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Journal of Molecular and Cellular Cardiology 147 (2020) 12–17

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Pathogenesis of SARS-CoV-2 induced cardiac injury from the perspective of the virus

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ARTICLE INFO

Keywords:
Myocarditis
COVID-19
SARS-CoV-2
SARS
Antivirals
Angiotensin-converting enzyme-2
ACE2

1. Introduction

The association between infection and cardiovascular disease has long been recognized in the form of Chagas Disease, Diptheria, tuberculous pericarditis, viral myocarditis, and others. Almost any infectious pathogen can cause myocarditis or heart disease [1]. Viral infection has been and is a predominant cause of myocarditis in the developed world, but viruses can also cause disease without the typical cellular inflammatory disease. During the influenza pandemic of 1918, a large number of patients had evidence of heart damage on autopsy [2]. Myocarditis was found in over 50% of patients who died of poliomyelitis infection during the years 1942–1951 [3,4]. Myocarditis has also been associated with outbreaks of mumps [5], measles [6], and enterovirus pleurodynia [7] before 1960. Association of Coxsackievirus with myocarditis has been recognized since at least the 1950s [8,9]. It has been demonstrated that viral infection can affect the heart by direct infection of cardiovascular organs and cells and is usually accompanied by a potent immune response. It is often challenging to determine the contribution of direct infection as compared to the immune response in viral-mediated cardiovascular disease since they frequently overlap.

A world pandemic has now turned attention to a novel viral infection, SARS-CoV-2, that primarily causes severe acute respiratory disease. However, the disease can be complicated by multiple cardiovascular abnormalities that are markers of a poor prognosis and most likely contribute directly to the severity of the disease. A better understanding of interactions between the virus and the host will ultimately guide the diagnosis and treatment of both pulmonary and cardiovascular complications seen in patients and ultimately contribute to the design of vaccines and other preventive strategies.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). It was identified in Wuhan, China, as the cause of an outbreak of acute respiratory distress syndrome (ARDS). At the time of writing, worldwide, there have been over 19 million confirmed cases and over 720,000 deaths caused by the virus [10]. The predominant manifestation of COVID-19 is ARDS. However, infection with SARS-CoV-2 is associated with multiple cardiac manifestations. These include: cardiac injury of uncertain etiology [11], and a thrombotic disease that may manifest as deep-vein thrombosis, pulmonary embolism, stroke, and peripheral arterial disease [12]. There is also growing evidence of an endothelial dysfunction that affects small vessels [13,14]. Recently, a form of Kawasaki disease, termed Multisystem Inflammatory Syndrome in Children (MIS-C), has been described in younger patients infected with SARS-CoV-2 [15]. MIS-C appears to have a direct effect on the vasculature and can be associated with cardiac dysfunction. While the associations between SARS-CoV-2 and the cardiovascular manifestations are clear, there is limited data that addresses how infection with SARS-CoV-2 affects the cardiovascular system.

By understanding the molecular pathways involved in virus replication, one can begin to understand how the virus may directly affect

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https://doi.org/10.1016/j.yjmcc.2020.08.002
Received 5 June 2020; Received in revised form 17 July 2020; Accepted 4 August 2020
Available online 06 August 2020

the host [1,16–18]. Activation of a potent immune response, both innate and adaptive, can actively inhibit viral infection, but can also damage the infected cell and adjacent cells [19]. It has been demonstrated in animal models of viral myocarditis that inhibition of innate immune mechanisms may be detrimental to the host by reducing the host antiviral immune response to virus infection and allowing unrestrained replication of the virus [20,21]. However, inhibition of the immune response has the potential to decrease immune mediated cytopathic effects. Maintaining the proper balance is crucial when using immunomodulators to treat viral infections.

A study of the viral life-cycle provides insight into viral tropism by understanding viral receptors and entry mechanisms. Direct cardiotoxic effects may involve the expression of virally encoded proteins such as viral proteases. Viral RNA-dependent, RNA-polymerases are crucial in the replication of the viral genome and, thus, the extent of viral-induced damage. Inhibition of mechanisms required for efficient viral replication is the primary clinical strategy for treating viruses such as HIV, Hepatitis B and C, influenza, and others [22,23].

2. SARS-CoV-2 viral life cycle

SARS-CoV-2 belongs to the genus *Betacoronavirus* [24]. The human beta-coronaviruses include the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV that will be referred to as SARS-CoV-1 throughout this document), and other coronaviruses that cause mild respiratory illnesses like the common cold. Coronaviruses are enveloped viruses in which the envelope glycoproteins reside in a lipid bilayer. These proteins include the spike (*S*)-protein, the membrane (M)-protein, the envelope (E) protein, and the nucleoprotein (N) as well as a few other accessory proteins. Enclosed in the viral envelope is a 30 kb positive-strand RNA [25] (Fig. 1).

The viral life cycle can be broken down into three significant steps: 1) virus binding and entry into the cell, 2) translation of the viral genome with associated viral polyprotein processing and replication of the positive-strand RNA via a negative-strand intermediate, and 3) assembly of the viral genome, and viral envelope with subsequent release from the host cell (For an overview, see Fig. 2).

Virus binding and entry into the cell: SARS-CoV-2 begins the infection process by binding of the viral envelop S-protein to angiotensin-converting enzyme-2 (ACE2) on the host cell membrane. Considerable investigation with SARS-CoV-1 and SARS-CoV-2 has demonstrated that cleavage of the S protein is required for efficient infection of the host cell. The binding and entry process is facilitated by cleavage of the full-length S-protein into S1 and S2 polyproteins. The S1 domain interacts with the receptor. The S2 domain is involved in the fusion of the viral envelope with the cell membrane [26]. In SARS-CoV-2, furin, a nearly ubiquitously expressed host proprotein convertase, participates in this cleavage [27]. Furin is typically involved in the processing of a cell's normal surface glycoproteins. Interestingly, the SARS-CoV-1 does not have a furin cleavage site. In both viruses, S1 and S2 polyproteins are cleaved by interaction with a host transmembrane protease serine 2 (TMPRSS2) and/or cathepsin L [28]. Both proteases can cleave the S-protein. A TMPRSS2 inhibitor has been demonstrated to block the entry of the virus into the cell [25]. It appears that coronaviruses have evolved to preserve redundant mechanisms by which the S protein can be processed into the S1 and S2 domains. This processing facilitates binding of S1 to the receptor (ACE2 for SARS-CoV-1 and SARS-CoV-2), and S2 mediates fusion of the virion envelope to the cell membrane. Receptor binding and S protein cleavage affects tropism and pathogenicity of coronaviruses [29].

Inhibition of this binding and entry process can inhibit viral replication. For example, monoclonal antibodies directed against the S-protein are expected to inhibit the virus from binding to ACE2. A protease inhibitor directed against TMPRSS2, Camostat Mesylate, is being tested in clinical trials [30].

Translation, processing, and replication of the viral genome: After binding, the virus enters into the cell through an endocytic process. The viral positive-strand RNA is released from the viral envelope into the cytoplasm and translated into polyproteins and structural proteins using host cell translational mechanisms. Importantly, the viral RNA encodes proteases that are involved in proteolytic cleavage of the viral polyproteins. One of the best characterized of these proteases in SARS-CoV-1 and SARS-CoV-2 is the main protease M^{pro}, also called $3CL^{pro}$. The x-ray structures of the SARS-CoV-2 M^{pro} without ligand and associated with an inhibitor was recently reported. Using the M^{pro} structure without ligand, the investigators developed a lead compound for a potent inhibitor of the SARS-CoV-2 M^{pro} [31].

Replication of the positive-strand viral genome requires the virally expressed RNA-dependent RNA polymerase that generates a negative-strand RNA using the positive-strand viral RNA as its template. The negative-strand serves as the template for replication of the positive-

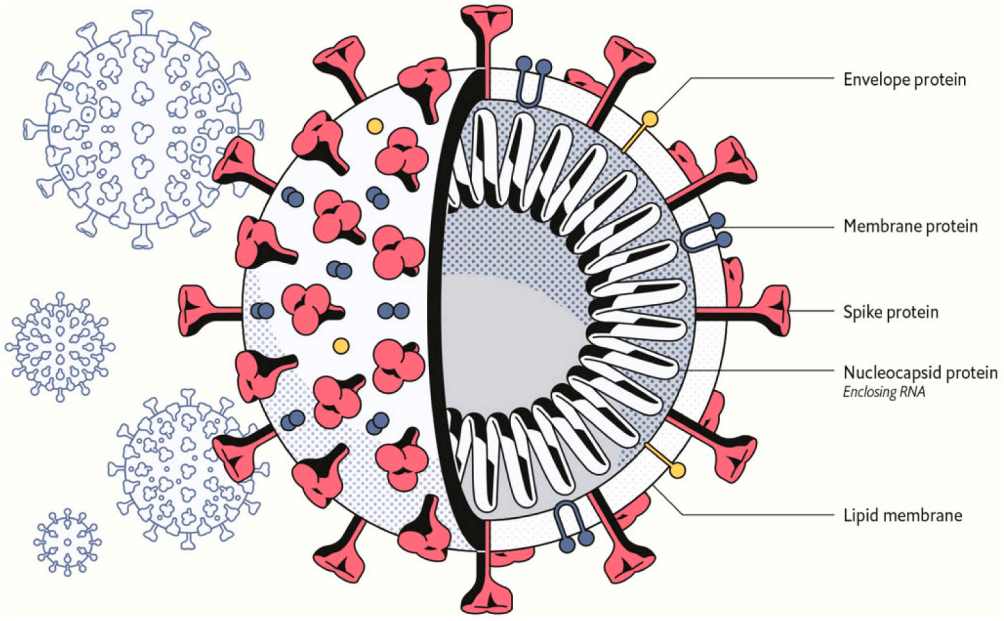

Fig. 1. Schematic of the coronavirus structure (Adapted from [64]).

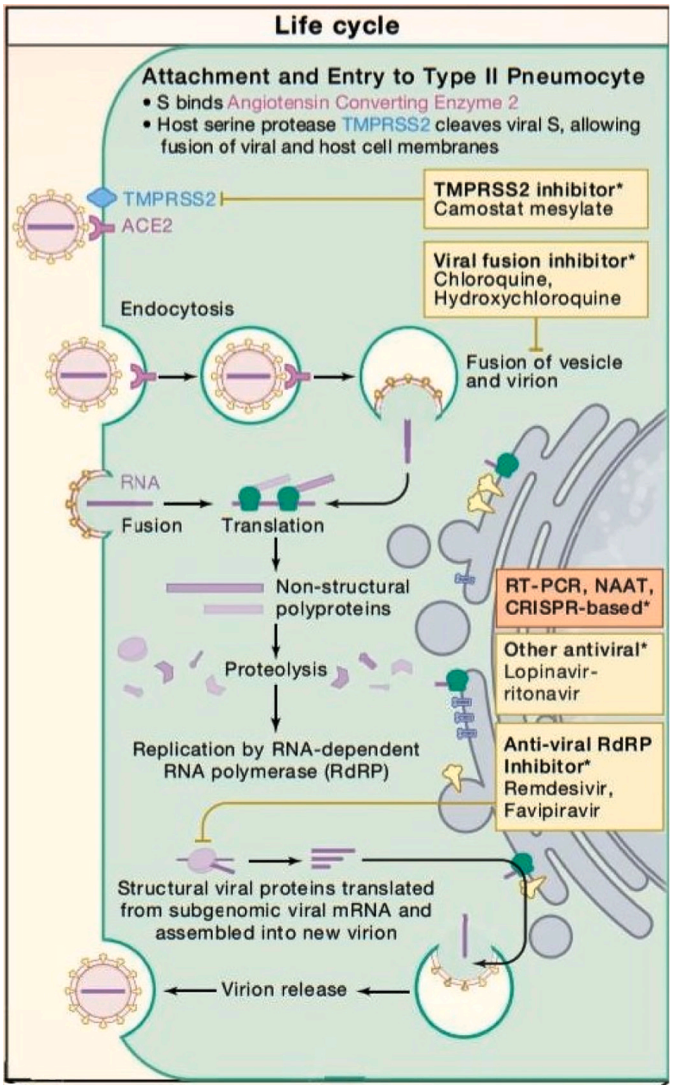

Fig. 2. Life cycle of the coronavirus and therapeutic targets-See text for details. (Adapted from [25]).

strand RNA genome that is assembled in the virion. M^{pro} proteolytic activity is required to process the viral RNA-dependent RNA polymerase into its mature, active protein. Remdesivir has been approved for COVID-19 therapy [32]. Remdesivir's primary mechanism of action is through inhibition of viral RNA-dependent RNA polymerase. An inhibitor of M^{pro} would prevent the maturation of multiple structural and non-structural proteins, including the RNA-dependent RNA polymerase, thus affecting the function of more than one essential viral protein. Inhibitors of RNA polymerases and proteases are the backbone of many antiviral strategies [22].

Assembly of the viral genome, envelope, and release from the host cell: Once the viral structural and non-structural proteins are expressed, and the viral genome has replicated, the structural proteins and viral genome migrate to the Golgi apparatus where assembly of the viral components and viral envelope begins. The immature virion migrates to the endoplasmic reticulum and fuses with the cell membrane for release from the cell. Hydroxychloroquine and chloroquine have been considered for the treatment of COVID-19. Though their use continues to be controversial [33–37], most studies have not shown significant improvement in disease progression. However, the presumed beneficial effects of hydroxychloroquine and chloroquine are thought to be via direct effects on organelle function. This includes the presumed inhibition of maturation and release of the virus in the endosomes and lysosomes of the cell by increasing the cellular pH and inhibiting endosomal maturation in the cell. Endosomes are also required for endocytosis of the virus; thus, there may also be an inhibitory effect on virus internalization [38].

3. Determinants of SARS-CoV-2 tissue tropism

While the precise determinants of SARS-CoV-2 tissue tropism are not fully understood, there are insights that can be gained by consideration of molecules involved in the entry of the virus into the host cell. Tissue tropism of the virus likely contributes significantly to the pathogenesis of SARS-CoV-2, including the cardiovascular manifestations of COVID-19. As has been previously mentioned, ACE2 is the predominant receptor for SARS-CoV-2. ACE2 is a transmembrane protein expressed in the lung and blood vessels. The expression of ACE2 is detected at high levels in alveolar, type II epithelial cells in the lung. There is also evidence that it is expressed in the heart, kidney, and intestines [39–41]. These are tissues that have been reported to be affected by SARS-CoV2 infection. Recent, single-cell RNA-seq analysis of ACE2 expression in healthy human tissues demonstrated that ACE2 mRNA was detected in lung epithelial cells, cardiac myocytes, kidney proximal tubular cells, esophageal epithelial cells, bowel, and bladder urothelial cells [42]. Another single-cell RNA-seq analysis of the heart found high levels of ACE2 in pericytes and low levels in cardiac myocytes. They also found that ACE2 was upregulated in failing hearts [43]. ACE2 has also been shown to be expressed in endothelial cells of many organs [14,39,40]. The infection of endothelial cells by SARS-CoV-2 could be important in vascular events that have been demonstrated in COVID-19 patients [14]. Also, in order to infect organs such as the heart or kidney, the virus may need to infect endothelial cells to reach other cells since the virion is moderately large at 80–100 nM in size. It has been recently shown that SARS-CoV-2 can directly infect engineered human blood vessel organoids derived from human induced pluripotent stem cells (iPSCs) [40]. Infection of the blood vessel organelle was inhibited using a previously developed, clinical grade, human soluble recombinant ACE2 (hrsACE2) [40].

Since ACE2 has been shown to be expressed in human cardiac myocytes, it is possible that SARS-CoV-2 could infect cardiac myocytes and induce a myocarditis phenotype or a cardiomyopathy without the traditional cellular inflammation of myocarditis. It is also possible that SARS-CoV-2 could infect endothelial cells, induce a cytopathic effect in the endothelial cells that could then contribute to vascular thrombosis formation, an entity that is being more commonly recognized in COVID-19 patients [12]. Finally, SARS-CoV-2 could infect pericytes cells in the heart, activating a virus-specific immune response.

While the expression of ACE2 is likely a significant determinant of tissue tropism for viral infection, there are other molecules that have a role in the entry of the virus within the cell, as is described above, including TMPRSS2. These have been implicated in determining viral tissue tropism for coronaviruses [28].

4. Cardiac injury

It was recognized early during the outbreak of COVID-19 that greater than 20% of patients with COVID-19 had elevations in cardiac troponin and other manifestations of cardiac injury, including impaired left ventricular ejection fraction and an elevation in type-B-natriuretic peptide [11]. The clinical aspects of these manifestations have been extensively reviewed elsewhere [44,45], but importantly, the manifestation of cardiovascular disease is a marker of a poor prognosis in COVID-19 [12,46]. A description of potential mechanisms by which these processes can occur following SARS-CoV-2 infection will be described with an emphasis on the role that the virus may have in the pathogenesis. Unfortunately, there is limited histologic information available about the pathologic changes that occur in the heart with SARS-CoV-2 infection. However, there are anecdotal reports that

provide early insight and new observations are reported on a regular basis.

At least four mechanisms have been proposed for the cardiac injury that has been described: 1) myocarditis, 2) cytokine storm, 3) coronary artery ischemia in the setting of underlying coronary artery disease, and 4) increased vascular thrombosis of small and large coronary arteries that could occur in the absence of coronary artery disease. It is also important to note that cardiac injury could also occur as a result of global ischemia related to multi-organ failure, respiratory distress, and associated hemodynamic and metabolic abnormalities. The major emphasis of this paper will focus on the current reports related to myocarditis or direct viral infection of the heart with variable evidence of cellular inflammation. Other reviews highlight the role of other mechanisms that will be briefly addressed herein [14,19,45,47].

5. Viral Infection of the Heart and Myocarditis

Viral infection, in general, has been previously identified as a cause of myocarditis that is generally defined by evidence of inflammation in the heart. It has also been recognized that there are forms of infectious viral heart disease that may not be associated with the typical inflammatory infiltrate [1]. Both forms of viral heart disease are often referred to, broadly, as myocarditis. Extensive work has defined significant interactions between viruses and the host myocardial cell. Also, there is a plethora of evidence that describes the activation of the immune system that is associated with viral infection that causes myocarditis. Given the large number of viruses that can cause myocarditis [1] and evidence that other coronaviruses can cause myocarditis, it is rational to hypothesize that a novel coronavirus that causes cardiac injury may be doing so by causing myocarditis, in some cases. The cardiac injury could occur because of direct viral-mediated cytopathic effects in the cardiac myocyte or by activation of an immune process that results in inflammatory cell infiltration in the heart.

The clinical diagnosis of viral myocarditis is most commonly defined by histologic evidence of inflammatory cells in the myocardium [1,48], abnormal cardiac magnetic resonance (cMR) imaging that meets the Lake Louise criteria and associated updates [49], or at the molecular level where there is direct evidence of viral infection and replication. However, given the difficulty obtaining cardiac tissue and advanced cardiac imaging during the COVID-19 pandemic, some papers utilize a clinical definition that might include decreased ventricular function, elevation in troponin in the absence of coronary artery disease, and elevation in BNP [50]. However, diagnosis from clinical criteria only is not as specific for myocarditis.

The most direct way to ascertain the presence of myocarditis is via histologic examination of the heart. Unfortunately, there are limited and at times conflicting reports of the myocardial histology in COVID-19 patients that had evidence of myocardial injury. An alternative manner to diagnose myocarditis is through cardiac magnetic resonance imaging (cMR) [49]. Cases of myocarditis have been reported using cMR in patients with SARS-CoV-2 infection.

For example, an autopsy report of three patients with COVID-19 published in the Chinese literature showed histologic evidence of limited interstitial fibrosis, and mononuclear inflammatory infiltrates in the heart, with positive staining for macrophages (CD68) and T-cells (CD4), but no significant CD8+ cells or B-cells (CD20). It was reported that SARS-CoV-2 was not isolated from the heart of these patients. They do not indicate whether there was an increase in markers of cardiac injury in these three cases [51].

In another report, a 37-year-old man with COVID-19 had evidence of severe myocardial injury, troponin T over 10,000 ng/L, markedly elevated BNP, ejection fraction of 27%, and an abnormal ECG consistent with STEMI. There was no evidence of obstructive coronary artery disease on CT scan. The patient was, therefore, treated for myocarditis and heart failure. The ejection fraction improved to 66% with normal systolic function by echocardiogram. The diagnosis of fulminant myocarditis was based on clinical presentation without cardiac MR or biopsy [52].

In another report of myocarditis with SARS-CoV-2 infection, a healthy 53-year-old woman in Italy had a prior history of a fever and dry cough the week before she presented with fatigue. Her chest x-ray was normal, but the electrocardiogram demonstrated diffuse ST-segment elevation, elevated troponin T and NT-proBNP. A coronary angiogram showed no obstructive coronary artery disease. Cardiac MR was consistent with myopericarditis, and the ejection fraction was 35%. The patient tested positive for SARS-CoV-2 and improved with treatment. No cardiac biopsy was performed [53].

A report from Germany relates details of a 79-year-old man who was hospitalized with fever, dyspnea, and recurrent syncope. He did not have a history of coronary artery disease. Troponin T was increased to 18.8 ng/L, but NT-proBNP was normal. Electrocardiogram, echocardiogram, and chest X-ray were reported as normal. CT scan of the chest was abnormal with pulmonary ground glass with pleural and pericardial effusions. He tested positive for SARS-CoV-2. His condition worsened, and cardiac magnetic resonance showed evidence of myocarditis with normal LV size, but decreased global ventricular function with an ejection fraction of 49% with decreased RV function. Thorough assessment for inflammation was clearly positive according to the Lake Louise criteria for myocarditis. There was no evidence of septic shock to account for myocardial injury, but cytokine storm could not be excluded [54].

Another case report presented autopsy findings from a 76-year-old woman that died from COVID-19 and demonstrated the presence of CD68+ macrophages in the myocardium and elevated serum troponin that were consistent with myocarditis [55].

A group from Germany reported that 4 out of 10 patients that died of COVID-19 had lymphocytic myocarditis, and 2 had signs of epicarditis on autopsy [56]. Another group from Germany performed autopsies on 39 individuals that died with SARS-CoV-2 infection. 24 (62%) had evidence of SARS-CoV-2 in the heart, but without myocarditis using the strict, Dallas criteria for myocarditis that included "massive cell infiltrates or necrosis." However, there was evidence of cytokine-mediated inflammation in the myocardium of those with highest levels of virus. Replication of the virus genome was identified in the myocardium of 5 patients [65]. A third group from Germany performed cMR post recovery on 100 patients that had presented as asymptomatic to moderate-severity disease from COVID-19. 78 had abnormal cMR findings and three patients that were referred for endomyocardial biopsy because of the severity of the abnormalities demonstrated active lymphocytic infiltration [66].

An autopsy series from New Orleans described heart and lung findings on nine African-American COVID-19 patients. 5 of 9 patients had elevated troponin T. Eight had increased cardiac mass on autopsy. However, there was no evidence of epicardial coronary artery disease or diffuse myocardial necrosis. There was a predominance of right heart enlargement. There were rare areas of lymphocytes adjacent to necrotic myocytes, but typical lymphocytic myocarditis was not observed [57]. All but one of the patients had pre-existing conditions, including hypertension, diabetes mellitus, renal failure, and heart failure.

A preliminary report of post-mortem analysis of the heart in 25 patients demonstrated “gross cardiac enlargement” in 24 of 25 cases. Many showing evidence of left ventricular hypertrophy and moderate to marked atherosclerotic narrowing of the coronary arteries. 15 of the 25 (60%) were reported to have evidence of a patchy epicardial mononuclear infiltrate with a predominance of CD4+ T-lymphocytes compared to CD8+ T-lymphocytes. Small vessel thrombi were observed in three cases, and one had hemophagocytosis within an area of epicardial inflammation [13].

Less is known about the incidence of myocarditis in children that are infected with SARS-CoV-2. However, 99 patients less than 21 years of age were identified in the New York State Department of Health database that met criteria for SARS-CoV-2 induced MIS-C. Of these 99

patients, 52 (53%) met their clinical criteria for myocarditis. 74 of 82 (90%) patients with MIS-C had elevated pro-BNP, and 63 of 89 (71%) had elevated troponin, indicating the presence of cardiac dysfunction and myocardial injury in a high percentage of the children and adolescents diagnosed with MIS-C. This was supported by the finding that 51 of 93 (52%) that underwent echocardiogram had some degree of ventricular dysfunction, 32 (32%) had a pericardial effusion [50], and 9 (9%) had coronary artery aneurysm [50].

Given the limited histopathologic data on SARS-CoV-2, and since both SARS-CoV-1 and SARS-CoV-2 enter the cell via similar mechanisms using ACE2 as their receptor, it is worthwhile to consider the evidence for myocarditis with SARS-CoV-1. In Toronto, 21 of 41 patients that died from SARS underwent autopsies. Of those that had SARS-CoV-1 in their lung, 35% had positive SARS-CoV-1 genome in their heart by rtPCR. Infection in the heart was associated with more rapid death. The presence of SARS-CoV-1 in the heart was associated with increased fibrosis and inflammation. Staining for macrophages (CD68) demonstrated considerable macrophage infiltration in those with SARS-CoV-1 and less, but present, in those who did not have detectable virus in the heart. There was only a minor increase in T-cells (CD3). Since in situ hybridization, or immune histochemistry were not performed, it is not clear which cell-types were infected [58]. MERS has also been demonstrated to cause a myocarditis documented by cardiac MR without histology [59].

While the cases and series described above provide limited evidence that infection with SARS-CoV-2 or SARS-CoV-1 can activate cardiac inflammarion that can cause myocarditis associated with cardiac injury, the incidence of myocarditis among COVID-19 patients is not known. Demographic data provide some insight into mechanisms for the myocardial injury on a larger scale. A potential explanation for myocardial injury is that patients hospitalized with COVID-19 had recognized or unrecognized coronary heart disease before infection with SARS-CoV-2 and that those patients manifested with increased cardiac injury when they became severely ill. However, in one series, the total percentage of patients with known coronary heart disease was only 10.6%, and only 29.3% of those with elevated troponins had a history of known coronary heart disease. Therefore, other potential mechanisms are likely to have a role in cardiac injury [11]. For example, the elevation in cardiac injury could be a result of myocarditis resulting from either direct infection of the cardiac myocytes or infection of non-non-myocytes such as fibroblasts, endothelial cells, or pericytes. Alternatively, myocarditis may occur from virus-specific inflammation or a generalized increase in inflammation that directly or indirectly affected the heart as a result of systemic infection with the virus.

6. Cytokine storm

The host immune response to SARS-CoV-2 infection results in an abundant inflammatory reaction that is associated with elevations in several cytokines that has been referred to as a cytokine storm. This cytokine storm correlates with lung injury, muli-organ failure and predicts an unfavorable prognosis [60]. There is evidence that cardiac injury may be a result of a severe cytokine storm with accompanying hemodynamic abnormalities that have been well-described with COVID-19 [61]. This cytokine storm may affect the heart, similar to the activation of the immune system that has been shown to occur with sepsis and cardiac dysfunction [62]. Modulation of the immune system with dexamethasone is likely to have a beneficial effect in hospitalized patients with COVID-19 [63].

7. Coronary artery ischemia in the setting of underlying coronary artery disease

As noted above, approximately 30% of patients with evidence of cardiac injury have been reported to have a history of coronary heart disease [11]. Cardiac injury could occur as a result of an oxygen supply-demand mismatch that results from increased oxygen consumption in the setting of severe illness combined with underlying obstructive coronary heart disease. Alternatively, the increase in inflammation associated with SARS-CoV-2 infection could contribute to plaque rupture and myocardial infarction. This may be especially true given the increase in thrombogenesis that has been associated with COVID-19 [12].

8. Large or small vessel coronary arterial thrombosis in the absence of underlying obstructive coronary atherosclerosis

One of the mechanisms shown to cause cardiovascular disease in COVID-19 is an increased thrombogenicity that has been demonstrated in venous and arterial circulations [12–14]. Abnormal endothelial cell function from activation of the immune system and probable endothelial cell infection, combined with increased thrombogenicity, are likely explanations for some patients with cardiac injury [12].

In conclusion, it is likely that SARS-CoV-2 can cause myocarditis and increased inflammation in the heart, but additional histologic and molecular analysis combined with cardiac MR investigation is needed to assess the characteristics and frequency of its presentation. It is also highly likely that the generalized, potent immune activation that occurs with SARS-CoV-2 infection has a significant role in the cardiac injury that may persist after recovery from the acute disease. In both situations, a thorough understanding of the viral life cycle, determinants of tissue tropism, and prioritizing therapeutic and preventive strategies that alter those processes will facilitate discoveries of pharmaceuticals and vaccines that will slow or stop the spread of COVID-19. The one sure thing is that infection with the virus is the initiating cause of this complex process that has affected so many lives. In the end, it all begins with infection by the virus.

Declaration of Competing Interest

Kirk U. Knowlton, M.D. –None.

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