COVID-19 x cardiovascular system: clinical evolution, risk factors and myocardial injury mechanism

COVID-19 x sistema cardiovascular: evolução clínica, fatores de risco e mecanismo de lesão miocárdica

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ABSTRACT
SARS-CoV-2 has driven the COVID-19 epidemic around the world, making it one of the most significant medical challenges of the last century. This infectious agent infects host cells by binding to ACE2 receptors (an enzyme present in several tissues, such as the heart, lung and kidneys) and can lead to pneumonia, acute myocardial damage and chronic damage to the cardiovascular system. Pre-existing conditions such as diabetes, hypertension and obesity are related to greater severity and a significant increase in the fatality rate of COVID-19. The exacerbated production of inflammatory cytokines such as IL-6 and TNF-α leads to systemic inflammation, which can directly affect the cardiovascular system. Acute myocardial infarction (increased risk), myocarditis, arrhythmias, venous thromboembolism and takotsubo cardiomyopathy are some of the most prevalent complications of the cardiovascular system described in patients with COVID-19.

Keywords: SARS-CoV-2, cardiovascular system, infectious diseases, cardiovascular diseases.

RESUMO
O SARS-CoV-2 tem impulsionado a epidemia de COVID-19 em todo o mundo, tornando-se um dos desafios médicos mais significativos do século passado. Esse agente infeccioso infecta as células hospedeiras ligando-se aos receptores ACE2 (uma enzima presente em vários tecidos, como coração, pulmão e rins) e pode causar pneumonia, lesão aguda do miocárdio e lesão crônica do sistema cardiovascular. Condições pré-existentes, como diabetes, hipertensão e obesidade, estão relacionadas à maior gravidade e a um aumento significativo na taxa de fatalidade da COVID-19. A produção exacerbada de citocinas inflamatórias, como IL-6 e TNF-α, leva à inflamação sistêmica, que pode afetar diretamente o sistema cardiovascular. Infarto agudo do miocárdio (risco aumentado), miocardite, arritmias, tromboembolismo venoso e cardiomiopatia de takotsubo são algumas das complicações mais prevalentes do sistema cardiovascular descritas em pacientes com COVID-19.

Palavras-chave: SARS-CoV-2, sistema cardiovascular, doenças infecciosas, doenças cardiovasculares.

1 INTRODUCTION

On December 31, 2019, an outbreak of a new viral pneumonia was reported to the World Health Organization (WHO) in Wuhan City, Hubei Province, People's Republic of China. A

week later, on January 7, 2020, Chinese authorities confirmed that they had identified a new type of coronavirus: SARS-COV-2. The outbreak started in a local seafood trade in Wuhan and so far the reservoir host is unknown[1].

On January 30, 2020, WHO declared the SARS-CoV-2 outbreak a Public Health Emergency of International Concern[1].

In February 2020, WHO established that the disease would receive the following name: "COVID-19", a reference to the viral class and the year of the beginning of the epidemic[1]: Coronavirus disease – 2019.

Evolutionary advantages such as high infectivity, asymptomatic transmission capacity and relatively low virulence are some of the characteristics that SARS-COV-2 presents in relation to other coronaviruses that explain its rapid transmission, with its infection being identified in all continents of the world.

SARS-CoV-2 infects host cells through angiotensin-2 converting enzyme receptors (ACE2)[2] and the dominant clinical manifestation of COVID-19 is respiratory involvement, which may have an asymptomatic, mild or severe presentation, with development of the syndrome of acute respiratory distress[3].

It is known that pre-existing conditions such as cardiovascular disease (CVD), diabetes, hypertension and obesity are correlated with greater severity and a significant increase in the fatality rate of COVID-19[3].

It is a consensus that the pathophysiology of the development of COVID-19 severe acute respiratory syndrome occurs due to the overproduction of inflammatory cytokines (IL-6 and TNF-α) leading to a state of systemic hyperinflammation and multiple organ dysfunction[4].

Cardiac damage, demonstrated by markers such as elevated troponin I[4], is associated with inflammation markers (IL-6 and C-reactive protein and leukocytosis), thus establishing a correlation between myocardial damage and the increase in inflammatory activity caused by the viral infection.

The main cardiovascular complications described in patients with COVID-19 were: increased risk of myocardial infarction, fulminant myocarditis with evolution of left ventricular systolic function depression, arrhythmias, venous thromboembolism and cardiomyopathies[5] that mimic presentations of STEMI. These conditions imply a worse prognosis in patients with COVID-19.

It is not known which mechanisms lead to myocardial injury. The hypotheses and evidence of its presence, based on current knowledge, will be discussed throughout the article.

Therefore, special attention should be given to cardiovascular protection during treatment for COVID-19.

This review aims to provide a brief review of the clinical evolution of COVID-19, emphasizing its impact and manifestations on the cardiovascular system, in addition to raising possible hypotheses for the emergence of cardiac lesions.

However, a lot of information is still based on experience with COVID-19 and on learning from previous coronavirus diseases, requiring constant updating to better support these patients.

2 METODOLOGY

The “PubMed” database was used to select articles for the bibliographic review on 04/29/2021. The following terms were used for active data search: “COVID-19”, “SARS-CoV-2”, “Myocardial Infarction” “Myocarditis.”, “Risk Factors”, “Arrhythmias”, “Heart Failure” and “ Coagulation".

2.1 ETHICAL CONSIDERATIONS

Submission to the Research Ethics Committee was not necessary due to the nature of the study

3 DISCUSSION

SARS-CoV-2 are single-stranded RNA viruses, approximately 30 kb in length and their virion is about 50–200 nm in diameter, with a large capacity for mutations[3].

Infection in humans occurs through the upper respiratory tract and the gastrointestinal tract[6]. SARS-CoV-2 infects human cells through the coupling of its spike protein, present on the surface of the virus, with the angiotensin-converting enzyme 2 (ACE2) of host cells[6]. Like ACE2, virus receptor, it is in its most, located in the lung, this appears to be the major site of infection. However, ACE2 is also present in large amounts in the heart, and can thus lead to cardiovascular involvement[2].

The most common symptoms of COVID-19 are fever, anosmia, ageusia, cough, diarrhea, muscle pain, shortness of breath or dyspnea[3]. Some cases evolve to acute respiratory distress syndrome (ARDS), a potentially fatal condition, in addition to decompensation of underlying chronic cardiac pathologies and also the onset of new cardiac complications[7].

Thus, among the relationship of the cardiovascular system with COVID-19 infection, we can cite as relevant topics: Cardiovascular risk factors and their prognosis, evidence and

hypotheses of the mechanism of cardiac injury and the appearance of cardiovascular comorbidities in previously healthy individuals.

3.1 ACE2 E COVID-19

The angiotensin-2 converting enzyme (ACE2) is a transmembrane protein that plays a vital role in the cardiovascular and immune systems, having a relevant role in the renin angiotensin aldosterone system[8,9]. ACE2 is involved in cardiac function and in the development of hypertension and diabetes mellitus (conditions where this protein seems to be more expressed), being present in several tissues, including heart, lung and kidney[10,11,12].

Furthermore, it was recently discovered that ACE2 acts as a functional receptor for the coronavirus[9] class, including SARS-CoV-2, the latter by coupling one of its membrane proteins (spike).

Thus, patients with previous cardiovascular disease may have more severe symptoms, thanks to the increased secretion of ACE2 in these patients compared to healthy individuals.

ACE2 levels may also be increased with the use of renin angiotensin aldosterone system inhibitors, thus raising doubts about their safety and potential effects of using ACE inhibitors or angiotensin receptor blockers in patients with COVID-19. Its possible suspension in this situation is still controversial, thus needing more evidence and should analyze the possible benefits and risks[9].

3.2 CLINICAL EVOLUTION

COVID-19 has different symptoms and clinical evolution, ranging from asymptomatic to severe acute respiratory syndrome requiring mechanical ventilation[7.]

The first stage of the disease, usually benign, lasts for 7 days with typical symptoms of upper respiratory tract infections. The symptoms presented are nonspecific, with runny nose, cough, fever, anosmia and ageusia. About 80% of the frames are resolved in this phase[7].

The second phase, present in about 15% of patients, begins on the tenth day of symptoms, with clinical worsening evidenced by the onset of dyspnea and progressive decrease in oxygen saturation, in addition to signs of lower respiratory tract infection and moderate pneumonia[7].

The laboratory evaluation of patients in this phase, in most cases, reveals an increase in inflammatory reagents such as C-reactive protein (CRP), ferritin and D-dimer, showing an important inflammatory activity and prothrombotic components of the disease. High-resolution computed tomography of the chest can demonstrate a bilateral peripheral pulmonary infiltrate in

a well-defined ground-glass pattern, indicating the development of viral pneumonia[7]. Chest radiography is not indicated due to its low sensitivity (30 to 69%) in evaluating these patients.

About 5% progress to the third stage, or severe pneumonia, with worsening of the respiratory condition, hypoxemia and fever[7].

From a pathophysiological point of view, this phase is characterized by hyperactivity of the inflammatory immune response, promoting hypercytokinemia, mainly at the expense of interleukin 6 and 2 (IL-6 and IL-2), and tumor necrosis factor-α (TNF-α)[4].

Cytokines cause endothelial damage and increase the activation of the coagulationcascade (tissue factor), leading to hypercoagulability, thromboembolic events and increased risk of bleeding from disseminated intravascular coagulation[13] (DIC). We can also observe at this stage cytopenia and increase in D-dimer[4].

The installed picture of respiratory failure will have as a natural path to severe acute respiratory syndrome.

It is also important to pay attention to the risk of sepsis due to viral spread and inflammatory hyperactivity, leading to multiple organ dysfunction.

Systemic inflammation, with increased cytokines and hypercoaguability, are highly harmful to the cardiovascular system, resulting in myocardial damage, demonstrated by the increase in troponin and the N-terminal of the pro-BNP prohormone (NT-proBNP), and consequent complications CV, which will be further clarified throughout this work [4].

3.3 RISK FATORS

Hypertension, obesity and diabetes mellitus are the most common comorbidities among hospitalized individuals with COVID-19, as demonstrated by a large case series study, among the 5,700 patients present, the proportion of hypertensive patients was 56.6%, 41.7% had obesity and 33.8% had diabetes[14].

A higher mortality was also demonstrated in the group of patients with arterial hypertension infected with COVID-19 when compared to non-hypertensive ones[15,16].

Hypertension, in addition to new evidence suggesting a higher risk of serious disease due to the increased presence of ACE2 [10,11] is a disease that favors the pro-inflammatory state, which is an important component of the pathogenesis and outcome of COVID-19.

Hypertension can also aggravate the inflammatory condition of these patients. This hypothesis is suspected after a retrospective cohort study revealed that hypertensive patients with COVID-19 had higher concentrations of C-reactive protein, procalcitonin and IL-6 compared to the control group[17].

3.4 CARDIAC INJURY IN COVID-19

Several studies have shown an elevated level of cardiac troponin T (cTnT) in the plasma of patients with COVID-19 and patients with preexisting cardiovascular complications compared to those patients without cardiovascular complications[18].

The relevance of measuring cTnT is due to its prognostic value and its levels are known to increase in conditions of acute myocardial injury. Studies show that non-surviving patients had a high level of cTnT, which continued to increase until death, whereas the levels of cTnT of surviving patients did not change significantly[19], thus, continuous monitoring of cTnT values may be useful under the point from a prognostic point of view in patients who do not yet have the disease in its most advanced state.

There is no concrete evidence whether the myocardial injury caused by COVID-19 is a consequence of a systemic or local and ischemic or inflammatory process[12].

Recently, using the RT-PCR detection method of heart samples from some patients, it was possible to identify the presence of SARS-CoV viral particles, suggesting the direct role of the virus in cardiac injury[20]. This remains a possibility, since cardiomyocytes express a high level of ACE2.

In other studies, an endomyocardial tissue biopsy was performed in patients with COVID-19 who had acute myocardial injury and the findings were mild myocardial inflammation and the absence of cardiomyocyte necrosis or signs of apoptosis, suggesting that the location of SARS-CoV-2 is not in cardiomyocytes, but in macrophages[2].

These data are important in supporting the idea that SARS-CoV-2 may reside in the heart, however, more studies are needed to know which heart cells are actually infected by the virus.

It was also recently demonstrated, in in vitro studies, that cardiomyocytes derived from pluripotent stem cells can undergo transfection with SARS-COV-2 and, because they have ACE2 on its cell surface, allowed the virus to enter the cell, replicate and produce several viral copies to proliferate to other cells[21].

In the same study, this mechanism was demonstrated through the immunofluorescence technique and also its cytotoxic effect of the virus on cell morphology and an increase in an apoptosis marker (caspase-3), suggesting an increase in cell death by apoptosis. In summary, it is suggestive that SARS-CoV-2 can infect human cardiomyocytes and exert cytotoxic effects[21].

Infection by SARS-CoV-2 decreased the regulation of ACE29 and, as a result of down-regulation, there is a significant reduction in the production of angiotensin 1-7, leading to an increase in the production of TNFα[22,23]. Angiotensin 1–7 is known to inhibit proinflammatory

cytokines such as IL-6, TNFα, IL-12, IL-5 and other inflammatory pathways such as NF-kB and JNK. Down-regulation of ACE2 can amplify for increased thrombotic and inflammatory risk[24].

Another hypothesis supports the idea that the severe inflammatory response in COVID-19 may be a potential mediator of damage to cardiomyocytes[18] thanks to findings of activation of pro-inflammatory pathways, C-reactive protein, elevated inflammatory markers, and plasma-like troponin in patients with underlying cardiovascular disease and high mortality. Recently, it was shown that significant pulmonary fibrosis occurred by the SARS virus through the activation of the molecular pathway TGF-β-SMAD, the same molecular pathway for the development of fibrosis in the myocardium[25].

Drugs or therapies used to treat patients with COVID-19 for severe multiple organ dysfunction in patients with COVID-19 can lead to cardiac toxicity.

In SARS-CoV-1 infections, it has already been demonstrated that there is a direct cellular viral infection of the myocardium and that the cells reside in the conduction pathways of the heart[20]. Other studies linking myocarditis to viral infections demonstrated the presence of cell damage due to viral entry into myocytes leading to myocarditis, later causing necrosis and myocardial damage[16]. It may lead, in the future, to contractile dysfunctions and heart failure.

The hyperinflammation state caused by cytokine storm viruses and the systemic ramifications of COVID-19 (such as sepsis, vascular inflammation and microthrombosis) together are events capable of developing cardiovascular complications in patients diagnosed with COVID-19[27,28].

COVID-19 can cause lung damage, leading to hypoxemia and vasoconstriction. This continuous decrease in oxygen supply to the heart can lead to myocardial ischemia and subsequent HF or heart disease.

More studies are needed to clarify whether myocardial damage occurs predominantly directly due to the infection of cardiomyocytes by SARS-CoV-2 or indirectly due to systemic release of cytokines or any other mechanism.

COVID-19 can induce cardiac damage beyond ischemic pathways, including stress cardiomyopathy, acute and fulminant myocarditis[25,28,29].

Thus, possible mechanisms of myocardial injury in COVID-19 may be direct systemic inflammation, direct damage to cardiomyocytes, exaggerated cytokine response by immune cells, hypoxia, myocardial fibrosis. These processes evolve into cardiac dysfunctions and HF. However, because most of the data obtained are the result of post mortem tissues or observational clinical samples, the persistence of investigations is necessary in order to bring more concrete evidence to promote their hypotheses in order to turn them into facts.

3.5 MYOCARDITIS

Severe forms of SARS-CoV-2 infection can result in aggression to the cardiac muscle, in the form of myocarditis[5,29].

A study by Shi et al[31] reported that patients with myocardial injury, identified by increased troponin levels, had a higher mortality compared to those without myocardial injury (51.2% x 4.5%; p <0.001), being , thus, a risk factor for mortality[31].

It was also identified that the presence of myocardial injury was associated with a higher incidence of ARDS development (58.5% x 14.7%), greater need for the use of both noninvasive ventilation (46.3% x 3, 9%) as invasive (22.0% x 4.2%)[31].

The same study reported that patients who had elevated troponin also had high levels of leukocytes, D-dimer, C-reative protein, ferritin and IL-6, thus demonstrating the relationship between myocardial damage and inflammatory hyperreactivity[30].

Thus, high troponin levels may be a marker of worse prognosis and mortality in SARS-CoV-2 infection. Inflammation of the cardiac muscle, depending on its extension, can generate a considerable reduction in cardiac contractility, reducing inotropism and increasing filling pressures, in other words: a picture of acute heart failure.

Some authors describe SARS-CoV-2 associated myocarditis as an acute ventricular disorder concomitant with diffuse myocardial edema[32].

There are also reports of presentation of myocarditis associated with pericardial effusion and cardiac tamponade[32].

Inciardi et al[33] emphasize that cardiac muscle involvement may be present even in the absence of symptoms of upper respiratory tract infection. Thus, the Society of Exercise Medicine and Sports (SBMEE) and the Brazilian Society of Cardiology (SBC) defend the performance of a cardiac assessment before returning to physical exercise[34].

Relevant findings reported in the physical examination of these patients were: hypotension, tachycardia, signs of low cardiac output and the presence of B3. The electrocardiographic evaluation may show diffuse ST-segment elevation with concave morphology in association with a significant increase in troponin, cerebral natriuretic peptide (BNP) / NT-proBNP and evidence of inflammatory activity[33].

Transthoracic echocardiography may reveal signs of diffuse hypokinesia and myocardial thickening, in addition to a decrease in the left ventricular systolic ejection fraction [33].

Therefore, the presence of myocardial injury is an indicator of worse prognosis and associated with higher mortality in COVID-19. Therefore, a rigorous cardiovascular assessment

should be performed, using data such as troponin dosage, ECG and bedside echocardiography, especially in patients with more severe signs[31,33,32].

3.6 HEART FAILURE

Mechanisms of myocardial aggression reported in patients with COVID-19, such as direct myocardial injury by viral action, inflammatory damage, imbalance between oxygen supply and demand, and increased atherothrombotic events are conditions that lead these patients to develop acute heart failure[18,33].

3.7 MYOCARDIOL INFARCTION

There are already many studies correlating acute myocardial injury (AMI) with COVID-19, however, these still present low levels of scientific evidence[31,35]. The Fourth Universal Definition of acute myocardial infarction says that clinical or laboratory evidence of myocardial ischemia can be considered AMI, being divided into five different pathophysiological types[35].

The hyperinflammatory and hypoxemic state can cause instabilities of the atherosclerotic plaque, causing thrombi in the coronary arteries and, consequently, infarction (type 1 AMI)[35,36].

Other mechanisms are also suspected. Some authors have shown that certain glycoproteins present in the viral envelope of SARS-CoV-2 can bind to porphyrin and the β chain of hemoglobin, which can decrease serum hemoglobin levels and thus lead to hypoxemia by reducing oxygen transport to tissues , thus causing significant pulmonary and cardiovascular damage[37].

Type 2 AMI, which arises from the imbalance between oxygen consumption and supply, can occur in COVID-19 due to increased oxygen demand (systemic infection) and decreased supply (lung damage and consequent hypoxemia).

Patients previously submitted to coronary angioplasty may develop thrombotic stent occlusion (AMI type 4B), since COVID-19 leads to a state of hypercoagulation due to its systemic infection[35,36].

3.8 TAKOTSUBO CARDIOMYOPATHY

Takotsubo cardiomyopathy, also known as transient left ventricular apical ballooning syndrome, stress cardiomyopathy or "broken heart syndrome", has clinical, electrocardiographic and laboratory characteristics similar to acute coronary syndrome and, therefore, is a differential diagnosis of myocardial injury .

Researchers found an increase in the number of Takotsubo cardiomyopathy cases (from 1.7% to 7.8% during the pandemic)[38].

The presence of electrocardiographic changes (T wave inversion and ST-segment elevation with normal coronary arteries on coronary angiography) and laboratory changes (increase in troponin, NTPro-BNP) are typical of this stress cardiomyopathy, which can be confused with acute myocardial infarction[38].

There is no well-established pathophysiological mechanism, however, the most widely accepted hypothesis is that personal reaction to stressful events (both physical and emotional) release stress hormones that lead to a temporary reduction in the heart's ability to pump.

Given the current pandemic scenario, the psychological, social and financial stress caused by the isolation period may have favored the increase in cases of Takotsubo cardiomyopathy [39].

3.9 VENOUS THROMBOEMBOLISM

Infection by COVID-19 leads to prothrombotic states through direct mechanisms (microvasculitis), indirect (hypoxia), and even behavioral (restriction of walking due to hospitalization in bed)[36,40].

This prothrombotic state may increase the risk of arterial thrombosis and venous thromboembolism (DVT and PTE) in patients with severe COVID-19[40] infection.

The most accepted hypothesis for the pathophysiological relationship between patients with pulmonary thromboembolism and covid-19 was the demonstration of thrombi on chest CT angiography in those patients with high dosage of D-dimer[40].

A study was carried out with 449 patients, of which 99 used low molecular weight heparin for a minimum period of 7 days[40]. Simultaneously, D-dimer levels and prothrombin time were monitored for a period of 28 days. Overall, mortality was similar between groups using and not using heparin. However, in the group with d-dimer dosage with values up to 6 times higher than normal, those who used heparin had lower mortality (40.0% vs. 64.2%, $p = 0.029$). Thus, anticoagulation was recommended in patients with severe COVID-19 and elevated D-dimer[41].

3.10 ARRHYTHMIAS

Although there are few reports in the literature, its potential pathophysiological mechanism seems to be the association of viral fulminant myocarditis caused by COVID-19 [42] and cardiogenic shock, which can lead to the development of ventricular and atrial arrhythmias, considering that this myocardial inflammation and the severe necrosis can develop reentry points

of the cardiac electrical circuit, which can lead to ventricular tachycardia and ventricular fibrillation[42,43].

In order to support this hypothesis, some studies describe the correlation between high troponin levels and a higher incidence of ventricular arrhythmias[42]. However, patients with severe hyperinflammatory state evolve with hypoxemia, a condition that can lead to acute kidney injury, causing hydroelectrolyte disturbances with arrhythmogenic potential, such as hypokalemia[42].

4 CONCLUSION

SARS-CoV-2 infection results from the interaction of the spike glycoprotein present without the viral envelope with ACE2 receptors and this is present in the nasal and oral epithelium, thus explaining its viral entry point, and also in large ones in the lung (site of symptomatic occurrence) and heart.

Evidence supports the idea of myocardial damage spread by the infection, although its mechanism has not yet been recovered. Its presence is more prevalent in hospitalized patients, and it may or may not be associated with previous cardiovascular disease, increased mortality and worsening the prognosis. Troponin revealed that it may be an important prognostic marker.

Although the airway is the main clinical manifestation of SARS-CoV-2 infection, several studies have proven the association of COVID-19 with cardiovascular complications such as myocarditis, acute myocardial infarction, heart failure, takotsubo cardiomyopathy and arrhythmias.

Thus, special attention to the cardiovascular system should be recommended in order to avoid complications of this system or even their early detection so that these patients meet the effective implementation and prognostic improvement.

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