Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Cardiac inflammation in COVID-19: Lessons from heart failure

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ABSTRACT

Cardiovascular disease (CVD) is the most common co-morbidity associated with COVID-19 and the fatality rate in COVID-19 patients with CVD is higher compared to other comorbidities, such as hypertension and diabetes. Preliminary data suggest that COVID-19 may also cause or worsen cardiac injury in infected patients through multiple mechanisms such as 'cytokine storm', endotheliosis, thrombosis, lymphocytopenia etc. Autopsies of COVID-19 patients reveal an infiltration of inflammatory mononuclear cells in the myocardium, confirming the role of the immune system in mediating cardiovascular damage in response to COVID-19 infection and also suggesting potential causal mechanisms for the development of new cardiac pathologies and/or exacerbation of underlying CVDs in infected patients. In this review, we discuss the potential underlying molecular mechanisms that drive COVID-19-mediated cardiac damage, as well as the short term and expected long-term cardiovascular ramifications of COVID-19 infection in patients.

1. Introduction

Corona **Vi**rus **D**isease-2019 (COVID-19) is an ongoing pandemic caused by **S**evere **A**cute **R**espiratory **S**yndrome **Co**rona**v**irus 2 (SARS-CoV-2) which originated in Wuhan province in China [1]. It is a highly contagious disease that has affected more than 187 countries across the globe, infecting around 32 million people and resulting in the death of over 966,000 people. In the US alone, we have had over 6.9 million people infected and around 200,000 deaths, and these counts continue to increase everyday (figures are current at the time of writing this manuscript) (Center for Systems Science and Engineering). To control its spread, strict quarantine measures have been adopted world-wide and there has been a strong push towards rapid development of diagnostics, therapeutics and vaccines.

Most patients infected with SARS-CoV-2 are asymptomatic, or develop mild to moderate symptoms, and recover in 1–2 weeks. The most common symptoms of COVID-19 include shortness of breath, low-grade hyperthermia and cough [2]. However, subsets of patients develop pneumonia and severe dyspnea, and many of these patients end up in the intensive care unit and require intubation [3]. Interestingly, it remains unclear why the degree of severity varies from patient to patient, and identification of the contributing factors that differentiate a moderate from a severe COVID-19 response remains an active and critical line of investigation. What we do know so far is that COVID-19 mainly attacks the respiratory system and that the hallmark features of severe COVID-19 infection include diffuse alveolar damage with Acute Respiratory Distress Syndrome (ARDS). Moreover, while the lung seems to be the most overtly affected organ in this disease, accumulating evidence suggests that SARS-CoV-2 also severely affects additional organs and tissues, including the heart, brain, large intestine, kidneys and spleen [4,5].

Initial reports suggested that systemic hyper-inflammation, which leads to Cytokine Release Syndrome (CRS, aka the 'cytokine storm'), is thought to be one of the main causal mechanism for the serious complications and high mortality associated with COVID-19. Inflammation is initially triggered in the lungs due to SARS-Cov-2 induced alveolar epithelial cell damage, evoking extensive immune cell infiltration [6]. However, this local inflammatory response also induces the release of systemic pro-inflammatory cytokines, resulting in the hyper-inflammation of multiple organs, and leading to

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome associated coronavirus; MERS-CoV, Middle East Respiratory Syndrome associated coronavirus; ARDS, Acute Respiratory Distress Syndrome; CRS, Cytokine Release Syndrome; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-TnI, high sensitivity cardiac troponin I; CRP, C-reactive protein; TMPRSS2, transmembrane protease serine 2

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subsequent tissue damage and death of patients [7]. While cytokine storm causes significant morbidity and mortality in COVID-19 patients, multiple pathophysiological mechanisms such as endotheliosis, dysregulation of Renin-Angiotensin-Aldosterone System (RAAS), thrombosis, lymphocytopenia, T-cell anergy might also contribute to the morbidity [8,9].

In addition to hyper-inflammation, multiple studies also report that comorbidities in COVID-19 patients potentiate poor prognosis. Around 94% of all COVID-19 patients have one or more underlying health conditions, and the most common comorbidities include hypertension, Chronic Obstructive Pulmonary Disorder (COPD), diabetes, CVD and cerebrovascular diseases [10]. Even though hypertension is the most common comorbidity, the case fatality rate is highest in patients with underlying CVD (Worldometer).

Preliminary reports suggest a significant CVD burden in COVID-19 patients that require hospitalization. Clinical data from COVID-19 patients indicate elevated levels of cardiac injury biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), high sensitivity cardiac troponin I (hs-TnI) and C-reactive protein (CRP) [11]. In addition, preliminary autopsy reports from patients that succumbed to severe COVID-19 infection show severe right ventricular dilation, cardiac necrosis and infiltration of immune cells into the myocardium [12–14]. While the exact sequela and the relationship between these cardiac pathologies are still undetermined, it is becoming increasingly clear that inflammation, in addition to other factors plays an important role in promoting COVID-19 related cardiac injury.

While inflammation plays an important role in pathogenesis of COVID-19, it is noteworthy that inflammation is also an important driver of cardiac pathological responses to stress, including following myocardial infarction (MI) and transition to heart failure (HF). In both ischemic and non-ischemic HF, immune cells infiltrate the myocardium and release pro-inflammatory cytokines which regulate maladaptive cardiac remodeling [15]. Recent studies in humans and animals have greatly advanced our understanding of the molecular mechanisms that drive these cardiac inflammatory responses, as well as the short-term and long-term consequences of the immune cell infiltration to the heart. In this review, we will discuss SARS-CoV-2 pathogenesis, disease mechanisms that mediate cardiac injury in COVID-19 and highlight the common inflammatory mechanisms that mediate HF between COVID-19 and ischemic/non-ischemic heart disease.

2. SARS-CoV-2 pathogenesis

SARS-CoV-2, which belongs to the Coronavirus family, is an enveloped positive single-stranded RNA virus, and is derived from a novel strain of Beta coronavirus[16]. Historically, human coronavirus infections, from strains such as hCOV-OC43, HKU, and 229E, caused mild common cold like symptoms [17]. However, since 2000, at least two highly pathogenic and deleterious coronavirus strains have emerged, including SARS-CoV in 2002–2003 and the **M**iddle **E**ast **R**espiratory **S**yndrome Coronavirus (MERS-CoV) in 2012. SARS-CoV originated in China and rapidly spread to five of the seven continents, mainly through air travel; it resulted in 8098 cases with death rate of 10%. MERS, on the other hand, originated in the Arabian Peninsula, and resulted in 2494 confirmed cases, but with devastating fatality rate of 35% [18].

Viral entry into host cells is a key determinant of infectivity and disease pathogenesis. While the virus entry is dictated by efficient binding of the virus to host receptor, severity of infectivity and disease pathogenesis are determined by the host immune system. Generation of viral specific neutralizing antibodies by the host can definitively dampen the viral load and infectivity.

SARS-CoV-2 shares significant structural and genetic similarity with the original SARS-CoV. Both viruses are spherical in shape and have multiple transmembrane spike (S) glycoproteins embedded in the virion envelope that form homotrimers [19]. In both cases, infection in humans is mediated mainly by binding of the viral surface spike protein (S) to the human angiotensin-converting enzyme 2 (ACE2) receptor following its cleavage and activation by transmembrane protease serine 2 (TMPRSS2) or cathepsins secreted by the host. [20–24]. The S1 harboring receptor binding domain binds to the cellular receptor ACE2, while the transmembrane unit S2 facilitates fusion of the viral membrane with host cellular membrane. Membrane fusion is facilitated by cleavage of S protein by host cell proteases such as TMPPRSS2 or cathepsin at the S1/S2 and the S2′ site, which results in S protein activation [21,25,26]. This cleavage of the S protein in the constitutive endocytic pathway of infected cells or during viral entry into target cells is a key determinant of viral infectivity and pathogenesis[27–29].

In addition, the SARS-CoV-2 spike protein also contains a polybasic cleavage site, allowing it to also be processed by furin-like proteases, a feature also shared by other highly pathogenic avian flu viruses [30,31]. Recent reports demonstrate that furin cleaves the S protein precursor of SARS-Cov2 virus to generate a polybasic ArgArg-Ala-Arg (RRAR) C-terminal amino acid sequence on S1 protein, which increases the association of the virus to neuropilin-1 (NPR-1), a cell receptor widely expressed in respiratory and olfactory epithelium. In vitro and in vivo experiments suggest that this binding of SARS-Cov2 to NPR-1 receptor enhances the infectability of SARS-Cov2 in cell culture [32] and may be a significant contributing factor for enhanced tropism and infectability of SARS-Cov2 in humans, [33]. Compared to previous corona viruses, this combination of high ACE2 receptor affinity and enhanced tropism due to the presence of a polybasic cleavage site in its spike protein enhances SARS-CoV-2's ability to infect multiple organs, including the heart and therefore entry receptors and proteases present good therapeutic targets to combat SARS-CoV-2 infection.

Furin itself is a ubiquitously expressed transmembrane protein and its function has been well- characterized in the heart [34–36]. In the case of COVID-19, protein-proofed single-cell RNA (pscRNA) profiling studies examining the effects of infection on expression of ACE2, TMPRSS2 or furin in the heart, revealed that cardiomyocytes are a critical target for infection by SARS-CoV-2, preceded only by lung alveolar type II (AT2) cells and macrophages [37]. Two additional studies demonstrated that SARS-CoV-2 can enter the cell membrane and replicate in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). Microscopy and immunofluorescence studies confirmed that the virus localizes in the perinuclear region and induces apoptosis in the infected hiPSC-CMs, suggesting a deleterious outcome for cardiac tissue in response to COVID-19 [38,39]. (Fig. 1).

3. COVID-19 and cardiovascular burden

Damage to cardiac tissue has been previously reported in response to the coronavirus outbreaks. Approximately 8% of all SARS patients had CVD comorbidities and the presence of CVD or diabetes mellitus in SARS-infected patients led to at least 12-fold increased death rate [40,41]. CVD (30%) and hypertension (50%) comorbidities were also significantly associated with MERS [122]. Recent reports from Wuhan, Italy and the US suggest that CVD is one of the most common comorbidities associated with COVID-19 [42–45]. In addition, COVID-19 patients with CVD have a higher mortality rate (around 10.5%) as compared to other comorbidities such as hypertension (6%), diabetes (7.3%), or chronic respiratory disease (6.3%) [46]. In a study of 416 hospitalized patients with confirmed COVID-19, approximately 20% had elevated hs-TnI levels, indicative of an increased pathological response in the heart. Patients with these elevated cardiac injury biomarkers also had significantly higher mortality rates (~50%), as compared to those without heart injury (~4.5%) [45]. Similar findings were reported in a separate independent study, where the mortality rate among patients with elevated Troponin T (TnT), another cardiac injury biomarker, was ~60%, whereas the mortality rate in patients with normal TnT levels was ~9% [47]. Examination of additional cardiac injury biomarkers, including CRP and NT-proBNP, all consistently point

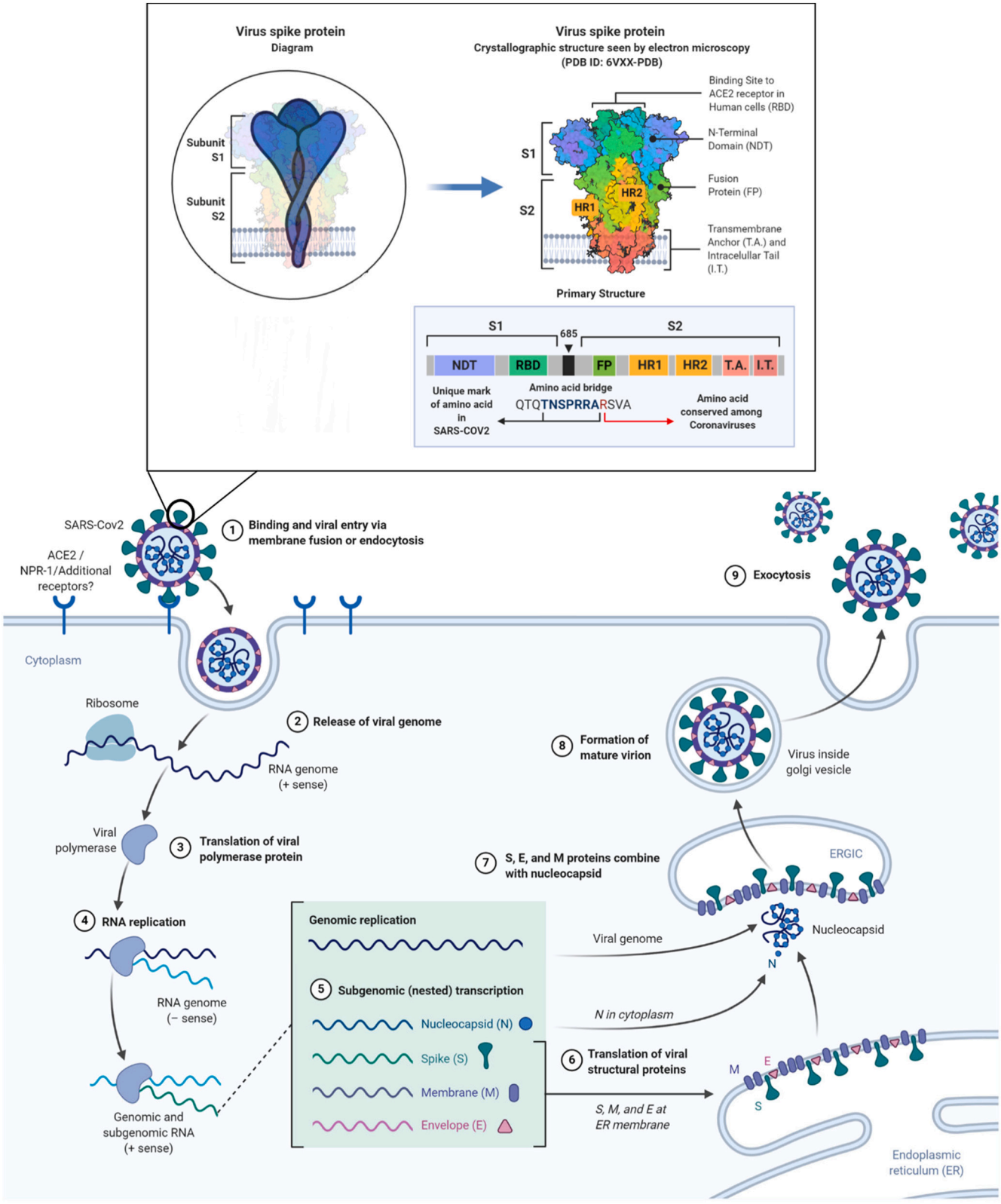

Fig. 1. SARS-Cov2 pathogenesis.
The life cycle of SARS-CoV-2 in the host cells. The S glycoproteins of the virion bind to the cellular receptors (E.g.: angiotensin-converting enzyme 2 (ACE2) or Neuropilin-1 (NPR-1)) and enters target cells through an endosomal pathway. Following the entry, the virus hijacks the host transcription and translation machinery to synthesize SARS-Cov2 structural proteins. Following the production of structural proteins, nucleocapsids are assembled in the cytoplasm and followed by budding into the lumen of the endoplasmic reticulum (ER)–Golgi intermediate compartment. Virions are then released from the infected cell through exocytosis. The insert highlights S1 and S2 domains of virus spike protein and the polybasic RRAR cleavage site that enhances its association with NPR-1 receptor. (Adapted from "Coronavirus Replication Cycle", by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates).

towards a similar conclusion [48].

While there was an increase in multiple cardiac injury biomarkers, the physiological and pathological manifestation of COVID-19 infection in heart spans a broad spectrum. In severe cases, direct acute myocardial injury characterized by concentric left ventricular hypertrophy with a dilated, severely hypokinetic right ventricle and cardiac amyloidosis has been reported [49]. Cardiac rhythm disorders have also been observed in patients with COVID-19. Guo et al. reported an overall ventricular tachycardia (VT)/ventricular fibrillation (VF) incidence rate of 7% during hospitalization [47] However in a larger clinical trial involving 700 COVID-19 positive patients, only 1.3% of the patients had cardiac arrests, 3.6% had atrial fibrillation, 1.3% had significant bradyarrhythmia and 1.4% had nonsustained VT [50]. Vascular complications of COVID-19 have also been reported including stroke, cutaneous lesions on the toes, and Kawasaki disease like systemic vasculitis in young children with severe COVID-19 [51,52].Preliminary autopsy and endocardial biopsy reports suggest low grade myocardial inflammation as evidenced by T-lymphocytic infiltration [53] and CD68+ macrophage infiltration in heart [13,54,55]. In addition, evidence of viral particles within vascular endothelial cells and diffuse vascular endothelial cell injury in lung, heart, and other organs have also been reported [56,57]. Histological evidence of acute myocarditis in COVID-19 patients is limited and additional autopsy and endomyocardial biopsy studies are needed to accurately estimate the pattern and proportion of cardiac damage caused by acute myocarditis versus other mechanisms.

In addition to being widely prevalent and at times, even being a prognostic comorbidity, CVD can also be triggered and caused by COVID-19 in patients with no prior history of heart disease. In a specific case study of a patient without previous history of cardiovascular disease, elevated levels of cardiac injury biomarkers high-sensitivity troponin T and NT-proBNP, acute myopericarditis with increased wall thickness and severe left ventricular dysfunction were reported one week after the respiratory symptoms were completely resolved [55]. Although underlying disease mechanisms are not well understood, these findings suggest significant cardiac involvement in COVID-19.

3.1. Potential disease mechanisms underlying COVID-19 induced cardiovascular dysfunction

Direct mechanisms: In addition to ACE 2 receptor, which serves as the main anchor point for SARS-CoV-2, cellular proteases such as serine protease TMPRSS2 and cathepsins (cathepsin B and cathepsin L) play an important role in viral entry by promoting viral fusion with host cells [21]. In humans, ACE 2 receptor expression is highest in the digestive tract, followed by kidney, testis, heart and lungs [58]. A detailed cellular level *ACE2* expression analysis in heart reported by two independent studies revealed that, among various cells in heart, *ACE2* was most highly expressed in pericytes, which line the microvasculature, followed by vascular smooth muscle cells, fibroblasts and cardiomyocytes [58,59]. In addition, cardiac expression analysis of viral entry promoting proteases TMPRSS2 and cathepsin L, encoded by genes *TMPRSS2* and *CTSL* respectively, revealed that *TMPRSS2* was minimally expressed across all cardiac cell types, while *CTSL* displayed low levels of expression in fibroblasts, macrophages, adipocytes and cardiomyocytes[60]. Recent articles report the presence of SARS-Cov2 viral particles in cardiac tissue including cardiomyocytes, endothelial cells, mesenchymal cells, and inflammatory cells [61].

Indirect mechanisms: In addition to the potential direct infection of the myocardium by SARS-CoV-2, cardiac damage can also be triggered by multiple indirect mechanisms in COVID-19 patients. Systemic hyperinflammation triggered by SARS-CoV-2 infection in the lungs, the 'cytokine storm', may indirectly lead to cardiac damage. Several clinical reports on COVID-19 patients reported significantly elevated inflammatory biomarkers in circulation, including interleukin (IL)-2, IL-6, IL-7, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), tumor necrosis factor-α (TNF-α), interferon-γ inducible protein (IP)-10, C-reactive protein (CRP), ferritin and procalcitonin [44,62]. Although triggered by local infection in the lungs, the increased systemic levels of these inflammatory cytokines activate inflammatory and maladaptive remodeling pathways in multiple organs, including the heart.

Increases in proinflammatory cytokines are involved in the development of cardiac disease. For example, aberrant expression of proinflammatory cytokines TNF-α, IL-1β, IL-6, and matrix metalloproteinases (MMPs) in the heart are also thought to contribute to the onset of myocardial infarction (MI) [63]. In addition, increases in inflammatory cytokine production has been correlated with aberrant intracellular Ca2+ regulation, a reduction in repolarizing potassium (K+) currents and altered expression of connexin 43 in cardiomyocytes lining the infarct border zone, leading to electrical disturbances in the heart, or cardiac arrhythmias [64]. Indeed, increased expression of CRP is associated with the development of atrial fibrillation (AF) [123]. With respect to COVID-19, multiple clinical studies now report a significant arrhythmogenic burden in severely infected patients including, heart palpitations and tachycardia [65].

Recent reports also highlight the presence of coagulation abnormalities in COVID-19 patients that led to blood clots and, ultimately to multi-organ failure, including HF. Coagulation is triggered by the activation of cascade of proteins that include coagulation factors, thrombin and fibrinogen. Once formed these blood clots are systematically degraded by specific enzymes such as plasmin, resulting in the formation of fibrin degradation products. D-dimer is one of the main fibrin degradation products and is used as a clinical marker for deep vein thrombosis (DVT), pulmonary embolism (PE) or disseminated intravascular coagulation (DIC). Patients with COVID-19 often have elevated D-dimer levels and high D-dimer levels correlate with disease severity and increased risk of death [66,67]. While the exact underlying mechanisms are not completely understood, multiple phenomena could contribute to this condition. Recent studies suggest that SARS-Cov2 can directly infect and kill endothelial cells exposing the thrombogenic basement membrane and activating the coagulation cascade. An autopsy study revealed that deep vein thrombosis is present in 7 of 12 patients who died of COVID-19 and in whom venous thromboembolism was not suspected prior to death [5]. In addition to direct endothelial cell injury, acute immobilization, especially in critically ill patients in ICU, increase in clotting factor VIII, fibrinogen, blood viscosity and presence of neutrophil extracellular traps (NETs) [68] can together contribute to hypercoagulable state in COVID-19 patients. Coagulation abnormalities triggered by COVID-19 can also directly and indirectly lead to cardiovascular problems. Micro-emboli caused by damaged endothelium or a hyper-coagulable state could destabilize existing coronary artery plaques precipitating a type I myocardial ischemia (MI) [69]. ARDS is the central feature of COVID-19 and the lungs are the most severely affected organ in these patients. Dyspnea has been reported in over 50% of all COVID-19 positive patients and is another common feature in patients with severe disease [70]. Pulmonary edema and severe inflammation in lungs lead to reduced gaseous exchanges and result in systemic hypoxemia that affects multiple organs, including heart. This respiratory derangement triggered by COVID-19 could lead to a mismatch between oxygen supply and demand, resulting in type 2 MI [71].

Significant immunological changes have also been reported in patients with severe COVID-19 infection, such as the cytokine storm, a decrease in lymphocyte count (both CD4+ and CD8+ T-cells) below the normal levels, also called as lymphopenia [72] [73] and T cell exhaustion [74,75]. Adaptive immunity, specifically through cytotoxic T-cells plays an important role in mounting an effective immune response against viral infections, including SARS-Cov2 and is therefore critical for effective recovery. Several studies have reported lymphopenia in a significant proportion of patients with confirmed COVID-19 infection [66,76–78]. Lymphopenia is now, a well-established hallmark feature

of COVID-19 infection [79]. While the precise underlying mechanisms of lymphopenia are unknown, recent reports demonstrate that SARS-Cov2 can directly infect and replicate in both B and T- lymphocytes triggering apoptosis in these cell types [80]. In addition to direct infection by SARS-Cov2, multiple other mechanisms such as cytokine storm [81] and elevated systemic lactic acid levels could contribute to lymphopenia [82]. In addition to a significant reduction in lymphocyte number, functional analysis of lymphocyte populations reveals that T cells from COVID-19 patients have significantly higher levels of PD-1 (programmed cell death 1) receptor protein compared to healthy controls suggesting that T-cell exhaustion or anergy could further contribute to the ineffective immune control over viral replication to facilitate disease progression [74].

Previously, lymphocytopenia has been associated with cardiovascular diseases, independent of COVID-19 infection. In a study on 392 patients with Heart Failure with Reduced Ejection Fraction (HFrEF), lymphocytopenia was strongly associated with more severe (NYHA Class III and IV) as compared to milder (NYHA Class I and II) heart disease [83,84]. In fact relative lymphocyte concentration is now recommended as a prognostic marker in patients with acute as well as chronic coronary artery disease [85,86]. Currently, there is no well-established causative relationship between lymphocytopenia and cardiovascular disease. However, animal studies suggest that interferon-γ secreted by T lymphocytes modulates smooth muscle proliferation during vascular repair. In addition, studies in rats which lack T-lymphocytes show larger arterial lesions after vascular injury, as compared to controls [87]. Together, these data all suggest that lymphocytopenia triggered by SARS-Cov2 infection can potentially add to the cardiovascular burden in COVID-19 patients.

4. Potential molecular mechanisms underlying COVID-19 induced cardiac remodeling: lessons from heart failure

COVID-19-associated systemic hyper-inflammation, cardiac arrhythmia, hemodynamic and respiratory derangement can induce cardiac stress. Sometimes, the stress can be severe enough to result in significant myocardial injury, which causes substantial cardiomyocyte death in the short term and potentially lead to onset of HF in the long run.

HF is a condition in which the heart can't pump enough blood to meet the body's needs due to aberrant cardiac structure and function, and affects nearly 6 million people in the US alone [88]. Significant research has been carried out to understand the molecular mechanisms that promote ischemic, non-ischemic and bacterial/viral triggered HF [89,90]. Chronic inflammation is an important pathogenic driver of HF, leading to cardiac fibrosis, an abnormal thickening and scarring of cardiac tissue, and eventually to cardiac dysfunction and patient death [91]. Different types of immune cells play an important role in promoting and regulating cardiac inflammation, and timing as well as identity of inflammatory cell infiltration in heart may vary, depending on the stimulus.

4.1. Inflammation mechanisms underlying ischemic cardiac injury

Cardiac ischemia caused by formation of an occlusive thrombus within the coronary artery leads to myocyte necrosis, triggering intense sterile inflammation and immune cell infiltration in hearts. In the case of an ischemic injury, neutrophils are the first immune cells to infiltrate cardiac tissue (between 12 h to 3 days post injury) [124,125]. In addition to secreting MMPs to help clear the dead cells and debris, neutrophils also produce IL-6, which plays a pivotal role in the recruitment of monocytes/macrophages to the heart. Two distinct phases of monocyte recruitment have been identified in healing myocardial infarcts. After ischemic injury in mice, the first phase of monocyte/macrophage infiltration comprises of C-C chemokine receptor 2 (CCR2) + monocytes which express high levels of lymphocyte antigen 6 complex ($Ly6c^{hi}$) on their membranes. These cells reach their peak infiltration by 3 days post MI and predominantly promote acute inflammation and further removal of dead cells. In the second phase, CCR2+ monocytes which express lower levels of Ly6C ($Ly6C^{low}$) reach peak infiltration by day 7 and are more reparative in nature; they promote the activation and transformation of fibroblasts to collagen producing myofibroblasts to generate scar tissue, a crucial step needed for wound healing [92]. In humans, classical monocytes are identified by membrane proteins that are Cluster of Differentiation (CD)14^{++} $CD16^{-}$ which are functionally similar to murine $Ly6C^{high}$ monocytes, whereas non-classical monocytes ($CD14^{+}CD16^{++}$) more closely resemble murine $Ly6C^{low}$ cells. In addition to the innate immune cell infiltration, adaptive immune cells, predominantly T-lymphocytes also infiltrate the injured myocardium. Specifically, CD3+ CD4+ helper, CD8+ cytotoxic, and Foxp3+ regulatory T-cell numbers in heart are significantly increased (up to 10 fold) by day 7 after coronary ligation in mice. During the early stages of MI, CD4+ T-cells are shown to promote wound healing and tissue repair [93]. However, in chronic ischemic HF, CD4+ T-cells impart pro-inflammatory stimuli on the heart that promote adverse remodeling. Antibody mediated CD4+ T-cell ablation alleviated pathological LV remodeling, suggesting pathological role for T-cells during these later stages of MI [94]. Replacement of dead cardiac tissue with fibrotic myocardial scar is absolutely crucial for maintaining the structural integrity of the cardiac wall and inhibiting scar formation can lead to ventricular dilation or even ventricular rupture [95]. However, conversely, persistent activation and propagation of myofibroblasts can lead to pathological fibrosis, decreasing cardiac function, stiffening the heart, and eventually causing HF and death [96,97]. Although the precise molecular mechanisms underlying onset of pathological fibrosis remain unclear, transforming growth factor-beta (TGF-β) is thought to play a central role in fibroblast proliferation and fibroblast-to-myofibroblast conversion. Inhibiting TGF-β inhibits pathological fibrotic remodeling in mice, suggesting it may be a viable therapeutic target, although this has yet to be determined in humans [98].

4.2. Inflammation mechanisms underlying non-ischemic cardiac injury

Hypertension is a common risk factor for non-ischemic cardiac injury and HF [99]. Hypertensive heart disease is associated with cardiac hypertrophy, cardiac fibrosis and manifests clinically as systolic or diastolic HF [100–103]. Transaortic Constriction (TAC), a surgical procedure that involves placing an elastic band around the aorta to induce cardiac pressure overload is a well-established model of non-ischemic HF in mice [104]. TAC induces low-grade cardiac inflammation, adverse cardiac remodeling, and progressive cardiac dysfunction. In addition, Angiotensin II (ATII) infusion is another well-established experimental model for pressure overload mediated non-ischemic injury to heart [105]. The contribution of inflammation to pressure overload induced HF is a well-studied phenomenon, with multiple immune cell types infiltrating the heart. In contrast to ischemic injury, non-ischemic injury causes minimal necrotic death of cardiomyocytes and negligible cardiac neutrophil infiltration to the heart. Recent studies have shown that F4/80+ CCR2+ monocytes are one of the first immune cell types to infiltrate the heart in significant numbers after TAC. The infiltration of these monocytes is mediated by a specific chemokine, monocyte chemoattractant protein – 1 (MCP-1) and they reach peak infiltration by 7 days post TAC [106]. Unlike ischemic cardiac injury, CCR2+ $Ly6C^{low}$ macrophage population significantly increases, in response to TAC, making up over 80% of all the macrophage population in heart, 6 days post TAC [107]. Blocking TAC induced cardiac infiltration of CCR2+ macrophages either pharmacologically, using a CCR2 antagonist (RS-504393) or with an antibody mediated CCR2+ monocyte depletion strategy, alleviates maladaptive cardiac remodeling and protects the heart from pressure overload induced failure [108]. The adaptive immune system also plays an

important role in regulating the cardiac microenvironment after TAC. Although temporal studies on adaptive immune cell infiltration in heart after non-ischemic stress have not been carried out extensively, multiple studies have highlighted the role of T-cells in reparative and maladaptive cardiac remodeling following pressure overload. Interestingly, while no significant T-cell infiltration in the left ventricle (LV) was observed, 48 h post TAC, infiltration of T cells became prevalent after 2 weeks, peaking at 4 weeks after TAC. Using a T-cell deficient mouse model (T-cell receptor knock out $TCR\alpha^{-/-}$), T-cell recruitment into the LV correlated with adverse remodeling; mice lacking T-cell receptor showed resistance to pressure overload induced maladaptive cardiac remodeling and had preserved cardiac function [109]. Similar results were observed when T-cells were deleted in normal mice using anti CD3 antibody suggesting that T-cell recruitment into the LV is a contributing factor to pathological cardiac remodeling in HF. Similar observations were reported in patients with NYHA class III and class IV non-ischemic HF, where CD3+ T cells infiltrated the LV of patients with nonischemic end stage HF, and this was associated with significant cardiac hypertrophy and fibrosis. Moreover, blocking T cell co-stimulation by antigen presenting cells in mice subjected to TAC using a monoclonal antibody that blocks T-cell activation (Abatacept). significantly preserved cardiac function and reduced fibrotic response, was demonstrated, highlighting the importance of the adaptive immune system in pathological cardiac remodeling [110].

4.3. Inflammation mechanisms underlying virus mediated cardiac injury

Viral infections are one of the common causes of myocarditis [111]. Several viruses including adenovirus, herpesviruses, and influenza can cause myocarditis in humans [112]. However, Coxsackievirus type B (CVB) has have high tropism for cardiomyocytes, endothelial cells, and leukocytes in humans and CVB mediated myocarditis has been well studied [113]. CVB particles can directly induce myocardial injury, even in mice with significantly low B and T-cells, as demonstrated by CVB induced myocarditis in mice with severe combined immune deficiency [114]. In addition, CVB viral particles also activate both innate and adaptive immune systems and cause cardiac injury through inflammatory mechanisms. CVB infection of endothelial cells upregulates the expression of lymphocyte function associated antigen 1 (LFA-1), which promotes leukocyte extravasation and inflammation in heart [115]. Significant upregulation of F4/80+ macrophages has been observed in mice infected with CVB3 on post infection day 12 [116] and cardiac infiltration of CD3+ T-cells has been reported by post infection day 7 [115]. Depletion of T lymphocytes decreases mortality rate and reduces cardiac inflammation and injury after CVB3 infection [117] highlighting the pathological role of T-cells in viral myocarditis. However, recent reports show that CD4+CD25+FoxP3+ Treg cells exert protective effects through TGF-β which is known to suppress inflammation [118]. Together, these data highlight the significant and complex interplay of immune cells in regulating cardiac function.

Although no direct experimental evidence exists for understanding the molecular mechanisms that regulate COVID-19 induced remodeling in heart as yet, there seems to be some commonality between the immunological mechanisms underlying COVID-19 induced myocardial injury and ischemic/non-ischemic HF and viral myocarditis. As reported in ischemic and to a lesser extent in non-ischemic HF, myocardial infiltration of neutrophils has also been reported in hearts of COVID-19 patients, however, their specific identity is currently unknown [14]. Recent data suggest that the network of extracellular fibers secreted by neutrophils, also termed neutrophil extracellular traps (NETs), aggravate myocardial ischemia/reperfusion injury in CVD patients. However, breakdown of NETs with DNase I reduces neutrophil influx into the infarcted heart and improves cardiac function [119]. Interestingly, a recent report demonstrated a higher level of biomarkers for NETs in COVID-19 patients that were on mechanical ventilation, as compared to hospitalized patients breathing room air [120]. Together, these preliminary data suggest that significant increases in neutrophil count can exacerbate disease severity in COVID-19 patients and may also promote myocardial damage.

Multiple autopsy studies report an infiltration of macrophages and CD4+ T lymphocytes in the myocardium of COVID-19 patients [14]. Myocyte damage and lymphocytic myocarditis have also been independently confirmed by recent autopsies carried out on multiple COVID-19 patients from Seattle and Germany [4,5]. Recently, SARS-CoV-2 viral particles have been identified in cardiac macrophages, suggesting that these cells can be directly infected by the virus, potentially transmitting the disease systemically to multiple tissues [13]. While the exact molecular identity of these macrophages is currently unknown, the correlation of macrophage infiltration with cardiomyocyte necrosis and the systemic hyperinflammatory conditions in patients suggest that these macrophages could be pro-inflammatory in nature. The infiltration of neutrophils, macrophages and CD4+ T lymphocytes in COVID-19 patients can promote the activation of fibroblasts to myofibroblasts in heart, which could lead to pathological cardiac remodeling and fibrosis in the long term, leading to development of HF and potentiating earlier death in infected (or even recovered) patients (Fig. 2). Recently, 78% of 100 recovering patients evaluated 71 days after confirmed COVID-19 diagnosis showed cardiovascular involvement as detected by magnetic resonance imaging, irrespective of pre-existing conditions and severity of COVID-19 disease. 76% of patients had detectable high-sensitivity troponin, a cardiac injury biomarker and 60% had myocardial inflammation, edema and/or diffuse myocardial fibrosis as determined by abnormal native T1 and T2 measures. Compared with both healthy and risk factor–matched controls, patients who recently recovered from COVID-19 had lower left ventricular and right ventricular ejection fractions, higher left ventricle volumes and masses [121] These findings highlight COVID-19 related cardiovascular burden in patients, even after recovery, and the possibility of residual left ventricular dysfunction and ongoing inflammation post-infection, which may lead to new-onset heart disease and other cardiovascular complications in the near future.

5. Conclusion

COVID-19 has already infected around 32 million people worldwide and has resulted in over 966,000 (figures are current at the time of writing these manuscript) deaths across the globe. This pandemic is nowhere near over or under control yet and continues to actively spread across the U.S. and rest of the world. Though tremendous efforts and resources have been dedicated towards developing a vaccine or a cure, there is yet no effective way to treat this disease. CVD remains the most significant comorbidity associated with increased mortality in COVID-19 infection. While the underlying disease mechanisms are not completely understood, preliminary data suggest that both local and systemic inflammation play a critical role in evoking and potentiating existing or new cardiac functional abnormalities. While myocardial infiltration of immune cells and cardiomyocyte necrosis are short term complications of COVID-19, the long-term effects remain to be seen. These could easily include cardiac hypertrophy, cardiac fibrosis and decreased cardiac output, leading to potentiated cardiac dysfunction. Therefore, patients who recover from severe COVID-19 could be at increased risk of developing HF, and there is a reason and need to continue monitoring these patients for cardiac health issues in the long run. Given the worldwide prevalence of this disease and the strong association with CVDs, additional studies are needed to gain a better understanding of the molecular mechanisms that drive COVID-19 related cardiac remodeling and to develop effective screening and therapeutic interventions against COVID-19-associated HF in the future.

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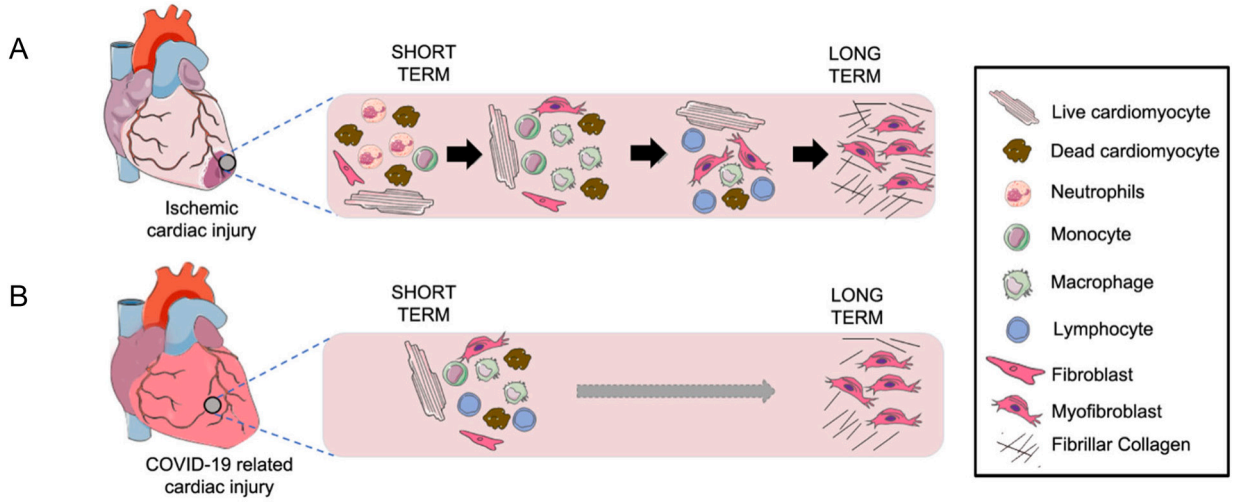

Fig. 2. Inflammation and potential remodeling mechanisms in COVID-19 heart.
Common mechanisms between ischemic injury and COVID-19 induced cardiac remodeling. A) Myocardial ischemia induces significant cardiomyocyte death followed by recruitment of innate (neutrophils, monocytes, macrophages) and adaptive immune cells (T-lymphocytes) which promote dead cell clearance and wound healing in the short term. In the long run, this immune cell infiltration and associated cytokine release transform fibroblasts to myofibroblasts, resulting in excessive fibrosis and maladaptive cardiac remodeling which may lead to HF. B) Preliminary autopsy reports of COVID-19 patients confirmed infiltration of both innate (monocytes and macrophages) and adaptive immune cells (lymphocytes) in myocardium. In the long run, this immune cell infiltration can potentially trigger maladaptive cardiac remodeling resulting in cardiac fibrosis and decreased cardiac function in patients who recover from severe COVID-19 disease.
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Declaration of competing interest

None.

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