REVIEW ARTICLE
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Cardiovascular damage due to COVID-19: what do we need to know?

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SUMMARY

Severe Acute Respiratory Syndrome Coronavirus 2 is part of the *Cononaviridae* family and is the causative agent of the 2019 (Covid-19) Coronavirus pandemic declared by the World Health Organization in March, 2020. This virus has a high rate of transmission, affecting several individuals, and has caused thousands of deaths. The clinical manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 infection are not restricted only to the respiratory tract, and there is an express involvement of the cardiovascular system with a higher risk of death in this group. In such patients there is an overactivation of renin-angiotensin-aldosterone system, which promotes an increase in the expression of angiotensin-converting enzyme – 2 that acts as a receptor for the SPIKE protein expressed by the virus and enables the interaction between the host cell and Severe Acute Respiratory Syndrome Coronavirus 2. This process of infection causes a hyperinflammatory state that increases the inflammatory markers of cardiac injury. Hence, an adequate understanding and clinical guidance regarding the monitoring, and controlling the damage in these patients is essential to avoid worsening of their clinical condition and to prevent death.

Keywords: SARS-CoV-2. Inflammation mediators. Shock, cardiogenic. Heart failure. Heart decompensation.

INTRODUCTION

At the end of December, 2019, a series of cases of pneumonia caused by a new virus was reported in the Chinese city of Wuhan[1,2]. The coronavirus 2 acute severe respiratory syndrome virus (SARS-CoV-2) has been identified as the etiological agent of coronavirus disease, officially named Covid-19 by the World Health Organization (WHO)[1]. This virus is part of the *Coronaviridae* family, and SARS-CoV-2 was the seventh identified member of this family.

The new coronavirus has a high dissemination potential, since it is transmitted from person to person through saliva and through the nasopharyngeal route by direct transmission. It can also infect people indirectly due to its ability to survive on different types of surfaces, which increases the infectious potential of the virus[3,4].

In the beginning, Covid-19 was known only for its high potential to infect the respiratory system. However, as it spread throughout Asia and Europe, turning into a pandemic, it was observed that the disease goes beyond the manifestations of the respiratory tract. Reports emerged about its effects of variable severity on the cardiovascular system including cardiac dysfunction, acute cardiac injury, tachycardia, arrhythmias, and heart failure, which were further aggravated in individuals with a previous history of heart disease[5].

Hence, we conducted a literature review to understand how the cardiovascular system is affected by the SARS-CoV-2 infection, and to identify the main phenomena and biochemical markers associated with the inflammatory response and cardiovascular damage. We also focused on the interaction between the angiotensin-converting enzymes with ACE inhibitors (ACE ACE) and angiotensin II receptor blockers (ARB) in the individuals infected by SARS-CoV-2.

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METHODS

Literature search for studies published between 2019 and 2020 involving patients affected by SARS-CoV-2 treated for cardiovascular complications.

In all, six studies were selected, two of which were case reports, three were retrospective cohort studies, and one was a case series. The data extraction was determined after analyzing the information available in the selected studies to understand the pathophysiological, clinical, and laboratory aspects of SARS-CoV-2. Additionally, we have grouped a series of clinical findings in Table 1, to provide information about the possible cardiovascular damage resulting from the clinical repercussions caused by Covid-19,

DISCUSSION

Relationship between Sars-Cov-2 and angiotensin 2 converting enzyme (ACE2)

The angiotensin-2 converting enzyme (ACE2) is mainly expressed in the lungs, more precisely in the alveolar epithelial cells of type II[6]. In patients with cardiovascular comorbidities such as hypertension, atherosclerosis, and congestive heart failure (CHF) that hyperactivate the renin-angiotensin system (RAS), overexpression of ACE2 occurs in the cardiac muscles[7].

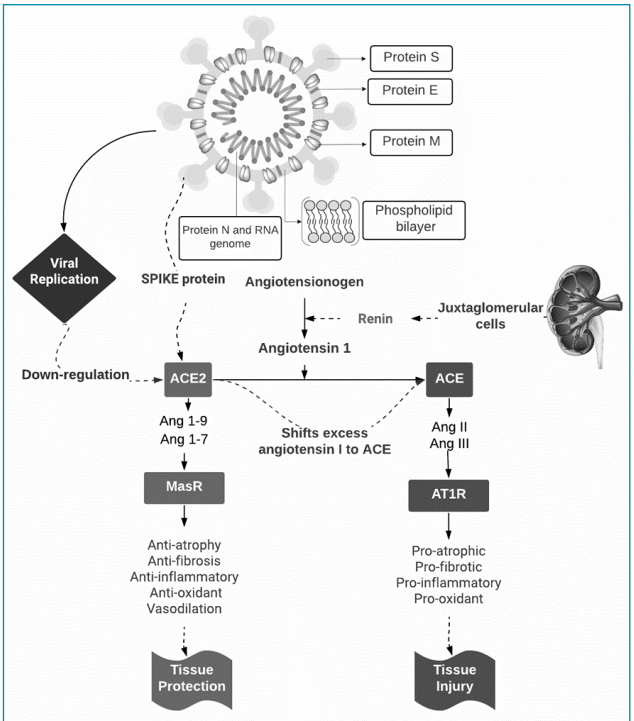
This is crucial because SARS-CoV-2 has surface proteins with high affinity for ACE2 receptors, which are expressed in

Table 1. Main cardiovascular repercussions in patients infected by covid-19.

Authors	Type of Study	Number of participants	Purpose of the study	Main clinical implications
Wang et al.[14], 2020	Case series	138	Describe the clinical and epidemiological characteristics of patients with the new coronavirus pneumonia.	Shock Acute Heart Injury Arrhythmia
Rente et al.[15], 2020	Case Report	01	Case report of a patient with diabetes mellitus who contracted the new coronavirus through community transmission, developed cardiac complications and died.	Thickening of the myocardial wall with slight increase in the cardiac area
Ruan et al.[18], 2020	Retrospective cohort	150	Investigating the cause of death of patients with SARS-CoV-2.	Myocarditis, Fulminant Heart Failure
Inciardi et al.[19], 2020	Case Report	01	Acute myocardial inflammation in a patient with Covid-19 who recovered from influenza-like syndrome and developed fatigue, and signs and symptoms of heart failure one week after recovering from upper respiratory tract symptoms.	Myopericarditis with ventricular dysfunction
Gho et al.[25], 2020	Retrospective cohort	187	To evaluate the association between previous cardiovascular disease and myocardial injury in patients who died of Covid-19.	Malignant arrhythmia – ventricular tachycardia with degeneration to ventricular fibrillation or hemodynamic instability
Zhou et al.[21], 2020	Retrospective cohort	191	To explore the risk factors of hospital death in patients with Covid-19 and describe the course of symptoms and changes in laboratory data during hospitalization.	Septic shock Coagulopathies Acute heart damage

high rate in the cardiac muscle and lung tissue, making these organs more susceptible to infection. This phenomenon is exacerbated in individuals with a pre-existing cardiac disease because they have a higher concentration of ACE2 compared to that in healthy individuals[7], as shown in Figure 1. Thus, it is assumed that the cardiac and lung injury is more severe due to the high concentration of ACE2 in these organs[7-9].

Some studies indicate that SARS-CoV-2 binds to ACE2 through one of its four structural proteins: *spike protein* (S), nucleocapsid protein (N), membrane protein (M), and the protein envelope[7], as shown in Figure 1. The viral protein that promotes interaction with the receptor of ACE2 is the S protein, and through this interaction it is able to infect the cells, and inactivate ACE2 causing lung injury, since the protective function provided by ACE2 is inhibited by the viral action. Thus, there is a displacement of angiotensin I to ACE type 1, causing an increase in the levels of angiotensin II and III. These have a harmful effect on the tissues, especially the cardiac tissue, because they have pro-apoptotic, pro-fibrotic, pro-inflammatory, and pro-oxidant activity, resulting in severe impairment of the cardiovascular function.



Ang: angiotensin; SARS-CoV-2: severe acute respiratory syndrome 2; ACE: angiotensin converting enzyme 1; ACE2: angiotensin converting enzyme 2; MasR: angiotensin receptor 1-7; At1R: angiotensin I receptor.

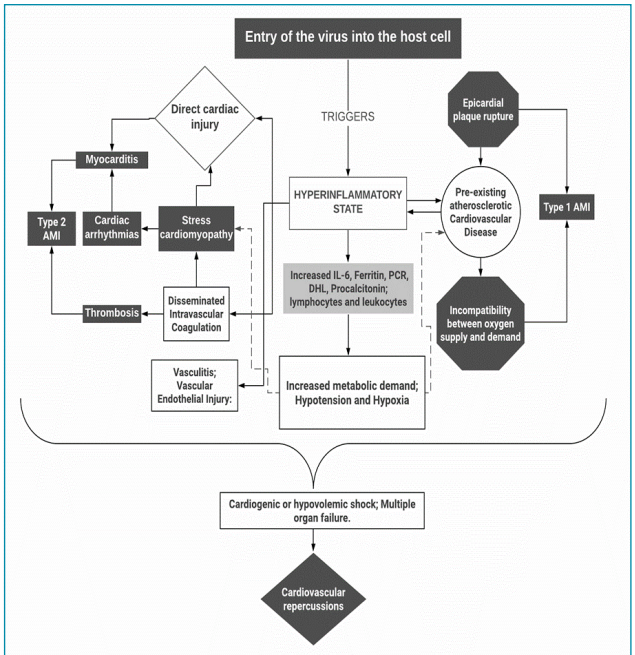
Figure 1. Molecular mechanism of the interaction between SARS-COV-2 and ACE2. The virus causes inactivation of ACE2, which results in the loss of its tissue protection function, displacing the angiotensin I to ACE1, leading to tissue injury.

Cardiovascular diseases and SARS-CoV-2 infection

Individuals with cardiovascular diseases (CVD) are more susceptible to infection due to the presence of proteins that act as viral receptors; in addition, CVD itself makes the individual more likely to develop clinical upsetting due to the hyperinflammatory state[10-13] as shown in Table 1. In individuals with hypertension with long-term intake of antihypertensives of the angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARB) class, the susceptibility to infection can increase and it can develop into a more aggressive form that leads to death[4].

Several clinical presentations resulting from cardiovascular damage in patients with Covid-19 have been observed. In a study that evaluated 138 individuals admitted for Covid-19, 16.7% presented arrhythmia and 7.2% presented acute cardiac injury[12]. The study could not identify a single cause for these changes, and the clinical and laboratory phenomena were interpreted as multifactorial causes resulting from the hyperinflammatory state caused by SARS-CoV-2, as shown in Figure 2.

In the case report by Rente et al. (2020)[15], a diabetic patient with Covid-19 presented with a severe cardiovascular involvement secondary to the inflammatory process. Computed Tomography (CT) revealed thickening of the myocardial wall with a slight increase in the cardiac area.



IL-6: interleukin-6; PCR: C-reactive protein; LDH: lactate dehydrogenase; AMI: acute myocardial infarction.

Figure 2. Main cardiovascular complications in patients infected with SARS-COV-2.

The study by Puntmann et al., (2020)[16], assessed the presence of myocardial injury in patients who had recently recovered from Covid-19, with a mean interval of 71 (64 - 92) days between diagnosis and cardiac magnetic resonance imaging (CMRI). Compared to individuals from a healthy control group, with patients presenting compatible risk factors with recently recovered patients from COVID-19, this last one had low left ventricular ejection fraction, high left ventricular volume, and left ventricular mass on native T1 and T2 MRI images. Of the 100 individuals in the study, 78 presented abnormal findings on CMRI, including 73 patients with myocardial elevation on native T1 and 60 on T2, in addition to delayed myocardial enhancement on gadolinium imaging in 32 and pericardial enhancement in 22 patients.

Increased native T1 values indicate the presence of diffuse myocardial fibrosis and/or edema, while native T2-weighted images are specific for edema. Thus, individuals with increased T1 and native T2-weighted sequences correspond to those with an active inflammatory process, while those with increased native T1 and normal native T2-weighted sequences no longer present with a hyperinflammatory state, but only diffuse residual damage to the myocardium[16]. However, native T1-weighted images might be increased in a variety of diseases involving different pathways leading to diffuse fibrosis, such as SAH or genetic cardiomyopathies[16].

In a study conducted and published by the Chinese Center for Disease Prevention and Control, involving data from 44,672 individuals who were positive for SARS-CoV-2, the mortality rate was 2.3%. The majority of deaths was seen among individuals above 70 years of age or those who had some comorbidity that compromised the cardiac function, such as CVD, SAH, and diabetes mellitus (DM)[17].

Other authors[4,10-11] reported venous thromboembolism in individuals infected by SARS-CoV-2, which is related to vascular inflammation, hypercoagulability, and endothelial dysfunction. In addition, cases of fulminant myocarditis and heart failure (HF) associated with SARS-CoV-2 infection were found[18].

However, in a study conducted in Germany involving the autopsy of 39 individuals infected with SARS-CoV-2, it was demonstrated that the virus does not necessarily infect the cardiomyocytes, but the interstitial cells or macrophages that end up invading the myocardium. The inflammatory response with increased cytokines was seen in cases with a viral load greater than 1,000 copies[20].

This indicates that the clinical manifestations of Covid-19 are not restricted to the lower and upper respiratory tract, and might have repercussions on other systems, such as the cardiovascular system. In some cases, it might not affect the respiratory system and compromise only the cardiac function, in which the patient with SARS-CoV-2 presents with myopericarditis with significant ventricular dysfunction, and absence of pulmonary manifestations[19].

Severe cases of rapid evolution can still occur in patients infected by SARS-CoV-2 in which 20% evolved to severe cases with shock[13,21].

Main biochemical markers of the impairment of cardiovascular function in patients infected with SARS-CoV-2

Direct injury to the heart occurs due to a systemic inflammatory response resulting from SARS-CoV-2 infection, in which high levels of cytokines involved with injury to the cardiovascular system are observed. Thus, there is an elevation of troponin I concomitant with the increase in other inflammatory markers such as D dimer, ferritin, IL-6, lactate dehydrogenase (LDH), C-reactive protein, procalcitonin, and lymphocyte count[22-24].

The increase in troponin I was indicated as a marker of severe Covid-19 infection compared to the non-serious form, in a meta-analysis of four studies including 341 patients. Malignant arrhythmias (ventricular tachycardia with degeneration to ventricular fibrillation or hemodynamic instability) were most frequent in individuals with high troponin I at 11.5% versus 5.2% in individuals in which it was not elevated[25].

In a study by SHI et al., (2020) which involved 416 patients admitted with Covid-19, the presence of myocardial injury was verified by increasing troponin I levels higher than the 99th percentile. This was associated with increased mortality and adult respiratory distress syndrome (ARDS), wherein the group of patients without cardiac injury had an average troponin I level of <0.006 μg/L (<0.006–0.009), while the group with cardiac injury had an average level of 0.19 μg/L (0.08–1.12)[25].

The mortality rate for individuals who developed Covid-19 without CVD involvement and with normal troponin levels was 7.6%[25]. However, the mortality rate for patients affected by Covid-19 with CVD and troponin normal levels was 13.3%, and in those infected by SARS-CoV-2 without prior CVD and with high troponin levels, the mortality rate was 37%[25]. In those who had prior CVD and were infected with SARS-CoV-2 with high troponin levels, the mortality rate was 69.4%[26]. Furthermore, patients who presented with increased troponin needed more mechanical ventilation and had a higher incidence of ventricular arrhythmias[25].

In a study by Puntmann et al. (2020)[16], high-sensitivity troponin T was correlated with native T1 ($r=0.35$; $p<0.001$) and native T2 mapping ($r=0.22$; $p=0.03$), showing significant results, which illustrates that during the active inflammatory process, troponin T levels are higher, being concordant with the findings of CMRI that reveals the presence of myocardial fibrosis and edema.

In another study, it was reported that patients who presented with D-dimer values higher than 1 µg/mL at admission had a higher risk of death, regardless of other laboratory parameters, as well as advanced age and high q-SOFA score[19].

In addition to the inflammatory markers, there is a concomitant increase in the levels of BNP (cerebral natriuretic peptide) or NT-proBNP (cerebral N-terminal natriuretic propeptide). These proteins have biological effects such as diuresis, decreased peripheral vascular resistance, inhibition of SARS, and sympathetic activity. However, when there is an impairment of the cardiac function, the values of these markers of myocardial dysfunction are quite high in patients of Covid-19 with previous cardiac dysfunction, which makes them more likely to develop a severe impairment.

Do patients who use ACE inhibitors have a greater risk of death than those who do not?

It should be noted that although ACE2 and ACE have homologous structures, the activation sites are different; hence, inhibition of ACE would theoretically have no effect on the activity of ACE2. The function of ACE2 is to promote recovery of the ventricular activity in patients with harmful damage to the cardiomyocytes, through the inhibition of angiotensin II activity[26]. However, some researchers cite that cardiac damage during infection by SARS-CoV-2 is due to angiotensin II, and one way to reduce this damage would be to administer recombinant ACE2 to stabilize the angiotensin II levels[26].

Given the fact there are few published studies, and numerous studies that are currently ongoing, the current recommendation of the Brazilian Society of Cardiology (2020)[27], the European Society of Cardiology, and the *American College of Cardiology* (2020)[28] is that ACE inhibitors and ARB should not be discontinued in patients who are stable and have been taking these medications regularly, given the proven efficacy of these drugs for the treatment of SAH and HF. However, in specific cases in which the patient presents with Covid-19 in its severe form, it is necessary to evaluate the hemodynamic stability and renal function, to make a decision about continuation or discontinuation of antihypertensive therapy.

CONCLUSION

The SARS-CoV-2 virus has a potential to cause several clinical repercussions in the body of an infected individual. Patients with pre-existing cardiac diseases need special attention, since they are at a high risk of complications and death. A possible increase in the chronic repercussions due to the cardiac lesions caused by an hyperinflammatory process triggered by the infection that alters the cardiovascular homeostasis should be considered. It is still recommended that users of ACE inhibitor or ARB should not discontinue their antihypertensive treatment, unless they develop hemodynamic or renal instability, and the decision to change the antihypertensive drugs should be taken by the specialist. In view of these findings, it is essential to maintain measures of social distancing, hands hygiene, protecting the mouth and nose when coughing or sneezing, and continued use of masks.

AUTHORS' CONTRIBUTIONS

CRN: Conceptualization, Methodology, Writing – Review & Editing. **SCL:** Methodology, Writing – Review & Editing. **RHAB:** Methodology, Writing – Review & Editing. **PPT:** Conceptualization, Supervision, Methodology, Writing – Review & Editing.

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