

## Review Article

# Cardiovascular Manifestations of COVID-19

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### Abstract

Novel Coronavirus 2019 (COVID-19) has spread within a short period of time from Wuhan, a city within central China, to cause a global pandemic. Treatment options remain limited and mortality is high in older patients. Although primarily linked to respiratory symptoms, cardiac complications have been found to be common and can also be severe. Various cardiac manifestations may include myocarditis, ST elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), pericarditis or myopericarditis, pericardial effusion, stress (Takotsubo) cardiomyopathy and

cardiac arrhythmias. COVID-19 related cardiovascular diseases present a diagnostic challenge, given overlapping features.

Fear of infection has resulted in more frequently seen late presentations to hospitals causing greater morbidity and mortality. In addition, regional and hospital workflows have been disrupted due to the virus which has also led to significant delay in patients receiving urgent care. Furthermore, optimal patient care delivery has to be balanced against the risk of infection to health care providers and limited resource management. In addition, regional and

hospital workflows have been disrupted due to the virus which has also led to significant delay in patients receiving urgent care. Furthermore, optimal patient care delivery has to be balanced against the risk of infection to health care providers and limited resource management.

Off-label drugs used to treat the infection have largely been unsuccessful. Initial proposed guidelines addresses some concerns; however, further comprehensive literature is required to develop standardized management. Vaccine development at this time remains the only proposed definitive prevention strategy though a definitive timeline for such a modality currently remains uncertain. Given the continued pandemic, health care providers are adjusting their practices to adapt with new social distancing guidelines and reduce the spread of disease. As medical literature and data proliferates, we may be able to reduce the rate of cardiac complications and develop effective strategies to combat the disease whilst at the same time protecting health care providers.

**Keywords:** COVID-19, Heart; Cardiovascular; Symptoms; Diagnosis; Management; Complications

## 1. Introduction

First described within central China, novel coronavirus 2019 (COVID-19) has rapidly evolved from an initial localized collection of pneumonia cases to a global pandemic [1]. Patients most commonly present with fever, cough, fatigue and shortness of breath although a wide array of clinical signs and symptoms have been reported [2]. COVID-19 enters human cells via the angiotensin-converting enzyme (ACE)-2 receptor within the nasal cavity, it

subsequently replicates and spreads throughout the upper conducting airways triggering an immune response which results in mild respiratory symptoms in a majority of patients [3]. Despite this, COVID-19 can also be associated with severe hypoxic respiratory failure from worsening pulmonary infiltrates and alveolar damage leading to acute respiratory distress syndrome (ARDS) [4].

The accurate reporting of COVID-19 infection related mortality has been challenging given the high prevalence of asymptomatic carriers, however initial estimates place the case fatality rate between 0 to greater than 20% based upon predisposing factors including age and underlying medical comorbidities [5]. Unfortunately, treatment options remain limited; although compassionate use of Remdesivir has been associated with some clinical improvement, other tried therapies including lopinavir-ritonavir, hydroxychloroquine and azithromycin have failed to demonstrate any mortality benefit [6-9]. Vaccination development against COVID-19 remains the only proposed definitive prevention at this time, although the process of manufacture is lengthy and complicated with limited detail available on efficacy if successfully produced [10].

Although well known as a respiratory pathogen, COVID-19 has complex interactions with the cardiovascular system; preexisting heart disease leads to increased susceptibility from the virus and cardiac complications from direct infectious insults or due to delay in seeking care [11]. Cardiac injury appears to be common with a reported prevalence of ~20% within hospitalized COVID-19 patients and is independently associated with mortality [12]. We

therefore conducted a comprehensive review of cardiac complications with COVID-19 infection.

## 2. COVID-19 Myocarditis

Myocarditis represents an inflammatory pathology of the heart in the absence of ischemia that can present with a wide variety of clinical signs and symptoms, with chest pain, heart failure and malaise commonly reported [13]. Unfortunately, fulminant myocarditis may also occur on rare occasions which carries an associated mortality ranging between 40 and 70% [14]. Viral infection is a well-established cause of myocarditis as a result of complex multiphasic pathogenesis initially involving direct injury to cardiomyocytes, subsequent immune dysregulation and possible progression to long-term dilated cardiomyopathy [15].

COVID-19 has been reported to instigate cardiac inflammation with suspected myocarditis considered as the likely cause of acute COVID-19 cardiovascular syndrome which comprises of acute cardiac injury, cardiomyopathy, ventricular arrhythmia and hemodynamic instability [16]. COVID-19 patients may also have elevated high-sensitive troponin T and N-terminal (NT)-pro hormone BNP (NT-proBNP), suggesting the development of myocardial injury and ventricular dysfunction [17]. Compared to those with normal troponin T levels, patients with elevated troponin T have been shown to have increased mortality in all patients, more frequently require glucocorticoid therapy and mechanical ventilation, in addition to being at higher risk to developing in-hospital complications such as acute respiratory distress syndrome, malignant arrhythmias, and acute kidney injury [18]. Data on the incidence of COVID-19 related myocarditis is limited however; an initial

study reported that 7% of infected patients died of myocarditis related circulatory failure alone whereas 33% lost their lives to both respiratory failure and myocarditis related circulatory failure [19].

The underlying pathogenesis for this cardiac injury is not well understood, however several mechanisms have been proposed including direct myocyte infection, systemic inflammation through increased production of tumor necrosis factor alpha (TNF- $\alpha$ ) from ACE-2 receptor downregulation, enhanced activation of transforming growth factor beta (TGF- $\beta$ ) leading to interstitial fibrosis, interferon mediated immune response, hypoxia due to underlying lung dysfunction and cytokine reaction with Type 1 and 2 helper T cells [20].

Current management of COVID-19 related myocarditis is based upon individual case scenarios given that recent literature is limited to only small studies with reported treatment approaches; there remains a lack of high-quality randomized data which is required to determine optimal therapy [21]. However, data from both small and large non-COVID-19 studies has been used to form a set of proposed new guidelines for the management of COVID-19 myocarditis; this includes the utilization of mechanical ventilatory and circulatory support, avoidance of immunosuppression in addition to the possible use of anti-interleukin 6 (IL-6) receptor monoclonal antibody to reduce inflammation such as tocilizumab [22].

## 3. Pericarditis/Cardiac Tamponade

Up to 90% of pericarditis cases can be attributed to viral causes, most often due to enteroviruses, herpesviruses, and parvovirus B19 [23]. With the

ongoing COVID-19 pandemic, cases of pericarditis associated to the coronavirus in addition to its life-threatening sequela of cardiac tamponade have been reported with inflammation of the pericardium likely occurring as a result of direct cytotoxic effects or immune-mediated mechanisms [24]. In addition to blood, feces, and the respiratory tract, isolation and detection of SARS-CoV-2 by reverse transcriptase polymerase chain reaction (PCR) has also been reported within pericardial fluid of a patient undergoing pericardiocentesis for cardiac tamponade, further contributing to the evidence of COVID-19 related myopericarditis [25]. Cardiac tamponade has been witnessed in patients with no prior cardiovascular risk factors, they were found to have significantly elevated troponin T levels after presenting with signs and symptoms of dyspnea, chest pain and hypotension; management with pericardiocentesis resulted in improved hemodynamic parameters, however also exposed a barrier to treatment as isolation may preclude transfer to a cardiac laboratory for fluoroscopic-guided paracentesis and may necessitate paracentesis under echocardiographic guidance [26].

#### 4. STEMI

The COVID-19 pandemic has caused a fear of acquired infection within the general population which in turn has resulted in a reduction of ST-segment elevation myocardial infarction (STEMI) related hospitalizations and consequent increase in morbidity and mortality [27]. In addition, overburdened emergency medical services (EMS), fear of improper medical management, use of personalized protective equipment (PPE), lack of trained EMS paramedics, non-availability of negative pressure cardiac catheterization laboratories and

uncertain diagnosis due to the high incidence of COVID-19 related myocarditis may delay STEMI care [28]. Presumed COVID-19 related myocarditis can mask underlying STEMI, whereas the opposite may also occur given similarly elevated cardiac biomarkers and electrocardiographic changes between the two diseases resulting in a diagnostic challenge; the use of non-invasive imaging modalities such as echocardiography and cardiac magnetic resonance imaging may help to aid in differentiation [29, 30].

The Society for Cardiovascular Angiography and Interventions (SCAI), American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP) recommend the continued use of percutaneous coronary intervention (PCI) as the mainstay of treatment for STEMI in the COVID-19 pandemic. If PCI is not available, thrombolytic therapy can be considered [31]. In addition, the following interventions are recommended during the COVID-pandemic: EMS should use personal protective equipment (PPE) in all patients regardless of symptoms and should rapidly perform an electrocardiogram (ECG) if heart disease is suspected; once in the emergency department, patients should be triaged to COVID-19 possible or negative pressure areas where testing may be considered although not at the expense of a delay to revascularization, low threshold intubation may be performed in patients at risk for respiratory decompensation. PPE should be used by all individuals in contact with the patient regardless of COVID-19 status. Lastly, post-procedure care should consist of an extended decontamination time of the cardiac catheterization laboratories, plans for early discharge, use of negative pressure rooms if available

and rationing of critical-care beds to those requiring intensive care [31, 32].

Broader goals include the initiation of a campaign on public awareness to remind the general population of seeking help immediately if they have symptoms indicative of a heart attack [32]. Additionally, regional STEMI systems of care should be considered including the establishment of macro-hubs to converge time-sensitive emergencies and dedicated personal; these changes may also simultaneously decompress smaller spoke hospitals [33, 34]. Finally, the implementation of telemedicine and virtual cardiac rehabilitation may be considered to help aid and follow-up patient recovery [32].

## 5. NSTEMI and Unstable Angina

A reduction in the number of observed non-ST segment elevation myocardial infarction (NSTEMI) cases presenting to hospital has been witnessed during the COVID-19 pandemic, as patients tend to stay at home given fear of infection and may only present to hospitals once symptoms worsen or remain persistent, with this unfortunately leading to a delay in treatment and subsequently results in adverse outcomes [35].

Management recommendations for NSTEMI remain largely similar but have also been adapted to reduce the risk of virus exposure to patients and health care professionals; all hospital personal should wear PPE based upon established institution guidelines, COVID-19 testing for suspected patients is recommended if available locally, medical management should be commenced at local non-PCI capable hospitals with avoidance of routine transfer to a designated PCI center unless patients have high risk electrocardiographic features or hemodynamic

instability. Lastly, high-risk transferred patients or those who present at designated PCI centers should be treated based upon standard revascularization protocols with either conservative or invasive therapies [36].

Of note, patients with NSTEMI and COVID-19 infection have a higher reported incidence of myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) suggesting that some cases of reported NSTEMI may in fact be secondary to viral mediated myocardial inflammation [37]. A careful review of risks and benefits for acute coronary intervention in NSTEMI is required before proceeding to reduce risk of transmission of COVID-19 to patients and health care workers, in those who require intervention isolated culprit vessel PCI is recommended [38].

## 6. Takotsubo Cardiomyopathy

The COVID-19 pandemic has resulted in significant stress within the general population with more than half of the general population describing a moderate to severe psychologic impact due to the disease; this may result in emotional triggers and subsequent takotsubo cardiomyopathy [39]. Post-menopausal women are considered to be most susceptible to takotsubo cardiomyopathy due to possible lack of estrogen replacement and may be at the highest risk for takotsubo cardiomyopathy during the course of COVID-19 infection [40, 41]. Most reported cases of takotsubo cardiomyopathy from COVID-19 infection are of post-menopausal women; several mechanisms of pathogenesis have been proposed including an adrenergic response to stress, though little is known about any specific pathologic changes which may occur with COVID-19 resulting in

takotsubo cardiomyopathy [42, 43]. Treatment of takotsubo cardiomyopathy predominantly consists of symptom management until left ventricular function has recovered [41].

## 7. Arrhythmias

Patients suffering from COVID-19 are at risk to suffer from arrhythmias as a result of hypoxia, fever, severe electrolyte abnormalities in addition to the adverse effects of medications used within management [44, 45]. Hydroxychloroquine, azithromycin and lopinavir-ritonavir are used for off-label treatment of COVID-19 but are all associated with significant risk of arrhythmia and QTc prolongation [46]. More recent studies have failed to demonstrate any significant clinical benefit with these medications which may result in a decline of their usage [7-9]. Currently remdesivir remains the only pharmacologic therapy which has shown promising results with severe COVID-19 infection, nonetheless information of the effect of the drug on QTc prolongation and arrhythmias remains limited, and further data is required to mitigate the risk of arrhythmia in patients with COVID-19 [6].

## 8. Conclusion

In summary, COVID-19 can present with a wide array of cardiovascular signs and symptoms which may be difficult to dissect from one another resulting in increased morbidity and mortality. Physicians should be aware of the cardiac manifestations of COVID-19 including myocarditis, pericarditis and cardiac tamponade, STEMI and NSTEMI, takotsubo cardiomyopathy and arrhythmias. Further guidelines and literature are required to allow for optimal cardiovascular management of COVID-19 patients.

## Conflict-of-Interest Statement

The authors have no conflict of interest to declare.

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