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Review

COVID-19 Pathophysiology: Inflammation to Cardiac Injury

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Abstract: Coronavirus disease 19 (COVID-19) is responsible for one of the worst pandemics in human history. The causative virus, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), can invade host cells in multiple organs by binding the angiotensin-converting enzyme (ACE) II expressed on the cell surface. Once inside the host cell, viral replication takes place, leading to cellular disruption and the release of signal molecules that are recognised by the innate immune system. Innate immunity activation leads to the release of proinflammatory cytokines and primes the adaptive immune system. The proinflammatory environment defends against further viral entry and replication. SARS-CoV-2 infection is thought to lead to myocardial injury through several mechanisms. Firstly, direct viral-mediated cellular invasion of cardiomyocytes has been shown in in vitro and histological studies, which is related to cellular injury. Secondly, the proinflammatory state during COVID-19 can lead to myocardial injury and the release of protein remnants of the cardiac contractile machinery. Thirdly, the hypercoagulable state of COVID-19 is associated with thromboembolism of coronary arteries and/or other vascular systems. COVID-19 patients can also develop heart failure; however, the underlying mechanism is much less well-characterised than for myocardial injury. Several questions remain regarding COVID-19-related heart failure, including its potential reversibility, the role of anti-viral medications in its prevention, and the mechanisms underlying heart failure pathogenesis in long COVID-19. Further work is required to improve our understanding of the mechanism of cardiac sequelae in COVID-19, which may enable us to target SARS-CoV-2 and protect patients against longer-lasting cardiovascular complications.

Keywords: coronavirus disease 19; SARS-CoV-2; cardiac injury; heart failure; pathophysiology

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1. Introduction

The coronavirus disease 19 (COVID-19) pandemic was one of the worst in human history [1]. Healthcare services worldwide were subjected to immense pressures with vast rises in hospital admissions, paralleled by significant loss of life globally [2]. At the core of the pandemic was the emergence of a virus which exhibited a number of properties that made it extremely contagious, difficult to treat, and ultimately, lethal [3]. We emerged from the pandemic with improved knowledge about the pathogenesis of COVID-19. However, the mechanisms underlying the pathogenesis of COVID-19 in patients with myocardial injury and heart failure remain unclear. Whilst the mortality rates from COVID-19 infections have fallen overall, the disease continues to mutate, and new variants of the causative agent continue to emerge [3]. COVID-19 is likely to stay as a disease entity. For healthcare professionals, there is a vast volume of the existing literature on the pathogenesis of COVID-19 and how it may affect the heart. Owing to the relevance of these healthcare issues to daily practice, a firm understanding of COVID-19 pathogenesis and myocardial injury is important. This review will summarise the processes by which COVID-19, as an infectious and inflammatory condition, affects the heart.

2. COVID-19 and Host Infection

The causative organism of COVID-19, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a single-stranded, positive-sense RNA virus [4–6]. The viral genome codes for several structural proteins [4–6]. Amongst these are viral membrane proteins, nucleocapsid proteins, spike glycoproteins, and envelope proteins [7]. SARS-CoV-2 invades the host cell first by using its spike protein to bind to the angiotensin-converting enzyme (ACE) II receptor expressed on the host cell [7]. The transmembrane serine protease 2 then cleaves the spike protein [8], which is followed by the fusion of the viral lipid bilayer with the host cell membrane, leading to the release of the viral material into the host cell [7].

Once inside the host cell, the SARS-CoV genome is replicated and translated into structural and accessory proteins [9]. The viral replication unit has membrane vesicles that act like shields during viral RNA replication, preventing the recognition of transcription intermediates by the host pattern recognition receptors [7]. The new SAR-CoV-2 viral particles then resurface on the host cell surface membrane via vesicles and are released to continue host infection [9]. ACE II receptors are found in many organ systems, such as the respiratory tract, the heart, the gastrointestinal tract, and the kidneys [10], allowing SARS-CoV-2 routes to affect multiple organs. Figure 1 summarises the invasion of the host cell by SARS-CoV-2.

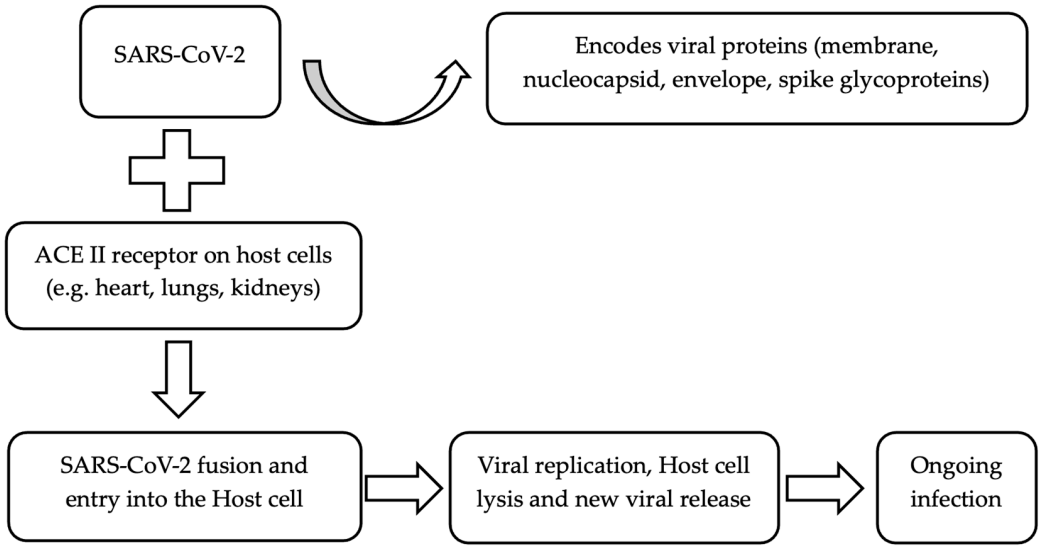

Figure 1. Host cell infection by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Angiotensin-converting enzyme (ACE).

3. Innate Immune Response to Infection

As the first line of defence against SARS-CoV-2 infection, innate immunity plays a part in inhibiting viral cellular entry, reducing viral replication, and facilitating the removal of infected host cells [9,11]. Innate immunity also triggers downstream proinflammatory pathways, which activate adaptive immunity and anti-viral processes [9]. Direct invasion of the host cells by SARS-CoV-2 can lead to host cell death [12] and the release of molecules collectively known as Pathogen Associated Molecular Patterns (PAMPs) and Damage Associated Molecular Patterns (DAMPs) [13].

PAMPs are signal molecules that can be recognised by pattern recognition receptors of the innate immunity system [13,14]. These include the Toll-Like Receptors [15] and the cytosolic-related receptors found on the surface of endothelial cells and macrophages [13,14]. Activation of pattern recognition receptions leads to proinflammatory cytokine cascades and interferon-dependent responses [13,14]. DAMPs are recognised by the nucleotide-binding domain leucine-rich repeat (NLR) proteins, which activate interleukin-1β (IL-1β) related inflammatory pathways [16].

Natural killer (NK) cells also contribute to the initial defence against SARS-CoV-2 infection [17]. NK cell activation is normally inhibited by the Major Histocompatibility Complex (MHC) class I molecules expressed in healthy host cells, and this leads to self-tolerance [17]. However, this self-tolerance is disrupted in the presence of infected host cells, which are destroyed by NK cells through cytotoxic degranulation and the release of proinflammatory cytokines [17].

The activation of the innate immunity by SARS-CoV-2 leads to a range of immune responses [18], including the release of proinflammatory cytokines, such as monocyte chemoattractant proteins, interferon γ (IFN-γ) and IL-6 [18]. Macrophages and dendritic cells are increasingly recruited to the infection hotspots, exerting further inflammatory activation and antigen presentation effects [7]. The influx of immune cells provides further cellular targets for SARS-CoV-2 invasion, and when these immune cells are penetrated and infected by the virus, they bring about more aggressive inflammatory cytokine and chemokine release [7]. Several interleukins, such as IL-2, IL-7, and IL-10, are implicated in the proinflammatory process of COVID-19 [7,18]. Further, granulocyte colony-stimulating factors (G-CSF), macrophage inflammatory proteins (MIP), and tumour necrosis factors (TNF) are also important mediators of the inflammatory response [7,18]. The innate immunity also activates adaptive immunity via cytokine release, leading to antigen-specific T lymphocyte recruitment, which can kill infected host cells and hinder viral propagation [19]. Figure 2 summarises innate immunity activation in response to SARS-CoV-2 infection.

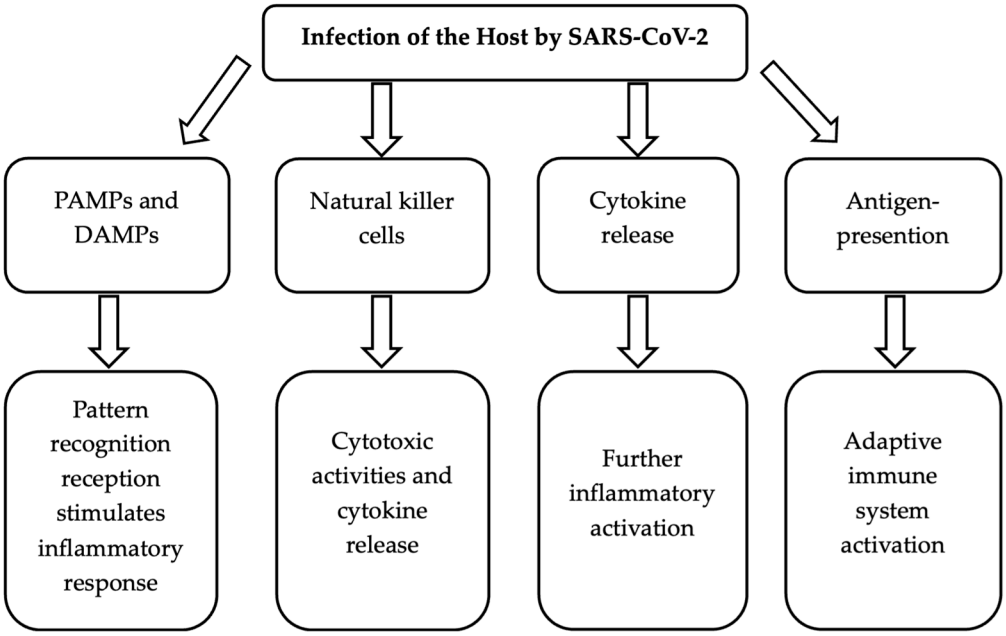

Figure 2. Inflammatory activation in response to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections. PAMPs: Pathogen Associated Molecular Patterns; DAMPs: Damage Associated Molecular Patterns.

4. Adaptive Immunity Activation in SARS-CoV-2 Infection

Activation of adaptive immunity is important in both direct viral clearance and the production of specific antibodies [15,20]. Class I MHC, expressed on host cells and platelets, can present viral antigens to the T-cell receptors (TCR) on naïve $CD8^+$ T lymphocytes [21]. This process causes the naïve $CD8^+$ T lymphocytes to activate, clonally expand, and differentiate into effector T lymphocytes, which can destroy infected host cells [21]. Class II MHC, expressed on the surface of antigen-presenting cells, such as macrophages, dendritic cells, and B lymphocytes, facilitate the activation, proliferation, and differentiation of B lymphocytes and $CD4^+$ T cells [20]. Further inflammatory activation leads to the production of antibodies against SARS-CoV-2 [15,20].

T-helper cells ($CD4^+$) play a major role in the regulation of the adaptive immune response to SARS-CoV-2 infections [15]. Naïve $CD4^+$ T lymphocytes are first activated by viral antigens and become follicular T-helper lymphocytes after migration and maturation in germinal centres [15]. T-helper cells facilitate the differentiation of follicular B cells into antibody-producing plasma cells and memory B cells [15]. Immunoglobulins (Ig) M against the SARS-CoV-2 spike protein are among the first antibodies to be produced in COVID-19, followed by IgGs [22]. Viral-specific antibodies are evident from 7 days post-infection [23]. Figure 3 summarises the adaptive T lymphocyte-mediated response against SARS-CoV-2 infection.

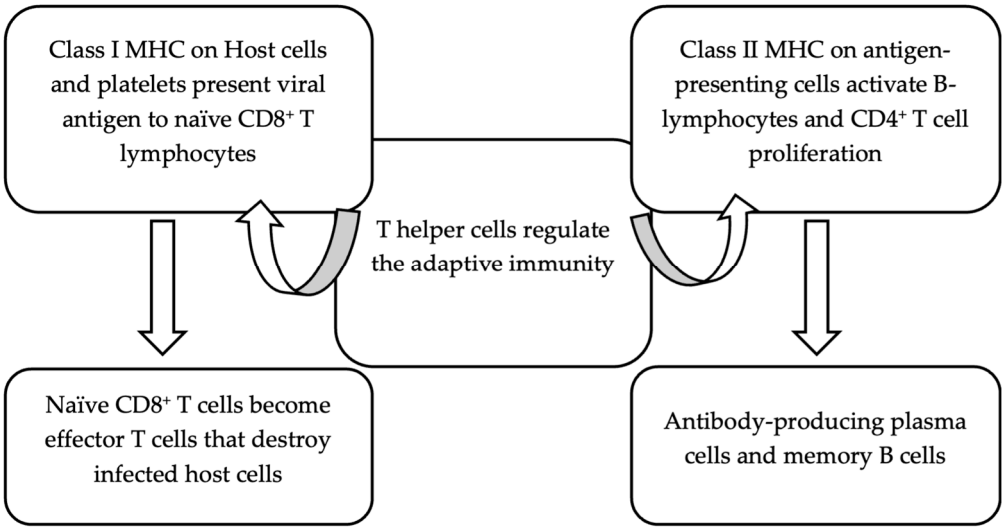

Figure 3. Adaptive immune system activation in Severe Acute Respiratory Syndrome Coronavirus 2 infections. MHC: Major Histocompatibility Complex.

5. Biomarkers of Inflammation in COVID-19

A number of markers of inflammation are implicated in the pathogenesis of COVID-19. Existing evidence suggests a role for these biomarkers in assessing both the severity and prognosis of patients with SARS-CoV-2 infections.

5.1. Interleukins

Several interleukins that are known to be involved in the activation and propagation of systemic inflammation have been shown to be elevated in COVID-19. A recent systematic review and meta-analysis showed that IL-2, IL-4, IL-6, and IL-10 were elevated in patients with COVID-19 [24]. Certain interleukins, such as IL-6 and IL-8, are higher in patients with severe disease manifestation and in those patients who require intensive care unit admissions [24], potentially conferring a prognostic value. Despite these results, routine assessment of serum interleukin levels has yet to translate into routine clinical practice, likely due to their non-specific nature (particularly in the presence of other confounding infections), the added cost implications of widespread clinical use, and the existence of other more clinically familiar markers of inflammation.

5.2. C-Reactive Protein (CRP)

Whilst considered a non-specific indicator of inflammation, serum CRP is an established biomarker with good clinical familiarity in practice [3]. Elevated CRP levels are found in COVID-19 patients as a possible predictor of clinical outcomes [25,26]. Patients with raised CRP are at risk of developing increased oxygen requirement [27] and inpatient mortality [26]. CRP is found to be elevated in patients with severe COVID-19 disease along with other makers of infection and inflammation, including erythrocyte sedimentation rate and procalcitonin [28]. Whilst the pattern of elevated CRP has been established in

COVID-19 patients, the use of CRP to solely risk-stratify patients has not materialised. This is likely due to the low diagnostic performance of CRP in predicting the occurrence of complications in the individual patient [3]. As a result, CRP may provide an indication of disease severity but should be used in conjunction with the overall clinical picture in patient management [3].

5.3. Combination Biomarkers

Owing to the non-specific nature of individual inflammation biomarkers, research efforts have emerged over the last 2–3 years in the development and use of combination markers for predicting prognosis in COVID-19 patients [3]. Work from our team, along with colleagues in other centres, showed that the ratio between lymphocyte and CRP (LCR) could predict adverse outcomes in COVID-19 [29–31]. LCR was originally developed to be a prognostic marker in patients with gastrointestinal cancers [32] and as an indicator of immune–tumour interaction [32,33]. In COVID-19, LCR theoretically exploits the combination of lymphopenia and CRP elevation (both are known prognostic markers) as a potentially viral-specific marker [29]. However, we did not show that LCR provided significant additional prognostic value when compared to CRP, which showed that it was not likely clinically viable without further work to improve its specificity towards COVID-19 [29]. Other combination markers, such as ferritin–lymphocyte ratio (FLR), have also been tested by both other teams and colleagues in other centres, but with varying degrees of success in predicting adverse outcomes in COVID-19, likely owing to factors such as expected variations in patient population and methods used in FLR estimation [34,35].

Other combination markers have also been tested for predicting clinical outcomes in COVID-19 patients [3]. These include a neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), monocyte–lymphocyte ratio, and eosinophil–lymphocyte ratio, which have been associated with severe disease manifestations in SARS-CoV-2 infections [36].

Non-serum-based combination markers, such as the CRB-65 risk score, have been shown to have prognostic value in COVID-19 patients [37]. Whilst these markers do not assess the degree of inflammatory activation through serum assays, the combination of confusional state, respiratory rate, and blood pressure reading can provide a clinical assessment of the manifestation of systemic sepsis [38]. The absence of abnormalities in the CRB-65 score may help to identify lower-risk COVID-19 patients without the need for blood tests [37]. This possible notion requires further validation.

6. Pathogenesis of Myocardial Injury in COVID-19

Three possible mechanisms are thought to be responsible for organ-specific injury in COVID-19 [9,39–47]. Firstly, direct viral host cell invasion can result in cellular damage that affects organ function [39–41]. Secondly, organ injury can result from the host immune activation by SARS-CoV-2 and the creation of a highly proinflammatory state within the body, involving cytokine storms and sepsis [9,42,43]. Thirdly, organ injury can be caused by the hypercoagulable state observed in COVID-19, leading to thromboembolic events [44–47].

6.1. Direct Myocardial Invasion in COVID-19

In patients with COVID-19, myocardial injury has been described since the early part of the pandemic [40,43,48–57]. The expression of ACE II receptors on cardiomyocytes means that the heart is vulnerable to direct invasion and cellular penetration by SARS-CoV-2 [10]. SARS-CoV-2 has been shown to target cardiomyocytes directly in vitro [58], and histological evidence of the SARS-CoV-2 genome has also been found in cardiac biopsy samples in patients [59]. The direct invasion of cardiomyocytes is linked to a reduction in ACE II, leading to excessive buildup of angiotensin II and dysregulation of the renin–angiotensin–aldosterone pathway [39]. This can lead to cardiomyocyte apoptosis [39]. Direct viral invasion has also been associated with the down-regulation of certain genes encoding for

cardiomyocyte contractile and sarcomeric proteins, which may lead to impaired cardiac function [60]. The clinically manifested disease is not a pre-requisite for myocardial injury since evidence of SARS-CoV-2 was present in cardiac autopsies of some patients who had displayed little or no symptoms during life [61].

6.2. Myocardial Injury in Systemic Inflammation

Myocardial injury has long been known to occur during systemic inflammatory responses and cytokine storms in sepsis [43]. Several mechanisms are thought to be implicated in this process, including immune cell recruitment, endothelial dysfunction, and hypoxia [43,62]. A similar mechanism may operate in myocardial injury related to COVID-19 [43,63]. Breakdown of the myocardial cellular structure due to necrosis and/or apoptosis leads to an increase in circulating protein remnants of the cardiomyocyte contractile machinery [64]. A rise in serum markers of myocardial damage is often seen to be associated with elevated inflammatory markers, including C-reactive protein (CRP) and ferritin [65]. These observations suggest that the systemic inflammatory response and myocardial injury may occur at the same time [65], although a causative relationship has yet to be definitively proven.

Systemic inflammatory response driven by interleukins (e.g., IL-2, IL-6, and IL-10) and TNF-α may accelerate atherogenesis and destabilise coronary artery plaques [44,66]. Catecholamine hyperactivity in the context of a proinflammatory state may also induce microvascular injury and stress-induced cardiomyopathy [67]. Systemic inflammation has been implicated in both Takotsubo cardiomyopathy and acute myocarditis in COVID-19 patients [68–75]. Indeed, both myocardial injury and systemic inflammatory state have prognostic implications in COVID-19 patients [3,29,34,64]. There is currently a paucity of therapeutic studies on anti-inflammatory treatments and their effects on myocardial injury.

6.3. Myocardial Injury and Thromboembolism in COVID-19

A significant proportion of COVID-19 patients presenting with acute coronary syndromes have unobstructed coronary arteries [76,77], which can be observed in both adults and children [78–81]. Occlusion of normal coronary arteries by thrombus has also been reported in COVID-19 patients [78–80], which suggests that the underlying mechanism may not be acute atherosclerotic plaque rupture [78–80]. Moreover, thrombotic occlusions can occur exclusively in the coronary arteries or in other parts of the cardiovascular system, such as left ventricular thrombus or embolic strokes [78–81]. These observations may be linked to a systemic hypercoagulable state seen in COVID-19 [78–82].

The formation of microthrombi and endothelial dysfunction has been postulated to result from the hypercoagulable state in SARS-CoV-2 infections [45,47]. Coronary artery microthrombi has been associated with myocardial necrosis in COVID-19 patients in autopsy studies [47]. Further, microthrombi aspirated from the coronary arteries of COVID-19 patients during acute myocardial infarction have high fibrin and complement content, implicating systemic inflammation in their pathogenesis [47]. Figure 4 illustrates the potential mechanisms for myocardial injury in COVID-19.

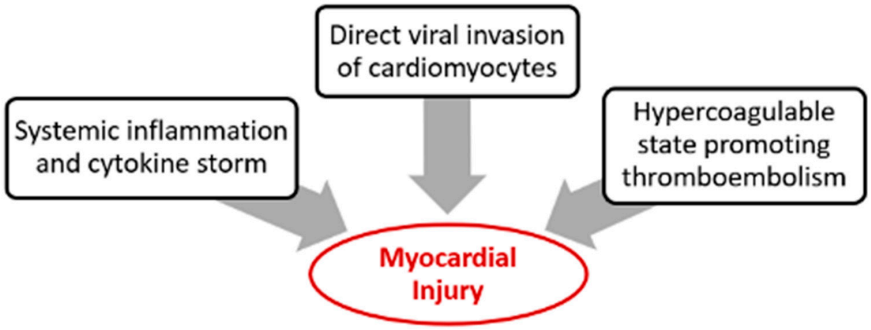

Figure 4. Potential mechanisms of myocardial injury in coronavirus disease 19.

6.4. D-Dimer and Thromboembolic Events in COVID-19

COVID-19 patients are at an increased risk of developing pulmonary embolism (PE), and a negative D-dimer test can help rule out PE [83]. However, a positive D-dimer does not necessarily rule in PE in COVID-19 sufferers [84]. There is no established threshold level of D-dimer that is recommended for the detection of PE in COVID-19 [85]. Part of the reason may be the heterogeneity of the D-dimer thresholds derived from different studies [3]. Whilst an elevated D-dimer level is linked to worse clinical outcomes in COVID-19 [86], there is currently insufficient evidence to link elevated D-dimer levels to myocardial injury during the acute SARS-CoV-2 infection. Although D-dimer may reflect a hypercoagulable state in patients with SARS-CoV-2 infections, the direct link between coronary thromboembolic disease and D-dimer remains tenuous and under-explored. Further mechanistic studies are required to elucidate such potential association.

7. Cardiac Troponins

Cardiac troponins are functional proteins and are components of the cardiomyocyte contractile machinery [3,64]. In the context of myocardial damage and necrosis, the breakdown of the contractile apparatus leads to the release of cardiac troponins into the bloodstream, which can be detected using serum assays [87,88]. Cardiac troponins already play an important role in the diagnosis and risk stratification of patients presenting with acute coronary syndromes [89,90].

During the pandemic, the use of cardiac troponins to risk-stratify patients with COVID-19 gained significant interest [3,52]. COVID-19 patients with elevated cardiac troponin levels have a worse overall prognosis than patients with normal troponins [57]. However, cardiac troponins did not enter the clinical arena for guiding clinical decision-making in COVID-19 owing to their poor positive predictive value for predicting adverse outcomes [64]. Further work is required to better understand the interplay between cardiac injury and cardiac troponin as a potential biomarker.

Work from our group showed that cardiac troponin had a high negative predictive value for predicting inpatient mortality, suggesting that it might be better used as a rule-out test to identify low-risk patients [64]. The low positive predictive value of cardiac troponin in the COVID-19 patient population studied suggests that it may be a non-specific marker of adverse outcomes in COVID-19 [64]. These results are in line with other studies and may offer some explanation as to why cardiac troponin has yet to enter routine clinical practice for risk-stratifying COVID-19 patients [57]. The use of cardiac troponins remains much better validated in acute coronary syndrome than in COVID-19, where the latter potential indication is mostly based on data from retrospective studies [57].

8. Electrocardiogram (ECG)

A number of ECG changes have been reported in COVID-19 patients, which relate to myocardial injury, atrioventricular heart block (AVB), atrial and ventricular arrhythmias, as well as QTc prolongation and QRS voltage changes [3]. The prognostic impact of ECG abnormalities has been studied in retrospective studies, which emphasises the importance of this bedside test [91].

Patients with COVID-19 can present with ST-segment and T-wave changes suggestive of acute myocardial ischaemia [76]. However, a significant proportion of these patients may have unobstructed coronary arteries [76]. Acute myocarditis can also present with non-specific ST/T-changes on ECG [3]. High-grade AVB occurs rarely in COVID-19, which is usually reversible and without the need for permanent pacing [92–98]. Atrial fibrillation and atrial flutter are common, with a reported prevalence of up to 13% in COVID-19 patients, which may reflect the effects of systemic inflammation and myocardial injury [3]. In COVID-19 patients, ventricular arrhythmias are much rarer, which may be triggered or exacerbated by systemic inflammation, underlying cardiac structural abnormalities or myocardial injury [99,100].

Prolonged QTc is a reported independent predictor of mortality in COVID-19 patients [101], whereby the longer the QTc, the greater the mortality risk [101]. The exact mechanism underlying the link between QTc and prognosis remains unclear, which may be related to arrhythmogenic risk or myocardial ischaemia [102,103]. Both low-voltage QRS complex and reduced heart rate variability are linked to adverse outcomes in COVID-19 patients [3]. There is currently no accepted consensus on the use of ECG in guiding the clinical risk-stratification of COVID-19 patients, and whether ECG findings should be considered in isolation or as the power of a wider risk scoring system also remains unclear.

9. Cardiac Imaging

The use of cardiac imaging has offered important insights into the diagnosis of cardiac injury in COVID-19 patients [104]. Several cardiac imaging-based biomarkers have also been tested on a retrospective basis for predicting adverse outcomes in COVID-19 [3]. One of the important challenges of performing cardiac imaging during the early periods of the pandemic rested on the risks of viral exposure to the operator and the imaging team [3]. As the pandemic progressed and as we emerged from it, the performance of imaging modalities previously considered logistically challenging, such as cardiovascular magnetic resonance (CMR), have offered significant novel insights into the cardiac effects of SARS-CoV-2 infection [105–107].

9.1. Echocardiography

Transthoracic echocardiography (TTE) was performed sparingly during the very early parts of the pandemic to limit infection risk to the operator, and imaging protocols were often abbreviated to reduce the duration of possible viral exposure [3]. Emphasis was also placed on appropriate triaging of TTE referrals, the use of appropriate personal protective equipment, equipment decontamination, and other infection control measures to minimise the likelihood of infection spread [108]. Despite these challenges, the clinical data gained from TTE proved invaluable in the assessment of patients with suspected cardiac involvement and altered clinical management in up to a third of the cases [109,110].

Left ventricular (LV) systolic function assessment by TTE enabled the diagnosis of heart failure in patients with COVID-19 [111], with prognostic implications [112]. Structural changes, as well as LV systolic dysfunction, can assist in the diagnosis of acute myocarditis, myocardial infarction, and stress-related cardiomyopathy [3]. In acute SARS-CoV-2 sufferers, up to 80% can have a subclinical reduction in TTE-based global longitudinal strain (GLS) [113]. COVID-19 patients with reduced LV GLS may be at a greater risk of developing fatal and non-fatal complications [114–116]. The reduction in GLS may be due to a range of aetiologies, such as myocardial infarction, inflammation, or severe systemic illness [114–116]. TTE also enables the detection of right ventricular (RV) dysfunction in COVID-19 patients who develop pulmonary complications, such as PE and artificial ventilation [117]. Severe RV failure, as detected by TTE, confers a high risk of adverse outcomes in COVID-19 patients [118]. Intra-cardiac thrombi have also been reported in COVID-19 patients, which calls for a high degree of suspicion in those with known cardiac disease and/or new-onset thromboembolism [119].

9.2. Cardiovascular Magnetic Resonance (CMR)

CMR enables the multi-parametric evaluation of cardiac structure, function, and tissue characterisation [120]. CMR was rarely performed in acute COVID-19 patients, likely due to concerns over infection control. Most CMR studies have focused on COVID-19 survivors and made heterogeneous findings, including evidence of myocardial infarction [106,107,121,122]. The use of CMR has enabled the identification of not only cardiac ventricular dysfunction but also myocardial scarring likely related to COVID-19 [106,107,122]. Further, myocardial ischaemia, microvascular disease, and pericardial involvement have all been reported in COVID-19 survivors [106,107,123].

The proportion of COVID-19 patients with myocardial inflammation suggestive of recent myocarditis is low, and the presence of myocardial fibrosis appears to be the independent predictor of adverse cardiovascular outcomes [124]. The estimated low prevalence of myocarditis in COVID-19 patients based on CMR appears in congruence with histological studies [74]. The presence of features such as elevated native myocardial T1 and T2 signals and non-ischaemic patterns of late gadolinium enhancement do not necessarily mean the presence or passing of acute myocarditis associated with COVID-19 per se [106,107]. The finding of elevated myocardial oedema signals on CMR could also be associated with changes that occur during septic conditions and/or critical illness [125,126]. Therefore, these findings should always be interpreted in the wider clinical context.

From a pathophysiological viewpoint, it remains unclear whether the CMR abnormalities observed in existing studies are due to direct viral invasion of the cardiomyocytes, bystanding injury due to systemic inflammatory sepsis or thromboembolic events, or a combination of these processes. Further work is required to elucidate the interplay between molecular mechanisms of myocardial injury and cardiac imaging findings.

10. Heart Failure and COVID-19

Patients with COVID-19 can develop new-onset heart failure through several mechanisms [127]. These include direct cardiomyocyte injury, myocardial ischaemia, and/or infarction, deleterious effects of the systemic inflammatory state leading to myocardial injury, sepsis-driven mismatch in circulatory supply and demand, systemic volume overload, and stress from critical illness [127]. Additionally, heart failure can develop in COVID-19 patients through endothelial dysfunction, microthrombi formation, and stress-induced cardiomyopathy [128]. New-onset heart failure has been observed in COVID-19 patients with severe systemic inflammation, suggesting that myocardial contractile depression can be induced in the context of cytokine storms and sepsis [129].

In patients without a previous history of heart failure, left ventricular systolic and diastolic dysfunction have been linked to acute myocardial injury in the context of COVID-19 [130,131]. Patients with severe heart failure and those who develop cardiogenic shock are more likely to have other underlying cardiac conditions, including ischaemic heart disease [132]. Further, COVID-19 patients who develop acute myocardial infarction have a greater propensity to descend into cardiogenic shock [133], which may be related to prolonged ischaemic injury due to delayed clinical presentation and persistent systemic inflammation [134].

Heart failure patients have high levels of ACE II expression, rendering them at a greater risk of developing COVID-19 [130,135,136]. Risk factors for developing acute heart failure during COVID-19 infections include a pre-existing history of heart failure [137]. Patients who develop arrhythmias during COVID-19 are also at risk of developing acute heart failure [137]. COVID-19 patients who developed acute heart failure and/or had withdrawal of their heart failure medical therapy have an increased risk of mortality [137].

In COVID-19 patients, pulmonary infection, hypoxaemia, and acute respiratory distress syndrome can lead to elevated right heart pressures and right heart failure [117,118]. Right ventricular strain can also result from mechanical ventilation required during acute infection [117] or thromboembolic events of the pulmonary vasculature, potentially leading to cor pulmonale and an adverse prognosis [118,138,139].

B-Type Natriuretic Peptides (BNP)

In patients with heart failure, BNP and N-terminal pro-BNP (NT-proBNP) have important diagnostic and prognostic roles in established clinical guidelines [140]. Elevated natriuretic peptides indicate the presence of myocardial injury and ventricular strain in patients with COVID-19 [141–144], even in patients without a previous history of heart failure [142]. Similar to findings in cardiac troponin, patients with severe manifestations of COVID-19 or those patients who develop adverse clinical outcomes have consistently shown a trend towards the development of elevated natriuretic levels [141–146].

Similar to the use of cardiac troponin in COVID-19, establishing an accepted single-point prognostic threshold using natriuretic peptides remains difficult [3]. A number of limitations remain in regard to both the patient population studies (which tend to be heterogeneous in geography and therapy received) and the nature of the clinical studies (which tend to be mostly retrospective and single-centred) [3]. The resulting natriuretic peptide levels considered "optimal" for predicting adverse outcomes vary according to the study performed, and the unification on a multi-centre basis into a single accepted threshold for widespread clinical use has yet to take place.

A summary of the pathophysiological processes (Figure 5) leading to myocardial injury and heart failure, as well as the conventional diagnostic tools, are summarised in the Central Illustration.

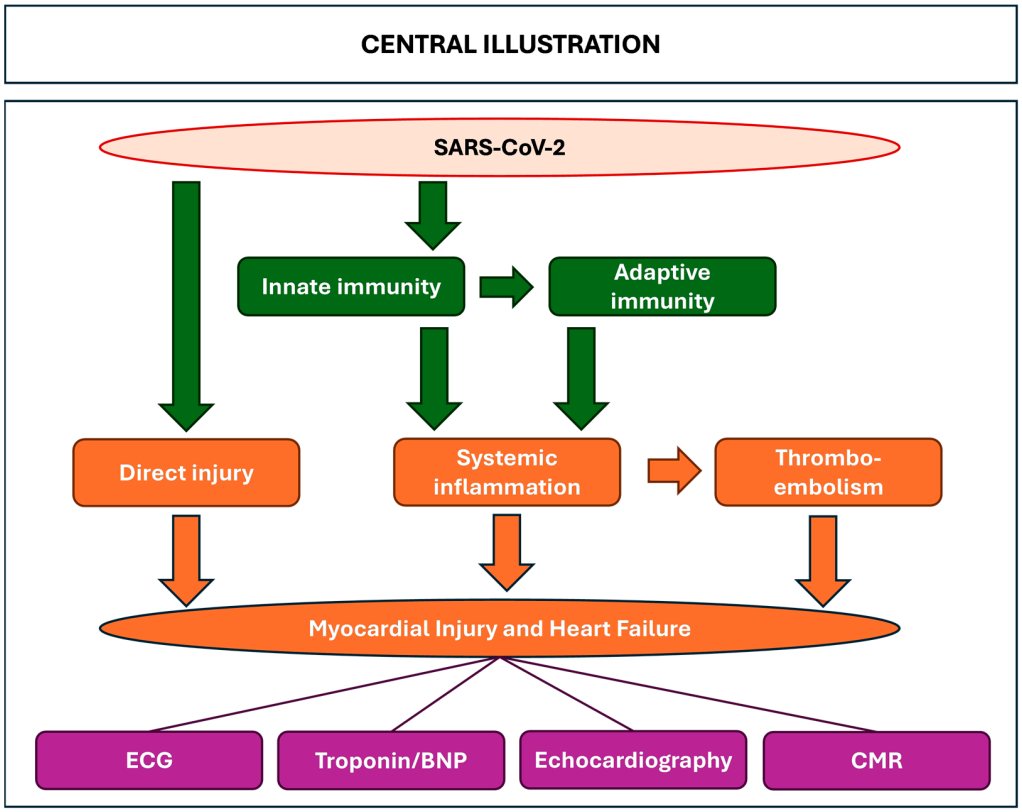

Figure 5. Central Illustration: BNP: B-type natriuretic peptide; CMR: cardiovascular magnetic resonance; ECG: electrocardiogram; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

11. Avenues for Future Research

As we emerge from the pandemic, many lessons have been learned about the pathophysiology of SARS-CoV-2. Forward steps have been taken to improve our defence against COVID-19 in the form of novel therapies and vaccination programs [3]. However, several uncertainties remain regarding the pathophysiology of COVID-19 and its associated cardiac sequelae, such as the recovery of cardiac function in new-onset heart failure and the mechanistic basis for the persistence of symptoms in long COVID-19 [3]. We must continue to search for the answers to these questions since SARS-CoV-2 will continue to mutate, and new viral strains will emerge.

The mechanistic link between acute and long COVID-19 remains unclear, which hinders the effective management of this debilitating condition. This is the subject of ongoing research. The effect of many contemporary COVID-19 therapies on suppressing myocardial injury or preventing the onset of heart failure also requires further exploration. This will enrich our understanding of the choice of therapies to use in acute infection while considering the need to minimise long-term cardiovascular complications.

12. Conclusions

COVID-19 leads to a range of proinflammatory processes linked to myocardial injury and heart failure. Mechanisms linking COVID-19 to myocardial injury include direct viral-mediated cardiomyocyte invasion, the deleterious effects of proinflammatory environment and thromboembolic events. Further work is required to improve our understanding of the mechanism of cardiac heart failure in COVID-19, which may enable us to better target both the SARS-CoV-2 infection and protect patients against longer-lasting cardiovascular complications.

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