may occur when SARS-CoV-2 binds to ACE2 receptors on heart cells, particularly cardiomyocytes, resulting in myocarditis and other forms of cardiac tissue damage [77,85]. Additionally, plaque macrophages and foam cells in coronary tissues, susceptible to infection through neuropilin-1, exacerbate this myocardial injury [48]. Secondly, a systemic inflammatory response, often described as a cytokine storm, leads to severe inflammation and a massive release of cytokines, potentially causing cardiomyocyte dysfunction and progressing to multiorgan failure. Furthermore, factors such as increased cardiometabolic demands coupled with hypoxia, plaque rupture, thrombosis, and electrolyte imbalances also contribute to cardiovascular complications [77,85,86].

The diversity of damage to heart cells induced by SARS-CoV-2 is considerable, impacting both the morphology and electrical functionality of cells. These structural and functional changes are closely interconnected, leading to a decrease in myocardial contractility which impairs the heart's ability to circulate blood and propagate electrical signals effectively. Structural damage is characterized by the disintegration of sarcomeres and the destruction of myofibrils, undermining the integrity of the myocardial architecture [87,88]. Moreover, the fusogenic nature of the SARS-CoV-2 Spike (S) protein facilitates cell-to-cell fusion, resulting in altered syncytia formation that complicates myocardial function [89,90].

The interaction between immune response mechanisms and SARS-CoV-2 infection is intricate and bidirectional. Lee *et al.* [32] found that pre-treatment of cardiomyocytes with TNF-alpha significantly increases ACE2 and TMPRSS2 expression, enhancing SARS-CoV-2 entry [32]. Infected cardiomyocytes secrete CCL2 (C-C motif chemokine ligand 2), attracting macrophages that secrete interleukin-6 and TNF, thereby increasing apoptosis in adult cardiomyocytes [69]. Additionally, Razaghi *et al.* [91] noted the presence of circulating endothelium-activating factors like VEGF in some deceased individuals without histological myocarditis. These factors could cause generalized hypoxia and endothelial leakage, exacerbating cardiac damage [91]. The involvement of the immune system supports the systemic inflammation hypothesis linked to COVID-19, alongside direct cardiac cell damage by SARS-CoV-2 [68,92-94].

As previously mentioned, the Spike protein of SARS-CoV-2 is crucial for the virus's ability to enter host cells because it is essential for attachment and fusion with host cell membranes. The Spike protein of the SARS-CoV-2 virus causes fusion of cardiomyocytes, the formation of syncytia, and subsequent impairment of cell function – altering the expression of mitochondrial genes, causing fibrosis, and affecting contractility [13,95]. The S1 subunit of the Spike protein is toxic to cardiomyocytes according to an *in vitro* experiment. Within 24 h, it increases ATP production and mitochondrial respiration, while after 72 h, the S1 protein decreases mitochondrial respiration, increases levels of ROS, mitochondrial and intracellular Ca^{2+}, and leads to mitochondrial fragmentation [96].

The connections between the Spike protein and cardiac tissue have also been explored in relation to vaccination. Researchers have identified the Spike protein of SARS-CoV-2 as the key antigen target for vaccination strategies. Some COVID-19 vaccines, which utilize a lipid nanoparticle platform to transport mRNA that directs cellular synthesis of the Spike protein, were among the initial vaccines to receive emergency authorization. Abnormalities on MRI scans of the heart have been observed in patients who developed myocarditis following vaccination against SARS-CoV-2 [97,98]. Nakahara *et al.* conducted an international study included 303 unvaccinated patients and 700 vaccinated patients, who underwent analysis using myocardial ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake on PET/CT, a sophisticated imaging tool that provides critical information on myocardial viability and

inflammation. Asymptomatic patients, vaccinated 1-180 days before the examination, showed increased FDG uptake in the myocardium compared to unvaccinated patients, with a median SUVmax of 4.8 [IQR: 3.0-8.5] vs. 3.3 [IQR: 2.5-6.2]; P<0.0001 [99].

Impact of SARS-CoV-2 E protein viroporins on cardiac calcium homeostasis

Viroporins are small, channel-forming integral membrane proteins found in various viruses, which notably facilitate the passage of Ca^{2+} ions [20]. The increase in cytosolic Ca^{2+} concentration activates Ca^{2+}-dependent enzymes and transcription factors, enhancing viral replication. Elevated Ca^{2+} levels within mitochondria augment energy production, supporting continuous viral replication [100]. Furthermore, the presence of viroporins in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) neutralizes its acidity, altering pH homeostasis and contributing to the virus's enhanced fitness and pathogenicity as noted recently [101].

In cardiomyocytes, Ca^{2+} plays a critical role in regulating both heart rhythm and contractility. Abnormal Ca^{2+} fluxes can lead to disturbances in cardiac function, potentially triggering arrhythmias or contributing to cardiac injury. Pacemaker cells, located within the sinoatrial node, are integral in orchestrating the cardiac cycle through the generation and propagation of electrical impulses, dependent on precise intracellular calcium dynamics. Recent research indicates that these primary pacemaker cells can be directly infected by SARS-CoV-2, which raises concerns about the virus's impact on cardiac functionality [102]. The disruption of Ca^{2+} homeostasis caused by the E protein's viroporin activity is particularly detrimental in pacemaker cells, where Ca^{2+} is crucial for regulating heart rhythm. This disruption can severely impair the functionality of infected pacemaker cells, leading to significant cardiac complications, including disturbances in the heart's rhythmic contractions.

Additional SARS-CoV-2 proteins that form viroporins include 3a, ORF8a, and ORF4a [103]. These viroporins can also damage host cells and lead to disruptions in organ functions, further complicating the pathophysiological landscape of COVID-19.

Cardiac manifestations and complications of COVID-19

Infection of heart cells by SARS-CoV-2 predominantly manifests as myocarditis [33,104-107], which can be associated with bradycardia [108], pericarditis, coronaritis [105], sarcomere rupture [106] or cardiac necrosis (ischemia) leading to cardiac failure [106]. Other severe symptoms include acute heart failure, major arrhythmias, acute coronary syndrome, and severe aortic stenosis [109]. In some rare instances, an accumulation of lipofuscin within cardiac tissue is observed [110]. COVID-19 is strongly associated with thrombosis. The occurrence of microthrombi and extensive areas of thrombosis is common, highlighting the disease's role in promoting coagulopathy [34,93,105,111,112]. Notably, SARS-CoV-2 infection has been linked to mechanical valve thrombosis, leading to serious complications and significantly impacting patient morbidity and mortality [113]. As the COVID-19 pandemic has progressed, there has been a noticeable decline in the frequency of cardiovascular complications associated with the virus. These complications, which include haemorrhage, myocardial necrosis, blood clots, and myocarditis, have shown a reduced incidence from the initial to subsequent waves of infection [79]. This decrease in incidence may be attributed to several factors, including improved treatment protocols, widespread vaccination, increased natural immunity in the population [114] and the emergence of the Omicron variant. The Omicron variant, in particular, has been associated with a lower risk of severe cardiovascular complications compared to earlier variants, likely due to its tendency to cause milder disease primarily affecting the upper respiratory tract [115]. These combined factors have contributed to a significant reduction in the severity and frequency of cardiovascular issues during the later stages of the pandemic.

During COVID-19 infection, various markers have been observed to increase, serving as potential prognostic indicators of clinical outcomes. A comparison between survivors and non-survivors of COVID-19 revealed elevated levels of d-dimers, creatine kinase, troponin, C-reactive protein, ferritin, and triglycerides in the latter group, underscoring their significance as risk factors or markers for mortality or poor clinical outcomes [116-118]. Moreover, specific markers have been identified for heart injury caused by SARS-CoV-2 infection. Levels of anti-heart antibodies (AHA), which are implicated in inflammatory and autoimmune heart diseases, were significantly increased in patients with post-COVID myocarditis [119,120]. Troponin, an organ-specific marker of myocardial injury, was found to be

elevated in both SARS-CoV-2 positive endomyocardial biopsies and the serum of infected patients [121-123]. Its increased levels persisting for several months post-diagnosis, suggesting ongoing, long-term myocardial damage [108,122]. Additionally, Maggialetti *et al.* demonstrated a correlation between coronary artery calcification and the mortality rate in COVID-19 patients suggesting calcific atheromasia of the coronary arteries in patients as a prognostic marker of clinical outcome of COVID-19 [124].

SARS-CoV-2 infection can have long-term impacts on patient health, often referred to as 'long COVID', which also affects cardiac tissue. Several underlying mechanisms can explain these effects. Primarily, the SARS-CoV-2 virus has been detected in cardiomyocytes, endothelium, and macrophages several months post-infection, potentially manifesting as post-COVID myocarditis [125]. Cardiac symptoms in post-COVID-19 patients can be attributed to a cytokine imbalance in myocardial tissue, characterized by a significant increase in CD68+ macrophages, and cardiac dysfunction due to angiopathy resulting from the acute infection [126]. Additionally, notable consequences have been observed from SARS-CoV-2-induced syncytia formation in cardiomyocytes, particularly affecting their contractility. It has also been found that thrombosis may persist even after the virus has been cleared [104].

Conclusions

In conclusion, SARS-CoV-2 has a profound and multifaceted impact on cardiac tissue, mediated primarily through the Spike protein's interaction with the ACE2 receptor. The virus not only causes direct damage to the heart by infecting cardiomyocytes but also triggers significant systemic effects that can exacerbate pre-existing cardiovascular conditions. The extensive expression of ACE2 in heart cells underpins the high susceptibility of cardiac tissues to SARS-CoV-2, leading to a range of complications from myocarditis to severe myocardial dysfunction. Long-term consequences, such as 'long COVID', further complicate the cardiovascular outcomes of survivors, highlighting the need for targeted therapeutic strategies and comprehensive management of cardiac health in COVID-19 patients. Future research should continue to explore the molecular dynamics of SARS-CoV-2 interaction with cardiac cells and the resulting clinical manifestations, which will be crucial for developing effective treatments and preventive measures.

Conflict of Interest

There is no conflict of interest.

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