COVID-19-associated myocarditis: Screening for early diagnosis

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Abstract
The SARS-CoV-2 virus (causing COVID-19), has infected about 770 million people, and caused the death of about 6.9 million people worldwide in the span of three years (John Hopkins Resource Center). Common symptoms of a patient infected with the virus include shortness of breath, fever, chills, fatigue, loss of taste or smell, and muscle aches. However, recent studies have also shown a prevalence of patients presenting with cardiac inflammation (endocarditis, myocarditis or pericarditis) as a potential comorbidity, both during the infectious stage as well as after the infection has subsided. A pattern of specific clinical markers may be indicative of potential heart inflammation, particularly myocarditis. Screening for these clinical markers, such as troponin and brain natriuretic peptide (BNP) in COVID-19 patients may allow for earlier identification, diagnosis, and treatment of a potentially life threatening comorbidity. This article briefly explains the underlying mechanisms of COVID-19-induced cardiac inflammation, and discusses prognostic indicators clinicians can take advantage of to effectively diagnose and treat patients.

Keywords
COVID-19, myocarditis, troponin, BNP

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Cover Page Footnote
We want to thank Dr. Mohammed Razzaque, PhD., MBBS, as a guide throughout our research process.
META-ANALYSIS/SYSTEMATIC REVIEW

COVID-19-associated Myocarditis: Screening for Early Diagnosis

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Abstract

The SARS-CoV-2 virus (causing COVID-19), has infected about 770 million people, and caused the death of about 6.9 million people worldwide in the span of three years (John Hopkins Resource Center). Common symptoms of a patient infected with the virus include shortness of breath, fever, chills, fatigue, loss of taste or smell, and muscle aches. However, recent studies have also shown a prevalence of patients presenting with cardiac inflammation (endocarditis, myocarditis or pericarditis) as a potential comorbidity, both during the infectious stage as well as after the infection has subsided. A pattern of specific clinical markers may be indicative of potential heart inflammation, particularly myocarditis. Screening for these clinical markers, such as troponin and brain natriuretic peptide (BNP) in COVID-19 patients may allow for earlier identification, diagnosis, and treatment of a potentially life threatening comorbidity. This article briefly explains the underlying mechanisms of COVID-19-induced cardiac inflammation, and discusses prognostic indicators clinicians can take advantage of to effectively diagnose and treat patients.

Keywords: COVID-19, Myocarditis, Troponin, BNP

1. Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is an enveloped, single stranded ribonucleic acid (RNA) virus, which can be transmitted through aerosols, direct/indirect contact, or in laboratory sample handling.\textsuperscript{1} The virus most commonly infects the lungs, via the angiotensin-converting enzyme 2 (ACE 2) which are on lung epithelium, venous endothelial cells, arterial smooth muscle, and many organs.\textsuperscript{2} As mentioned, common symptoms of COVID-19 include shortness of breath, fever, chills, myalgias and loss of taste.

Myocarditis is the inflammation of the muscle layer of the heart, which can progress to dilated cardiomyopathy in 30\% of cases.\textsuperscript{3} Myocarditis remains underdiagnosed because it may be asymptomatic, but what is concerning is that it is one of the most common causes of sudden cardiac death, especially in young adults.\textsuperscript{3} Its etiology can be infectious or non-infectious, and common symptoms include fever, mild chest pain and arrhythmias. There are four main categories of myocarditis: acute, fulminant, chronic active, or chronic persistent. Among these, acute myocarditis is the most prevalent, occurring 65\% of the time, usually as a result of a viral infection.\textsuperscript{4}

The COVID-19 inflammatory responses can lead to significant molecular and gross cardiac changes. COVID-19 may access cardiac myocytes via ACE-2 receptors to infect them directly.\textsuperscript{5} This cellular dysfunction and inflammatory response can lead to elevated serum troponin levels.\textsuperscript{6} Additionally, COVID-19 spike protein accesses the ACE-2 receptor on myocytes, which leads to imbalances in the Renin Angiotensin Aldosterone System (RAAS). These imbalances further enhance inflammation, leading to an increase in cardiomyocyte...
Recent studies have shown a higher prevalence of patients presenting with cardiac inflammation (endocarditis, myocarditis or pericarditis) as a comorbidity with a COVID-19 infection, both during the infectious stage as well as after the infection has subsided. Patients with COVID-19 have been reported to have a 16 times greater risk of developing myocarditis than patients without COVID-19. The main documented symptoms in COVID-19 related myocarditis were tachycardia and dyspnea.

There are two major mechanisms of cardiac inflammation due to COVID-19. The first being SARS-CoV-2 directly infecting myocytes and pericytes of the heart, since they have a large amount of ACE2 receptors. On a molecular level the virus can travel through the hematogenous route where it reaches the myocytes of the heart. Oudit et al. found that “35% (7/20) of human hearts from patients infected with SARS possessed viral RNA”. The spike protein of the COVID-19 virus can bind to the ACE-2 receptor on lung tissue and myocytes, which leads to imbalances in the RAAS system, increased generation of aldosterone, and further enhancing inflammation and degeneration of cardiac tissue due to high blood pressure and a proinflammatory state. These imbalances can lead to hypertension, left ventricular hypertrophy, and endothelial dysfunction. Extensive inflammation can lead to tissue damage which leads to a robust immune response consequently causing the second major mechanism of myocarditis, which is via systemic cytokine storm.

COVID-19 infection has also been found to be correlated with gross cardiac changes affecting cardiovascular function specifically inducing parenchymal lung disease and pulmonary vascular congestion. Szekely et al. found that all parameters of right ventricular function were reduced in patients with COVID-19. Pulmonary hypertension has also been found to be common in COVID-19 patients leading to elevated left heart filling pressure and cardiovascular damage in over one third of patients. COVID-19 infection is also associated with acute myocarditis, leading to fulminant cardiogenic shock in up to 32% of patients. Overall, COVID-19 infection can lead to drastic cardiovascular dysfunction, such as impaired ejection fraction and cardiac pressures, which may significantly affect survival and recovery of the patients with COVID-19. As a result of this fatal association, a further investigation of the molecular and clinical consequences of COVID-19 and myocarditis is warranted.

2. Methods

To analyze the effectiveness of using troponin as a biomarker for COVID-19 related myocarditis, a broad literature search and review was completed with an examination of over 45 articles regarding the screening of troponin among various patients. Articles pertaining to the pathogenesis and healthcare burden associated with COVID-19, and cardiovascular testing were also explored. Literature was found by utilizing PubMed and Google Scholar search engines to target articles with the keywords “troponin,” “COVID,” “inflammation,” “cytokine storm,” and “management strategies.” Additionally, filters were utilized to target journal articles published after 2020 and in the English Language. This targeted approach to an article search allowed for a concise overview of the current literature on the pathogenesis of COVID-19 in the heart, and troponin screening.

2.1. COVID-19 and myocarditis

COVID-19 can clinically induce myocarditis by two likely mechanisms. Firstly, cytokines, which are immune system signaling molecules, are released in response to the viral infection, can injure heart muscle, leading to myocarditis. Many patients with COVID-19 also develop an overactive immune response, called a “cytokine storm,” which can also cause myocarditis and other systemic complications.

Secondly, the virus may directly infect the heart cells via ACE2 receptors to initiate an immune response that causes inflammation and injury to the heart muscle. A buildup of Angiotensin II (1-8) also promotes oxidative stress, hypertrophy, vasoespasm and cardiac fibrosis (Fig. 1). While direct infection of myocytes is technically possible, there have been few proven reported cases confirmed via endomyocardial biopsy.

Many studies have shown that high troponin levels were seen in patients infected with COVID-19 which could be indicative and used as a biomarker for detecting myocarditis. Patients were also seen to have elevated ANP (Atrial natriuretic peptide), T-cells, macrophages, lymphocytes, and intercellular adhesion molecules (ICAMs). Necrosis of the cardiomyocytes and interstitial cells, along with granulation tissue were detected in analyzed tissue samples. It is hypothesized that SARS-CoV-2 infection may cause arterial obliteration and ischemia of the heart, secondary to cardiac inflammation.

This figure displays that once the ACE2 receptor is activated, the body responds with a pro-
inflammatory state, with increased oxidative stress. SARS-CoV-2 activates the ACE2 receptor and causes dysregulation of this system.\textsuperscript{16}

2.2. Molecular cardiac events

SARs-COV-2 can bind to the ACE-2 receptor of the heart, gaining entry into the myocardial cells. A hyperinflammatory state was present in these patients, with an abundance of generalized inflammatory markers including IFN-g, IL-1RA, IL-6, IL-10, IL-19, and monocyte chemoattractant protein (MCP)-1, MCP-2, MCP-3, CXCL9, CXCL10, CXCL5, ENRAGE, and poly (ADP-ribose)polymerase 1. The exact mechanism of how COVID-19 causes inflammation in the heart is not well understood, but can be interpreted based on normal immune response to a viral infection. It is hypothesized that COVID-19 can cause a cytokine storm mediated by IL-6 within the heart itself leading to massive inflammation and edema of the heart via direct cell injury and T-lymphocyte-mediated cytotoxicity.\textsuperscript{20} Furthermore, it is hypothesized that T-lymphocytes can be primed for viral antigens when exposed to COVID-19. These primed CD8+ T cells can then travel to cardiomyocytes and cause inflammation within the myocardium via cell-medical cytotoxicity.\textsuperscript{21} This proposed mechanism sends back a positive feedback loop for the immune response to exacerbate inflammation even further.

2.3. Gross cardiac changes

As mentioned previously, cardiac tissue biopsies of COVID-19 infected patients have been noted to have elevated T-cells, macrophages, lymphocytes, and ICAMs along with myocyte necrosis, interstitial necrosis, and granulation tissue.\textsuperscript{19} Consequently, roughly 60\% of biopsies were noted to have hypertrophy with tissue edema.\textsuperscript{22} SARS-CoV-2 infection
may cause arterial obliteration and ischemia of the heart secondary to cardiac inflammation. Gross cardiac changes involved left ventricular dysfunction which included decreased left ventricular ejection fraction on echocardiography. Acute right ventricular dilatation was also noted in one study with a higher level of BNP. Other common gross findings seen were related to an increase in the number of blood clots within the right atrial appendage as well as clots found in the cardiac veins. Other common comorbidities include diabetes, gross ventricular hypertrophy of the heart, hypertension, pericarditis, as well as atherosclerotic related coronary artery disease. All these factors aid in progressing mortality rates in patients.

2.4. Prognostic indicators

In addition to microscopic and gross cardiac changes, a highly sensitive key laboratory finding reflecting myocardial damage has been elevated troponin levels in patients infected with COVID-19. Elevated cardiac troponins have been found in 38% of patients infected with COVID-19. Cardiac troponins (cTnT and cTnI) are proteins that regulate the calcium-dependent interactions between actin and myosin, so when myocardial damage or inflammation ensues, troponins leak out into the serum. Additionally, elevated atrial natriuretic peptide (ANP) was found in 56% of patients infected with COVID-19. ANP works with NT-proB-type Natriuretic Peptide (BNP) which are hormones mainly released from the atrium and ventricles respectively in response to stretch and hypovolemia. This causes a decrease in renin release, and vasodilation to lower cardiac stress and promotion of regeneration on damaged cardiomyocytes.

The ECG findings most commonly seen in COVID-19-associated myocarditis are: Sinus tachycardia, Diffuse T wave inversions, and ST segment elevation without reciprocal depression. T wave inversions are especially indicative of myocarditis. ECG findings were mostly identical in all 51 COVID-19 related myocarditis cases reviewed by Haussner et al.

Patients with COVID-19 and myocarditis have also been found to have significantly worse clinical outcomes compared to matched controls without myocarditis. Specifically, patients with COVID and myocarditis have a higher 6-month all-cause mortality, rehospitalization rates, and acute myocardial infarction. COVID-19 patients have also been found to be at risk of delayed-onset myocarditis, even after the resolution of COVID-19 infection. Bajaj et al. found in their study that patients who tested negative on PCR test for COVID-19, but still had some respiratory symptoms, developed myocarditis soon after the infection had resolved highlighting possible multisystem effects COVID-19 can play a roll in.

3. Discussion

COVID-19 myocarditis is a sequelae of inflammation mainly due to cytokine activation or direct myocardial invasion via ACE-2 receptors. The Cytokine storm can be attributed to IL-6 leading to T cell mediated cytotoxicity causing cellular injury as well as T cell priming for viral antigens that facilitate myocyte inflammation. The pathogenesis suggests that immunotherapy may prove to be a viable treatment for COVID-19 cardiac inflammation. This is used in other causes of cytokine storm, such as patients that are undergoing chemotherapy. Tocilizumab is a monoclonal antibody that acts against human IL-6 and has been proven as a viable treatment for severe CRS. Corticosteroids are effective but are second line to tocilizumab for CRS due to slower onset of activation but are frequently used as an initial treatment for severe CRS. A 2022 review studied tocilizumab usage in COVID-19 patients and determined that significantly decreased the risk of mortality by 48% as well as “clinical failure” (intubation, ICU admission, death). ACE-2 also contributes to the immune response leading to inflammation and cardiac injury via oxidative stress. Consequently, therapies targeting the SARS-COV-2 Spike protein-ACE-2 receptor subunits have been explored as potential entry blocking agents. Further studies with larger and diverse populations are needed to evaluate the benefits of these therapies as an intervention for COVID-19 myocarditis.

In addition to molecular changes, COVID-19-induced inflammation also leads to gross changes in the cardiac tissue. Numerous studies have documented left ventricular dilatation with decreased left ventricular ejection fraction as cardiac changes from myocarditis. Right ventricular dilatation could also be a gross presentation. This can be exacerbated in patients with comorbidities including coronary artery disease, hypertrophy, diabetes, and hypertension. A recent review found that 58% of patients with COVID-19 myocarditis had one of these comorbidities, making them useful for predicting severe cases and guiding therapy. Patients that present with fulminant myocarditis and shock should be treated according to the shock protocol including positive inotropes, vasopressors, and mechanical ventilation if necessary and arrhythmias should be managed with pacing or antiarrhythmics.
by Hausner et al. are variable, and supportive treatments with fluids, beta blockers, and diuretics were the most common.\textsuperscript{10} Corticosteroids were also shown to be effective at reducing mortality in the small sample size of 7 patients.\textsuperscript{10}

Patients with COVID-19 and myocarditis have been found to have significantly worse clinical outcomes, 6-month all-cause mortality, rehospitalization and infarction rates.\textsuperscript{32} Therefore, determining a specific biomarker for assessing myocarditis in COVID-19 patients can assist in expediting treatment and improving clinical outcomes. Trends in troponin as a marker for cardiac injury have been shown to be a viable prognostic indicator in COVID-19 patients.\textsuperscript{25} Elevated troponins have been determined to be highly sensitive in identifying cardiac injury in patients with COVID-19.\textsuperscript{19,25,26} BNP may also be viable highly sensitive in identifying cardiac injury in patients with COVID-19.\textsuperscript{25} In the 2020 case report by Doyen et al., researchers advocate for timely measurement of troponin in cases of COVID-19 patients with evolving ECG changes and clinical evidence of acute coronary syndrome.\textsuperscript{31} In studies such as the review from Haussner et al., troponins and ECG changes were the inclusion criteria for COVID-19 patients with myocarditis.\textsuperscript{10} In the 2020 case report by Doyen et al., researchers advocate for timely measurement of troponin in cases of COVID-19 patients with evolving ECG changes and clinical evidence of acute coronary syndrome.\textsuperscript{31} Patients with COVID-19 pneumonia can also present with delayed onset myocarditis.\textsuperscript{33,34} Therefore, the measurement of troponin and ECG changes could be an effective diagnostic method for these patients with a recent positive history for COVID-19 and further research would be beneficial if directed toward this patient population.

The development of an effective cardiac screening panel which assesses troponin levels and other cardiac biomarkers, patient's clinical status, along with imaging studies in COVID-19 patients may be an effective means of reducing cardiac related COVID-19 complications. Special consideration should also be given to patients with underlying cardiovascular disease or associated risk factors. Earlier identification and diagnosis of myocarditis in patients with COVID-19 allows for prompt supportive care and treatment of a potentially life-threatening comorbidity. Based on elevated troponin levels (and other serum markers) being found in COVID-19 infected patients, early identification of at-risk patients should be considered, even in patients with subclinical presentation.

COVID-19 patients have also been found to be at risk of delayed-onset myocarditis, even after the resolution of respiratory symptoms.\textsuperscript{33,34} Cases of myocarditis have been reported in the weeks following recovery from COVID-19 pneumonia suggesting lingering systemic inflammation lingers after recovery. This should be kept in mind in patients reporting new-onset cardiovascular symptoms following recovery of COVID-19. Despite recent controversy, Singer et al. demonstrate that myocarditis related to COVID-19 infection is at a significantly higher rate than cases attributed to vaccine administration, especially in younger individuals.\textsuperscript{39} Vaccination is recommended as a preventative measure. Early identification and supportive care of COVID-19 myocarditis is recommended to prevent the progression of the disease.

4. Conclusion

Cardiac implications of COVID-19 infection are ever-evolving. A large cytokine activation during infection has been demonstrated to lead to structural, molecular and functional cardiac changes which could have everlasting implications on COVID-19 patients. In order to treat these patients more effectively, clinicians must maintain a high-index of suspicion for cardiac injury in COVID-19 patients. Specifically, the use of troponin levels, cardiac cytokine levels, and c-reactive protein may be useful in identifying COVID-19 patients with cardiac manifestations. This heightened diagnostic approach may lead to an earlier identification, diagnosis, and subsequent treatment of potential life-threatening cardiac manifestations of COVID-19.

Conflicts of interest

The authors declare there are no conflicts of interest.

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