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Cardiovascular injury in COVID-19: An extension of pulmonary disease

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Abbreviations
ACE: Angiotensin-converting enzyme
AMI: Acute myocardial infarction
ARDS: Adult respiratory distress syndrome
COVID-19: Coronavirus disease 2019
ICU: Intensive care unit
NT-proBNP: Amino-terminal pro-brain natriuretic peptide.
RAAS: Renin-angiotensin-aldosterone system
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

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ABSTRACT

Faced with a pneumonia outbreak in 59 suspected patients at a local seafood market in Wuhan, China, the first case of a novel coronavirus was laboratory-confirmed on December 1, 2019. On January 7, 2020, a new type of virus of the family Coronaviridae called SARS-CoV-2 −causative agent of COVID-19− was identified. The few initial reports restricted involvement to the lower respiratory tract. Both, disease progression and build-up of scientific evidence, proved the crucial role played by cardiovascular involvement in the development and prognosis of the infection. Age is an independent predictor of mortality and an association between pre-existing cardiovascular disease and severe forms of the disease has been demonstrated. Cardiovascular involvement may be either direct or indirect; acute myocardial injury, myocarditis, acute myocardial infarction, heart failure, arrhythmias and venous embolic events stand out among others. Adverse effects of treatment for cardiac complications and drug testing in therapeutic protocols may be contributing aspects. This paper addresses cardiovascular involvement due to COVID-19.

Keywords: SARS-CoV-2, COVID-19, Cardiovascular complications, Risk factors, Mortality

Daño cardiovascular en la COVID-19: Una extensión de la enfermedad pulmonar

RESUMEN

Ante la ocurrencia de un brote de neumonía en 59 pacientes sospechosos en un mercado local de mariscos en Wuhan, China, el 1 de diciembre de 2019 fue confirmado por el laboratorio el primer caso de un nuevo coronavirus, hasta entonces desconocido. El 7 de enero de 2020 fue identificado un nuevo tipo de virus de la familia Coronaviridae denominado SARS-CoV-2, agente causal de la enfermedad conocida como COVID-19. Los escasos informes iniciales limitaban la afectación al tracto respiratorio inferior. Con el progreso de la enfermedad y el cúmulo de evidencia científica, se demostró el papel fundamental que desempeña la afectación cardiovascular en el desarrollo y pronóstico de la infección. La edad es un predictor independiente de mortalidad y se ha demostrado una asociación entre la enfermedad cardiovascular preexistente y las formas graves de la enfermedad. La afectación cardiovascular puede ser directa o indirecta, se destacan el daño miocárdico agudo, la miocarditis, el infarto agudo de miocardio, la insuficiencia cardíaca, las arritmias y los eventos tromboembólicos venosos. Se añaden los efectos adversos del tratamiento de las complicaciones cardíacas y el ensayo con fármacos en los protocolos terapéuticos. En esta monografía se revisa el daño cardiovas-

cular por la COVID-19.
Palabras clave: SARS-CoV-2, COVID-19, Complicaciones cardiovasculares, Factores de riesgo, Mortalidad

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) identified in 2019 in Wuhan, China, is a new strain of coronavirus responsible for the Coronavirus Disease 2019 (COVID-19) pandemic.

The main manifestation of this disease is respiratory involvement, which in its clinical spectrum can range from asymptomatic patients with mild respiratory symptoms (80%), to adult respiratory distress syndrome (ARDS) (20%) with potentially fatal outcomes[1].

During the initial stages of the pandemic and given the limited scientific evidence available, it was thought that this coronavirus caused symptoms limited to the respiratory tract. With the publication of reports on large series of the disease in different countries, it was observed that cardiovascular involvement plays a fundamental role in the development and prognosis of the infection.

Patients with pre-existing cardiovascular disease and other cardiovascular risk factors are more susceptible to COVID-19 infection and its clinical complications, thus being the group with the highest risk of morbidity and mortality. However, it is important to know that the direct myocardial involvement that takes place in the course of severe infection in healthy individuals favors acute cardiovascular damage[2,3]. Its expression through *de novo* cardiac complications, such as acute myocardial injury (8-12%), myocarditis and arrhythmias (16.7%), highlight the need to study the pathophysiological mechanisms related to cardiovascular damage in SARS-CoV-2 infection (COVID-19), its diagnosis and therapeutic interventions in this particular group of patients[1,4].

History of coronavirus infection

In 1965, Dorothy Hamre, a researcher at the University of Chicago, while studying tissue cultures of students with cold, discovered a new type of virus, now known as 229E. This turned out to be a coronavirus, the first one in infecting humans and the responsible for the common cold. Two years later Dr. McIntosh's team discovered what is now known as OC43, another coronavirus affecting humans that causes the common cold[5].

In 1968, the term "coronavirus" was coined, based on how, under an electronic microscope, its surface resembled the outer layer of the Sun, called corona. In 2004, NL63 was discovered in Netherlands, causing mild to moderate infection in the upper respiratory tract as well as more severe infection in the lower respiratory tract. One year later HKU1 was discovered in Hong Kong, which causes mild to moderate infection in the respiratory tract.

Of the seven species of the *Coronaviridae* family, the following strains cause mainly mild respiratory symptoms: 229E, OC43, NL63 and HKU1. There are three strains of coronavirus capable of triggering a severe and fatal systemic disease: SARS-CoV-1, responsible for the severe acute respiratory syndrome (SARS) epidemic in 2003; MERS-CoV (Middle East Respiratory Syndrome), identified in 2012 in the Middle East; and SARS-CoV-2 discovered in China, in 2019, responsible for the current COVID-19 pandemic.

SARS-CoV-2 infection

The first laboratory-confirmed case of SARS-CoV-2 infection took place on December 1st, 2019, during the presence of a pneumonia outbreak in 59 suspected patients at a local seafood market in Wuhan, this event triggered the epidemiological alert with the isolation of a new coronavirus in the lower respiratory tract, initially named 2019-nCoV2[6]. Just one month later, on January 7th, 2020, a new type of virus of the *Coronaviridae* family named SARS-CoV-2 was identified as the causative agent of the outbreak. The exponential increase in transmissions and its worldwide spread led the World Health Organization (WHO) to declare the infection as a pandemic on March 11th, 2020[7].

EPIDEMIOLOGY

The SARS-CoV-2 (COVID-19) infection currently affects more than 215 countries, with more than 77 228

903 million of cases, about 44 300 000 recovered patients and more than 1 718 470 deaths. Until today (December/2020), the most affected country in terms of number of cases is the United States of America, with about 18 090 260 diagnosed patients and 320 180 deaths. The first Latin American country affected was Brazil, which reported the first case on February 26th; the first death was recorded in Argentina on March 7th. Brazil is today the Latin American country with the highest number of cases, with nearly 7 318 821 cases and 188 259 deaths[8].

Cuba registers to date, on the official government website of the Ministry of Public Health (MINSAP by its acronym in Spanish)[9], 10 500 patients diagnosed with COVID-19, of which 9 307 patients (88.6%) have recovered and 139 have died.

RISK FACTORS

The most accurate data have been taken from published studies on the Chinese population that experienced the first SARS-CoV-2 infection[4,10,11] and included "in its first report" 72 314 confirmed cases (44 672 laboratory-confirmed, 16 186 suspected, 10 567 clinically diagnosed, and 889 asymptomatic cases).

Age

Age over 80 years old was documented as the main risk factor for mortality; 87% were aged between 30 and 79 years old, with a mortality of 14.8%. In one of the Chinese cohorts, age was identified as an independent predictor of mortality, with an odds ratio (OR) of 1.1 (95% confidence interval [95% CI], 1.03-1.17) per year[12]. A WHO report on 55 924 confirmed cases in China showed a mortality rate of 14.8% in patients over 80 years old and 8% in those aged 70-79 years old, compared to rates of less than 0.5% in those under 50 years old[13].

Age is a risk factor for both cardiovascular disease and progressive deterioration of the immune system's capacity, and disturbances in the immune response have been associated with a higher prevalence of cardiovascular disease[14]. This fact may be influenced both by the physiological aging process and, especially, by the greater prevalence in elderly patients of frailty and comorbidities that contribute to a decrease in functional reserve, which in turn reduces intrinsic capacity and resilience, and makes it more difficult to cope with diseases and, in particular, infections. This explains why in the current SARS-CoV-2 infection the elderly populations and those with pre-existing medical comorbidities, or both, are the most vulnerable ones and who more frequently present more severe forms of the disease[4,6,15].

Comorbidities

To establish the true prevalence of comorbidities and cardiovascular mortality among the patients infected with SARS-CoV-2 is difficult. The data are variable and they are influenced by several demographic, social and epidemiological circumstances in each country, in addition to possible differences in the approach of the diagnosis and treatment of patients[13]. Despite this, the number of available studies suggests an association between pre-existing cardiovascular disease and severe cases of COVID-19 infection. Between 32% and 48% of patients in the published cohorts present some type of comorbidity, the most prevalent being high blood pressure (15-30%), diabetes mellitus (19-20%) and cardiovascular disease (8-15%)[6,12]. A meta-analysis of six studies with a total of 1 527 patients reported a prevalence of high blood pressure of 17.1%, cardiovascular and cerebrovascular disease of 16.4% and diabetes mellitus of 9.7%. Patients who required admission to intensive care units (ICU) were more likely to have these comorbidities[16].

Among the risk groups with adverse clinical evolution and high mortality in the first report from China, which included 72 314 confirmed cases, the following stand out: presence of cardiovascular disease (10.5%), diabetes mellitus (7.3%), chronic pulmonary disease (6.3%), high blood pressure (6%) and a history of neoplastic disease (5.6%). The 81.4% presented mild infection, with a total mortality of 2.3%, the 13.9% presented severe infection and the 4.7% critical infection. In the group of patients with critical infection a mortality rate near the 50% was documented[8]. In another cohort from Wuhan, the ICU requirement was 26%; 60% due to ARDS, 40% due to arrhythmias and 30% due to shock[4].

SARS-CoV-2

Virus structure

The SARS-CoV-2 is a single-stranded RNA virus of

the beta-coronavirus genus, *Coronaviridae* family with envelope. The 2/3 of the genetic material translates into 16 non-structural proteins and 1/3 corresponds to four structural proteins: S protein, which presents a S1 subunit that intervenes in the virus affinity for the angiotensin-converting enzyme 2 (ACE2); the S2 subunit, which facilitates cell membrane fusion; the M protein, which allows the RNA release into the host cell and the N and E proteins, which are structural proteins responsible for interacting with the innate immunity of the host[17].

Role of the renin-angiotensin-aldosterone system in SARS-CoV-2 infection and the development of complications

The renin-angiotensin-aldosterone system (RAAS) contributes to the regulation of blood pressure through the vasoconstrictive properties of angiotensin II and the sodium-retaining properties of aldosterone (**Figure 1**).

Renin is an aspartyl protease synthesized in the form of an inactive proenzyme, in renal afferent arterioles. Active renin, once released into the circulation, cleaves a substrate: angiotensinogen, to form an inactive decapeptide: angiotensin I. Angiotensin-converting enzyme (ACE) is an ectoenzyme that promotes the conversion of angiotensin I into an active octapeptide: angiotensin II, and it is found predominantly in the lung and vascular endothelium, although it is almost universally distributed[18]. The ACE separates other peptides (and consequently inactivates them) including bradykinin which is a vasodilator. Angiotensin II, by acting predominantly on type 1 angiotensin II (AT1) receptors distributed in cell membranes, ends up being a potent pressor substance, the main trophic factor for aldosterone secretion by the glomerular area of the adrenals and a potent mitogen that stimulates smooth muscle cells in vessels and myocyte proliferation. Angiotensin II, regardless its hemodynamic effects, is also involved in the pathogenesis of atherosclerosis, through a direct cellular action on the vascular wall.

A type 2 angiotensin II receptor (AT2) has been identified, that is widely distributed in the kidneys, exerting functional effects opposite to those of the AT1 receptor. The AT2 receptor induces vasodilation, sodium excretion and inhibition of cell proliferation and matrix formation.

Experimental data suggest that the AT2 receptor increases vascular remodeling by stimulating smooth muscle cells apoptosis and contributes to the regulation of glomerular filtration. The block of the AT1

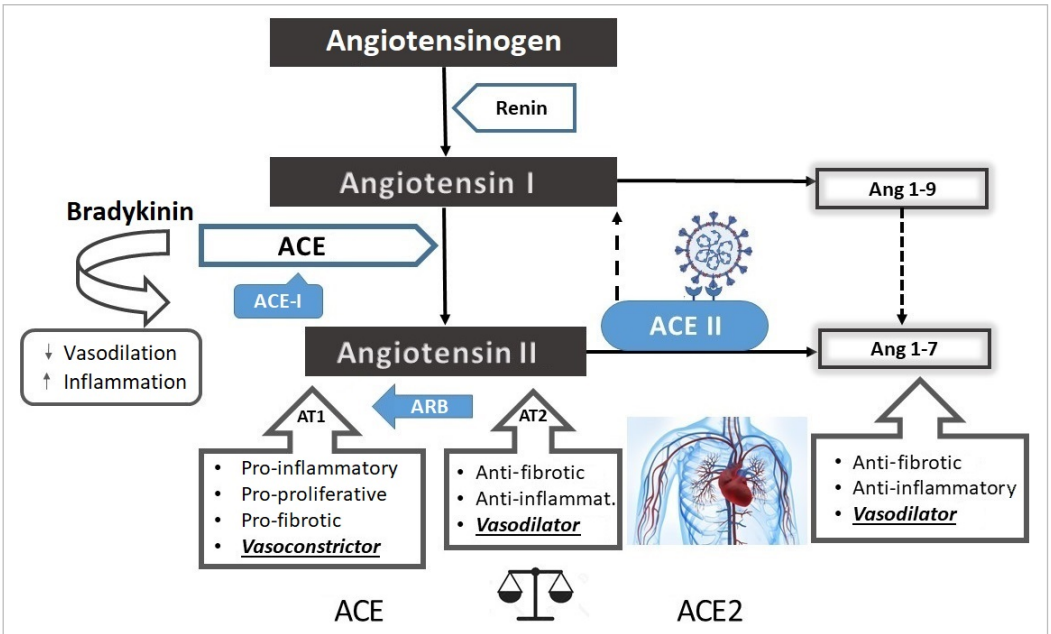

Figure 1. COVID-19 effect on the activation of the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitors; Ang, angiotensin; ARB, angiotensin II receptor blockers; AT1 and AT2, angiotensin II receptors. Taken from: de la Torre Fonseca LM. CorSalud. 2020;12(2):171-183[21].

receptor induces an increase the AT2 receptor activity.

The ACE2 is an important link in the genesis of COVID-19 disease and the main cardiovascular complications that this virus causes. This enzyme is widely disseminated in the pulmonary alveolar cells (type II), the heart, the vascular endothelium, the testicles, the intestine and the kidneys[19]. It is an ACE carboxypeptidase analogue that acts by degrading angiotensin II into angiotensin I-7 (Ag 1-7), and angiotensin I into angiotensin I-9 (Ag 1-9); with a counterbalancing role to the pro-inflammatory, pro-fibrotic and vasopressor effect of angiotensin II in the RAAS[20,21] (**Figure 1**). The Ag 1-7, which is one of the degradation products of angiotensin II, acts as an antagonist to the vasoconstrictive effects of angiotensin II, from a potent vasodilator effect.

Both angiotensin converting enzymes are analogous, ACE plays a determining role in the conversion into angiotensin II and ACE2 in its degradation. The balanced concentration of both angiotensin-converting enzymes in the kidneys and the heart ensures the proper regulation of urine output and blood pressure.

This balance is usually broken under certain conditions and shifts towards an increase in ACE2 in the heart, as it happens with the use of drugs that act on the RAAS or due to hemodynamic disturbances in the organism. The ACE inhibition, which leads to a decrease in angiotensin II concentrations, and the treatment with aldosterone antagonists increases ACE2 genetic expression in the heart[18,22].

Cardiovascular comorbidities such as those associated to SARS-CoV-2 infection (high blood pressure, heart failure, coronary artery disease), increase ACE expression and alter this ratio (ACE/ACE2) with the resulting vasoconstrictive effects. This imbalance leads to attenuation of their vasodilator, antifibrotic and anti-inflammatory effects and contributes to endothelial dysfunction and myocardial damage, which are cardiac and vascular complications frequently observed in these patients[18,21,23].

The relationship between the SARS-CoV-2 and the RAAS is given due to the fact that the ACE2 is considered to be the site of entry of SARS-CoV-2 into the cell. The entry of the virus into the organism, its internationalization, replication and the cardiovascular manifestations caused by COVID-19 are largely signaled by the binding of the virus to ACE2 receptors and the deregulation of the system, which increases the expression of ACE and, therefore, of angiotensin II with the deleterious effects that this causes[21,24].

Once the susceptible host is exposed to SARS-CoV-2 virus, and based on the arrangement of its structural proteins, the virus binds to the ACE2 receptor through the surface protein subunit (S): the S1 subunit mediates the affinity of the virus for ECA2 and the S2 subunit allows fusion with the cell membrane, so that this protein (S) undergoes a change in its structure that facilitates the binding of the virus surface to the target cell[17,25]. As a result of this binding of the virus to the host cell, the concentration of available ACE2 decreases and the ratio (ACE/ACE2) is altered with the consequent vasoconstrictive effect secondary to the increase in angiotensin II.

From the above analysis, the idea could be derived that patients receiving ACE inhibitor (ACEI) drugs, or AT1 receptor blockers (angiotensin II receptor antagonists [ARAII]) for the treatment of chronic cardiovascular diseases, such as high blood pressure, heart failure or coronary artery disease, may be susceptible to a greater impact of SARS-CoV-2 infection; this associated with the overexpression of ACE2. This hypothesis would explain the increase in the mortality observed in infected patients who present a pre-existing heart disease. However, the increase in the concentrations of Ag 1-7 and Ag 1-9, also generated by these RAAS blockers, could have a probable "beneficial effect"[26]. This last result has been demonstrated in animal models infected with SARS-CoV-1, where block of the RAAS resulted in a decrease in the appearance of pulmonary edema and ARDS. However, this consequence has not been confirmed in SARS-CoV-2 infection[24].

To date, the available scientific evidence does not support the postulate in favor of an increased risk of infection and the appearance of cardiovascular complications in patients with these therapies[27,28].

CARDIOVASCULAR INJURY

Pathophysiological mechanisms related to cardiovascular injury

In addition to the interaction of the virus with the ACE2 receptor in pulmonary alveolar cells, that is the main scenario of transmission and infection, which explains why the respiratory system is the most frequently affected, there is a high incidence of cardiovascular involvement in these patients. Sev-

eral mechanisms have been stated in order to try to explain the damage to the heart and vessels (**Figure 2**)[29].

I. Direct myocardial injury

The ACE2 shows a wide organic distribution: heart and vascular endothelium. The SARS-CoV-2 enters host cells via spike (S) protein binding and it interacts with the ACE2 receptor on the myocardial surface. Its effect on cardiovascular homeostasis through the RAAS directly generates myocardial injury by this mechanism[3].

II. Indirect myocardial injury

In these cases the infection is not caused due to direct viral invasion to the myocardium. There are other mechanisms that indirectly affect the myocardium, among which are: inflammatory, neurogenic, vascular hyperreactivity, endothelial dysfunction, hypoxia, procoagulant activity, microvascular injury, thrombosis, adverse drug effects and electrolyte alterations[30,31].

Systemic inflammation: COVID-19 disease, in its most severe form, causes an acute systemic inflammatory response, subsequent to the release of proinflammatory cytokines (TNF-α, IL-1β, IL-2R, IL-6, IL-12, ferritin, chemotoxins) responsible for myocardial damage and secondary multi-organ failure[1,6].

Type 1 acute myocardial infarction: the systemic inflammatory response can cause increased stress in the coronary circulation, leading to ulceration, fissure, erosion or dissection and rupture of a plaque; resulting in intraluminal thrombus in one or more of the coronary arteries, triggering reduced myocardial blood flow or distal platelet embolism with subsequent myocyte necrosis. In 5 to 20% of cases angiography shows non-obstructive coronary artery disease or the absence of such disease, especially in

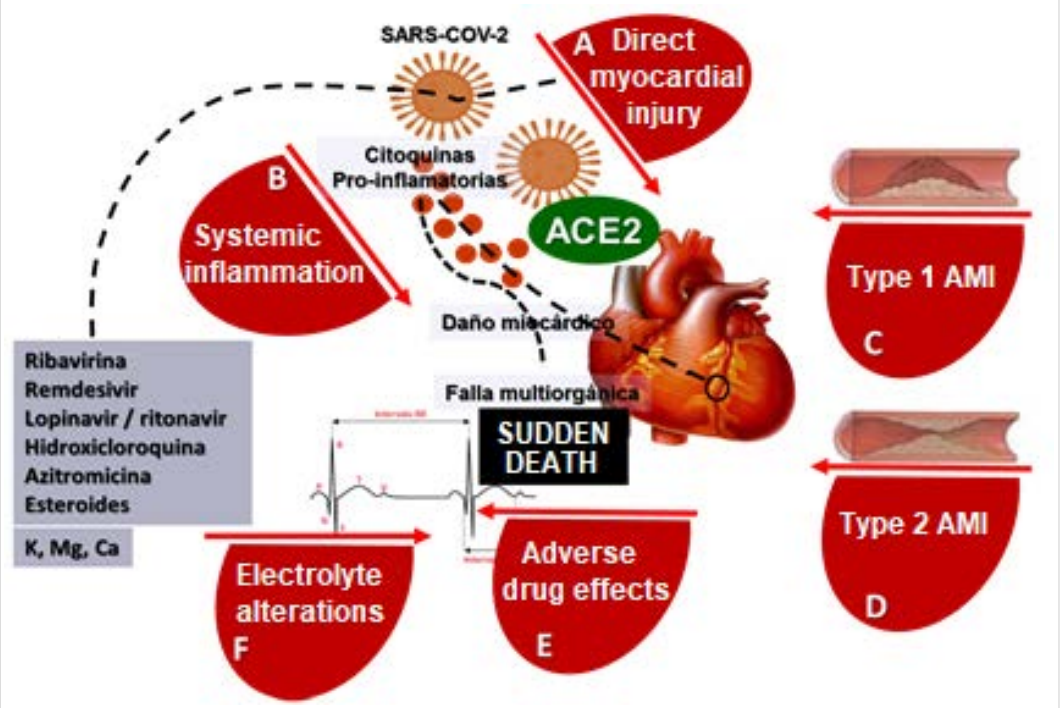

Figure 2. Pathophysiological mechanisms related to cardiovascular damage in COVID-19. **A**. Direct myocardial injury caused by viral infection to the myocardium. **B**. Systemic inflammation secondary to severe sepsis with release of inflammatory mediators. **C**. Type 1 myocardial infarction: acute changes in the vulnerable plaque secondary to the stress in the coronary circulation. **D**. Type 2 myocardial infarction: imbalance between myocardial oxygen demand and supply secondary to hypoxia. **E**. Effects of drugs used in the treatment scheme for COVID-19 on the myocardium and the cardiac conduction system. **F**. Electrolytic disturbances of the critically ill patient. ACE: angiotensin-converting enzyme; AMI, acute myocardial infarction.

women[32,33].

Type 2 acute myocardial infarction: the systemic inflammatory response syndrome in the critically ill patient, with the consequent increase in oxygen demand associated with hypoxia due to pulmonary involvement, generates an increase in myocardial demand, creates an imbalance between myocardial oxygen supply and demand, and causes myocardial injury with necrosis. Coronary vasospasm and endothelial dysfunction are other mechanisms at work[32,34].

Adverse effects of pharmacological therapies: the treatments for COVID-19 that are being currently studied can have cardiovascular side effects (antivirals, anti-malarials, steroids, antibiotics) as well as causing myocardial injury or IV conduction disturbances, such as prolonged QT interval and ventricular arrhythmias *torsades de pointes* type, which can lead to sudden death[35].

Electrolyte disturbances: multisystemic disturbances in the critical patient can generate imbalance of the internal environment, the most common ones being calcium, magnesium and potassium disturbances. Hypokalemia resulting from the interaction of the virus with the RAAS is a factor that conditions the appearance of cardiac arrhythmias[36].

Cardiovascular complications in COVID-19

The COVID-19 can cause a severe infection with significant implications in patients with heart disease. Patients with cardiovascular disease have a higher risk of presenting severe symptoms and death. Furthermore, SARS-CoV-2 infection has been associated with multiple direct and indirect complications in the cardiovascular system, such as acute myocardial damage, myocarditis, acute myocardial infarction (AMI), heart failure, arrhythmias and venous thromboembolic events[3,12]. In addition, treatment protocols in which drugs for treating COVID-19 with possible beneficial effects are being tested can have cardiovascular side effects; these interactions frequently lead to hospitalized patients being withdrawn from their usual pharmacological treatment and all this can lead to acute cardiological decompensation. Furthermore, in the elderly patient, polypharmacy, with the use of antipsychotic drugs and other antibiotics that lengthen the QT, could contribute to cardiotoxicity derived from these combinations[35,37,38].

Myocardial injury

The damage caused to the heart cells by SARS-CoV-2 infection defines myocardial injury. The frequency of this complication varies from 7.2% to 28%, largely influenced by its definition and by the type and severity of hospitalized patients. It is usually associated with non-ischemic etiology, such as acute inflammatory cardiomyopathy or takotsubo syndrome, and ischemic with infarction types 1 and 2[3].

Myocardial injury or damage is defined as the detection of cardiac troponin (T or I) value above the 99th percentile of the upper reference limit, which can respond to an acute or chronic damage depending on the enzymatic curve values[32]. In addition to presenting high values of cardiac enzymes, these patients with myocardial injury often have electrocardiographic alterations of the ST segment and the T wave, and disorders of regional motility of the left ventricle walls as well as of the cardiac function, identified through echocardiogram[39].

An association between cardiac injury and mortality in admitted patients has been found. Myocardial injury was documented in five of the 41 first patients diagnosed with COVID-19 in Wuhan[6]. In a cohort of 416 patients in this same city, 19.7% had high troponin I levels above the reference value, predominant in elderly patients (74 vs. 60 years old) and a higher number of comorbidities: high blood pressure (59.8%), diabetes mellitus (24.4%) and coronary artery disease (29.3%). These patients needed more non-invasive mechanical ventilation (46.3% vs. 3.9%) and invasive mechanical ventilation (22% vs. 4.2%); they also received treatment with corticosteroids, antibiotics and immunoglobulin more frequently and acute renal failure was the most common complication. The risk of death for patients with myocardial injury was 4.26 times higher than that found in patients without myocardial injury at symptom onset (HR 4.26, 95% CI: 1.92-9.49), as well as between the admission and the fatal outcome (HR 3.41, 95% CI: 1.62-7.16). A higher mortality was evidenced in patients with myocardial injury (51.2% vs. 4,5%). These findings suggest a correlation between the infection severeness, the myocardial involvement degree and mortality[39,40].

Proposed pathophysiological mechanisms

Although severe hypoxemia secondary to respiratory dysfunction can, by itself, explain myocardial in-

jury through the oxidative stress, mitochondrial damage and right ventricular failure that it causes, other mechanisms are proposed. A hypothesis links ACE2, this signaling pathway could play a role in the direct myocardial damage mechanisms (**Figure 2**)[3]. Another suggested mechanism involves the cytokine storm triggered by the imbalance between the type 1 and type 2 response of T helper lymphocytes[41]. This pathway is characterized by an increase in circulating levels of pro-inflammatory cytokines: gamma interferon (γ), alpha tumor necrosis factor (TNFα), interleukins (IL-1β, IL-6, IL-12) and chemokines. This generalized inflammatory response, associated to inflammation and extensive lung damage, promotes, among its most notable effects, a large decrease in myocardial contractile force; which plays an important role in calcium homeostasis, excitation-contraction junction, nitric oxide metabolism and signaling through second messengers; in addition to facilitating cell apoptosis, when ischemic damage has been established, which contributes to cardiac dilation[1,3,41].

Disturbances caused by vascular endothelial dysfunction in patients with COVID-19 lead to inadequate vasodilation of the coronary microcirculation, which is an expression of the imbalance between vasodilator and vasoconstrictive substances, which results in the loss of the regulatory capacity of the normal vascular tone. This deregulation leads to a decrease in the reserve of the coronary flow. In patients with previous heart disease and severe forms of the virus infection, the imbalance accentuated by these disorders between the (inadequate) supply and (increasing) demand of oxygen to the myocardium explains the final myocardial damage[21].

Multiple factors are involved in the initiation and perpetuation of endothelial dysfunction with its effects on the coronary and systemic vasculature, from the overexpression of angiotensin II and endothelin to the entry of SARS-CoV-2 into host cells, when interacting with the ACE2 receptor on the myocardial surface (direct pathway)[3], to the release of pro-inflammatory mediators[42], dysregulation of nitric oxide metabolism, and microvascular injury with microthrombi in myocardial capillaries due to disseminated intravascular coagulation (indirect pathway)[1,30,31].

Another mechanism invoked in patients with myocardial damage due to COVID-19 is that resulting from an imbalance between myocardial oxygen supply and demand. In COVID-19 positive patients (with or without known coronary artery disease) the hemodynamic changes that take place in severe forms of the disease favor an imbalance, which in basal conditions, even with the presence of coronary obstruction, would allow the patient to meet his or her needs. The increase in myocardial oxygen consumption, favored by severe sepsis, tachyarrhythmias, high blood pressure, hypoxia, coronary spasm, right ventricular claudication and secondary biventricular claudication, requires significant increases in coronary flow (demand). This increase in flow (supply) cannot be supplied, especially in patients with coronary artery disease where there is already compromised flow due to underlying coronary stenosis, aggravated by infectious-inflammatory, neurogenic, humoral mechanisms, endothelial dysfunction and dysregulation, and vascular hyperreactivity[21,24,32].

The cardiologist or intensive care specialist taking care of critically ill patients with myocardial damage in the course of COVID-19 faces, in these authors' opinion, three important challenges. The first one is to be able to make the diagnosis of myocardial damage and to avoid the classic initial tendency to diagnose this condition as acute myocardial ischemia. The second one is to identify whether myocardial damage takes place in the context of a pre-existing heart disease, where prognosis and mortality are usually higher, or whether it takes place in the absence of preceding cardiac involvement. And the third one is to unravel when the enzymatic increase corresponds to primary damage to cardiac cells, and when it is secondary to critical stages of the disease[21,32].

CARDIAC BIOMARKERS IN COVID-19

Troponins T and I

The increase in troponin levels in patients with acute respiratory distress syndrome (ARDS) is a known and documented fact[43]. In the identification and stratification of the risk of cardiovascular complications in patients with COVID-19, the role of this biomarker is decisive in the management of COVID-19 infection and its cardiovascular repercussions. The data available on the pandemic allow us to assert that patients with myocardial injury evidenced by high cardiac troponin levels (T or I) above the normal range (10 000 ng/L) show a direct and proportional relationship with the severeness of the dis-

ease and increased hospital mortality. The study by Shi, *et al.*[39] with a retrospective design, included 416 patients admitted in Wuhan province (China) with a diagnosis of COVID-19; the 19.7% had high troponin I levels, with a mean age of 64 years old and hospital mortality was quantitatively higher than those with normal troponin values (51.2% vs. 4,5%). It is also illustrative the Guo *et al.*[44] report in 187 patients with confirmed diagnosis for COVID-19, where the 27.8% presented high values of troponin T with a hospital mortality of a 52% respect to an 8.9% of those who had enzymatic values within the range of normality. In this study the 69.4% of cases with myocardial damage had a history of cardiovascular disease. Mortality is higher in patients with a history of heart disease and high troponin levels and it is high as well in patients without a history of heart disease but with high troponin levels. Patients with a history of heart disease without troponin increase have a better prognosis although they are not exempt from the risk of mortality[45].

Creatine kinase (CK-MB)

Despite having a lower sensitivity and specificity, other biomarkers could also be used in the detection of the damage to the heart cells, such as the creatine kinase MB fraction (CK-MB). The CK-MB levels greater than 12.9 ng/l are also significantly higher in patients requiring ICU versus those treated in other services. These findings suggest a correlation between the severeness of COVID-19 disease and the myocardial involvement degree[4,24,31].

Natriuretic peptides

The natriuretic peptides BNP (brain) and NT-proBNP (Amino-terminal pro-brain natriuretic peptide) are biomarkers of myocardial stress. As well as the troponin, their increase suggests a worse prognosis in patients with ARDS. Individuals who present severe SARS-CoV-2 infection frequently have high levels of BNP and NT-proBNP[24,46]. The prognostic value of NT-proBNP levels in 54 patients with severe COVID-19 pneumonia was analyzed, and it was found that values greater than 88.6 pg/ml are associated with increased risk of in-hospital mortality; after adjusting according to gender and age (HR of 1.32, 95% CI: 1.11-1.56, p=0.001), patients with COVID-19 and high NT-proBNP were more likely to have high blood pressure and coronary artery disease[46]. The prognostic value of these biomarkers is limited, given the high frequency of positive values and low specificity, as it happens in patients with severe acute respiratory diseases in the absence of high ventricular filling pressures or signs and symptoms of heart failure[47]. For this reason, some authors suggest that troponin and natriuretic peptide measurements should only be performed to patients with COVID-19 who have signs and symptoms suggestive of AMI or heart failure[48,49].

D-dimer

Increased D-dimer is considered a risk factor for the development of ARDS and its progression to death in patients with COVID-19[11]. In a series of 201 patients published by Wu, *et al.*[10], D-dimer concentration correlated directly with mortality, suggesting that possibly disseminated intravascular coagulation is one of the mechanisms of death in these patients[11]. A retrospective analysis including 191 patients hospitalized due to COVID-19 reported among the most important risk factors related to in-hospital mortality: D-dimer (OR 18.4, 95% CI: 2.64-128.5)[12]. D-dimer together with the other described biomarkers helps to identify patients with COVID-19 and the increased risk of in-hospital mortality[24].

Other biomarkers

Despite their limited prognostic value given their low specificity, other biomarkers such as interleukin 6, lactate dehydrogenase and ferritin are also associated with poor prognosis in hospitalized patients with COVID-19. Increase of C-reactive protein, transaminases and bilirubin have also been reported[6,38].

CLINICAL PRESENTATION

Myocarditis and cardiomyopathy

Previous viral diseases, including Middle East respiratory syndrome coronavirus (MERS-CoV), have been associated with myocardial injuries and myocarditis[50], contributing to the impact on morbidity and mortality in these patients[2,51]. However, in the current COVID-19 pandemic, the absence of endo-

myocardial biopsies for histological diagnosis of this disease makes it difficult to register cases[29] and limits the information in the literature on patients with acute and fulminant myocarditis due to SARS-CoV-2[50,52].

Myocarditis refers to myocardial inflammation with focal or global extension, presence of necrosis, biomarkers increase and ventricular dysfunction resulting from myocardial involvement. Increase of myocardial necrosis markers (troponins T and I, CK-MB) is usually associated with severe forms of the disease, such as fulminant myocarditis and left ventricular dysfunction; which justifies its usage as a predictor of complications risk and mortality in critically ill patients with COVID-19[52].

One of the earliest reports of myocardial injury associated to SARS-CoV-2 was a study of 41 patients diagnosed with COVID-19 in Wuhan, in which five patients (12%) had a high-sensitivity troponin I above the threshold of 28 pg/ml[6]. Subsequent studies have found that myocardial injury with a high troponin level can take place in 7% to 17% of patients hospitalized with COVID-19 as well as in 22% to 31% of those admitted to ICU[4].

Myocarditis has also been identified with high viral loads and mononuclear infiltrates identified at autopsy in some SARS-CoV-2 infected patients. Tian *et al.*[53] performed histological studies of the myocardium in two patients who died of COVID-19 and found edema, interstitial fibrosis and hypertrophy, without inflammatory cellular infiltration.

Primary myocardial involvement during the course of COVID-19 is usually explained by two mechanisms (**Figure 3**), there is a direct involvement of cardiac tissue caused by binding of SARS-CoV-2 to the ACE2 receptor of myocardial cells, with internalization and replication of capsid proteins and the viral genome. There is indirect cytokine storm-mediated involvement during systemic inflammation secondary to severe sepsis, with subsequent myocardial damage and multi-organ failure[1,6,52]. This last mechanism justifies the evolution to the fulminant clinical form, with circulatory failure and high mortality (40-70%)[54,55].

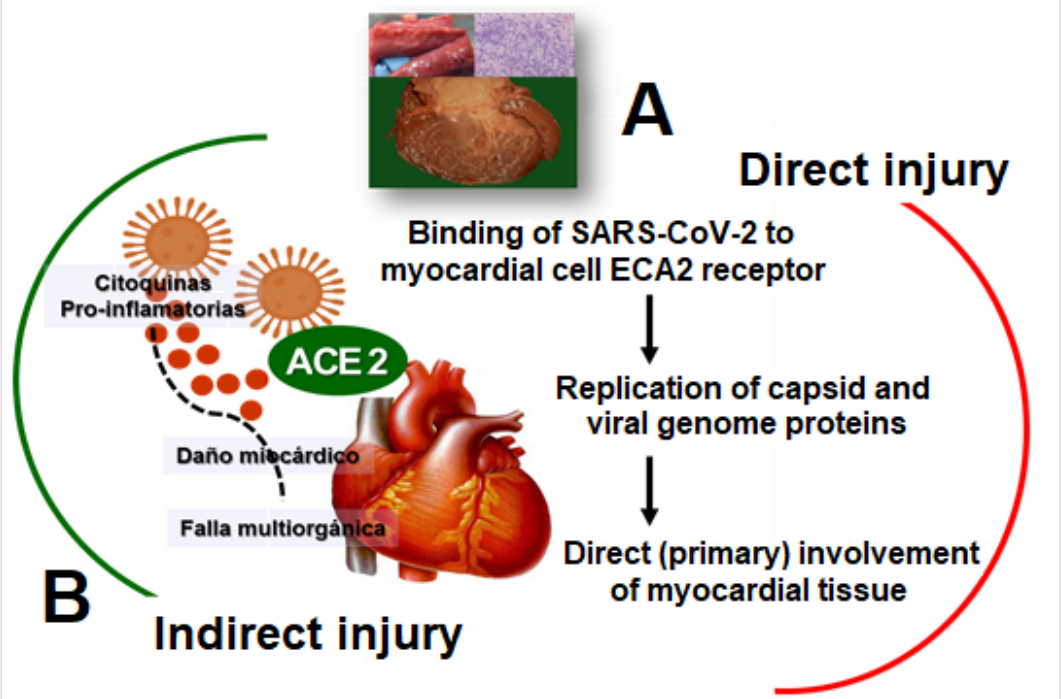

Figure 3. Myocardial damage in COVID-19. **A**. Direct myocardial injury: binding of SARS-CoV-2 to the ACE2 receptor of myocardial cells, internalization and replication of capsid proteins and viral genome, which explains the direct (primary) involvement of myocardial tissue. **B**. Indirect myocardial injury: systemic inflammation secondary to severe sepsis with release of inflammatory mediators, subsequent myocardial damage and multiple organ failure.
ACE: angiotensin-converting enzyme.

Acute coronary syndrome

Kwong, *et al.*[56] in 2018 documented an increased risk of AMI in patients with influenza acute respiratory disease, with an incidence rate of 6.1 (95% CI: 3.9-9.5) versus other respiratory infections of viral origin that included coronavirus species (incidence rate 2.8, 95% CI: 1.2-6.2).

The cause of AMI in patients affected by SARS-CoV-2 is unknown. Two postulates are basically invoked (**Figure 4**). In patients with atherosclerotic plaques susceptible to rupture (vulnerable), the systemic inflammatory response caused by severe sepsis can cause increased stress in the coronary circulation, leading to dynamic changes in these plaques (ulceration, fissure, erosion, dissection and rupture) with the formation of an intraluminal thrombus as final event (type 1 AMI)[32,33]. In this group of patients, a history of coronary artery disease and atherosclerotic vascular risk increase the probability [56].

Apparently, pathophysiologically, type 2 AMI is the most important modality related to viral infection (**Figure 4**), where coronary blood flow compromise predominates, resulting from the imbalance between myocardial oxygen supply and demand; this last variable, increased by severe hypoxia, a consequence of extensive lung damage, is what causes myocardial injury with necrosis. Other mechanisms, different from coronary thrombosis, in patients with epicardial coronary arteries without significant angiographic lesions, positive for COVID-19, are vasospasm and endothelial dysfunction[32,34].

The reduction in mortality —due to ST-elevation AMI (STEMI)— shows its most critical point and, at

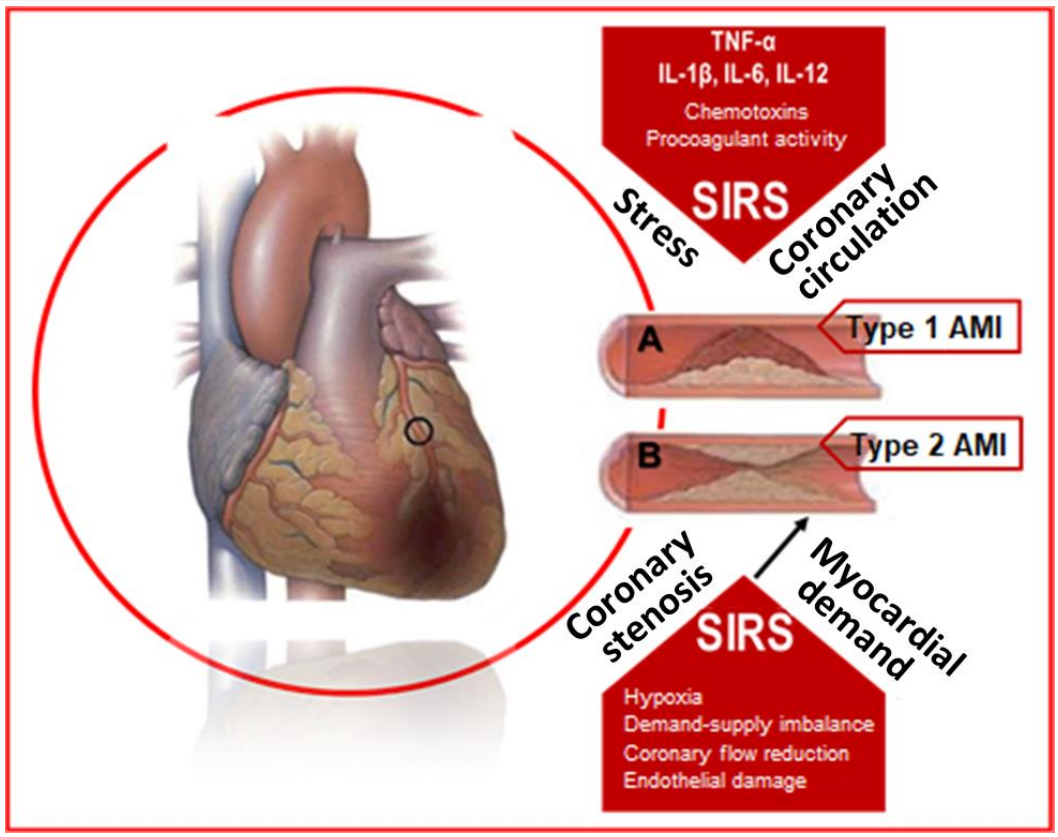

Figure 4. Acute coronary syndromes in COVID-19 disease. **A**. Type 1 AMI caused by increased stress in coronary circulation due to systemic inflammatory response originated from severe sepsis, leading to dynamic changes of vulnerable atherosclerotic plaques (ulceration, fissure, erosion, dissection and rupture) with final formation of an intraluminal thrombus. **B**. Type 2 AMI with predominance of coronary blood flow disturbances, resulting from the imbalance between oxygen supply and demand to the myocardium; this last variable increased by severe hypoxia, which is a consequence of extensive pulmonary injury.
AMI, acute myocardial infarction; IL, interleukin; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor.

the same time, its greatest therapeutic opportunity, in the prehospital phase. Minimizing the time that it takes for the patient to identify his or her symptoms and consequently to request medical assistance; the early arrival of a well-equipped ambulance, with trained personnel capable of making the diagnosis at the site of first contact; the application of the initial pharmacological treatment and the transfer of the patient to an appropriate cardiac care center should be the pillars of care in this initial stage[57]. Tam *et al.*[58] described the impact of COVID-19 infection in patients with STEMI, they recorded an increase in the time from symptom onset to first medical contact, as well as delayed care and diagnosis of patients after the arrival to the hospital, which contributes negatively to an increase in mortality. In their analysis, they suggest as main factors the fear of the patient to go to the hospital emergency system or of the health personnel of acquiring SARS-CoV-2 infection, as well as the time required for the implementation of protective and biosecurity measures by the interventional cardiology team.

The most recent recommendations on the care and management of patients with COVID-19 in the cardiac catheterization laboratory are gathered in the consensus of the American College of Cardiology (ACC) and the Society for Cardiovascular Angiography and Interventions (SCAI)[59].

Given that the clinical scenario of patients with COVID-19 and AMI is highly probable, recommendations have been developed for their care[60]. In the epidemiological phase in which there is community transmission[61], sampling to confirm SARS-CoV-2 infection is indicated as an initial step. It is essential to evaluate the presence of severe pneumonia and both confirmed and suspected cases should be treated equally.

There is a benefit in reducing mortality when comparing patients undergoing primary percutaneous coronary intervention (PCI) versus patients receiving thrombolysis[57,62]. However, this benefit should be balanced against the risk of exposure of the health care personnel (risk-benefit ratio). Hence the importance of performing rapid tests in patients with respiratory symptoms[59]. In this context a conservative medical management is proposed.

In stable patients with STEMI and COVID-19 in the first 12 hours of symptom onset and without contraindications for thrombolysis, this reperfusion strategy should be chosen. If the time of evolution is longer than 12 hours or there is a contraindication for thrombolysis, the risk and benefit of PCI should be evaluated on individual basis[59]. This option should be reserved for those patients in whom it is considered that these procedures will significantly modify clinical behavior and prognosis[48]. Primary PCI is a valid option as long as adequate personal protective equipment is guaranteed in the catheterization room and the risks of transmission are assessed[59].

In the epidemiological phase where the absence of community transmission is demonstrated, the intervention of patients with STEMI and low clinical probability for COVID-19 will be based on the recommendations of the current guidelines[62].

Heart failure

Heart failure is the main cardiovascular complication in patients with COVID-19. Its appearance in the course of the disease represents a bleak prognosis[29,63]. In a multicenter cohort in China that included 191 patients, 23% developed heart failure and of these, 63% did not survive[64].

It is important for the treating attending physician to identify whether this is an disease exacerbation in patients with pre-existing (chronic) heart failure, favored by severe sepsis, release of inflammatory mediators, adrenergic stimulation, increased myocardial oxygen demand and coronary flow compromise or if the patient's symptoms are attributable to acute heart failure of recent onset, associated with de novo cardiac complications during COVID-19, such as a fulminant myocarditis event or an acute coronary ischemic or hemodynamic event[29] (**Figure 5**). In a series of 416 patients in China, 4.1% of patients were identified as having a history of chronic heart failure. Among patients in whom myocardial injury was demonstrated, a history of heart failure was frequent (14.6% vs. 1.5%) and correlated with high NT-proBNP levels (689 vs. 139)[40].

Heart rhythm disturbances

Prospective studies of COVID-19 pandemic have described heart rhythm disturbances, together with ARDS and shock among the major complications during hospitalization of patients[6,11,12]. This complication varies in the different registries from 7 to 17% of cases[4,53], with a higher frequency in patients hospitalized in the ICU (44.4% vs. 6.9%)[4]. Atrial fibrillation, paroxysmal supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation and car-

diac arrest have been described most frequently. Its appearance is often due to multiple factors. Sinus tachycardia may be an expression of hypoperfusion, fever, hypoxia and anxiety. In the context of SARS-CoV-2 viral infection, factors such as hypoxia, inflammatory stress and abnormal metabolism are intertwined. When increased cardiac biomarkers such as troponins (T and I), CK-MB or NT-proBNP are added to its appearance, myocardial injury, acute myocarditis and acute coronary syndromes should be considered among the diagnostic hypotheses[63].

In its genesis there are factors not directly dependent on the infection, among these the most common ones are associated to the therapeutics used in the treatment of complications such as shock, where some drugs such as dopamine offer an increased risk of arrhythmias and mortality from this cause (RR 2.34, 95% CI: 1.46-3.78)[24.65]. In severely ill patients with electrolyte and internal environment disorders, further enhanced by the inadequate use of diuretics and vasodilators, the probability of occurrence of arrhythmias increases.

Suspension of the patient's basic medical treatment or interaction with new drugs that are being tested for COVID-19, show a greater propensity for the occurrence of life-threatening arrhythmias[37,38].

Lopinavir/ritonavir, an antiviral drug combination included in the therapeutic protocol for these patients, exerts its effect by inhibiting viral RNA replication[66]. This drug can prolong the PR and QT intervals, particularly in patients with basal PR and QT disturbances (long QT) and in those who show an added risk due to the use of therapeutics capable of prolonging this interval[67].

Chloroquine and its derivative hydroxychloroquine are antimalarial agents that block virus infection by increasing the endosomal ph required for the virus-cell fusion. Their inhibitory activity against SARS-CoV-2 has been demonstrated *in vitro*[68]. However, both compounds show a potential (intermediate to late) for myocardial toxicity, which manifests as restrictive or dilated cardiomyopathy or conduc-

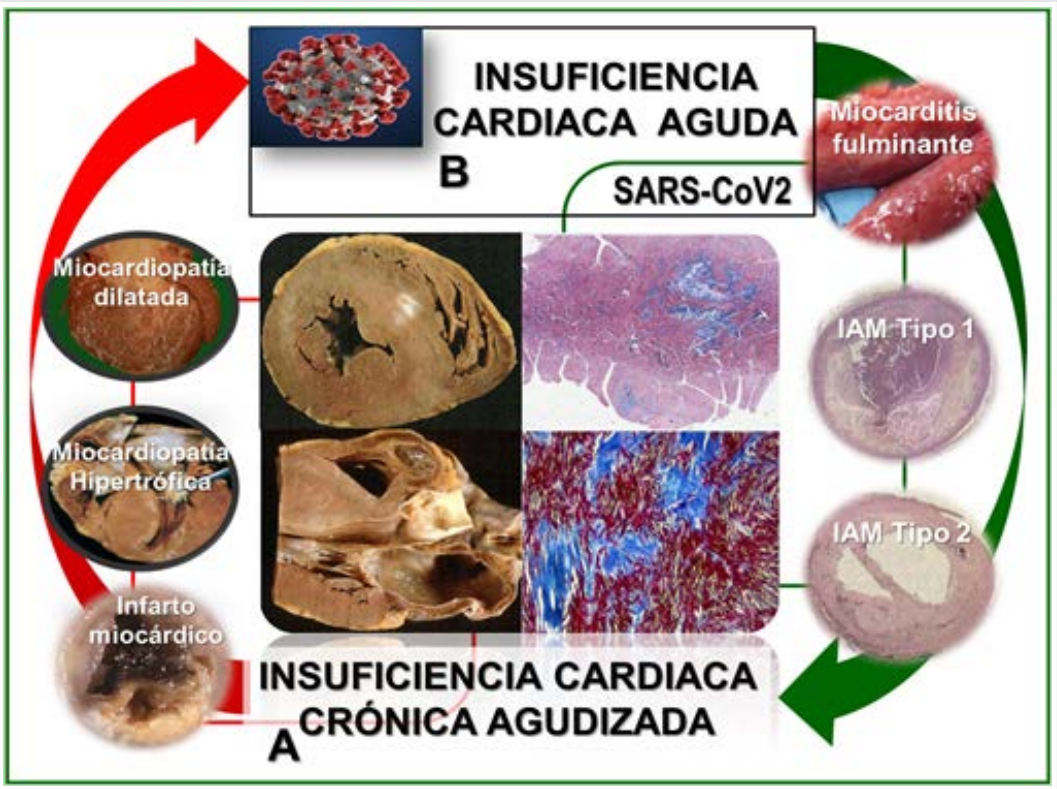

Figure 5. Heart failure as a complication of COVID-19 disease. **A**. Exacerbation of chronic heart failure, favored by severe sepsis, release of inflammatory mediators, adrenergic stimulation, increased myocardial oxygen demand and coronary flow compromise. **B**. Acute heart failure of recent onset, associated with cardiac complications during COVID-19, such as: fulminant myocarditis or an ischemic or hemodynamic acute coronary event.

tion disturbances, attributed to intracellular inhibition of lysosomal enzymes in the myocyte. Both agents are associated with an increased risk of sudden death events in these patients during the pandemic, due to complex ventricular arrhythmias of *torsades de pointes* type, triggered by the presence of prolonged QT[64,67].

In the race against time in pursuit of effective therapies against COVID-19, the use of antibiotics such as azithromycin in combination with other drugs (lopinavir/ritonavir and chloroquine/hydroxychloroquine)[7] has become available. This drug included in group B, with isolated reports of *torsades de pointes* and prolongation of the corrected QT (QTc) interval[69] is responsible for sudden death especially in association with factors such as age, gender and disturbances of the internal environment, frequent conditions in severely ill patients, in the course of the current pandemic due to COVID-19[64].

The administration of chloroquine, hydroxychloroquine, azithromycin and lopinavir/ritonavir shows, among its adverse effects, prolongation of the QT interval and appearance of complex ventricular arrhythmias such as *torsades de pointes*[35]. If we consider that most of patients who died from COVID-19 were elderly adults[12,13] with cardiac comorbidities[4,6,12,16], the use of these drugs could potentially increase the risk of drug-induced sudden death[10,64,70].

A thorough review of the pathophysiological mechanisms of cardiovascular complications in patients with COVID-19 leading to the occurrence of sudden death is called for in a forthcoming paper.

Venous thromboembolic disease

In patients admitted due to severe COVID-19 disease there is a high risk of venous thromboembolism. Factors such as advanced age, critical disease, prolonged immobilization, obesity, systemic inflammation, hypoxemia, abnormal coagulation status and multi-organ dysfunction increase its probability[63,71]. A multicenter study in China showed that high D-dimer levels (> 1 g/L) were significantly associated with in-hospital mortality, with an effect measure OR 18.4 (95% CI: 2.64-128.5, p=0.003) after a multivariate adjustment[12].

The diagnosis of pulmonary embolism, that is a challenge even under normal conditions, is often more difficult in the course of COVID-19 infection, so it is advisable to consider as a reasonable diagnosis of pulmonary thromboembolism any patient with unexplained acute respiratory worsening, new-onset tachycardia, low blood pressure not attributable to sepsis, hypovolemia or arrhythmia, suggestive electrocardiographic changes and signs of deep vein thrombosis[31,72].

Another comparative study between living and deceased patients with COVID-19 showed that patients who did not survive the disease had significantly higher levels of D-dimer and fibrin degradation products, hence 71.4% of the cases met the clinical criteria for disseminated intravascular coagulation[73]. This result allows to infer that this coagulation disorder is one of the death mechanisms in these patients[11].

CONCLUSIONS

The scientific evidence that is emerging in parallel with the evolution of the COVID-19 pandemic as a result of multicenter studies and epidemiological series worldwide, allows a better understanding of the systemic effects of the disease beyond the initial pulmonary damage and its extension to the cardiovascular system, which determines the prognosis and survival of patients. Identifying the factors related to cardiovascular disease, the pathophysiological mechanisms of infection that facilitate myocardial and vascular damage, and the effects of treatment are important in this disease care. The correct evaluation and stratification of patients, prevention, diagnosis and early treatment of complications are essential pillars in the reduction of morbidity and mortality due to COVID-19.

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