



An Investigation into the Association of COVID-19 and Viral Myocarditis: A Literature Review

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ABSTRACT

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Myocarditis, or inflammation of the muscle layer in the heart wall, is caused by several factors including viral infection. Although the literature briefly alludes to a method of viral entry into cardiomyocytes, this work provides further detail into subsequent novel mechanisms leading to the development of myocarditis following infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The keywords "COVID-19", "SARS-CoV-2", "Myocarditis", "viruses", and "human" were used to run searches on OVID Medline, as well as Google Scholar. Resulting papers were subject to further analysis. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor which is found on type 2 pneumocytes and cardiomyocytes. Infection of cardiomyocytes can overregulate the immune response resulting in a cytokine storm: an uncontrolled increase of proinflammatory cytokines, as is commonly seen in respiratory infections. Cytokines can enter established biological pathways, creating positive feedback, which causes increased inflammation leading to myocarditis. SARS-CoV-2 viral envelope (E) proteins present an alternate association with myocarditis. Less severe myocarditis manifests common symptoms, and detecting it before it worsens may be difficult. Understanding the pathogenesis of myocarditis in COVID-19 could help find and implement preventative measures during future treatment.

In December 2019, the first case of viral infection by SARS-CoV-2 was detected in China; starting the coronavirus disease of 2019 (COVID-19) pandemic [1]. Over 500 million cases and over 6 million deaths due to coronavirus have been reported globally since December 2019 [2]. SARS-CoV-2 is a positive-sense stranded RNA virus, spherical in shape, with a diameter of 60-140 nm, and enveloped in a membrane protein [3, 4]. Since SARS-CoV-2 is composed of positive-sense stranded RNA, the genetic material entering the host cell is single-stranded and is able to interact with host cell translation machinery to produce viral proteins [5]. Among the CoV viruses, SARS-CoV-2 is also the 7th one found, which is able to infect humans [3]. Others include the Mers and SARS-CoV viruses [3]. Out of the 29 proteins which are encoded in SARS-CoV-2, the following major genes produce proteins like the spike surface glycoprotein (*S* gene), the small E protein (*E* gene), the membrane protein (*M* gene), and the nucleocapsid protein (*N* gene), all of which play a major role in the functioning of the virus [6, 7, 8, 9]. The spike protein is integral for the virus's entry into the host cell, while the others mentioned serve to strengthen the structural integrity of the virus [6, 7, 8, 9]. The spike protein has an S1 domain which attaches to the ACE-2 receptor on the host cell, and an S2 domain, which primarily promotes the fusion of the virion and host cell membrane [10].

The E protein plays a multifunctional role and has been shown to transport calcium (Ca^{2+}) ions, triggering inflammasome activation, which, as described later, may be important in the association between COVID-19 and myocarditis [11, 12]. An inflammasome is a multiprotein intracellular complex that can detect pathogenic microorganisms and sterile stressors. It activates the highly pro-inflammatory cytokines interleukin-1b and interleukin-18, which establishes a link between inflammasome induction by the E protein and the cytokine-storm related symptoms seen in COVID-19 patients [11, 12].

Many spike proteins cover the surface of SARS-CoV-2 [13]. When SARS-CoV-2 is in proximity to cells in the respiratory tract like type II pneumocytes, the Receptor Binding Domain (RBD) situated within the S1 subunit of the spike protein is able to bind to the ACE2 receptor on the host cell [13, 14]. At this time, the S2 subunit of the spike protein is cleaved at two spots: at the boundary between the S1 and S2 subunits and at an area within the S2 subunit [13]. This activates the S2 subunit, allowing it to change conformation in order to bring the viral envelope and cell membrane into proximity for viral fusion and entry [15, 16, 17]. The virus may then expel viral material into the host cell [15, 18, 19]. This is one of the multiple mechanisms of entry that have been proposed. Another method includes uptake through endocytosis which may come about in many ways [15, 18, 19]. Production of viral proteins and viral release occurs at the Endoplasmic Reticulum Golgi Intermediate Compartment (ERGIC) membrane and the Golgi region as early as 3 hours after infection [20, 21]. This may contribute to SARS-CoV's fast infection rate [20, 21].

Myocarditis is the inflammation of the middle layer of the heart wall or the myocardium [22]. The heart wall, situated deep in the pericardium, comprises three layers [23]. The innermost layer is the visceral layer of the serous pericardium and is also called the epicardium [23]. The middle layer is called the myocardium and is mostly composed of mononucleated muscle cells called cardiomyocytes or cardiac myocytes, which are striated like myocytes [23]. Coronary arteries, veins, lymphatic vessels, and nerves lay between the epicardium and the myocardium [23]. The outermost layer, the endocardium, is composed mostly of endothelium and subendothelial connective tissue [23]. Myocarditis may be acute, subacute, or chronic,

depending on the disease process [22]. Acute myocarditis is defined by direct viral cytotoxicity and myocardial necrosis, subacute by heightened autoimmune-mediated injury, and chronic by cardiac dysfunction and fibrosis of the myocardium [22].

Recently, the association between COVID-19 and myocarditis has become more prevalent in vaccine administration, with subsequent doses of the COVID-19 vaccine leading to an elevated risk of myocarditis in some groups [24]. Therefore, this association is crucial to understanding COVID-19 treatment and comorbidity prevention. This association is also unclear within the current literature. This review aims to provide theories of plausible associations based on evidence found within the literature.

Method

Initially, an investigation into the relevant medical subject headings (MeSH) was conducted through OVID Medline. Scope notes and related terms were reviewed to create a comprehensive list of accurate search terms. The resulting list of keywords (COVID-19, SARS-CoV-2, myocarditis, viruses, human) along with appropriate Boolean Operators was used to run searches on OVID Medline, as well as Google Scholar.

Titles and abstracts were subjected to an exclusion criterion, including articles not relevant to the keywords, those not in English, and those not formally published. The body-text of the remaining papers was analyzed next for relevance. Information from this literature search was supplemented with literature on the cytokine storm as well as the hierarchy in viruses.

Results

Causes of COVID-19 Infection

The immune system comprises two parts: the innate and adaptive systems [25]. The innate immune system comprises the first line of defense and includes physical barriers, fever, inflammation, and Pattern Recognition Receptors (PRRs) [25]. PRRs are membrane proteins not specific to a certain pathogen and provide a rapid response to antigens [25]. They can recognize Pathogen-Associated Molecular Patterns (PAMPs), which can trigger a cytokine response [25]. This part of the system also includes mononuclear phagocytes and granulocytic cells which help link it to the adaptive immune system [25]. The adaptive immune system's actions are specific to a certain pathogen [25]. The system is composed of B-cells, antibodies, and T-cells [25]. B-cells and antibodies are used for antibody-mediated immunity, while T-cells relate to cell-mediated immunity [25]. The B-cells and antibodies function against extracellular pathogens and toxins [25]. T-cells can be classified as T-Helper cells or T-Cytotoxic cells (also referred to respectively as CD4 or CD8 cells) [25]. These cells function primarily against intracellular pathogens [25].

SARS-CoV-2 is transmitted by inhalation of aerosols or respiratory droplets containing the virus or by contact between the mucosal membrane and fomites [26, 27]. Initially, the virus populates nasal and pharyngeal epithelial cells, which have a high expression of ACE2, and proliferates if it has not already been eliminated by the innate immune system [26, 27]. The virus then moves into the lower respiratory and gastrointestinal tract [26, 27]. Type II pneumocytes in the lungs are heavily populated with ACE2, making them a prime target [26, 27]. SARS-CoV-2 infection is promoted when SARS-CoV-2 spike protein is proteolytically cleaved and binds to ACE2 [26, 27]. Viral replication in these cells may cause cell apoptosis

and vascular leakage, causing cytokines and chemokines to release [26, 27]. Pyroptosis may also occur in lymphocytes and macrophages, leading to the release of proinflammatory factors [26, 27].

Type II pneumocytes share the same basement membrane with capillary endothelial cells that express high levels of ACE2 [26, 27]. Therefore, the damage that is caused here is thought to be the primary site of the SARS-CoV-2 entrance [26, 27]. Once SARS-CoV-2 enters the circulatory system, it is spread to other susceptible organs [26, 27].

Acute myocardial injury induced by SARS-CoV-2 is thought to involve one or more of the following mechanisms: direct cell injury due to the virus, cytokine-mediated injury, microvascular injury or stress-related cardiomyopathy or myocardial infarction [26].

Signs and Symptoms of COVID-19 Infection

COVID-19 symptoms vary with every individual; however, common symptoms of COVID-19 include cough, tiredness, fever, as well as a loss of taste and smell [28]. Many individuals, specifically 80% - 90%, who have developed COVID-19 remain asymptomatic and are unaware of it unless they have explicitly tested positive through reverse transcription polymerase chain reaction (RT-PCR) [29]. Upon hospital admission, laboratory reports suggest that those with COVID-19 present with lymphocytopenia, thrombocytopenia, and leucopenia [30, 31, 32]. According to radiology reports, those with COVID-19 often present with ground-glass opacities in various segments of the lungs, namely the peripheral and lower lobes, among others [33]. The amount of lung segments engaged can highlight the severity of the disease [29].

Causes of Myocarditis

Myocarditis can occur through many avenues such as viral infection, rheumatic fever (ex. streptococcus), and radiation [22, 34]. Bacterial myocarditis is uncommon but can result from extreme cases such as sepsis or a bacterial syndrome where bacterial invasion occurs [35]. Viral myocarditis is a more common cause of myocarditis [36]. Through the use of animal models, it has been speculated that viruses can invade cardiomyocytes and macrophages to incite a cytotoxic effect and impact the heart wall or directly damage cardiomyocytes [36, 37]. Typically, entry of the virus into the blood (i.e., viremia), precedes cardiomyocyte infection and results in innate immune response activation [37]. If patients have not recovered by the time the innate immune system has been put into effect, the adaptive immune system acts to produce antibodies to combat viral proteins and effector T cells multiply [37]. Infection by a virus (e.g., Influenza, Adenovirus) can cause immune cells such as lymphocytes to enter the myocardium, causing inflammation as well as cardiomyocyte necrosis [37, 23]. Myocarditis is speculated to be an underlying etiology of myocardial injury in COVID-19 cases [38]. In fact, in one retrospective multicenter study conducted by Ruan et al., it was found that 40% of 68 fatalities by COVID-19 were attributed to an underlying case of myocarditis [39].

Signs and Symptoms of Myocarditis

Symptoms of myocarditis vary among patients, and detection is difficult unless abnormalities are present in medical screening tools such as an electrocardiograph [37]. Others may have a mild viral illness, while some experience sudden cardiac death before it is detected [37]. However, most myocarditis patients are asymptomatic, and if abnormalities are detected, they

can easily mimic signs of other diagnoses [40, 37]. Therefore, it is imperative to gain a deeper understanding of how SARS-CoV-2 may induce myocarditis.

Discussion

Association between COVID-19 and Myocarditis

As mentioned previously, type II pneumocytes, a primary target for SARS-CoV-2 in the lungs, share a basement membrane with capillary endothelial cells, which express high levels of ACE2 receptors [25, 26]. Therefore, SARS-CoV-2 has access to the circulation through type II pneumocytes without difficulty. SARS-CoV-2 may be able to reach the vasculature situated between the epicardium and myocardium due to its presence in circulation. Viral infection of cardiomyocytes in the myocardium can occur due to their proximity to the endothelial cells within the heart's vasculature and through the leveraging of ACE2 receptors which are present on both these cells [40, 41]. Upon infection, as is seen in COVID-19, activation of the innate immune response and, consecutively, the adaptive immune response may overregulate the immune system response. The severe overregulation of proinflammatory cytokines, which are a normal part of the immune system's response to infection, can also be called the cytokine storm [42, 43]. Cytokines are a diverse group of small proteins which are secreted by cells and occupy a role in intercellular signaling and communication. Through receptor binding, cytokines can elicit a variety of responses including control of cell proliferation, regulation of immune responses, and inflammatory responses [42, 43]. Cytokines that may be relevant to the inflammation of the myocardium in myocarditis include proinflammatory cytokines such as interleukins and Tumor Necrosis Factors (TNF) [42, 43]. Proinflammatory cytokines are largely responsible for the growth and differentiation of leukocytes for immune response, while TNFs are responsible for activating the cytotoxic T lymphocytes [42, 43]. In cases of severe COVID-19, interleukins such as IL-1, IL-6, IL-12, and TNFs such as TNF- α have been found to target lung tissue [44]. These cytokines have also been shown to be produced by macrophages when exposed to inflammatory stimuli [45]. Macrophages are mononuclear effector cells of the innate immune system, and they play an important role in eliminating damaged cells through apoptosis or programmed cell death [46]. During infection, it is characteristic for macrophage levels to be elevated as the innate immune response is initiated. The presence of such inflammatory mononuclear cells (i.e., macrophages), along with elevated CD4+ T lymphocytes, has also been observed near the myocardium in past autopsies of COVID-19 patients [47, 38]. This presents a potential association between COVID-19 infection and myocarditis. These proinflammatory cytokines may then transcribe more proinflammatory agents through established pathways such as the NF- κ B pathway, causing further inflammation to the myocardium. This may result in signs and symptoms that warrant a myocarditis diagnosis [41].

Future Directions

Another interesting mechanism to explore includes the role of the inflammasomes in myocardial inflammation through SARS-CoV-2 infection. Inflammasomes are said to be activated by the release of Ca²⁺ in CoV infection [48]. Replication of the viral E protein upon SARS-CoV-2 infection is involved with Ca²⁺ release from the Golgi apparatus, as previously stated [48]. The increase in Ca²⁺ is critical in activating the NLRP3 inflammasome, which is found within cardiomyocytes [49, 50]. The NLRP3 inflammasome is then capable of activating

proinflammatory cytokines including IL-1 β , which is part of the IL-1 family [51]. Recently, greater attention has also been paid to the role of inflammasomes in various heart diseases [48]. Investigating this mechanism further for reasonable causality can inform treatment approaches in mitigating the harmful effects of the viral E protein.

Limitations

Potential associations between COVID-19 infection and viral myocarditis have been presented in this paper. However, it is important to note that this paper serves only to highlight possible links, and further clinical studies are needed to validate certain hallmarks within the proposed pathways. This can be achieved through certain experiments which allow for the detection of the movement and position of viral proteins.

Conclusion

This review discusses possibilities for the induction of viral myocarditis after SARS-CoV-2 infection by examining receptor concentration and placement, established feedback loops, as well as viral protein mediated inflammasomes. Understanding the association between COVID-19 and myocarditis is incredibly important since it is very difficult to predict myocarditis, and this disease has the potential to become fatal quickly. An understanding of these associations can allow for the development of preventative measures in treatment, especially given the widespread use and importance of COVID-19 vaccines around the world.

Declarations

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No potential conflict of interest was reported by the authors.

Ethics Approval

Ethics approval and consent is waived for this paper.

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