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**ORIGINAL RESEARCH ARTICLE**

# Coronavirus and cardiovascular system

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## ABSTRACT

The current pandemic caused by the new coronavirus (SARS-CoV-2) has been the focus of worldwide health concern since its appearance. Its high transmissibility associated with the absence of an effective treatment implies a hard impact in the research area. Reports on atypical forms of presentation, associated risk factors and drugs tested to reduce morbidity and mortality saturate the media. The cardiological community is actively involved, since cardiovascular manifestations are frequent and varied, and an increased risk of poor outcome has been observed in individuals with previous cardiovascular disease. The aim of the review is to provide the available evidence on this topic, with the caveat that the information is dynamic.

***Keywords:*** SARS-COV-2; COVID-19; cardiovascular disease

## 1. Introduction

Since the appearance in December 2019 in Wuhan, China, of COVID-19, the disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), more than 2.3 million cases and 160,000, as of the writing of this article, have been reported. Given its rapid worldwide spread, COVID-19 was declared a pandemic by the World Health Organization on 11 March[1], and in our country the first cases were confirmed on 13 March, currently numbering more than 500[2].

Although it usually presents with mild respiratory symptoms, some patients have pneumonia and, in severe cases, acute respiratory distress syndrome (ARDS) and shock are observed[3]. Multiple studies have shown that patients with underlying cardiovascular (CV) comorbidities, such as hypertension (HT) and coronary artery disease, are more prone to severe coronavirus infection, which requires intensive care unit (ICU) admission and is associated with increased mortality[4].Based almost exclusively on data from China, cardiac injury appears to be a prominent feature of the disease, occurring in 20%–30% of hospitalized patients, and contributing to 40% of deaths. Elevation of cardiac biomarkers is common in this infection and is associated with worse prognosis[4].

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A bibliographic search was carried out in the main scientific societies using the words "COVID and CARDIOVASCULAR DISEASE". In the following paragraphs, the pathophysiology of the infection and its affectation will be explained.

## 2. Pathophysiology

SARS-CoV-2 belongs to the Coronauiridae family, whose members cause respiratory, enteric, hepatic and neurological diseases. It consists of a single-stranded RNA with a spiculated, corona-like glycoprotein envelope[5]. It is sensitive to ultraviolet radiation and can be inactivated by lipid solvents such as 75% ether, ethanol, chlorine disinfectants, peroxyacetic acid and chloroform; except chlorhexidine. Several related coronavirus strains have been discovered in bats and a working hypothesis is that these constitute the initial zoonotic host. SARS-CoV-2 and other coronaviruses can use angiotensin-converting enzyme 2 (ACE2) to enter host cells. ACE2 is abundant in lung alveolar cells among other tissues, providing the primary entry site for the virus. After ligand binding, SARS-CoV-2 enters cells through an endocytosis-mediated receptor. ACE2 also plays a role in lung protection that is impaired by infection, contributing to viral pathogenicity[1].

Like other respiratory pathogens, transmission occurs through aerosolized droplets during coughing and sneezing[5]. Disease progression can be divided into three phases: a) an early infection phase; b) a pulmonary phase; and c) a severe hyperinflammatory phase. During the early phase of infection, the virus infiltrates the lung parenchyma and begins to proliferate. This stage is characterized by mild symptoms and marks the onset of the innate immune response, mediated by monocytes and macrophages[6]. SARS-CoV-2 can cause direct damage to pneumocytes through a cytopathic effect, but also diffuse alveolar damage leading to ARDS. Data from multiple studies show that inflammatory markers are elevated during infection (C-reactive protein, interleukin 6, interferon, tumor necrosis factor a, procalcitonin and ferritin, among others), favoring the sustained inflammatory response[4].

Collateral tissue injury and the inflammatory processes that follow (vasodilatation, endothelial permeability, leukocyte recruitment) can lead to further lung damage, hypoxemia and CV stress. In a subset of patients, the host inflammatory response continues to amplify (even with decreasing viral loads) and causes systemic inflammation. This systemic toxicity in turn has the potential for distant organ damage. Lymphopenia is commonly seen in critically ill patients, suggesting that viral particles may invade lymphocytes and cause their destruction[4,6].

While the mechanism of cardiac injury is not fully understood, it is theorized that SARS-CoV-2 may cause cardiac involvement through multiple mechanisms: 1) indirect cardiac damage due to an exaggerated immune inflammatory response and cytokine storm; 2) direct damage through cardiomyocyte invasion; and 3) severe hypoxia due to acute respiratory damage caused by the virus, which can lead to oxidative stress and myocardial injury due to increased myocardial oxygen demand in the presence of ARDS[4].

## 3. Cardiovascular manifestations

It has been observed that SARS-CoV-2 infection has a worse prognosis in patients with pre-existing CV disease. In different studies the most frequent co-morbidities were HT, diabetes mellitus (DM) and CV disease, being significantly higher in those who required admission to the ICU or died[7,8].

About 12% of patients infected by the virus have cardiac involvement as evidenced by increased levels of myocardial damage markers[9]. It has been shown that patients with SARS-CoV-2 and associated myocardial injury are older and have more comorbidities such as hypertension, DM, heart failure (HF) and cerebrovascular disease than those patients infected but without myocardial involvement. In turn, they more

frequently present ARDS, require non-invasive and invasive mechanical ventilation, and have higher mortality[10]. In a study conducted in Wuhan, a mortality of 10.5% was observed in patients with antecedents of CVD, 7.3% in patients with DM, and 6% with AHT. All these figures far exceed the reported overall mortality of 2.3%[11].

Different mechanisms have been proposed to explain this increased susceptibility. The presence of diseases such as dyslipidemia has an impact on the immune system by different mechanisms of action that make these patients more vulnerable to infection and its complications[12]. On the other hand, although it is controversial, patients with ETS express a higher number of ACE2 and since the virus uses this enzyme to enter host cells, it could generate amplified responses to infection[13]. Specifically, the role of renin-angiotensin-aldosterone system (RAAS) inhibitor drugs has been discussed. However, despite the structural similarity of ACE 1 and 2, their active sites are different and as a result, the use of ACE inhibitors would not directly affect ACE2. It has been further postulated that angiotensin II is partly responsible for the SARS-CoV-2 insult and could be limited by the use of ACE inhibitors[14]. In a retrospective study of 1128 hypertensive patients diagnosed with COVID-19, all-cause mortality was lower in those under treatment with RAAS inhibitors[15].

As a result of campaigns emphasizing social distancing, urging patients to consult only in emergencies, reducing the number of outpatient consultations, and preparing health care teams (measures to reduce contagion in the population and care of health care personnel), an increase in the time to consultation has been observed in patients with previous pathologies. Specifically, in the case of acute coronary syndrome (ACS), there has been a considerable increase in the time from the onset of symptoms to the first medical contact, from emergency consultation to admission to the catheterization laboratory, and in door-to-balloon time, with the negative consequences that this entails[16].

Although patients with SARS-CoV-2 frequently present with respiratory symptoms, clinical presentation with CV-oriented symptoms is not unusual. The most common forms of presentation are listed below.

### 3.1. Myocarditis

There is evidence of direct myocardial involvement by coronavirus[17]. One of the clinical forms of presentation of COVID-19 may be chest pain, accompanied by alterations in the PR and ST segments on the electrocardiogram, with elevated blood biomarkers that raise suspicion of myocarditis. Although case reports provide evidence of myocardial inflammation in infected patients, there are doubts about the mechanism responsible since, although viral genome has been observed in tissue samples, it is also associated with decreased levels of ACE2. Current evidence is insufficient to determine whether these patients present preferentially with preserved or reduced ejection fraction. In addition to treatment of myocarditis, studies should be performed to confirm infection[3]. The severity of the clinical picture will depend on the extent of myocardial damage and the levels of inflammatory mediators, such as interleukin-6. The evolution can be dramatic in those who develop fulminant myocarditis, with cardiogenic shock. The first case reported evolved favorably after antiviral therapy and use of a ventricular assist device. It is interesting to note that the improvement in left ventricular ejection fraction was observed together with a decrease in troponin and interleukin 6 values[18].

### 3.2. Decompensated heart failure

Presentation as HF is frequent, reaching about 23% of those infected with SARS-CoV-2. However, doubts persist as to whether it is more frequently due to an exacerbation of previous pathology or to a de novo phenomenon, secondary to myocarditis or stress cardiomyopathy[1]. Not surprisingly, as in other respiratory conditions, patients with SARS-CoV-2 and a history of chronic HF present with decompensation of HF. These

cases usually occur with low blood troponin levels and inflammatory response markers, suggesting that direct myocardial involvement is not the main culprit.

### 3.3. Acute coronary syndrome

Patients with a history of ischemic heart disease or those with a likelihood of ischemic disease atherosclerotic, present a higher risk of developing ACS. Infection produces an increase in myocardial oxygen requirements, usually linked to respiratory failure, and can trigger acute myocardial infarction type II, secondary to an imbalance in oxygen supply/demand. On the other hand, the systemic inflammatory response can destabilize coronary atherosclerotic plaques causing acute myocardial infarction type I[19].

In a series of 19 patients with ST-elevation ACS and SARS-CoV-2 infection, wide variability in presentation was observed, with a high prevalence of nonobstructive coronary artery disease and poor prognosis (72% in-hospital mortality). The authors highlight the almost constant presence of elevated D-dimers (18/19 patients)[20].

A fundamental aspect to consider is reperfusion treatment. There is currently no agreement among different scientific societies as to which strategy should be applied. Some maintain primary angioplasty as the treatment of choice while others postulate pharmacological treatment. The use of one or the other is based on the material and human resources of each country, and on the capacity of their centers to apply protocols of protective equipment to personnel[21]. In those presenting with non-ST-segment elevation ACS, the treatment strategy should be based on risk stratification, while determining whether or not the patient is a SARS-CoV-2 carrier[21,22].

### 3.4. Arrhythmias

Cardiac arrhythmias are another common manifestation in infected patients, with an approximate incidence of 16%, which increases significantly with the severity of the disease (44% in ICU patients). The presence of malignant arrhythmias such as ventricular tachycardia/fibrillation was reported in 5.9% of cases[23]. Myocardial injury, manifested by troponin elevation, has also been observed in these patients. Although the underlying mechanisms remain under investigation, it is attributed to hypoxia, metabolic alterations, inflammatory and neurohumoral stress[1,23]. Brugada-like electrocardiographic patterns have also been described, making a correct differential diagnosis even more complex[24].

Another recognized aspect is the proarrhythmic role of some treatments used off-label. The administration of chloroquine/hydroxychloroquine (antimalarial agents), lopinavir/ritonavir (protease inhibitors used in HIV) and azithromycin (there are in uitro reports of SARS-CoV-2 inhibition) has an impact on ventricular repolarization directly and indirectly, prolonging the QT interval, with the consequent risk of spike torsion[23]. Concomitantly, there is evidence that inflammation per se could favor arrhythmic vulnerability. Interleukin 6, among other cytokines, is able to modulate the expression of inon channels in cardiomyocytes in inflammatory heart disease[25]. Undoubtedly, the lack of proven efficacy of the treatments and their association with these potential risks should be considered in each patient according to their previous arrhythmic profile.

### 3.5. Thromboembolic events

Patients infected with SARS-CoV-2 present an increased risk of venous thromboembolism, reaching 25% in those admitted to the ICU[26]. Alterations in coagulation parameters and a prognostic association with elevated D-dimers* have been reported. As research progresses, the hypothesis that endothelial damage produces activation of the inflammatory and coagulation cascade with consequent microvascular thrombosis, initially pulmonary and subsequently at a distance, is becoming increasingly attractive[27]. In view of the above,

it is recommended that infected patients receive thromboprophylaxis, not only during hospitalization, but it has also been proposed to extend treatment for 45 days in individuals at high risk (reduced mobility, active cancer, elevated D-dimers). Although information is limited, full-dose anticoagulation therapy has been postulated to be useful in preventing microvascular thrombosis. However, in a prospective, multicenter study of patients with COVID-19 admitted to the ICU, severe thromboembolic events (including pulmonary embolism) were observed despite the use of anticoagulation, suggesting that doses should be higher than usual[28].

## 4. Conclusions

The current SARS-CoV-2 coronavirus pandemic may have presentations suggestive of CV pathology, so it is important to maintain a high level of suspicion in all patients with this form of presentation. Those with previous cardiopathies are at risk of decompensation and have higher morbidity and mortality. Continued research in the coming months will be crucial to improve the outcome of affected individuals.

## Conflict of interest

The authors declare no conflict of interest.

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