COVID-19 e Doença Cardiovascular: O Impacto da Pandemia

The Impact of COVID-19 Outbreak on Cardiovascular Disease

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Resumo:

SARS-CoV-2, o novo coronavírus, surpreendeu o mundo com a sua capacidade de infecção, causando uma preocupação emergente de saúde pública com mais de 3 milhões de pessoas afetadas em apenas quatro meses. A taxa de mortalidade é variável entre os países, considerando as suas estruturas etárias e o percentual de comorbilidades. Os Idosos e as pessoas com doenças subjacentes são mais suscetíveis ao desenvolvimento de casos graves de COVID-19 e têm maior taxa de mortalidade. As doenças cardiovasculares têm uma importância particular, uma vez que a sua prevalência é elevada e considerando a fisiopatologia da infecção. O vírus usa os receptores da enzima de conversão da angiotensina (ECA) 2 para invadir as células humanas. Esses receptores estão principalmente nos pulmões e no coração. Além do dano viral direto, a hipóxia, a tempestade de citocinas e a libertação de catecolaminas também afetam esses órgãos. No coração, estudos mostraram que a COVID-19 pode causar miocardite, arritmias ventriculares, síndrome coronária aguda e insuficiência cardíaca. Além disso, a lesão cardiovascular pode ser a primeira manifestação de infecção viral em alguns casos, motivo de maior preocupação durante esta pandemia. Os inibidores da ECA e os bloqueadores dos receptores da angiotensina (BRA) são medicamentos de suma importância no tratamento de doenças cardiovasculares. No entanto, alguns estudos sugeriram preocupação com esses medicamentos na COVID-19, pois eles poderiam causar um aumento da ECA2 e aumentar a gravidade da infeção. Até onde sabemos, nenhum estudo demonstrou que inibidores da ECA ou ARA são prejudiciais e as principais sociedades cardiovasculares recomendam a continuidade do tratamento.

Palavras-chave: COVID-19; Doenças Cardiovasculares; Infecções por Coronavírus; SARS-CoV-2.

Abstract:

SARS-CoV-2, the novel coronavirus, surprised the world with its capacity of infection, causing a public health emergency concern with more than 3 million people affected in only four months and forcing public institutions to search for ways of obtaining the contention of the virus. The mortality rate is very different among the countries, considering their age structure and the percentage of comorbidities. Elderly and people with underlying diseases are more susceptible to develop severe cases of COVID-19 and have higher case fatality rate. Cardiovascular diseases have a particular importance, given that their prevalence is elevated and considering the infection pathophysiology. Virus uses angiotensin-converting enzyme (ACE) 2 receptors to invade the human cells. These receptors are mainly in the lungs and the heart. Besides the direct viral insult, hypoxia, cytokines storm and catecholamine's liberation also affect these organs. In the heart, studies have shown that COVID-19 can cause myocarditis, ventricular arrhythmias, acute coronary syndrome and heart failure. Moreover, the cardiovascular insult may be the first manifestation of viral infection in some cases, which is a matter of increased concern during this pandemic. ACE inhibitors and angiotensin receptor blockers (ARB) are drugs of paramount importance in the treatment of cardiovascular diseases. However, studies suggested concern about these medications in COVID-19 because they could cause an ACE2 upregulation and increase the severity of the infection. To the best of our knowledge, no study demonstrated that ACE inhibitors or ARB are harmful and the main cardiovascular societies are recommending the continuity of the treatment.

Keywords: *Cardiovascular Diseases; Coronavirus Infections; COVID-19; SARS-CoV-2.*

Introduction

Infections by the coronavirus family are common in the population and they have been a recognized cause of colds,[1] bronchiolitis and gastroenteritis.[2] However, in December 2019 at Wuhan, China, a "novel coronavirus" infection was noticed for the first time in humans, with the official name SARS-CoV-2 (severe acute respiratory syndrome – related coronavirus 2).[3] The disease, which can be caused by this virus, was called COVID-19, the name being the abbreviation of coronavirus disease and the date from the year of the first diagnosed case. It is important to note that this new virus is a betacoronavirus,

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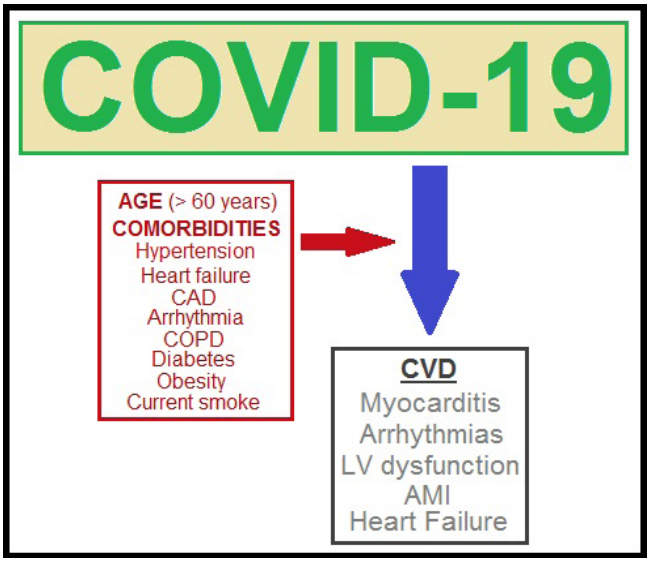
which appears to be more aggressive than alphacoronavirus.[4]

In the last 20 years, two severe betacoronaviruses epidemics were recorded: SARS-CoV, in 2002 arousing in China,[5] and MERS-CoV, in 2012 at Saudi Arabia.[6] The current outbreak, also within this period of 20 years, has become a public health emergency of world concern,[7] a pandemic that has been spreading quickly around the world with more than 10 million cases in six months.[8]

With the aim to flatten the incidence curve and reduce the chances of an overload on the health system, public institutions defined ways to try to obtain the contention of the virus, like travel restrictions and social distancing.[9] Nevertheless, those actions were not able to avoid an enormous number of deaths namely in specific groups, mainly in elderly people and those with underlying diseases, most of all cardiovascular diseases.[9,10]

Among the comorbidities in patients with COVID-19, which can cause severe acute disease and death, it is worth to mention arterial hypertension, coronary artery disease, cardio--cerebrovascular disease and diabetes mellitus.[11,12] Regarding cardiovascular diseases, they are connected to COVID-19 not only as a complication of the previous disease but also as the consequence of the involvement of the heart as a target organ (Fig. 1). The result will be the worsening of the prognosis. Although the more common symptoms of this disease are a respiratory infection with symptoms of fever and dry cough,[13] SARS-CoV-2 infected patients also may have cardiac symptoms related to acute coronary syndrome, heart failure and myocarditis.[12,14]



CAD = coronary artery disease. COPD = chronic obstructive pulmonary disease. COVID-19 = coronavirus disease 2019. CVD = cardiovascular diseases. LV = left ventricle.

Figure 1: Relation between CVD and COVID-19 AMI = acute myocardium infarction.

Methods

A literature review was performed using PubMed to identify relevant English-language articles published through October 6, 2020. Search terms/Keywords included coronavirus, severe acute respiratory syndrome coronavirus 2, 2019-nCoV, SARS--CoV-2, SARS-CoV, and COVID-19 in combination with hypertension, myocarditis, cardiovascular insult, heart failure, left ventricular dysfunction, ventricular arrhythmias.

The search resulted in 1090 total articles. Due to the lack of RCTs, the authors also included case reports, case series and review articles. The authors independently reviewed the titles and abstracts for inclusion. The selection criteria were the relation of the article with cardiovascular disease in the COVID-19 context, in addition to the relevance of the journal. Additional relevant articles were identified from the review of citations referenced.

Epidemiology

Although most of the first cases were mild (80.9%) and the total case fatality rate [(CFR) - deaths per total number of confirmed cases] at the beginning was 2.3%, Chinese reports of February and March 2020 have shown that this infection attack some groups of people with more severity, predominantly elderly, above 80 years.[15,16] At this latter age, the CFR overcame 13.4%.[16] However, in China 86.6% of those infected are between 30 and 79 years,[15] but this reality change according to the demographic profile of the area we are talking about.[9] The age cut-off to define if a person belongs to the elderly group is not clear, considering the big differences in criteria and the wide disparities between developed and developing countries; for this review, it was accepted 60 years.[17]

According to "World Population Prospects 2019" of United Nations, China has 17.4% of its population with more than 60 years.[18] In the case of Italy, one of the countries with more elderly in the world, 29.8% of its population is more than the same age. Obviously, there was a possibility of more severe cases in Italy, and the CFR was 12.8% as of April 2020. In Spain, where 26.3% of people are more than 60 years old, the CFR was 10.2% until the same month, and in the United Kingdom, with 24.4% of elderly, the CFR was 12.1%. Taking into account that the virus came later in some European regions, its governments could take time to determine rules to tackle the infection. Considering the previous government's rules in Portugal, the total CFR was 2.8% as of April 2020, in a country where the elderly population correspond to 29.4%.[18-20] New Zealand, one of the "smart countries", those that face the pandemic with efficacy, the total CFR was only 1.3%, with 22.2% of elderly.[21,22]

Evaluating the country that is now having the greater absolute number of cases, United States of America (USA), the total of its population over 60 is 22.9% and its CFR is 3.7% as of April 2020.[18,19] This country has 154 deaths/million habitants. However, specifically about New York State, the numbers are most worrisome: 1063 deaths/million habitants; in the capital of the state, there are 1162.90 deaths/million habitants, the highest value in the world through April 2020.[19,23] In Brazil,

another big country in America, only 14% of its population are elderly and the CFR is 5.4% as of April 2020.[18,19]

Children's cases are difficult to report and mostly they are mild or asymptomatic.[24] Studies have shown that less than 10% of children evolved to critical disease and several of them had comorbidities, like congenital heart disease, for instance.[25,26] Apart from these severe cases, the symptoms more common in children are the same as the adults, that is, fever and dry cough.[25] Importantly, though the most cases in children are not severe, it is essential to take care to avoid the transmission.[27]

About gender, in most reports the fatalities are more frequent in men, but the reason is not clear yet. In a study, it was suggested that one reason could be that men smoke more than women.[9]

About the spectrum of COVID-19 confirmed cases, a report showed that 80.9% are mild, 13.8% severe and 4.7% critical.[28] As far as the severity of the disease is concerned, we could conclude that mild cases, the majority, received house treatment, severe cases would be the patients hospitalized in common beds and critical cases would be patients in intensive care. Finally, 2.3% of the patients required endotracheal intubation and invasive ventilation, 0.5% needed extracorporeal membrane oxygenation (ECMO) and 1.4% deceased.[29]

PATHOPHYSIOLOGY OF THE VIRUS IN THE LUNG AND THE HEART

The coronavirus has a particular way to infect people; SARS-CoV has high affinity to angiotensin-converting enzyme 2 (ACE2) receptors and use these to invade the humans cells.30,31 Knowing SARS-CoV-2 spike proteins (S proteins) are 76.47% similar to that of the SARS-CoV and considering the 3-D structure of both virus are almost the same,[32] we can assume that the infection mechanism in both cases is the same above-mentioned: ACE2 receptors. The viral invasion mechanism is in the Fig. 2.

Moreover, the attraction force between the virus and ACE2 is stronger in SARS-CoV-2 than SARS-CoV, causing SARS-CoV-2 to be more infectious.[32,33] Furthermore, a study concluded that SARS-CoV-2 does not use other receptors used by others coronavirus, among them aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4),[31] being mostly dependent of ACE2 to entry into the cells.

It is important to explain in this moment the physiological difference between ACE2 and simply the angiotensin-converting enzyme (ACE). Both are related to the renin-angiotensin system, but they have different roles. ACE is responsible, namely, for the conversion of angiotensin I in an active peptide, angiotensin II. AT1 receptor-mediated by angiotensin II activation is responsible for vasoconstriction, sodium retention and fibrosis.[34]

On the other hand, ACE2 is able to convert angiotensin II in angiotensin 1-7, a peptide with vasodilators functions,[35] promoting a balance with ACE. Summarizing, the SARS--CoV-2 target is the ACE2[30,31] and the ACE inhibitors appear to work predominantly against ACE.[36] These interactions can be seen in the Fig. 3.

Although ACE2 is present freely in the blood circulation, it is mostly expressed in organs, like a cell receptor.[37] In search of the pathophysiology of the SARS-CoV, studies[38,39] found the ACE2 receptors distribution in the human body, by immunolocalization or real-time PCR. Arterial and venous endothelial cells, stomach, small intestine, colon, skin, testis, kidney, lungs and heart express them. ACE2 was also found in myofibroblasts and the membrane of fat cells in various organs.

The respiratory system is full of ACE2: nasal and oral mucosa, nasopharynx, bronchial epithelial cells and type I and type II pneumocytes in the lungs, mainly in the type II cells.[38] A study with small animal model showed that the mouse models with more ACE2 in their lungs had more intense respiratory disease.[40] Therefore, ACE2 is not only the virus entry mechanism, but it is important to determine the disease severity. The heart also express ACE2 in significant quantity,[39] both in the endothelium and in the cardiomyocytes.[36]

When the virus interacts with ACE2 receptors of pneumocytes, it enters in the pulmonary epithelial cell and begins its

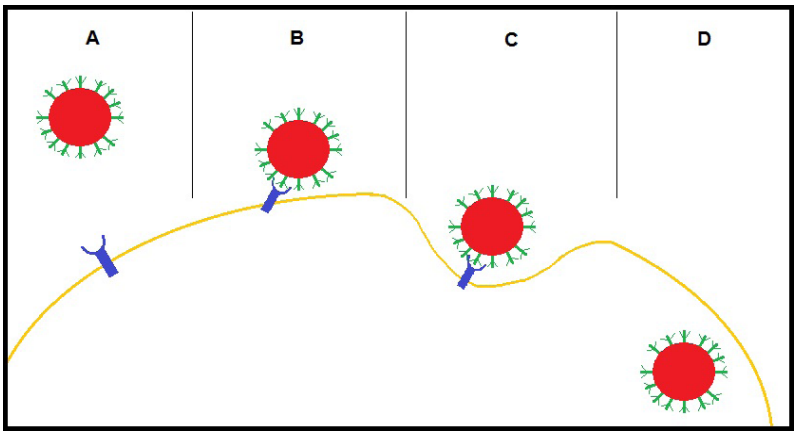
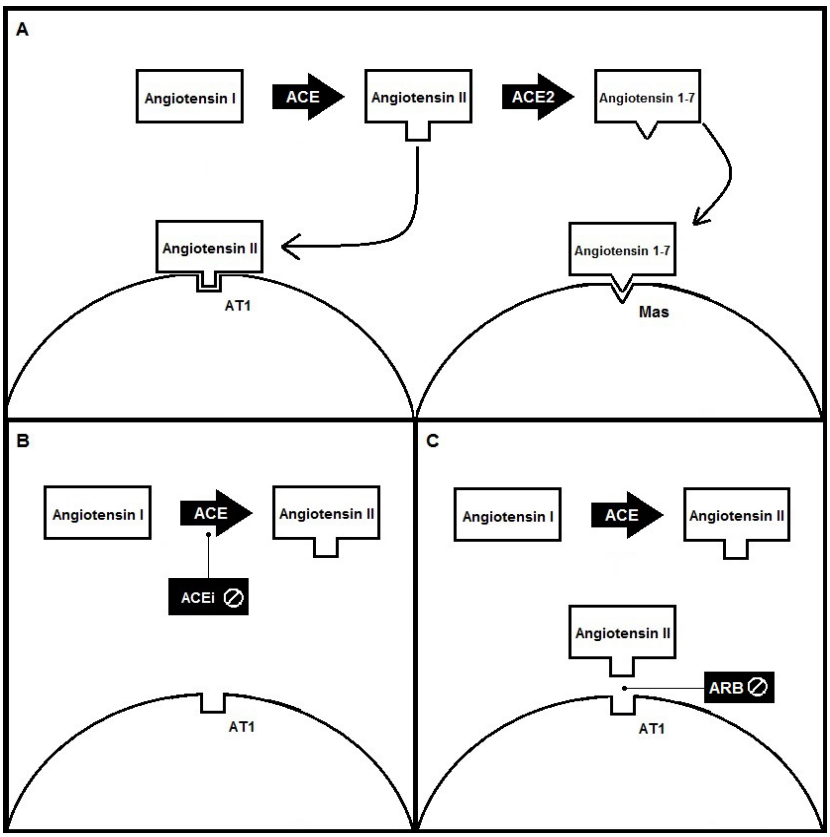


Figure 2: Viral invasion by ACE2 receptors (A) Free virus in circulation. (B) Binding of the virus to the ACE2 receptor. (C) Endocytosis process. (D) Virus inside the cell.



ACE = angiotensin-converting enzyme. AT1 = angiotensin II receptor type 1. Mas = angiotensin 1-7 receptor.

Figure 3: Angiotensin-converting enzymes and their blockers drugs (A) Physiological conditions. (B) Action of angiotensin-converting enzyme inhibitor. (C) Action of angiotensin II receptor antagonist.

replication, it quickly occurs an inflammatory response and a structural change in the cells. With many receptors, the lung cells are destroyed in short period of time.[38] This mechanism explains the diffuse and bilateral alveolar damage and the acute respiratory distress syndrome (ARDS) installation. Indirectly, the systemic immunological response induced by the virus also contribute to the respiratory failure in these patients.[41]

The pulmonary damage also occurs due to the ACE2 receptors in the endothelial cells. The virus causes an inflammatory response in the vessels in all the body and the thrombotic potential of these events is established in reason of this endothelial dysfunction,[42] one of the components of Virchow's Triad. Thus, thrombotic events like pulmonary thromboembolism happen in COVID-19 patients. A histological study showed that COVID-19 infection is able to cause nine times more alveolar capillary microthrombi than other viral infections, like Influenza A (H1N1).[43]

It is relevant to highlight the SARS-CoV-2 prothrombotic potential. A review showed that all the coronavirus could cause a deregulation at the coagulation cascade.[44] In an attempt to avoid the diffuse alveolar hemorrhage, it occurs the development of fibrin clots, which is noticed, for instance, by the D--dimer elevation and low platelets count. In addition, these laboratorial finds are higher in severe COVID-19 patients than in mild cases and they are related to a worse prognosis, in which we could notice disseminated intravascular coagulation.

The relation between coronaviruses and the heart is more complicated. Although the direct viral attack occurs in SARS--CoV,[45] it is not clear if this happens in SARS-CoV-2. Even if the direct viral attack could occur in the heart, pathologic samples had not shown the viral presence in the cardiomyocytes, but only mononuclear inflammatory infiltrates,[46] that justify the myocarditis, as in other viral infections. However, more recently study was able to show that SARS-CoV-2 can entry in the cardiomyocytes. Researchers demonstrated the virus in endocardial biopsy of a COVID-19 patient.[47]

The cardiac damage also occurs by others mechanisms. Hypoxia, caused by the pulmonary injury, leads to cellular acidosis and cardiomyocytes apoptosis,[11] causing cardiac dysfunction. The famous cytokines storm syndrome and the inflammatory markers elevated allow us to understand that the inflammatory response is systemic and it also interfere with the heart.[13] Moreover, the stress related to the illness and the medications used in the treatment are able to promote catecholamine's liberation, favoring cardiac damage.[11]

Left ventricular dysfunction can occur due to myocarditis48 or the cytokine storm syndrome,[49] as noticed in the SARS-CoV. Severe cardiac arrhythmias, like ventricular

tachycardia/fibrillation, also occurs due to the cardiac injury related to the mechanisms above.[50]

COMORBIDITIES AND COVID-19

Since the first reports from China, a correlation between underlying comorbidities and COVID-19 was established. These illnesses might be cardiovascular, cerebrovascular, respiratory, metabolic or immunological diseases and they are related to more severe clinical conditions and death.

A meta-analysis[11] with 1527 Chinese cases, most of them occurred in January 2020, showed that the most common comorbidities were hypertension (17.1%), cardiovascular/cerebrovascular diseases (16.4%) and diabetes *mellitus* (9.7%). Considering that patients in ICU (intensive care unit) have a more severe expression of the disease, a comparison was carried out between comorbidities prevalence in ICU patients versus non-ICU patients. For hypertensive patients and those with cardiovascular/cerebrovascular disease, the difference was statistically significant ($p < 0.00001$). For diabetic patients, the difference was also high, but it was not statistically significant, according to the authors ($p = 0.09$). Finally, they had shown that ICU patients presented more cardiac injury than non-ICU ($p = 0.0001$), considering the troponin I/T altered levels.[11] In addition, another study[51] showed about the acute respiratory distress syndrome (ARDS) that patients with hypertension ($p = 0.02$) and diabetes ($p = 0.002$) had more chance to develop this severe condition.

Regarding the prevalence of comorbidities, hypertension (21.1%), diabetes (9.7%) and cardiovascular disease (8.4%) were also cited in a meta-analysis[52] like the mainly conditions associated to COVID-19. Hypertension (OR: 2.36; 95% CI: 1.46-3.83) and cardiovascular disease (OR: 3.42; 95% CI: 1.88–6.22) were related to more severity.

The mortality in patients with underlying comorbidities is greater than in the general population. The "COVID-19 Clinical Guidance for the Cardiovascular Care Team",[10] elaborated by the American College of Cardiology, show that, while the general CFR was 2.3% in the world, in patients with comorbidities was higher: hypertension (6%), diabetes *mellitus* (7.3%), respiratory disease (6.3%) and cardiovascular disease (10.5%). A study[53] of 113 individuals demonstrated that comorbidities like hypertension, cardiovascular disease and cerebrovascular disease were more common in the deceased people than in those that recovered themselves. Other study[54] with 187 patients had a general mortality rate of 22.9%. However, to people with underlying cardiovascular disease (hypertension, coronary heart disease and/or cardiomyopathy) associated with high troponin T levels, this number rise up to 69.44%. This report show that comorbidities are a big problem to COVID-19 patients, mainly if these patients develop acute cardiac insult.

Furthermore, obesity also might be a risk factor for the development of COVID-19 severe cases and death, considering that ACE2 receptor was also identified in the membrane of fat cells in various organs.[38] Even so, this relation is unclear. One author expressed the idea that the correlation between COVID-19 and obesity is bigger than between H1N1 and obesity in influenza epidemics (2009/2010) simply because there are more obese people in the world nowadays.[55] However, we can see in the same report that obesity is related to decreased respiratory system compliance and more difficult ventilation. Obesity is also associated with a systemic inflammatory process.

Smokers are also more susceptible to COVID-19 infection and have a worst prognosis than healthy people.[56] It is important to highlight that smoking cause injury to respiratory (decreased lung function, emphysema, airway remodelling), cardiovascular (hypertension, acute myocardial infarction, atherosclerosis, endothelial dysfunction) and immunologic systems (rising inflammatory cells, macrophage activation, deficit in cell-mediated immunity), not to mention cancer in several organs.[57] These systemic changes are enough to cause illnesses easier, among them the virus disease.

In short, although people previously sick do not seem to be more susceptible to be infected by coronavirus,[11] the comorbidities rate in the population, associated to their elderly percentage, contribute directly to the severe cases and deaths proportion.[9] As reported, it is especially important that the health care team look for these comorbidities in the patients with COVID-19 and provide special attention to them.

CARDIOVASCULAR INSULT AND MORTALITY

Among the cardiovascular events in COVID-19 patients, we can cite namely myocarditis, arrhythmias, acute coronary syndrome (ACS) and heart failure (HF). Table 1 shows the occurrence of these manifestations.

Myocarditis occurs in about 7.2% – 17.2% of the COVID-19 patients, as an acute cardiac injury.[58,59] It is manifested by chest pain, dyspnea, ventricular arrhythmias and acute left ventricular dysfunction.[60,61] A histological sample of heart obtained from autopsies have shown only mononuclear inflammatory infiltrates[46] in COVID-19 patients. Despite that, 35% of SARS-CoV patients in Toronto/Canada had viral RNA detected in their hearts and died earlier than other subjects.[45] Thus, the direct viral cardiac attack may be dangerous to the patients because it can lead to a more aggressive case. It is unclear until now where the viral invasion in SARS-CoV-2 occur. However, mononuclear

Table 1: Cardiac manifestations in COVID-19.

Wang *et al* [54] Zhou *et al* [55]	Myocarditis	7.2 – 17.2%
Wang *et al* [54]	Cardiac arrhythmias	44.4% [a]
Huang *et al* [13] Wang *et al* [54]	Acute coronary syndrome	7.2 – 12%
Chen *et al* [49] Zhou *et al* [55]	Heart failure	25%

Legend: aICU patients.

inflammatory infiltrates are enough to justify the presence of the cardiomyocytes inflammation during COVID-19.

Other finding in favour of myocarditis is the troponin elevation without ACS. A relevant case report[48] presented a COVID-19 patient that had risen troponin levels during the hospitalization. Electrocardiogram showed minimal diffuse ST-segment elevation and in the coronary angiography was not found obstructive artery disease. Transthoracic echocardiography (TTE) revealed an increased wall thickness, diffuse hypokinesia, mildly impaired left ventricular diastolic function and pericardial effusion. Cardiac magnetic resonance imaging (MRI) showed ventricular walls thicker than common and biventricular hypokinesia, with severe left ventricular dysfunction, biventricular myocardial interstitial oedema, slow gadolinium washout and pericardial effusion. These findings allow us to diagnose acute myocarditis. Considering that TTE is not so specific and its accuracy is limited,[62] MRI is important to increase the diagnostic specificity. However, MRI is not available in all hospitals and is not essential to the management of the patient with an acute cardiac injury. Note that the myocarditis definitive diagnosis is given by histologic analyses.

Cardiac arrhythmias in general may occur in 44.4% of ICU patients with COVID-19.[58] They may be previously sick (hypertension, diabetes *mellitus*, cardiovascular diseases, etc.) or healthy individuals. Obviously, underlying comorbidities rise the chance to develop arrhythmias. Ventricular arrhythmias, hypoxia and the cytokines storm can also lead to atrial fibrillation.[63] Lastly, malignant arrhythmias (ventricular tachycardia/fibrillation) are an important cause of cardiac arrest and death and they are more frequent in patients with myocardial injury and troponin T elevation.[14,54]

Acute coronary syndrome (ACS) is characterized in the COVID-19 context by type I or type II acute myocardial infarction (AMI). Type I AMI occurs due to the atherosclerotic plaque instability and its rupture in patients with coronary artery disease. In infectious illnesses like SARS-CoV-2, the systemic cytokines storm contributes to this case. On the other hand, type II AMI occurs when there is an increase in the cardiac demand – increased heart rate and inotropism in infectious illnesses – associated to hypoxia, both factors related to this viral infection.[64] Studies showed that the acute cardiac injury incidence vary between 7.2% – 12.0%,[13,58] but it is not specified as a diagnosis of AMI.

Despite these findings, most of AMI still occurs in non-COVID-19 patients[65] and this must be considered relevant by medical teams. A study showed that pandemic causes a delay in the minutes between symptoms onset and the first medical contact in until 3.5 times[66] and this may mean an increase in cardiac muscle death; as we know, "time is muscle". Hospitals around the world prepared themselves to face the coronavirus disease and many restrictive protocols for access have been created, which can cause a delay in the medical care. Besides that, people are worried about leaving their homes, even in face of chest pain, for example.

Heart failure can appear in the patients as the first viral disease manifestation. About 25% of all patients presented this condition during hospitalization in the studies of Chen *et al*[53] and Zhou *et al*.[59] The risk was 80% higher for those that had cardiovascular comorbidities. Besides that, 50% of the deceased patients presented heart failure regardless they had comorbidities (hypertension or cardiovascular diseases) or not.

This cardiac manifestation may be acute or an exacerbation of chronic heart failure. However, in a study[53] among 43 subjects that had heart failure only one patient was aware of the disease. We can conclude that according to some reports the acute form is more common than the chronic disease in the COVID-19 cases.

Although the mechanisms are unclear, coronaviruses are also able to cause long-term cardiovascular damage. This happened with SARS-CoV and there is a potential to occur with SARS-CoV-2, considering their similar pathophysiology. A study[67] showed that recovered patients developed hyperlipidaemia (68%), increased triglyceride levels (44%), cardiovascular abnormalities (44%), and abnormal glucose metabolism (60%) about 12 years after the SARS-CoV infection. Other study[49] concluded that there was subclinical diastolic dysfunction in patients with SARS-CoV, but no systolic dysfunction was observed. Importantly, these changes may be reversible later in the viral illness. These two studies express different realities, the first showed that almost half of the patients developed non-reversible cardiovascular abnormalities after 12 years and the second concluded that the cardiac dysfunctions might be reversible.

In addition to the cardiovascular injury, 64% of survivors had lung infections along one decade.[67] A study[68] in 2003 noticed others SARS-CoV respiratory complications several weeks after hospital discharge: pulmonary fibrosis (by chest computer tomographic imaging) at least in 50% of patients, lung function testing with mild or moderate restrictive pattern (about 8 weeks after hospital discharge) in until 20% of the patients and mild decrease in carbon monoxide diffusing capacity in a minority of subjects.

During SARS-CoV epidemic, researchers suggested that lung abnormalities would improve over time. However, another study[69] showed that survivors still presented a reduction in diffusion capacity and a lower exercise endurance capacity when submitted to pulmonary function testing one year later.

The mortality causes were related to cardiorespiratory system: 52.9% died of respiratory failure, 7.3% died of circulatory failure and 32.3% died of both causes.[70] A study[59] of 191 patients also showed that deaths might be related to the increase in age, rise in D-dimer levels and high punctuation in Sequential Organ Failure Assessment (SOFA) on hospital admission.

Other study[71] showed that D-dimer levels were statistically higher among the non-survivor patients (mean of 2.12 µg/mL) compared to the survivors (mean of 0.61 µg/mL). In these case reports, 71.4% of the deceased patients presented disseminated intravascular coagulation criteria. Thus, severe and death

cases may be related to coagulation changes and venous thromboembolism.

In another study, considering the SOFA, we can conclude that sepsis is another mortality cause, related to viral infections or bacterial secondary infections. This complication appeared in 59% of the patients. If we consider only the non-survivors, all of them had sepsis criteria.[53,59]

Several studies showed that cardiovascular insults in patients with COVID-19 are particularly important for their prognosis and recovery, taking into account that the cardiac manifestations may be the first clinical expression in a COVID-19 case and the long-term outcomes may be gloomy.

COVID-19, ACE2 AND ACE INHIBITORS/ARB TREATMENT

Previously, we noticed that ACE2 receptors are the entry door to coronavirus infection.[30,31] Additionally, the more ACE2 receptors, the more severity of the illness.[40]

People with underlying comorbidities like hypertension, diabetes *mellitus*, coronary artery disease, heart failure and chronic kidney disease frequently take drugs like ACE inhibitors or angiotensin receptor blockers (ARB). These medications might increase ACE2 expression in their users[12,72] promoting a cardiovascular benefit, given that ACE2 initiate vasodilator and antioxidant functions. In diseases with a renin-angiotensin system exacerbation, ACE2 is decreased, worsening the illness.[73] ACE2 upregulation may be harmful in coronaviruses disease, considering the pathophysiology. However, this hypothesis needs to be proved by clinical studies.

A Chinese study[54] showed that 21.1% of the patients with higher troponin during COVID-19 infection were using these medications, against 5.9% with normal troponin, demonstrating the elevated rate of cardiovascular disease in these subjects. Despite that, this elevation was not significantly different for the mortality rate. On the other hand, an Italian study[74] with more than 37 000 patients demonstrated that ACE inhibitors/ARB were neither related to higher risk for infection nor to severe or fatal outcomes. Others three studies[75-77] also concluded it: deaths during the hospitalization were not related to these drugs and there was no relation between antihypertensive medications and severe coronavirus disease.

A study[78] showed that hypertensive patients treated with ACE inhibitors/ARB evolved less frequently to severe COVID-19 than hypertensive patients without these drugs. These findings weaken the hypothesis that these antihypertensive drugs can cause damage in patients infected by SARS-CoV-2.

A report suggested the treatment with calcium channel blockers as an alternative to the hypertension treatment.[79] However, ACE inhibitors/ARBs are not used only to this illness. In heart failure with reduced ejection fraction, for instance, ACE inhibitors/ARBs change the prognosis and reduce the mortality rate.[80] Importantly, the abrupt suspension of these drugs could cause clinical instability and the consequences could be catastrophic.[81]

Lastly, cardiovascular societies around the world indicate the maintenance of ACE inhibitors/ARBs for cardiovascular diseases,[82-85] taking into account the importance of these drugs to control patients' comorbidities and avoid complications. Considering that there is no demonstration of harm of these drugs in COVID-19 context, they must be kept.

Conclusion

Although coronavirus infections are common in the population, SARS-CoV-2 is an aggressive form with a high rate of contagiousness and the virus outbreak implies prevention actions that must be taken by the governments in order to avoid the spread of the infection.

COVID-19 may cause important cardiovascular manifestations, like myocarditis, acute myocardial infarction, ventricular arrhythmias and heart failure. Cardiac symptoms may be the first presentation of the disease, regardless of the fact that the patient has previously underlying cardiac disease. This circumstance may however contribute to more severe prognosis. ■

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