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Myocardial injury in patients with COVID-19

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ARTICLE INFORMATION

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Abbreviations
ACE: angiotensin-converting enzyme
ACE2: angiotensin-converting enzyme 2
COVID-19: Novel coronavirus infection disease 2019
IL: interleukin
MERS-CoV: Middle East respiratory syndrome coronavirus
RAAS: renin-angiotensin-aldosterone system
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
TNFα: tumor necrosis factor-alpha

ABSTRACT
Since the first reports of patients infected with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) appeared in the Chinese province of Wuhan, the infection by the new coronavirus has infected more than 4.7 millions of people, and the amount of deaths is greater than 315,000, until May 18, 2020. The myocardial injury or damage is defined as the detection of a value of cardiac troponins (T or I) above the 99th percentile of the upper reference limit. The exact mechanism, from which this infection by the new coronavirus causes damage to the heart cells, has not been completely clarified; however, numerous factors could be taken into account: imbalance between the supply and the demand, systemic inflammatory response, hypoxia, microvascular dysfunction and the direct myocardial injury caused by the virus.
Keywords: COVID-19, Angiotensin-converting enzyme, Myocardial injury, Cytokine storm

Lesión miocárdica en el paciente con COVID-19

RESUMEN
Desde los primeros informes de pacientes infectados con el SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) en la provincia China de Wuhan, la infección por el nuevo coronavirus ha contagiado a más de 4,7 millones de personas y los fallecidos superan los 315000, hasta el 18 de mayo del 2020. La lesión o daño miocárdico queda definido, como la detección de un valor de las troponinas cardíacas (T o I) por encima del percentil 99 del límite superior de referencia. El mecanismo exacto a partir del cual esta infección por el nuevo coronavirus le infringe un daño a las células del corazón no ha quedado totalmente esclarecido; no obstante, numerosos podrían ser los factores a tener en cuenta: desequilibrio entre el aporte y la demanda, la respuesta inflamatoria sistémica, hipoxia, disfunción microvascular y el daño miocárdico directo ocasionado por el virus.
Palabras clave: COVID-19, Enzima convertidora de angiotensina, Lesión miocárdica, Tormenta de citocinas

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GENERAL INFORMATION ABOUT THE VIRUS

Since the first reports of patients infected with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) appeared in the Chinese province of Wuhan, in December 2019[1-2], the infection by the new coronavirus has spread to more than 4.7 millions of people, and the amount of deaths is greater than 315,000, until May 18, 2020, according to data from the Johns

Hopkins University[3]. On March 11 of that very same year, the World Health Organization (WHO) decided to declare the COVID-19 (Novel Coronavirus Infectious Disease 2019) infection as a pandemic[4].

This new pathogen belongs to the family of coronaviruses affecting humans and animals. It can provoke symptoms going from the common cold to potentially fatal illnesses such as the SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome) and the COVID-19. It is a zoonotically transmitted virus and it has a sequence, similar in an 87-92%, to the one found in bats[5], thus generating the hypothesis that this animal could be the primary source of infection in humans[6,7].

COVID-19 is one of the seven beta-coronaviruses that affect humans. It has a spherical shape and its molecular structure is composed of a single-stranded positive-sense RNA, a lipid bilayer that covers it and four major protein subunits: spike surface protein (S), nucleocapsid protein (N), membrane glycoprotein (M), and envelope protein (E)[8]. Starting from the protein (S), the virus joins the angiotensin-converting enzyme 2 (ACE2) receptor of the respiratory cells[9] and this way, it starts the invasion of the target cell and its subsequent replication.

Although it shares similar properties with other coronaviruses in terms of genome and clinical manifestations, COVID-19, due to its high virulence and power of infection of asymptomatic or mildly symptomatic patients, has had a fast transmission in European countries and the United States. The R_0 estimate (the average number of secondary cases produced from one case) is equal to 3 in the susceptible populations[10-12].

Transmission occurs from person to person, and it has an average incubation period of 2 to 14 days after the exposure to the virus[13]. Most patients (81%) present mild manifestations of the disease: fever (88%), dry cough (67.7%), rhinorrhea (4.8%) and gastrointestinal symptoms[14]; however, a 14% develops the more severe symptoms and about 5%, the critical ones (respiratory failure, shock, multiple organ dysfunction)[15].

ROLE OF THE ACE2 AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The relationship between SARS-CoV-2 and the renin-angiotensin-aldosterone system (RAAS) has two key moments that have an influence in the virus's entry

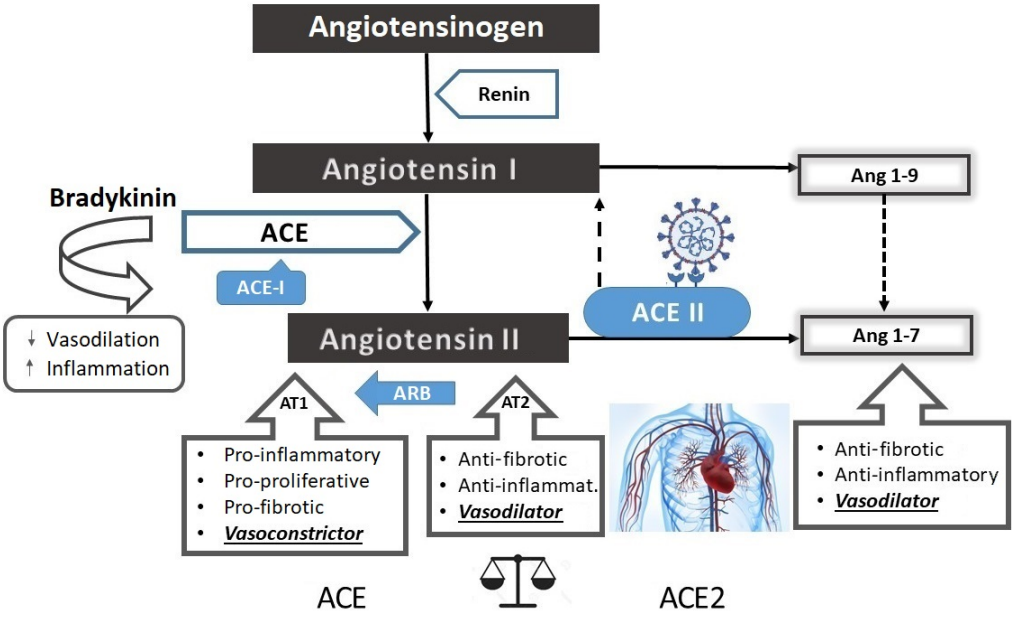

Figure 1. Effect of COVID-19 on the activation of the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ACE-I, angiotensin-converting enzyme inhibitors; Ang, angiotensin; ARB, angiotensin II receptor blockers; AT1 and AT2, angiotensin II receptors.

into the body, its replication and, the cardiovascular manifestations that the disease causes:

1. The formation of angiotensin II from angiotensin I, with the action of the angiotensin-converting enzyme (ACE).
2. The joining of the virus to the ACE2 receptors.

An important link between the genesis of the disease and the main cardiovascular complications that this virus causes is the ACE2. This enzyme is widely disseminated in the pulmonary alveolar cells (type II), the heart, the vascular endothelium, the testicles, the intestine and the kidneys[16,17]. It is an ACE- analogue carboxypeptidase which acts by degrading the angiotensin II into angiotensin-(1-7), and the angiotensin I into angiotensin-(1-9); with a counterbalancing role to the pro-inflammatory, pro-fibrotic and vasopressor effect of the angiotensin II in the RAAS[18] (**Figure 1**). The angiotensin-(1-7), which is one of the degradation products of the angiotensin II, acts as an antagonist to the vasoconstrictive effects of angiotensin II, from a considerable vasodilatory effect.

Why are angiotensin II formation and regulation of RAAS important in the COVID-19 infection? It is enough to remember that both angiotensin-converting enzymes are analogous, one playing a key role in the conversion of angiotensin II and the other one 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.

In certain situations, this balance is often broken, either due to the use of drugs that act on RAAS or due to hemodynamic alterations in the body. When ACE inhibition occurs with the aim of lowering the concentrations of angiotensin II, genetic expression of ACE2 in the heart increases[19]. The same happens with the treatment of the aldosterone antagonists, which increases the cardiac activity of this enzyme[20]. Any alteration in our body, such as high blood pressure and heart failure, capable of increasing the production of vasoconstrictive substances, alters the ACE/ACE2 ratio in a value higher than 1[21,22].

Once the concentration of ACE2 decreases, its counterbalancing effects on angiotensin II (its vasodilatory, anti-fibrotic and anti-inflammatory effect) are lost; at the same time, this same deregulation contributes to the endothelial dysfunction and the myocardial damage[23].

After the exposure of the COVID-19 infection susceptible host, the SARS-CoV-2 virus joins the ACE2 receptor via the surface protein subunit (S). This protein, when joining the receptor, suffers a conformational change that facilitates the joining of the virus surface to the target cell[24]. From this union of the virus with the host cell, the concentration of ACE2 decreases, the balance is broken and the production of angiotensin II increases, with the corresponding catalytic activity of ACE.

Regardless of the effect that ACE inhibitor (ACEI) drugs or AT1 receptor blockers (angiotensin II receptor antagonists) may have on increasing the ACE2 receptors, this effect is not associated to a significant increase in the risk of COVID-19 infection. There is no current evidence relating the use of these drugs to the risk of infection by the novel coronavirus[25,26].

What would be the results of the COVID-19 infection in the RAAS? a) decrease in the concentration of ACE2 and the attenuation of its protective effects on the heart and b) increase in the activity of ACE and the production of angiotensin II.

ETIOPATHOGENESIS OF MYOCARDIAL INJURY

Myocardial injury: Definition

The damage caused to the heart cells by SARS-CoV-2 infection is relatively common, between 8-20% according to the consulted series[27], especially, in the severe forms of the disease. In a retrospective study of 416 patients admitted in Wuhan Province (China), who were tested positive for COVID-19, the 19.7% showed an elevated troponin I values over the reference value, with an average age of 64 years old[28].

Although the mechanisms by which these alterations occur in the cardiac cell have not been fully clarified, many authors do agree on the relationship existing between myocardial damage and the future evolution of the patient and the short-term mortality. Patients with myocardial damage had a hospital mortality quantitatively higher than those who did not: 51.2% *vs.* 4.5% respectively; according to the study by Shi *et al*[28]. Similar results were obtained by Guo and coworkers in 187 patients admitted, positive for SARS-CoV-2, where the 27.8% presented elevated values of troponin T with a hospital mortality of a 52%, *vs.* an 8.9% of those who had enzymatic values within the range of normality. Another significant detail was the number of patients with myocardial damage and history of a cardiovascular disease (69.4%).

Myocardial injury or damage is defined as the detection of a cardiac troponins (T or I) value over the 99th percentile of the upper reference limit[30], which may respond to acute or chronic damage depending on the values of the enzymatic curve[31]. Despite having a lower sensitivity and specificity, other biomarkers could also be used in the detection of the damage on the heart cells, such as the creatine kinase MB fraction (CK-MB).

In addition to presenting elevated 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 and of the cardiac function, identified during the echocardiogram[28]. Discerning how much the enzymatic elevation corresponds to a primary damage to heart cells, and how much is secondary to the critical disease states, is a real challenge.

Although, the exact mechanism from which this infection by the novel coronavirus causes damage to the heart cells has not been completely clarified, numerous factors could be taken into account: imbalance between the oxygen supply and the demand, systemic inflammatory response, hypoxia, microvascular dysfunction and the direct myocardial damage caused by the virus (**Figure 2**).

Imbalance between oxygen supply and demand

Recently published studies have proven that the myocardial damage in patients with COVID-19 was more frequent among those admitted to Intensive Care Units and, at the same time, these patients presented more severe forms of the disease[32]. Regardless of the rise in markers of myocardial damage in severely ill patients without taking into account the underlying disease[33,34], this rise may also be related to increased myocardial oxygen demands, in patients positive to COVID-19, with or without previously known coronary disease.

This increase in myocardial output, secondary to SARS-CoV-2 infection, can lead to significant increases in the coronary flow and the oxygen demand, enough to provoke myocardial ischemia, especially in patients with coronary disease. The increase in the metabolic activity of the myocardium produces a significant oxygen extraction from the arterial blood, and it implies the need to generate increases in the flow from precise and complex regulatory mechanisms[35], capable of guaranteeing an adequate balance between the oxygen supply and demand, where nervous, humoral, mechanical and electrical

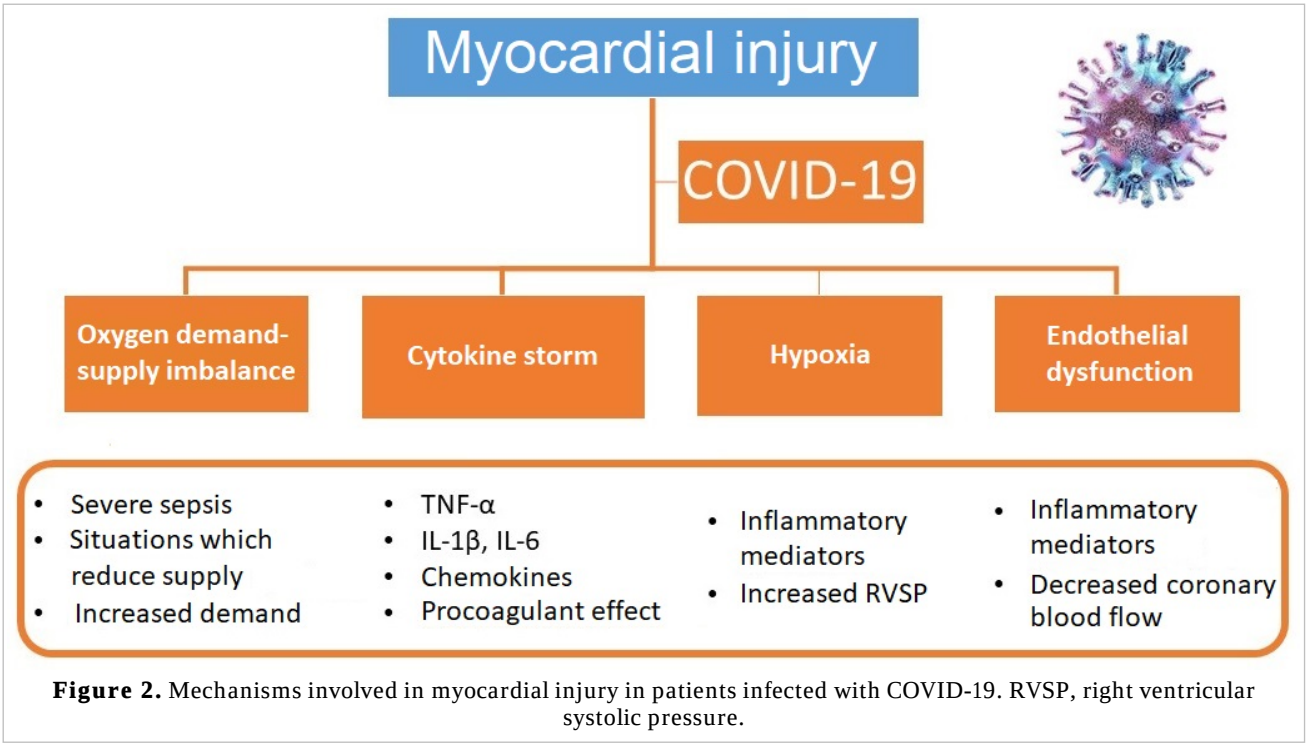

Figure 2. Mechanisms involved in myocardial injury in patients infected with COVID-19. RVSP, right ventricular systolic pressure.

phenomena are involved. Circumstances such as tachycardia and severe high blood pressure, whether or not accompanied by situations that reduce the oxygen supply (significant anemia, severe hypoxia, coronary spasm, coronary dissection) contribute to break this necessary balance and cause injury to the myocardial cells.

Cytokine storm

One of the characteristics of COVID-19 infection is that it evolves into severe forms. In these circumstances, high serum values of the inflammation mediators, secondary to a dysfunctional and uncontrolled immune response, may cause serious damage to the heart function. However, what cardiovascular disturbances occur in the body during the release of these inflammatory mediators? What effects do they specifically have on patients infected with SARS-CoV-2?

In the infection by the novel coronavirus, it has been proven that, patients with more severe presentations, trigger an acute systemic inflammatory response with fatal and fulminant hypercitokinaemia; which is what many authors, in their scientific publications, have called "cytokine storm"[36]. This new state of inflammatory response can be found in a wide spectrum of conditions, not only infectious, and it was in 2005 that it was related to a respiratory virus[37].

The cytokine storm is characterized by an increase in circulating levels of pro-inflammatory cytokines: gamma interferon (γ), tumor necrosis factor alpha (TNFα), interleukins (IL-1β, IL-6, IL-12) and chemokines. It is a generalized inflammatory response, associated with lung inflammation and extensive lung affection in SARS, very similar to the one found in MESR-CoV infection[38]; in addition, they are associated with the myocardial damage and the cardiac remodeling[39,40].

From the beginnings of COVID-19 infection, authors such as Huang *et al* reported an increase in proinflammatory cytokines, especially in patients admitted to Intensive Care Units.

The TNFα is one of the most studied cytokines, it is secreted into the cardiac tissue by macrophages, endothelial cells and cardiomyocytes, and it has a strong effect in decreasing the contractile force of the myocardium, in addition to its role in the calcium hemostasis[41], the excitation-contraction joining[42], the nitric oxide metabolism[43] and the signaling through second messengers[44]. In addition, this cytokine may facilitate the cellular apoptosis, once ischemic damage occurs[45], and contribute to cardiac dilatation[46,47].

Large amounts of interleukin IL-6 and IL-1β are also released. Both increase their synthesis when severe myocardial damage occurs due to ischemia/reperfusion, endotoxemia and other cardiovascular conditions. They have a depressant effect on myocardial contractility and, although their exact mechanism is not known yet, it is thought to be related to the nitric oxide pathway[48,49].

Chemokines, as well as interleukins and TNFα, are other mediators of the inflammation released during COVID-19 infection. High concentrations of these mediators are also present in the ischemic myocardial damage in cardiac surgery with extracorporeal circulation and in the cardiac arrest. What role do they play in the severe sepsis by COVID-19 and weather they share or not the same mechanism of the TNFα and the IL-1β and IL-6, remains still unproven.

Studies carried out in patients with this type of surgery have proven the myocardial damage provoked by ischemia/reperfusion, with the release of free radicals and the increase in the factor of transcription kappa B[50] that, once activated, induces the transcription of genes of activation of proinflammatory cytokines (IL-2, IL-2β, IL-6, IL-8, TNFα and interferon and), in addition to taking part in the production of chemokines. Many of these inflammatory mediators are also present in the myocardial damage.

The inflammatory response provoked by COVID-19 infection not only has a depressant effect of the contractile force, but also has a direct action on the heart vessels and the artherosclerotic disease. It is capable of increasing the inflammatory activity of the coronary vessels' walls and inside the atheroma plaques, which contributes to the unstable plaques to be more susceptible to rupture[51]. In addition, it generates an increase in the blood procoagulant activity, which might contribute to the occlusive thrombus formation on a fractured coronary plaque[52].

Hypoxia

The acute progression of the disease by COVID-19 is divided into three phases: early infection phase, pulmonary phase and severe hyperinflation phase[53]. During the first phase, the virus infiltrates the lung parenchyma and begins its proliferation. An innate inflammatory response occurs and the first manifestations of the disease begin to appear. In the pulmonary phase, there is an extension of the damage to

this organ, hypoxia and cardiovascular stress appear; while in a group of patients, the host's inflammatory response continues to be amplified until systemic inflammation develops[54]. This state of systemic toxicity has the capacity of damaging distant organs.

During the pulmonary phase, when the increased cardiac output is not enough to restore the oxygen delivery, cells begin to draw a higher percentage of the content in circulating blood. If this new situation is not corrected on time, the difference between the oxygen supply and demand will continue to increase; thus creating the so-called oxygen debt and, subsequently, the cellular hypoxia.

As this hypoxia worsens and the available reserves of ATP (adenosine-triphosphate) are exhausted, the cells transform their metabolism from aerobic to anaerobic. Although this metabolism represents an alternative for the organism, it only produces one-eighth of the energy needed. As a result, this causes an imbalance between the oxygen supply and demand in the tissues, especially the heart. The oxygen debt also triggers an intracellular metabolic acidosis with mitochondrial damage; the mitochondria suffer a high amplitude swelling and an irreversible damage in its membrane that finally leads to an acute cardiac injury[55].

In the systemic inflammatory response phase, there is an increase in the endothelial permeability and the occupation of the alveolus by a protein-rich edema. This decreases the alveolar surface available for the gas exchange and the perfusion through them. Once the respiratory distress syndrome is established, there is an increase in cardiac output and the perfusion of the non-ventilated areas, where previously closed capillaries are recruited, thus worsening the shunt effect and hypoxemia[56].

The released inflammatory mediators can affect gas exchange in a variety of ways: while some produce bronchoconstriction with increased inequalities in ventilation/perfusion, others cause pulmonary vasoconstriction; which, if becomes severe, produces right ventricular failure due to acute *cor pulmonale* and aggravates the deterioration of oxygen saturation and hypoxemia[57]; all of which leads to an increase in right ventricular afterload with increased wall tension, dilation and finally, ischemia.

Either as a consequence of the hypoxemia generated by lung disease with oxidative stress and mitochondrial damage, or by right ventricular failure; the pulmonary infection in COVID-19 is capable of causing severe myocardial damage in a group of patients.

Endothelial dysfunction

Another mechanism outlined to account myocardial damage in SARS-CoV-2 infected patients is the endothelial dysfunction. The vascular endothelium is a cellular monolayer that covers the blood vessels, responsible for the control and functioning of the coronary microcirculation, which are small-caliber vessels, smaller than 200 microns, impossible to visualize in a coronary angiography. Based on numerous nervous, mechanical, chemical and humoral stimuli, this endothelium guarantees normal vascular tone with a balance between vasodilatory and vasoconstrictive substances[58].

The endothelium, and its effect on coronary microcirculation, plays a decisive role in the perfusion of the heart muscle, by ensuring an optimal coronary reserve: that is the heart's ability to increase the coronary flow from the rest to its maximum vasodilation in response to a given stimulus. How does this happen? By reducing coronary resistance five times under its normal value in a healthy heart, the basal coronary flow can be increased in an equal number of times.

Alterations in the vascular endothelium lead to an inadequate vasodilation of the coronary microcirculation and, as a consequence, to a decrease in the reserve of coronary flow. This inability to increase the flow through these small arteries, especially in circumstances of increased oxygen demand, could result in myocardial damage.

Among the factors involved in this complex phenomenon are: alterations in the metabolism of nitric oxide, deregulation of the inflammatory cytokines, estrogen, adrenergic receptors and alterations in the expression or vasoactive substances production such as angiotensin II and endothelin[59].

How does this phenomenon occur in COVID-19 infection? The joining of the virus to the ACE2 receptor decreases the concentration of this enzyme in the body and causes an increase in the concentrations of angiotensin II. The release of this powerful vasoconstricting substance reduces the vasodilatory capacity of the coronary microcirculation. In some studies of patients with acute respiratory distress syndrome and sepsis, elevated serum ACE and angiotensin II values have been associated with certain degrees of microvascular dysfunction[60,61].

In addition to vasodilator and vasoconstrictor substances, inflammation mediators are involved in endothelial function. Their deregulation could lead to serious alterations in the vasodilation of coronary microcirculation and finally, to myocardial damage.

Post-mortem histological studies in patients with COVID-19 found accumulation of endothelium-associated inflammatory cells, as well as apoptotic bodies in the heart, the small intestine and the lung[62].

In addition, immune cell recruitment, either by direct viral infection of the endothelium or mediated by the immune system, may also result in widespread endothelial dysfunction associated with apoptosis.

COMPLICATIONS

Complications and situations that cause myocardial damage

During SARS-CoV-2 infection, different cardiovascular conditions and complications are triggered, with the common denominator being the myocardial injury. For one reason or another, or even a combination of more than one mechanism, they cause major alterations in the heart function and contribute to increased mortality. Among the different situations or complications presented in this disease by the novel coronavirus are: septic shock, type 2 myocardial infarction and myocarditis.

Although about 80% of patients infected with COVID-19 develop mild forms of the disease, another group requires invasive mechanical ventilation, suffers hemodynamic impairment and even dies from coronavirus. Among the consulted series, cardiovascular risk factors, diabetes mellitus, smoking habit and elderly predispose to myocardial damage and increase the risk of complications and mortality.

In a study of four meta-analyses involving 314 patients positive for the novel coronavirus, the patients with myocardial damage were those with most severe presentations of the disease[63]. The same happens to patients admitted in intensive care and the history of cardiovascular diseases. In Wuhan province, of 138 patients admitted with COVID-19, 72% of those admitted to intensive care had comorbidities, mostly cardiovascular[64].

Septic shock and myocardial damage

Until nowadays, with the accumulated data from the outbreak in China and the European Union, 6.1% of patients diagnosed with COVID-19 in China developed critical forms (respiratory failure, septic shock and multiorgan failure, or both)[65]; while in Europe 4% did so. Of the series of 1099 hospitalized cases in China, 31 suffered severe respiratory failure (distress), 11 septic shock and 6 renal failure[66].

The SARS-CoV-2 often causes, in some patients, serious conditions such as septic shock; characterized by an increased cardiac output, the oxygen transport and reduced systemic vascular resistance and oxygen withdrawal. From the first studies by Parrillo *et al*[67], that used pulmonary flotation catheters, to the current use of echocardiography and nuclear magnetic resonance, many authors have tried to explain the relationship between severe sepsis and myocardial damage. Important humoral phenomena are involved in the complex system of metabolic activity regulation in patients with severe sepsis.

Classically, it has been considered that the metabolic signals are in charge of regulating the balance between supply and demand in the heart. One of the most important agents is adenosine[68-69], which like other chemical mediators (prostaglandins, endothelial relaxation factor, natriuretic peptide and nitric oxide) provoke vasodilation and control the contraction of the muscle fibers of the blood vessels[70]. Although the exact mechanism is unknown, it is thought that the effect they produce on microcirculation is capable of responding to metabolic changes, decreasing resistance and increasing perfusion[71,72].

Among the theories that attempt to justify the damage caused by the state of sepsis in the heart is the cardiosuppressive effect produced by local and systemic mediators of inflammation, as explained in cytokine storm. An infectious stimulus (endotoxin), induces in the body the release of TNFα, IL-1β and IL-6 derived from monocytes/macrophages. These cytokines, in turn, stimulate polymorphonuclear leukocytes, macrophages and endothelial cells to the release of the platelet-activating factor and nitric oxide[73].

The TNFα, IL-1β and IL-6 have a strong myocardial depressant effect, characterized by low blood pressure and decreased peripheral resistance[74]. It has also been postulated, although still under study, that nitric oxide has a deleterious action on long-term cardiac contractility.

Other authors[75-77] propose that prolonged beta-adrenergic stimulation induces myocardial injury by calcium overload. Endotoxin and cytokines inhibit cytosolic calcium movement in cardiac myocytes isolated and open potassium-dependent ATP channels that shorten the action potentials and thus reduce the availability of intracellular calcium, events that decrease calcium reserve and the contraction

strength[76-77].

The state of severe sepsis caused by COVID-19 is capable of inducing significant myocardial damage in the body, aggravated by a history of cardiovascular diseases and poor immune response. Through the mediators of inflammation and adrenergic stimulation involved in this type of infection, serious alterations in cardiac function occur.

Acute myocardial infarction

Currently, there are no studies that have described the real incidence of acute myocardial infarction with ST-segment elevation in patients with COVID-19, although it seems to be low. Bangalore *et al*[78] published a series of 18 patients with ST-elevation and COVID-19 in six hospitals in New York; of these, 9 (50%) underwent coronary angiography, 6 (67%) had obstructive coronary disease, and 72% died in the hospital.

The cause of acute myocardial infarction in patients affected by this novel coronavirus is unknown, although the rupture of an atheroma plaque is possible, especially from the effect of inflammatory mediators on the coronary vessels. It is also important to note that the pathological history of coronary artery disease, and the risk of atherosclerotic cardiovascular disease, increase the probability of suffering an acute coronary syndrome during acute infection[79-81].

So far, type 2 acute myocardial infarction (not related to coronary atherothrombosis) is the most frequent in SARS-CoV-2 positive patients. Regardless of the inflammation mediators effect in cytokine storm (TNFα, IL-1β, IL-6), capable of causing myocardial damage by depression of the contraction force, the large increase in myocardial oxygen demand, the decrease in coronary flow reserve secondary to endothelial damage and the decrease in oxygen supply by severe hypoxia, are the most likely mechanisms to provoke an imbalance between the oxygen supply and demand[82].

Viral myocarditis

The first reports of myocarditis associated with viral infections took place during the outbreaks of influenza, polio, measles and mumps[83]. Within that group, the respiratory viruses most commonly associated with this disease have been the influenza, parvovirus B-19[84], and MERS-CoV[85]; however, currently there are only reports of isolated cases of SARS-CoV-2[86]. In a series of 151 patients studied with 68 deaths, 7% of the deaths were attributed to myo carditis with circulatory failure[87].

Myocarditis refers to any inflammation of the myocardium with focal or global extension, presence of necrosis and, eventually, ventricular dysfunction. Because of the high resistance to endomyocardial biopsy, it is a highly underestimated disease.

Among the diagnostic tests used to confirm acute myocarditis are the markers of myocardial necrosis (troponins T and I, CK-MB). Although earlier studies demonstrated the low sensitivity of troponins for the diagnosis of acute myocarditis[88], their high concentrations were associated with more severe forms of the disease −including fulminant myocarditis− and left ventricular dysfunction[89]. Nowadays the detection of myocardial necrosis markers, it is often used in critical patients, as risk predictor of complication and mortality, with very good results

Infection by COVID-19 and a possible joining of the virus to an ACE2 receptor of the myocardium cells could favor the internalization and subsequent replication of the viral capsid proteins and genome[90] with a direct involvement of the virus in the myocardial tissue[91]. However, so far, it is thought that the cytokine storm triggered by the infection by the novel coronavirus is responsible for the myocarditis, especially the fulminant one, a rare presentation of this disease with circulatory failure and high mortality (40-70%)[92].

EPILOGUE

During the infection by COVID-19, the joining of the virus to ACE2 receptors, invasion into the lung cells and its replication, has triggered multiple manifestations in the body. From cytokine storm, severe hypoxia, endothelial dysfunction or imbalance between the oxygen supply and demand, multiple mechanisms attempt to demonstrate why COVID-19 infection causes myocardial injury in infected patients.

The estimated fatality rate for this disease has varied from 3 to 7%, depending on the region, the spread of the virus and the affected populations. The cardiovascular risk factors, the diabetes mellitus and the smoking habit since the beginning of the pandemic have been directly related to the number of deaths and complications of all kinds. The early detection of this myocardial damage and the rational use of treatments and therapeutic measures repre-

sent a key point for the control of the pandemic and the minimization of its consequences.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet, publicado 11 Mar 2020]. World Health Organization [cited 8 May 2020]. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020
3. Coronavirus Resource Center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Internet]. Johns Hopkins University of Medicine [cited 10 May 2020]; 2020. Available at https://coronavirus.jhu.edu/map.html
4. Biondi Zoccai G, Landoni G, Carnevale R, Cavarretta E, Sciarretta S, Frati G. SARS-CoV-2 and COVID-19: facing the pandemic together as citizens and cardiovascular practitioners. Minerva Cardioangiol. 2020;68(2):61-4.
5. Berry M, Gamieldien J, Fielding BC. Identification of new respiratory viruses in the new millennium. Viruses. 2015;7(3):996-1019.
6. Paules CI, Marston HD, Fauci AS. Coronavirus Infections - More Than Just the Common Cold. JAMA. 2020;323(8):707-8.
7. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res [Internet]. 2020 [cited 11 May 2020];7(1):11. Available at: https://doi.org/10.1186/s40779-020-00240-0
8. Fehr AR, Perlman S. Coronaviruses: An overview of their replication and pathogenesis. En: Maier H, Bickerton E, Britton P, eds. Coronaviruses. Methods in Molecular Biology [Internet]. Vol 1282. New York: Humana Press [cited 11 May 2020]; 2015. Available at: https://doi.org/10.1007/978-1-4939-2438-7_1
9. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, *et al*. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450-4.
10. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199-207.
11. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet. 2020; 395(10225):689-97.
12. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Euro Surveill [Internet]. 2020 [cited 12 May 2020];25(4):2000058. Available at: http://doi.org/10.2807/1560-7917.ES.2020.25.4.2000058
13. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. Euro Surveill [Internet]. 2020 [cited 12 May 2020];25(5):2000062. Available at: http://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062
14. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. Ginebra: WHO; 2020 [En línea 28 Feb 2020]. Available at: https://www.who.int/publications/i/item/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)
15. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46(4):586-90.
16. Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, *et al*. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur Heart J. 2020;41(19):1804-6.
17. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochem J. 2004; 383(Pt 1):45-51.
18. Soler MJ, Lloveras J, Batlle D. Enzima conversiva de la angiotensina 2 y su papel emergente en la regulación del sistema renina-angiotensina. Med Clin (Barc). 2008;131(6):230-6.
19. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, *et al*. Effect of angio-

tensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111(20): 2605-10.
20. Keidar S, Gamliel-Lazarovich A, Kaplan M, Pavlotzky E, Hamoud S, Hayek T, *et al*. Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients. Circ Res. 2005;97(9):946-53.
21. Trask AJ, Averill DB, Ganten D, Chappell MC, Ferrario CM. Primary role of angiotensin-converting enzyme-2 in cardiac production of angiotensin-(1-7) in transgenic Ren-2 hypertensive rats. Am J Physiol Heart Circ Physiol. 2007;292(6):H3019-24.
22. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, *et al*. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature. 2002;417(6891):822-8.
23. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, *et al*. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009;39(7):618-25.
24. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, *et al*. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
25. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med [Internet]. 2020 [cited 13 May 2020];8(4):e21. Available at: http://doi.org/10.1016/S2213-2600(20)30116-8
26. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020;38(5):781-2.
27. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58(7):1131-4.
28. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, *et al*. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10.
29. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al*. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):1-8.
30. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, *et al*. Third universal definition of myocardial infarction. Eur Heart J. 2012;33(20):2551-67.
31. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al*. Consenso ESC 2018 sobre la cuarta definición universal del infarto de miocardio. Rev Esp Cardiol. 2019;72(1):72.e1-e27.
32. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229): 1054-62.
33. Guest TM, Ramanathan AV, Tuteur PG, Schechtman KB, Ladenson JH, Jaffe AS. Myocardial injury in critically ill patients. A frequently unrecognized complication. JAMA. 1995;273(24):1945-9.
34. Babuin L, Vasile VC, Rio Perez JA, Alegria JR, Chai HS, Afessa B, *et al*. Elevated cardiac troponin is an independent risk factor for short- and long-term mortality in medical intensive care unit patients. Crit Care Med. 2008;36(3):759-65.
35. Hoffman JI. Transmural myocardial perfusion. Prog Cardiovasc Dis. 1987;29(6):429-64.
36. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012;76(1):16-32.
37. Yuen KY, Wong SS. Human infection by avian influenza A H5N1. Hong Kong Med J. 2005;11(3): 189-99.
38. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-39.
39. Nian M, Lee P, Khaper N, Liu P. Inflammatory cytokines and postmyocardial infarction remodeling. Circ Res. 2004;94(12):1543-53.
40. Sirera R, Salvador A, Roldán I, Talens R, González-Molina A, Rivera M. Quantification of proinflammatory cytokines in the urine of congestive heart failure patients. Its relationship with plasma levels. Eur J Heart Fail. 2003;5(1):27-31.
41. Janczewski AM, Kadokami T, Lemster B, Frye CS, McTiernan CF, Feldman AM. Morphological and functional changes in cardiac myocytes isolated from mice overexpressing TNF-alpha. Am J Physiol Heart Circ Physiol. 2003;284(3):H960-9.
42. Yokoyama T, Vaca L, Rossen RD, Durante W, Hazarika P, Mann DL. Cellular basis for the negative inotropic effects of tumor necrosis factor-alpha in the adult mammalian heart. J Clin Invest. 1993; 92(5):2303-12.
43. Balligand JL, Ungureanu D, Kelly RA, Kobzik L, Pimental D, Michel T, *et al*. Abnormal contractile function due to induction of nitric oxide synthesis in rat cardiac myocytes follows exposure to activated macrophage-conditioned medium. J Clin

Invest. 1993;91(5):2314-9.
44. Thielmann M, Dörge H, Martin C, Belosjorow S, Schwanke U, van De Sand A, *et al*. Myocardial dysfunction with coronary microembolization: signal transduction through a sequence of nitric oxide, tumor necrosis factor-alpha, and sphingosine. Circ Res. 2002;90(7):807-13.
45. Krown KA, Page MT, Nguyen C, Zechner D, Gutierrez V, Comstock KL, *et al*. Tumor necrosis factor alpha-induced apoptosis in cardiac myocytes. Involvement of the sphingolipid signaling cascade in cardiac cell death. J Clin Invest. 1996;98(12): 2854-65.
46. Sivasubramanian N, Coker ML, Kurrelmeyer KM, MacLellan WR, DeMayo FJ, Spinale FG, *et al*. Left ventricular remodeling in transgenic mice with cardiac restricted overexpression of tumor necrosis factor. Circulation. 2001;104(7):826-31.
47. Kubota T, McTiernan CF, Frye CS, Slawson SE, Lemster BH, Koretsky AP, *et al*. Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumor necrosis factor-alpha. Circ Res. 1997;81(4):627-35.
48. Yu XW, Chen Q, Kennedy RH, Liu SJ. Inhibition of sarcoplasmic reticular function by chronic interleukin-6 exposure via iNOS in adult ventricular myocytes. J Physiol. 2005;566(Pt 2):327-40.
49. Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science. 1992;257(5068):387-9.
50. Castaño Ruiz M. Papel de la pravastatina en el daño miocárdico por isquemia y reperfusión [tesis doctoral]. Salamanca: Universidad de Salamanca; 2010 [cited 16 May 2020]. Available at: http://hdl.handle.net/10366/76414
51. Madjid M, Vela D, Khalili-Tabrizi H, Casscells SW, Litovsky S. Systemic infections cause exaggerated local inflammation in atherosclerotic coronary arteries: clues to the triggering effect of acute infections on acute coronary syndromes. Tex Heart Inst J. 2007;34(1):11-8.
52. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. Lancet. 2013;381(9865):496-505.
53. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, *et al*. COVID-19 and cardiovascular disease. Circulation. 2020;141(20):1648-55.
54. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, *et al*. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361(9371):1767-72.
55. Nava HJ, Zamudio P, Quiroz Y, Martínez I, Espinosa A, García A, Domínguez ED. Nava RHJ, et al. La disfunción mitocondrial como posible causa de la falla orgánica múltiple asociada a la sepsis severa. Rev Inst Nal Enf Resp Mex. 2009;22(1):37-47.
56. Baigorri-González F, Lorente Balanza JA. Oxigenación tisular y sepsis. Med Intensiva 2005;29(3): 178-84.
57. Fernández Fernández R. Fisiopatología del intercambio gaseoso en el SDRA. Med Intensiva. 2006; 30(8):374-8.
58. Vallance P, Collier J, Moncada S. Nitric oxide synthesised from L-arginine mediates endothelium dependent dilatation in human veins in vivo. Cardiovasc Res. 1989;23(12):1053-7.
59. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J. 2014;35(17):1101-11.
60. Wenz M, Hoffmann B, Bohlender J, Kaczmarczyk G. Angiotensin II formation and endothelin clearance in ARDS patients in supine and prone positions. Intensive Care Med. 2000;26(3):292-8.
61. Doerschug KC, Delsing AS, Schmidt GA, Ashare A. Renin-angiotensin system activation correlates with microvascular dysfunction in a prospective cohort study of clinical sepsis. Crit Care [Internet]. 2010 [cited 16 May 2020];14(1):R24. Available at: https://doi.org/10.1186/cc8887
62. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al*. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-8.
63. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis. 2020;63(3):390-1.
64. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11): 1061-9.
65. Coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK − Seventh update [Internet]. Estocolmo: European Centre for Disease Prevention and Control; 2020 [En línea 25 Mar 2020]. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-seventh-update-Outbreak-of-coronavirus-disease-COVID-19.pdf
66. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX,

et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18): 1708-20.
67. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, *et al*. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med. 1990;113(3):227-42.
68. Kanatsuka H, Lamping KG, Eastham CL, Dellsperger KC, Marcus ML. Comparison of the effects of increased myocardial oxygen consumption and adenosine on the coronary microvascular resistance. Circ Res. 1989;65(5):1296-305.
69. Kuo L, Davis MJ, Chilian WM. Myogenic activity in isolated subepicardial and subendocardial coronary arterioles. Am J Physiol. 1988;255(6 Pt 2):H1558-62.
70. Kuo L, Davis MJ, Chilian WM. Endothelium-dependent, flow-induced dilation of isolated coronary arterioles. Am J Physiol. 1990;259(4 Pt 2): H1063-70.
71. Kuo L, Davis MJ, Chilian WM. Longitudinal gradients for endothelium-dependent and -independent vascular responses in the coronary microcirculation. Circulation. 1995;92(3):518-25.
72. Chilian WM, Kuo L, DeFily DV, Jones CJ, Davis MJ. Endothelial regulation of coronary microvascular tone under physiological and pathophysiological conditions. Eur Heart J. 1993;14(Suppl I): 55-9.
73. Court O, Kumar A, Parrillo JE, Kumar A. Clinical review: Myocardial depression in sepsis and septic shock. Crit Care. 2002;6(6):500-8.
74. Eichenholz PW, Eichacker PQ, Hoffman WD, Banks SM, Parrillo JE, Danner RL, *et al*. Tumor necrosis factor challenges in canines: patterns of cardiovascular dysfunction. Am J Physiol. 1992; 263(3 Pt 2):H668-75.
75. Böhm M, Kirchmayr R, Gierschik P, Erdmann E. Increase of myocardial inhibitory G-proteins in catecholamine-refractory septic shock or in septic multiorgan failure. Am J Med. 1995;98(2):183-6.
76. Shepherd RE, Lang CH, McDonough KH. Myocardial adrenergic responsiveness after lethal and nonlethal doses of endotoxin. Am J Physiol. 1987; 252(2 Pt 2):H410-6.
77. Tang C, Liu MS. Initial externalization followed by internalization of beta-adrenergic receptors in rat heart during sepsis. Am J Physiol. 1996;270(1 Pt 2):R254-63.
78. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, *et al*. ST-segment elevation in patients with covid-19 - A Case Series. N Engl J Med. 2020;382(25):2478-80.
79. Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, *et al*. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. Eur Heart J. 2007; 28(10):1205-10.
80. Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal Influenza Infections and Cardiovascular Disease Mortality. JAMA Cardiol. 2016;1(3):274-81.
81. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, *et al*. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018;378(4):345-53.
82. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, *et al*. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol. 2020;75(18):2352-71.
83. Knowlton KU, Savoia MC, Oxman MN. Myocarditis and Pericarditis. En: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's – Principles and Practice of Infectious Diseases. 7ª ed. Philadelphia: Churchill Livingstone/Elsevier; 2010. p. 1153-72.
84. Fung G, Luo H, Qiu Y, Yang D, McManus B. Myocarditis. Circ Res. 2016;118(3):496-514.
85. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, *et al*. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med. 2013;369(5):407-16.
86. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2.
87. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-8.
88. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation. 1997;95(1):163-8.
89. Al-Biltagi M, Issa M, Hagar HA, Abdel-Hafez M, Aziz NA. Circulating cardiac troponins levels and cardiac dysfunction in children with acute and fulminant viral myocarditis. Acta Paediatr. 2010; 99(10):1510-6.

90. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, *et al*. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):1-6.
91. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J [Internet]. 2020 [En línea 16 Mar 2020]:ehaa190. Available at: https://doi.org/10.1093/eurheartj/ehaa190
92. Ammirati E, Veronese G, Brambatti M, Merlo M, Cipriani M, Potena L, *et al*. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2019;74(3):299-311.