



# Pericardial Diseases in COVID19: a Contemporary Review

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## Abstract

**Purpose of Review** Coronavirus disease 2019 (COVID19) involves the heart, including pericardium. This article reviews the possible pathophysiological mechanisms in pericardial involvement in COVID19 and pericardial manifestations of COVID19. It also summarizes the patients with pericarditis secondary to COVID19 and outlines the contemporary treatment strategies in this patient population.

**Recent Findings** A high degree of suspicion is required to identify the pericardial involvement in COVID19 patients. It is proposed that an underlying hyperinflammatory reaction in COVID19 leads to pericardial inflammation. Acute pericarditis with or without myocardial involvement is diagnosed on clinical presentation, serum inflammatory markers, electrocardiogram, and echocardiogram. Multimodality imaging may also have an additional diagnostic value. Patients are usually managed medically, but some patients develop a life-threatening pericardial tamponade necessitating pericardial drainage.

**Summary** Pericardial involvement is an important clinical manifestation of COVID19 requiring a proper workup. Timely diagnosis and a specific management plan based on the presentation and concomitant organ involvement usually lead to a complete recovery.

**Keywords** Pericardial disease · Pericardial effusion · Pericarditis · Myocarditis · Pericardial tamponade · COVID19

## Introduction

Coronavirus disease 2019 (COVID19) has infected more than 80 million people worldwide and caused more than 1.5 million deaths in 2020 [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes COVID19. COVID19 primarily affects the lungs, and the

severity of the disease ranges from mild respiratory symptoms to acute respiratory distress syndrome [2]. There is growing literature on the involvement of other organs, mainly the heart, kidneys, gastrointestinal tract, brain, and skin [3, 4]. Cardiac manifestations of COVID19 include acute heart failure, myocarditis, acute coronary syndrome, Takotsubo cardiomyopathy, arrhythmias, pericardial involvement, and cardiac arrest [5–7]. Pericardial diseases typically caused by viruses include pericarditis, pericardial effusion, and life-threatening pericardial tamponade (PT). A few cases of pericardial involvement in patients infected with other members of the coronavirus family have also been reported [8, 9, 10]. As the body of literature is expanding for COVID19, it is essential to understand some uncommon manifestations of the SARS-CoV-2 virus that require a high degree of suspicion. This review aims to identify COVID19-associated pericardial disease and briefly describe the underlying pathophysiological mechanisms. We have also summarized management strategies for COVID-19 associated pericardial diseases.

## Pathophysiologic Mechanisms

The pericardium is a double-layered protective membrane around the heart with an inner visceral (serosal) and outer parietal (fibrous) layer. The pericardial sac between these

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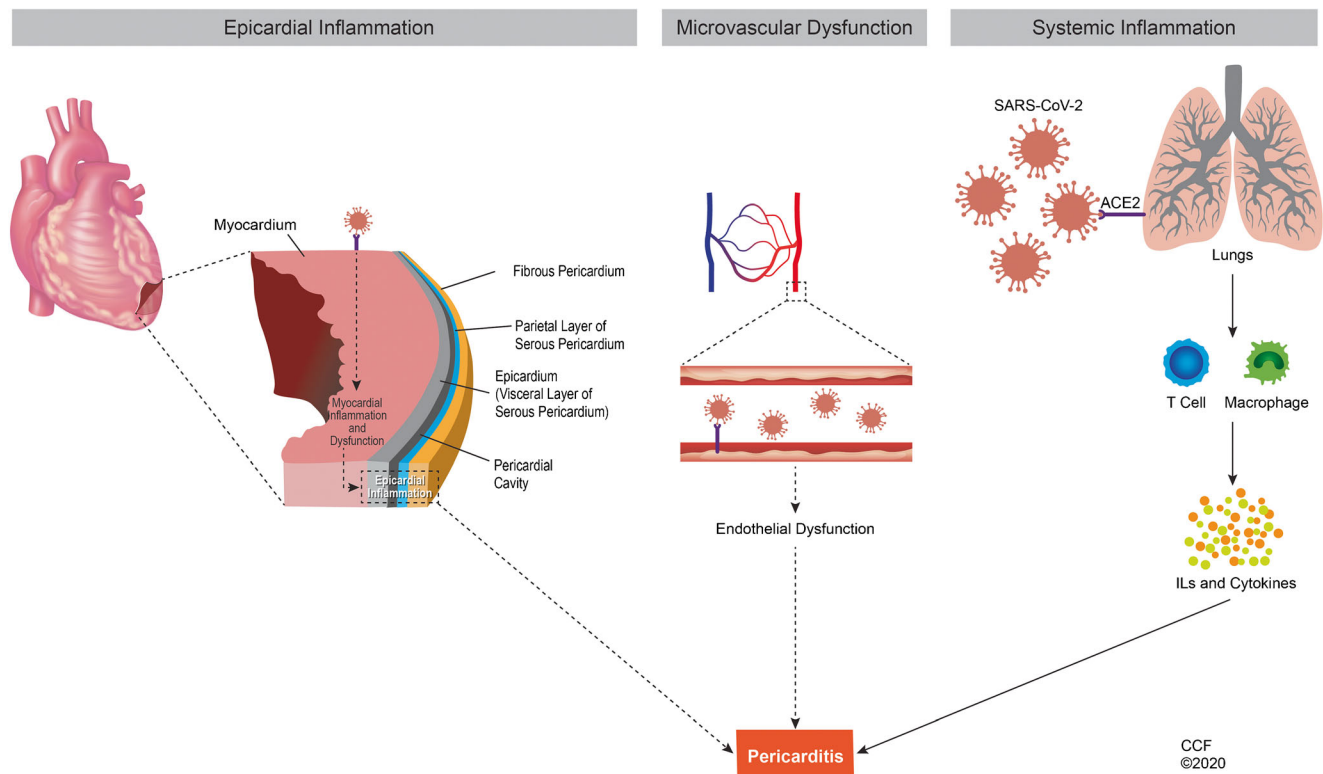
two layers usually contains around 50cc of serous fluid [11]. The pericardium is relatively avascular, and increased vascularity is the hallmark of inflammation [12]. COVID19 is primarily a disease of respiratory epithelium, and endothelial cells play a crucial role in the involvement of other organs, including the heart [13]. The exact pathophysiological mechanism of pericardial involvement in patients with COVID-19 has not been fully elucidated. At present, there is no evidence of direct infection of the pericardium and myocardium by SARS-Cov2. However, it is proposed that systemic inflammatory reaction induced by SARS-CoV-2 leads to cardiac involvement, including pericarditis. Endothelial damage as a result of heightened inflammation may also be responsible for pericardial manifestations. Although SARS-CoV-2 has also shown cardiotropic properties, the direct damage to the cardiac structures is rare (Fig. 1).

### COVID-19 mediated increased inflammation

The levels of various inflammatory markers and cytokines are elevated in COVID19 infection. The hyperinflammatory syndrome in COVID19 is characterized by increased interleukins (IL-1, IL-2, IL-6, IL-7), granulocyte-macrophage colony-stimulating factor, interferon- $\gamma$ , inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- $\alpha$ , and tumor necrosis factor (TNF)- $\alpha$  [14]. In a

multicenter retrospective study, elevated IL6 and ferritin levels in COVID19 patients were associated with mortality [15]. This suggests hyper-inflammation and mortality associated with the systemic effects of inflammation in a subset of COVID19 patients. A cytokine storm is defined as an activation of an auto-amplifying cascade of cytokines due to unregulated host immune response to various triggers. This so-called cytokine storm is triggered by damage-associated molecular patterns and pathogen-associated molecular patterns, including infections, malignancy, autoimmune diseases, and drugs [16]. These triggers cause an imbalance of type 1 and type 2 T helper cells resulting in a hyperinflammatory response that causes a multi-organ involvement, including the heart in COVID19 patients [17]. The main mechanisms by which this heightened inflammation causes end-organ damage are mainly endothelial dysfunction, systemic cytokine circulation, and T-cell mediated immunopathology [18].

A recent study also found the activation of NLRP3 inflammasome in moderate and severe COVID19 cases [19]. Neutrophils and C-reactive protein are also significantly higher in severe cases [2, 20]. Similarly, higher levels of pro-inflammatory cytokines such as IL-6, IL1-B, IL-2, IL8, IL17, G-CSF, GM-CSF, IP10, MCP1, MIP1a, and TNF are seen more frequently in symptomatic COVID19 patients with severe cases as compared to the moderately ill patients [20] [21]. Higher levels of inflammatory markers and cytokines are also



**Fig. 1** Mechanisms of pericardial inflammation caused by SARS-CoV2. SARS-CoV2, severe acute respiratory syndrome coronavirus 2; ACE 2, angiotensin-converting enzyme; ILs, interleukins. (Reprinted with

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associated with poor prognosis in COVID19 [22, 23]. Chemokines such as CXCL10 and CCL2 are found in the bronchoalveolar lavage fluid cells of patients with SARS-CoV-2 infection [24]. Immunohistochemical endomyocardial biopsy (EMB) analysis of COVID19 patients revealed a high number of T-cells, macrophages, lymphocytes, T-memory cells, and cell adhesion molecules (CD54/ICAM-1). It also showed vascular damage and obliteration, leading to myocardial necrosis [25]. Pericardial biopsy of a COVID19 positive patient showed reactive mesothelial cells, lymphocytes, and macrophages [26]. Postmortem histopathological analysis of the heart in patients who died of COVID19 also showed lymphocytic proliferation in the pericardium mainly composed of CD8+ lymphocytes within the visceral epicardium [27]. Cytokines such as IL1 and TNF- $\alpha$  are well established in the pathogenesis of pericarditis. The elevated levels of these interleukins in the activated inflammatory cascade setting predispose to pericardial inflammation [28]. The current evidence suggests that in addition to other organs, systemic inflammation may also involve the pericardium.

### Cardiac tropism of SARS-Cov2

Histopathological analysis in a patient who died from COVID19 multi-inflammatory syndrome showed the infiltration of inflammatory cells in the pericardium. The inflammation was composed primarily of macrophages with a few lymphocytes and neutrophils. Viruses were identified from capillary endothelial cells and endocardial cells. Viral particles were also found in macrophages, neutrophils, and fibroblasts [29]. Tavazzi and colleagues showed SARS-CoV-2 particles in the interstitial macrophages, but not in cardiomyocytes [30]. A post-mortem analysis detected SARS-CoV-2 RNA in the heart samples of 82% of patients who died of COVID19, but no myocardial injury was found [31]. SARS-CoV-2 genome was present in 5% of patients with suspected myocarditis or unexplained heart failure. Myocardium also had inflammatory cells, increased expression of cell adhesion molecules (CD34/ICAM-1), and myocardial necrosis [25]. The virus was also identified from the pericardial fluid of a patient with COVID19 [32]. Angiotensin-converting enzyme-2 (ACE2) receptors are considered the main portals of entry by which SARS-CoV-2 enters the organs. ACE2 is also present in the heart, endothelium, cardiomyocytes, and epicardial adipose tissue adjacent to the visceral pericardium [33–35]. The presence of the virus in the cardiac endothelial cells indicates that SARS-CoV2 can render direct damage to cardiac structures. The extent and exact pathways by which the virus potentially causes this direct damage to cardiac structures will need further exploration (Fig. 1).

## COVID-19 Associated Pericardial Involvement

### Pericarditis

The exact incidence of pericarditis in COVID19 patients is unknown, but the risk of pericardial involvement is higher in patients with clinical suspicion of COVID19 than in the general population [36]. Post-mortem studies have identified pericarditis in about 20% of the COVID19 cases [27, 37]. Cardiac magnetic resonance imaging (CMR) of recently recovered COVID19 patients showed pericardial LGE in 22% of patients [38]. In athletes recovering from COVID19 disease, 40% had pericardial late gadolinium enhancement (LGE), and 58% had pericardial effusions identified on CMR [39]. Chest pain was positive in 29% of the healthcare workers infected with SARS-CoV2 at baseline, and they were evaluated for the presence of pericarditis and myocarditis after 10 weeks of viral infection. Only 19% of the participants had persistent chest pain, and 14% of the total participants fulfilled the pericarditis criteria at week 10. Around 37% of these healthcare workers were also diagnosed with myocarditis based on the CMR criteria [40].

Pericarditis in COVID19 presents with chest pain and viral symptoms [41, 42]. Some pericarditis patients may not have chest pain even with an associated myocarditis [43]. Many acute pericarditis cases also had a large pericardial effusion necessitating pericardial drainage [26, 42, 44–47]. Recently, many case reports have identified acute pericarditis in COVID19 patients without myocardial involvement. A synopsis of studies reporting acute pericarditis secondary to COVID19 disease is described in Table 1.

### Pericardial Effusion and Tamponade

Pericardial effusion is found in 5% of patients with coronavirus disease on chest computed tomography (CT) [55]. Pericardial effusion develops as a result of various insults to the myocardium or pericardium and has variable clinical presentations. Pericardial tamponade was identified in COVID19 patients with deteriorating renal and respiratory function [56, 57]. Pericardial tamponade in the setting of acute pericarditis in COVID19 patients is managed with pericardiocentesis, and occasionally a pericardial window is also required (Table 1).

A patient also developed pericardial tamponade after myocardial infarction. Interestingly, SARS-CoV-2 ribonucleic acid (RNA) was found in the pericardial fluid, but patient's nasopharyngeal analysis was negative for the virus [32]. Pericardial analysis of another patient with COVID19-associated polyserositis also detected SARS-CoV-2 in the pericardial fluid [48]. However, other case reports evaluating pericardial effusions have not found any viral RNA in the pericardial fluid [45, 57, 58].

**Table 1** Studies reporting acute pericarditis in patients with SARS-CoV-2 infection

Study	Year/country	Age/ gender	Presentation	Cardiac enzymes	ECG	TTE	CMR	Other	Management	Outcome
Amoozgar et al. [26]	2020/USA	56/male	Chest pain and dyspnea	NL	Atrial fibrillation	Large circumferential pericardial effusion	N/A	Cardiomegaly on CXR	Pericardial window + ibuprofen	Resolution
Ortiz-Martínez et al. [42]	2020/Columbia	25/male	Chest pain and dyspnea	NL	Sinus rhythm	Pericardial effusion	N/A	Pericardial effusion on CT	Ibuprofen and colchicine + morphine/-oxycodone	Improvement
Asif et al. [44]	2020/USA	70/female	Chest pain, dyspnea, myalgia	NL	Diffuse ST elevation and PR depression	Circumferential pericardial effusion/+ tamponade physiology	N/A	Cardiomegaly on CXR	Pericardiocentesis and colchicine	Resolution
Fox et al. [45]	2020/USA	43/male	Chest pain, orthopnea, dyspnea	NL	Diffuse ST elevation and PR depression	Circumferential pericardial effusion/+ tamponade physiology	N/A	Cardiomegaly on CXR	Pericardiocentesis and ibuprofen + colchicine	Resolution
Walker et al. [46]	2020/USA	30/female	Chest pain, fever, cough, shortness of breath	NL	Sinus tachycardia	Moderate pericardial effusion	N/A	Pericardial effusion on CT	Pericardial window + colchicine initially and aspirin added at day 7	Improvement
Blagojevic et al. [47]	2020/Serbia	51/male	Chest pain	NL	ST elevation and PR depression	Pericardial effusion and hypercholesterolemic pericardium	N/A	N/A	Aspirin, beta blocker, lopinavir/ritonavir, ceftriaxone	Resolution
Sauer et al. [48]	2020/France	51/male	Chest pain, dyspnea	NL	Anterolateral ST-elevation and low QRS voltage	N/A	Circumferential pericardial LGE	Polyserositis on chest CT	Pericardiocentesis + colchicine	Resolution
Kumar et al. [49]	2020/Ireland	66/male	Chest pain	NL	ST elevations in most leads and PR depression	Pericardial brightening (thickened?)	Pericardial thickening on CMR	Normal	Colchicine	Resolution
Dabbagh et al. [50]	2020/USA	57/male	Cough, shortness of breath, left shoulder pain	NL	Non-specific ST changes	Circumferential pericardial effusion/+ tamponade physiology	N/A	Cardiomegaly on CXR	Pericardiocentesis and hydroxychloroquine + colchicine + glucocorticoids	Serial ECHO and troponins concerning for Takotsubo cardiomyopathy that resolved eventually
Tung-Chen et al. [51]	2020/Spain	35/female	Chest pain, cough,	NL	T wave inversions	Pericardial effusion	N/A	N/A	Colchicine	Resolution

**Table 1** (continued)

Study	Year/country	Age/ gender	Presentation	Cardiac enzymes	ECG	TTE	CMR	Other	Management	Outcome
Karademiz et al. [52]	2020/Turkey	33/male	malaise, fever, anosmia Chest pain	N/A	Non-specific	Circumferential pericardial effusion	N/A	Pericardial effusion on chest CT	Hydroxychloroquine and indomethacin + colchicine. Anakinra added at day 5	Resolution
Raymond et al. [53]	2020/ USA	7/female	Chest pain, cough, orthopnea	NL	Sinus tachycardia and low voltage QRS with electrical alternans	Large circumferen- tial pericardial effusion	Enlarged cardiac silhouette with pleural effusions	N/A	Pericardioentesis and NSAIDS + colchicine. Pericardiectomy was done eventually	Worsening symptoms leading to pericardiectomy and no follow-up available after surgery
Ashwin et al. [54]	2020/UK	63/female	Chest pain	NL	ST segment elevation and PR depression in inferolateral leads	Large pericardial effusion (four days later)	N/A	Pericardial thickening with no pericardial effusion on CT (baseline)	Pericardioentesis and NSAID + colchicine	Developed pericardial effusion and then complete resolution

ECG electrocardiogram, TTE transthoracic echocardiogram, CMR cardiac magnetic resonance imaging, CXR chest X-ray, NL normal, YO year old

## Myopericarditis

Acute cardiac injury is found in 7%-17% of COVID19 patients, and mortality is higher in the patients with cardiac injury [2, 59, 60]. Concomitant pericardial inflammation in patients with myocardial injury is also reported [29, 61]. COVID19-associated myopericarditis may present with or without respiratory tract symptoms [43, 62]. Chest pain is a common symptom, but some patients do not report chest pain and pose a diagnostic challenge [48, 63, 64]. Myopericarditis can also lead to cardiogenic shock and may require extracorporeal membrane oxygenation support and a left ventricular assist device for cardiac failure [65]. In a patient with myopericarditis associated with COVID19, a life-threatening cardiac tamponade was managed with pericardiocentesis [66]. Another severe case of myopericarditis was treated with intravenous immunoglobulin and methylprednisolone [67].

## Diagnosis of Pericardial Involvement in COVID19

The suspicion of pericarditis must be high in patients experiencing symptoms of chest pain or raised inflammatory markers. A chest x-ray (CXR) shows an enlarged cardiac silhouette in patients with moderate to severe pericardial effusion. An electrocardiogram (ECG) may show diffuse ST-segment elevation and PR depressions, especially with concomitant myocardial involvement. However, a normal ECG does not exclude the diagnosis, and an echocardiogram may yield important information such as the presence of pericardial effusion and its hemodynamic impact [68]. Multimodality imaging, including CMR and CT scan, can show the pericardial inflammation and edema in addition to the pericardial effusion [69]. A case series of COVID19-associated pericardial diseases used a multimodality imaging-based approach to diagnose the pericardial conditions accurately [48]. Pulmonary embolism should be in the differential diagnosis of COVID19 due to an increased prothrombotic risk. These patients also develop pleuritic left-sided chest pain.

Several COVID19 patients with pericarditis had typical ECG changes associated with pericardial inflammation. Most of these patients had an enlarged cardiac silhouette on CXR, and echocardiography usually confirmed pericardial effusion (Table 1).

## Management of pericardial involvement in COVID19

### Anti-Inflammatory Therapies in Pericardial Diseases

The mainstay for the treatment of acute and recurrent pericarditis is NSAIDs and colchicine. Corticosteroids are used in cases of treatment failure, resistance, or contraindications to first-line therapy [68]. IL1 receptor antagonists (anakinra and riloncept),

intravenous immunoglobulins, and azathioprine are recommended in refractory recurrent pericarditis patients [70••, 71••]. Some additional drugs such as azathioprine and intravenous immunoglobulins are also used in selected refractory cases [72, 73].

### Safety of Anti-Inflammatory Drugs in COVID19

The safety of NSAIDs in COVID19 patients was questioned after reports of worsening symptoms in a few patients [74]. Ibuprofen is linked to an increased expression of ACE2 receptors, but this does not establish any causative link to the severity of symptoms and warrants further investigation [75]. Observational studies on the use of aspirin in COVID19 patients have shown conflicting results. Chow et al. [76] reported decreased mortality, ICU admission, and mechanical ventilation, but Sahai et al. [77] found no change in mortality and an increased thrombotic risk in COVID19 patients taking aspirin. Current World Health Organization and Food and Drug Administration guidelines do not recommend stopping NSAIDs in symptomatic COVID19 patients [78, 79]. Recurrent pericarditis patients usually taper the anti-inflammatory drugs slowly over several months and are at risk of flare if anti-inflammatory drugs, such as NSAIDs, are stopped abruptly [80]. Colchicine is also safe to use in COVID19 patients and is currently explored as a potential treatment for COVID19. Various randomized trials have established on colchicine's safety and efficacy in the early phases of COVID19 and show that it may also decrease complications and mortality [81•, 82, 83••]. Corticosteroids are recommended for severe or complicated COVID19 cases or concomitant disease with specific indications for steroids [84]. Moreover, anakinra (an IL1 receptor antagonist) is also used safely in COVID19 patients [70••] [85].

### Patients with Established Pericarditis Developing COVID19

Patients with pericarditis (acute or recurrent) developing mild to moderate COVID19 may continue their NSAIDs and colchicine for pericardial inflammation. Recurrent pericarditis patients may also continue to use corticosteroids and anakinra. Continuous monitoring is warranted in all patients taking corticosteroids or anakinra; however, these treatments are also potential therapies for COVID-19 [86].

### COVID19 Patients Developing Pericarditis

There is no concrete evidence on the management of COVID19-associated pericarditis. Physicians usually avoid the use of aspirin, but ibuprofen and colchicine are considered safe. Corticosteroids may also be used in COVID19-associated pericarditis, as dexamethasone has also been shown to improve mortality and increased ventilator-free days in COVID19 [87].

There are a few cases of successful use of anakinra in COVID19 pericarditis [52]. In our review of literature, the majority of COVID19-associated acute pericarditis cases were treated with colchicine and NSAIDs. Corticosteroids were also added in complicated cases (Table 1).

## Future Directions

The current evidence shows that pericardial involvement is an important clinical manifestation of COVID19, requiring a proper workup and a specific management plan based on the presentation and concomitant organ involvement. Most pericarditis treatments (e.g., colchicine, corticosteroids, and anakinra) are safe and efficacious also for COVID-19. Further studies evaluating the incidence and pathophysiology of pericardial diseases in COVID19 patients will help understand the disease burden and refine appropriate treatment strategies.

**Abbreviations** COVID19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; RNA, Ribonucleic acid; PT, Pericardial tamponade; IL, Interleukin; TNF, Tumor necrosis factor; ACE2, Angiotensin-converting enzyme-2; ECG, Electrocardiogram; CMR, Cardiac magnetic resonance; LGE, Late gadolinium enhancement; CT, Computed tomography; NSAID, Non-steroidal anti-inflammatory drug

## Declarations

**Conflict of Interest** Muhammad M. Furqan and Beni R. Verma and declare that they have no conflict of interest.

Paul C. Cremer reports grants and personal fees from Kiniksa Pharmaceuticals, and grants from Novartis Pharmaceuticals.

Massimo Imazio has been on Advisory Board for Sobi and Kiniksa Pharmaceuticals.

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
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