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REVIEW

# Possible Mechanisms of SARS-CoV2-Mediated Myocardial Injury

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## Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has rapidly become a global health emergency. In addition to causing respiratory effects, SARS-CoV-2 can result in cardiac involvement leading to myocardial damage, which is increasingly being explored in the literature. Myocardial injury is an important pathogenic feature of COVID-19. The angiotensin-converting enzyme-2 receptor plays a key role in the pathogenesis of the virus, serving as a "bridge" allowing SARS-CoV-2 to invade the body. However, the exact mechanism underlying how SARS-CoV-2 causes myocardial injury remains unclear. This review summarizes the main possible mechanisms of myocardial injury in patients with COVID-19, including direct myocardial cell injury, microvascular dysfunction, cytokine responses and systemic inflammation, hypoxemia, stress responses, and drug-induced myocardial injury. Understanding of the underlying mechanisms would aid in proper identification and treatment of myocardial injury in patients with COVID-19.

**Keywords:** Cardiovascular disease; COVID-19; myocardial injury; possible mechanisms

## Introduction

Coronavirus disease 2019 (COVID-19) is an epidemic disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 has spread rapidly worldwide and led to a massive outbreak of novel coronavirus pneumonia. The number of recent SARS-CoV-2 infections has significantly increased with the emergence and prevalence of the novel Omicron coronavirus variant. SARS-CoV-2 affects primarily the respiratory system, thus causing presentations ranging from asymptomatic subclinical infection or mild upper respiratory illness to non-life-threatening pneumonia, which may progress to interstitial pneumonia and severe acute respiratory distress syndrome. Some studies have shown that this virus can cause cardiovascular damage [1]. SARS-CoV-2 can lead to cardiovascular system

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diseases such as myocarditis, heart failure, acute myocardial infarction, thromboembolic events, and shock. Additionally, some hospitalized patients have primary symptoms of chest tightness and palpitations. A large cohort study [2] including 4526 people worldwide has reported an overall incidence of arrhythmias after COVID-19 of 18.3%, and indicated that most of the arrhythmias developed are atrial arrhythmias; in addition, the incidence of atrial fibrillation was 61.5%. New-onset atrial fibrillation is a common complication, particularly in patients with severe disease [1, 3, 4]. However, the mechanism of myocardial injury caused by SARS-CoV-2 remains unclear. This article reviews the existing possible mechanisms leading to myocardial injury.

## Possible Mechanisms of Myocardial Injury

SARS-CoV-2 is a single-stranded RNA coronavirus belonging to a novel beta lineage that shares 82% nucleotide sequence similarity with human SARS-CoV [5]. SARS-CoV-2 invades cells by binding angiotensin-converting enzyme-2 (ACE2) [6]. Spike (S) protein is a host cell recognition protein consisting of two functional subunits, which are responsible for receptor binding (S1 subunit) and membrane fusion (S2 subunit). This protein plays an important role in mediating the binding of viruses to the ACE2 receptor and is a major target of attack by the human immune system [7]. When humans are infected with SARS-CoV-2, the coronavirus S protein promotes viral entry into target cells. Entry requires priming of S protein by cellular proteases, such as the transmembrane protease serine 2 (TMPRSS2), histone protease B/L (cathepsins B/L, CTSB/CTSL), and other trypsin-like proteases, thus resulting in cleavage of S protein at the S1/S2 and S2′ sites. The surface unit S1 of S protein then binds the cellular receptor and facilitates viral attachment to the target cell surface, whereas the S2 subunit enables viral fusion with the cell membrane [8, 9]. After entering a cell, the virus exploits the host cell's internal environment to self-replicate, synthesize structural proteins, and assemble particles, which are then released via cytosolic ejection. During this process, the function of the host cell may be damaged or even disrupted, thus leading to a series of adverse reactions.

ACE2 serves as a "bridge" allowing SARS-CoV-2 to enter the body. The role of ACE2 receptors in SARS-CoV-2 involvement in the heart is now well established. ACE2, a major enzyme in the renin-angiotensin system (RAS), is similar to ACE. However, although ACE2 has considerable homology with ACE, the two enzymes have different physiological functions [10]. In the heart, ACE2 is expressed mainly in cardiomyocytes, cardiac fibroblasts, and coronary endothelial cells. It serves not only as a functional receptor for SARS-CoV-2 but also as an important endogenous RAS antagonist [11]. ACE2 converts angiotensin II (Ang II) to angiotensin-(1–7) [Ang-(1–7)] and metabolizes angiotensin I (Ang I), thus generating angiotensin-(1–9) [Ang-(1–9)] [11, 12]. ACE2 binds Ang-(1–7) and its specific Mas receptor (MasR), thus forming the ACE2-Ang-(1–7)-Mas axis, which exerts its biological functions. The main effects of ACE2 are vasodilatation, anti-inflammatory effects, antioxidant effects, anti-ventricular remodeling, anti-myocardial fibrosis, and other cardioprotective effects, which in turn prevent the development and progression of cardiovascular disease.

Angiotensin converting enzyme inhibitors (ACEI) or Ang II receptor blockers (ARB) are widely used in the treatment of hypertension. In vitro animal experiments [13] have demonstrated that ACEI and ARB lead to the upregulation of ACE2 expression through RAS inhibition. On the basis of this finding, patients with COVID-19 may be prone to severe disease progression because of elevated ACE2 expression while using ACEI/ARB. In contrast, several clinical studies have shown that patients with COVID-19 treated with ACEI/ARB do not have elevated risk of disease severity [14–16]. Furthermore, in animal models [17], ARB-mediated ACE2 upregulation has been found to play a beneficial role in treatment by decreasing Ang II and increasing Ang-(1–7), thus antagonizing the over-activated RAS. Larger clinical studies in patients with COVID-19 are needed to determine whether the benefits of ACEI/ARB treatment outweigh the risks.

## SARS-CoV-2 Causes Direct Myocardial Injury via ACE2

As described earlier, SARS-CoV-2 infection is dependent on the ACE2 receptor, which is widely distributed in various tissues and expressed at different levels in different organs [18, 19]. ACE2 is expressed at high levels in the heart, thus leading to a hypothesis that SARS-CoV-2 might directly invade the heart. In support of this hypothesis, Viveiros et al. [20] have detected viral nucleocapsids in mouse heart tissue and observed downregulation of myocardial tissue ACE2 protein expression, which might decrease the cardioprotective effect of ACE2 against RAS (see Table 1). In addition, SARS-CoV-2-infected cardiomyocytes have been found to have a substantial inflammatory cell load, on the basis of histological staining. Bailey et al. [21] have detected viral proteins and RNA from SARS-CoV-2 spikes and nucleocapsids in the myocardium, and have observed infiltration of inflammatory cells such as macrophages in areas with myocardial cell injury (see Figure 1). In an autopsy study of deceased patients with COVID-19, Jum'ah et al. [40] have found that increased macrophage density correlates with the degree of necrosis of cardiomyocytes. Cao et al. [22] have found that invasive cellular S proteins induce long-term transcriptional repression of mitochondrial metabolism-associated genes in cardiomyocytes, thus leading to cardiac fibrosis, diminished myocardial contractility, and eventually myocardial injury. These observations suggest that SARS-CoV-2 can infect human cardiomyocytes and consequently lead to direct cardiomyocyte death and myocardial inflammation. ACE2-mediated direct myocardial injury and inflammation are considered important contributors to myocarditis associated with SARS-CoV-2 infection. In addition, SARS-CoV-2 infection can cause shedding of ACE2 from cell membranes, thereby producing soluble ACE2, which also acts as a receptor for SARS-CoV-2, and further mediates viral entry into cells and expands the area of infection [41]. However, Zhou et al. [23], through in vitro co-culture experiments with human cardiomyocytes (AC16), have recently shown that SARS-CoV-2 has little ability to directly infect AC16 cells. Analysis of serum markers has indicated that the immune storm caused by serum infection may increase the risk of DNA damage in cardiomyocytes. Whether direct myocardial damage by SARS-CoV-2 is due to ACE2 tropism or cardiotoxicity caused by indirect cytokine activation remains unclear. Therefore, further studies are needed to demonstrate the specific myocardial injury mechanism.

## Microvascular Dysfunction and Thrombosis

SARS-CoV-2 damages multiple systems in humans, including causing severe endothelial injury, hypercoagulability, and thrombotic microangiopathy [42, 43]. When the integrity of the endothelial barrier is compromised, collagen under the endothelium is exposed, thereby activating platelets and coagulation factors, which consequently initiate the clotting process and ultimately lead to the formation of microthrombi. Studies have shown [44] that endothelial cells, particularly pericytes, express abundant ACE2, and SARS-CoV-2 can lead to microvascular and macrovascular endothelial dysfunction by damaging endothelial and pericytes. If microvascular circulation is impaired, further local tissue inflammation, cardiac fibrosis, and thrombosis, may result, thus directly or indirectly affecting the entire atrium and/or causing cellular structure changes, and ultimately leading to the development of atrial fibrillation [45]. Simultaneously, downregulation of ACE2 expression diminishes the protective effect of the ACE2-AngII-Mars axis, and Ang II hyperactivity promotes the production of pro-inflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and transforming growth factor-βc (TGF-β) [46]. Decreased release of nitric oxide and prostacyclin also plays a role in promoting thrombosis. Beyond the ACE2-mediated injury mechanism, Avolio et al. [24] have found that S protein triggers extracellular signal-regulated kinase 1/2 (ERK1/2) signaling by interacting with CD147 receptors on pericardial cells, thus leading to pericardial dysfunction, and potentially increasing vascular permeability and coagulation capacity. Yu et al. [25] have found that the SARS-CoV-2 S protein inactivates the alternative pathway of complement (APC) convertase on the tissue cell surface, thereby directly activating the APC pathway, and triggering complement-mediated endothelial injury and thrombosis. In addition to directly causing endothelial injury, SRAS-CoV-2

**Table 1** Main Conclusions Regarding Cardiac Injury in COVID-19.

| First author [Ref] | Study area | Year | Sample size | Main conclusion |
|---|---|---|---|---|
| Viveiros [20] | Canada | 2022 | Sample of hamsters not described;<br>10 human myocardial samples | Infected hamsters showed increased mononuclear infiltration as well as focal fibrosis, and the viral nucleocapsid was detected in the heart.<br>The hamsters exhibited similar downstream effects of SARS-CoV-2 infection to those in human patients with COVID-19, thereby recapitulating myocardial damage, ACE2 downregulation, and a consistent pattern of immune cell infiltration.<br>Basic histological staining revealed extensive mononuclear infiltration and interstitial and vascular fibrosis in the myocardium in patients with COVID-19, with viral nucleotide staining predominantly in the perivascular area. In addition, ACE2 was significantly downregulated and showed a marked inflammatory cell burden, favoring neutrophils and macrophages. |
| Bailey [21] | USA | 2020 | 4 myocardial samples | SARS-CoV-2 spike protein and nucleocapsid RNA were detected in the myocardium of each participant with COVID-19 myocarditis.<br>Macrophage abundance was highest in areas of cardiomyocyte injury. |
| Cao [22] | USA | 2023 | 18 mice | Spike protein induced long-term transcriptional suppression of gene families associated with mitochondria metabolic pathways, and facilitated cardiac fibrotic development and myocardial contractility reduction in obese mice. |
| Zhou [23] | China | 2022 | 18 serum samples | Incubation of SARS-CoV-2 with AC16 cells and cellular immunofluorescence assays suggested that SARS-CoV-2 may not directly infect human cardiomyocytes.<br>Analysis of serum from patients with severe SARS-CoV-2 infection in the acute phase treated with AC16 cells showed that serum with excess immune factors induced cellular stress. |
| Avolio [24] | UK | 2021 | 3 myocardial samples<br>64 serum samples | S protein stimulated phosphorylation/activation of ERK1/2 through the CD147 receptor in pericytes.<br>S protein induced the production of pro-inflammatory cytokines by cardiac pericytes. |
| Yu [25] | USA | 2020 | Not described | SARS-CoV-2 spike proteins (S1 and S2) induced cell killing through the APC. |
| Duan [26] | China | 2022 | 62 serum samples | LL-37 was upregulated by SARS-CoV-2 infection and showed elevated concentrations in the plasma in patients with COVID-19 that activated coagulation factors. |
| Apostolidis [27] | USA | 2022 | 10 serum samples | Plasma from patients with COVID-19 showed activation of platelets at least partially through IgG-mediated activation of FcγRIIa. This effect was augmented by signals from complement, including C5a. |
| Blasco [28] | Spain | 2021 | 10 thrombus tissue samples | Thrombi from patients with COVID-19 were found to be composed primarily of fibrin and to present some degree of polymorphonuclear cell infiltration (mild to intense). |
| Arhontoulis [29] | USA | 2022 | 4 human organoids | Cytokine multiplex results indicated a fold change in cytokines in the supernatant with respect to hCOs. |
| Hartmann [30] | USA | 2021 | 6 myocardial samples | Myocardial postmortem biopsies of patients with COVID-19 showed myocardial interstitial edema, mast cell accumulation; and increased indicators of inflammation, apoptosis, and fibrosis. |

**Table 1** (continued)

| First author [Ref] | Study area | Year | Sample size | Main conclusion |
|---|---|---|---|---|
| Couselo-Seijas [31] | Spain | 2021 | 43 epicardial and subcutaneous adipose tissues | The study provides the first report of differential expression of ACE2 and ADAM17 between epicardial and subcutaneous fat. In fact, ACE2 was not detectable in most subcutaneous fat samples. |
| Won [32] | US | 2022 | 7 lung samples | Endothelial cells and immune cells in the lungs of patients with COVID-19 exhibited elevated HIF1α and $GLUT_1$ expression, thereby confirming hypoxic stress in the lungs. Hypoxia caused by infected epithelial cells led to endothelial cell dysfunction in COVID-19. |
| Maximilian [33] | Germany | 2020 | 7 lung samples | First, severe endothelial injury was associated with the intracellular SARS-CoV-2 virus and disrupted endothelial cell membranes. Second, the lungs of patients with COVID-19 had widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries. Third, the lungs of patients with COVID-19 had substantial new vessel growth through a mechanism of intussusceptive angiogenesis. |
| Titi [34] | Italy | 2021 | 16 myocardial samples in 1 person | The myocardium showed diffuse edema, multiple foci of contraction band necrosis in both ventricles, and occasional coagulative necrosis of single cardiac myocytes. No lymphocytic infiltrates were observed; however, abundant CD68+ macrophages were detected in the myocardial interstitium. |
| Stute [35] | USA | 2021 | 16 patients | Compared with healthy controls, young adults recovering from SARS-CoV-2 exhibited higher resting muscle sympathetic burst frequency, burst incidence, and total activity; had higher MSNA burst incidence, but suppressed total MSNA responses during a cold pressor test, and interestingly rated their pain significantly lower; and displayed higher MSNA throughout an orthostatic challenge. |
| Wallukat [36] | Germany | 2021 | 31 serum samples | Several different GPCR-fAABs were identified in the sera of 31 patients who recovered from COVID-19. |
| Chorin [37] | USA | 2020 | 84 patients | QTc prolongation from a baseline average of 435 ± 24 ms to a maximal average value of 463 ± 32 ms, occurred on day 3.6 ± 1.6 of therapy. |
| Fresse [38] | France | 2021 | 176 patients | Over an 8-week period, 176 cases of cardiotoxicity involving drugs targeting COVID-19 were reported. Of these, 22 cases were associated with lopinavir/ritonavir use, and 17 cases of QT prolongation and 5 cases of ventricular arrhythmias were observed. |
| Chan H [39] | USA | 2020 | 24 patients | Of 24 patients, 18 had D-dimer elevation after tocilizumab administration, whereas all inflammatory markers (ferritin, LDH, and CRP) showed decreasing trends. |

*Abbreviations: AC16, human cardiomyocytes; ERK (1/2), extracellular signal-regulated kinase 1/2; APC, alternative pathway of complement; LL-37, antimicrobial peptide LL-37; hCOs, human organoids; ADAM17, A disintegrin and metalloprotease 17; MSNA, muscle sympathetic nerve activity; GPCR-fAABs, functionally active autoantibodies targeting G-protein coupled receptors; LDH, lactate dehydrogenase; CRP, C-reactive protein.

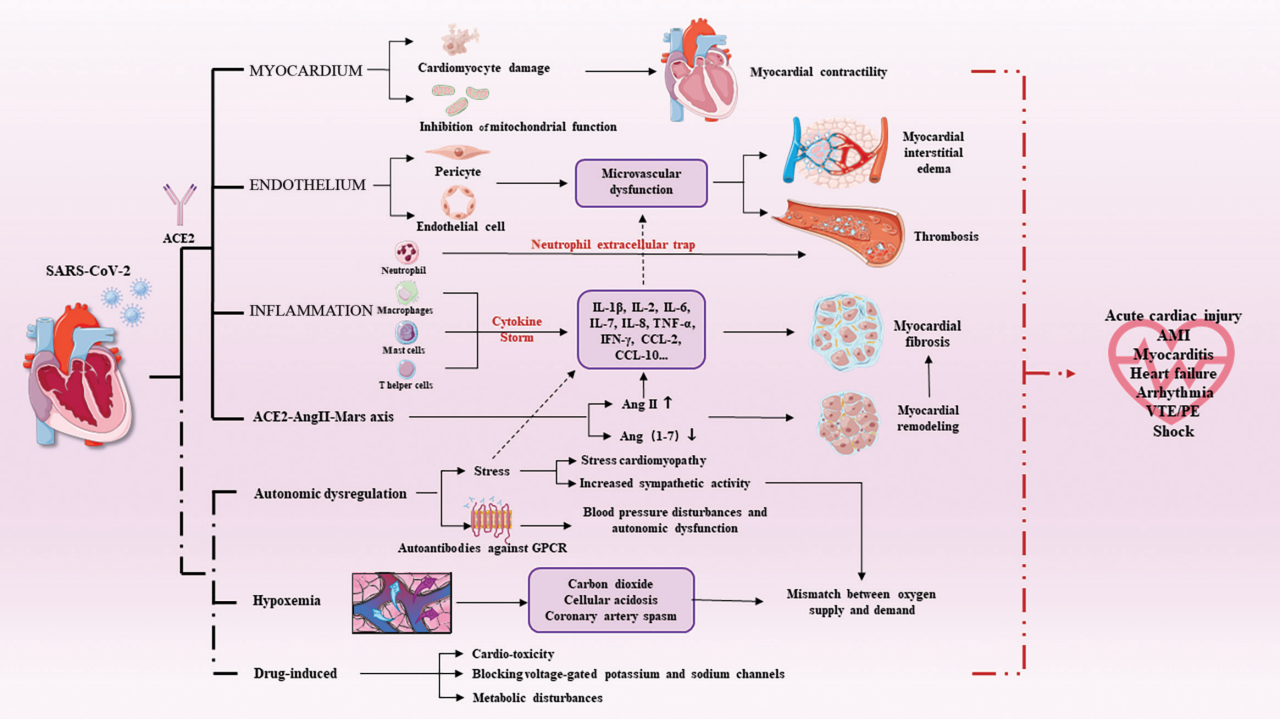


**Figure 1** Possible Mechanism of Myocardial Injury.

infection can lead to elevated serum levels of various cytokines, particularly IL-1β, IL-6, and TNF-α. Elevated cytokines indirectly activate complement and may subsequently cause endothelial cell dysfunction and increased permeability. Cytokines can also lead to platelet activation and leukocyte recruitment, thus resulting in new thrombus formation [47, 48]. Duan et al. [26] have found that the SARS-CoV-2 S protein significantly increases plasma levels of the cathelicidin antimicrobial peptide LL-37, thereby potentially enhancing the activity of coagulation factors and eliciting a hypercoagulable state in the body. Apostolidis et al. [27] have found that platelets in critically ill patients with COVID-19 show high levels of activation and that the FcγRIIa-Syk and C5a-C5aR axes are key mediators of platelet hyperactivation in COVID-19. As an important bridge between the immune system and hemostasis, platelets integrate signals from different immune cell subpopulations, soluble inflammatory mediators, and complement cascade responses; consequently, they play important roles in micro-thrombosis and inflammatory responses. Furthermore, the interaction between overactive coagulation and complement systems ultimately contributes to micro-thrombosis and consequent myocardial injury.

In addition to endothelial and coagulation system dysfunction, markers of neutrophil activation are frequently present in myocardial thrombosis in patients with COVID-19 [28, 49]. Neutrophils participate in inflammatory responses and thrombosis by releasing their DNA and various granule proteins, which in turn form neutrophil extracellular traps. In light of these findings, decreasing the neutrophil response may be an important target for therapeutic intervention in thrombosis.

## Cytokine Storm and Inflammation

A cytokine storm is an acute hyperinflammatory response, which is an excessive immune response caused by a dramatic increase in the amounts of pro-inflammatory cytokines. In patients with severe COVID-19, circulating cytokine levels are significantly elevated [50, 51], and the dynamic changes in IL-6 and IL-8 are closely associated with disease progression. The main cytokines and chemokines involved in inflammation include IL-1β, IL-2, IL6, IL-7, IL-8, TNF-α, interferon-γ (IFN-γ), interferon (IFN)-gamma-induced protein 10 (IP-10)/chemokine (C-X-C motif) ligand (CXCL)-10

(CXCL10), monocyte chemoattractant protein-1 (MCP-1)/chemokine (CC-motif) ligand 2 (CCL-2), regulated upon activation, and normal T-cell expressed and secreted (RANTES)/C-C chemokine ligand 5 (CCL5). The presence of a cytokine storm is associated with disease severity.

Arhontoulis et al. [29] have found that increased expression of the upstream cytokine IL-1β in cardiopulmonary tissue in patients with COVID-19 promotes the release of downstream cytokines and subsequently triggers cytokine storms. Hartmann et al. [30], in an autopsy study, have found that intercellular adhesion molecule-1 (ICAM-1), IL-1β, IL-6, matrix metalloproteinase-9 (MMP-9), TNF-α, and other cytokines in the hearts of patients with COVID-19 are also elevated, thus suggesting inflammatory activation. In addition, many mast cells can be observed in the damaged myocardium, and may contribute to increased capillary permeability, microvascular leakage, and the formation of interstitial myocardial edema. Hu et al. [46] have proposed a potential mechanism of AngII-triggered cytokine storm involving down-regulation of ACE2, increased serum AngII levels, and production of inflammatory cytokines such as TNF-α and IL-6.

Cytokine storms directly damage the myocardium, thereby causing myocardial fibrosis and decreased contractile function. In addition, they promote the expression of macrophages and leukocyte adhesion molecules in endothelial cells in tissues, thus increasing the risk of endothelial cell injury and causing acute coronary syndrome [52]. Furthermore, several studies [31, 53, 54] have shown that epicardial adipose tissue cells with dense macrophage infiltration and high enrichment of proinflammatory cytokines express more ACE2 than subcutaneous adipocytes. In a previous experiment [55], ACE2, TNF-α, and IL-6 have been found to be expressed at high levels in the epicardial adipose tissue of obese patients. Epicardial adipose tissue, a reservoir of many inflammatory mediators, may play an important role in SARS-CoV-2 cardiac injury.

## Hypoxemia Induced Injury

Hypoxemia, a major manifestation of SARS-CoV-2 infection, has important effects on organs with high oxygen and energy requirements. Some patients with COVID-19 have atypical clinical manifestations of hypoxemia, which are often referred to as asymptomatic hypoxemia [56, 57]. Prolonged hypoxia can aggravate the disease. ACE2 is a protective factor against the RAS and also has multiple physiological functions in the lungs, including prevention of lung injury [58]. When SARS-CoV-2 virus replication causes the infection to migrate from the upper respiratory tract to the lungs, the virus attacks ACE2-rich type II alveolar epithelial cells in the lungs causing cell necrosis, increasing airway resistance, decreasing alveolar ventilation, increasing local infiltration of inflammatory cells, increasing secretion of airway mucus, and decreasing secretion of alveolar surface active substances. The formation of alveolar hyaline membranes and thickening of the alveolar wall also inhibit the diffusion of oxygen while increasing carbon dioxide retention, thus decreasing the oxygen supply [58–60]. Hypoxia not only leads to endothelial cell dysfunction but also places the body in a hypercoagulable state; consequently, pulmonary vasculitis with extensive vascular thrombosis, microangiopathy, and alveolar-capillary occlusion may result. In addition, hypoxia enhances the inflammatory response and pulmonary vasoconstriction, which increase the severity of hypoxemia [32, 33]. A decrease in cardiac oxygen supply affects adenosine triphosphate (ATP) hydrolysis, thereby diminishing the energy supply to cardiomyocytes, increasing anaerobic glycolysis, raising intracellular lactate levels, and leading to cellular acidosis. In addition, the increase in reactive oxygen species disrupts the structure of the phospholipid layer, and can lead to membrane damage and mitochondrial damage, which in turn further decrease ATP synthesis. Hypoxia also affects ion channel activity, and increased calcium influx leads to calcium overload, thereby damaging cardiomyocytes and exacerbating cardiovascular dysfunction in patients with COVID-19 [61, 62]. Cytokine storms and cardiac microvascular endothelial dysfunction also affect cardiac energy metabolism. Cytokine storms increase not only the heart rate and cardiac oxygen consumption, through the release of IL-6 and catecholamines, but also the core body temperature. In addition, both synergistically affect the cardiac microenvironment, thereby causing pathological changes such as coronary artery spasm and thrombosis, and decreasing the coronary

blood and oxygen supply. A subsequent mismatch between myocardial oxygen supply and demand and ultimately leads to myocardial damage.

## Stress and Autonomic Dysregulation

Stress is involved in the progression of SARS-CoV-2-associated myocardial injury. Zuin et al. [63] have observed a high incidence of stress cardiomyopathy in the 2020 COVID-19 pandemic, thus suggesting a strong direct and/or indirect role of COVID-19 in the pathogenesis of stress cardiomyopathy. Titi et al. [34] have reported the case of a patient with COVID-19 Takotsubo syndrome death, in whom abundant CD68+ macrophages were detected in the myocardial interstitium by autopsy. Moreover, the finding of diffuse systolic area necrosis supports the pathogenic role of elevated catecholamine levels. Patients with COVID-19 are well known to be prone to severe inflammatory responses and cytokine storms, which may be a possible mechanism underlying stress cardiomyopathy. The immense emotional stress caused by the SARS-CoV-2 pandemic and SARS-CoV-2-induced respiratory infections may also be potential triggers for stress cardiomyopathy [64]. The stressful state in the organism is often accompanied by autonomic dysregulation. Stute et al. [35], through a comparison of autonomic and cardiovascular function between SARS-CoV-2 infected patients and healthy controls, have found that adults can develop autonomic dysfunction after SARS-CoV-2 infection. This dysfunction manifests primarily as increased sympathetic activity, and can lead to increased myocardial oxygen consumption and further exacerbate myocardial injury. Wallukat et al. [36] have identified functionally active autoantibodies against different G-coupled receptors in SARS-CoV-2-infected patients; these autoantibodies act as receptor agonists and include the β2-adrenoceptor, α1-adrenoceptor, Ang II receptor type 1 receptor, and Ang-(1–7) Mas receptor. This autoimmunity against the nervous system may be the root cause of autonomic dysfunction and/or cardiovascular disease after SARS-CoV-2 infection. In addition, Goldstein et al. [65] have noted that SARS-CoV-2 infection may disrupt normal blood pressure regulation mediated by ACE2 as well as extracardiac postganglionic sympathetic noradrenergic system neurons, thus leading to blood pressure disturbances and autonomic dysfunction in the presence of autonomic dysfunctional postural tachycardia syndrome.

## Drug-induced Cardiotoxicity

Owing to the rapid transmission and high infectivity of COVID-19, many drugs for the treatment and prevention of SARA-CoV-2 infection have been used in clinical therapy. The combined use of Hydroxychloroquine and Azithromycin may increase the risk of cardiotoxicity, thereby prolonging the QT interval, and increasing the risk of drug-induced tip-twist tachycardia and sudden death [37]. Lopinavir/Ritonavir is an antiretroviral drug that increases the risk of cardiac arrhythmias, such as a prolonged QT interval, bundle branch block, and bradycardia, by blocking voltage-gated potassium and sodium channels [38]. Nirmatrelvir/Ritonavir (Paxlovid) is able to interfere with metabolic disorders, and interactions with multiple drugs may cause severe adverse effects, thus providing a basis for the adverse cardiac effects of this drug [66]. Tocilizumab is an IL-6 antagonist that causes a transient increase in serum D-dimer, and the potential thrombus-associated adverse effects may increase the incidence of micro-thromboembolic events [39]. Furthermore, excessive glucocorticoids may also increase the risk of adverse cardiovascular events in patients with COVID-19 through immune damage and effects on cardiometabolism [67].

## Conclusion

COVID-19 is among the most severe viral infectious diseases and has become a widespread global epidemic. SARS-CoV-2 infection is associated with myocardial injury, which in turn is associated with more severe disease progression and even death. The myocardial injury mechanism of SARS-CoV-2 is multifactorial, and both direct and indirect mechanisms of SARS-CoV-2 injury may synergistically contribute to cardiovascular injury. The ACE2 receptor, which specifically

binds SARS-CoV-2, plays an important role in the mechanism of SARS-CoV-2 myocardial injury; however, the detailed mechanism remains unclear, and various compound mechanisms must be further explored. Physicians' understanding of myocardial injury in patients with COVID-19 must be improved, to avoid serious adverse reactions caused by drug administration, and enable appropriate prevention measures to be taken in a timely and precise manner to benefit patients with COVID-19.

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## Author Contributions

All listed authors made substantial intellectual contributions to the work and approved it for publication.

## Competing Interests

The authors declare that no competing interests exist.

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