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Cardiovascular effects of new coronavirus infection SARS-CoV-2 (COVID-19)

Repercusión cardiovascular de la infección por el nuevo coronavirus SARS-CoV-2 (COVID-19)

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CORONAVIRUS 2 DISEASE (COVID-19)

Beginnings of a pandemic

On 7 January 2020, the new SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was officially recognized by the Chinese authorities as the causal agent of a series of pneumonia cases diagnosed in Wuhan, China, during the previous month (December/2019)[1]. The disease causing the virus has been named Novel Coronavirus Infectious Disease 2019 in its original language giving rise to its well-known acronym COVID-19. The World Health Organization (WHO) declared the outbreak as a public health emergency of international concern on 30 January 2020[2], and a pandemic on the following 11 March[3].

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The COVID-19 virus efficiently replicates in the upper respiratory tract and its epidemiological characteristics make it actually different from conventional human coronaviruses, which are those responsible for many of the all too common winter season colds[4]. Since the onset of symptoms is slower, the incubation period in infected people is likely to be longer (up to 2 weeks). As long as individuals remain asymptomatic or oligosymptomatic, they maintain their mobility and usual activities. This contributes to the spread of the infection; which seems to have some affinity for the lower respiratory tract cells. After migrating there, the virus continues to replicate and may produce radiological manifestations of inflammatory condensation without the typical symptoms of pneumonia[5].

By the time this article was completed, there were a total of 1.840.093 confirmed cases globally, according to the COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)[6] and the World Health Organization coronavirus world map (**Figure 1**)[7]; and Cuba was reporting 669 cases with 18 deaths[6,7].

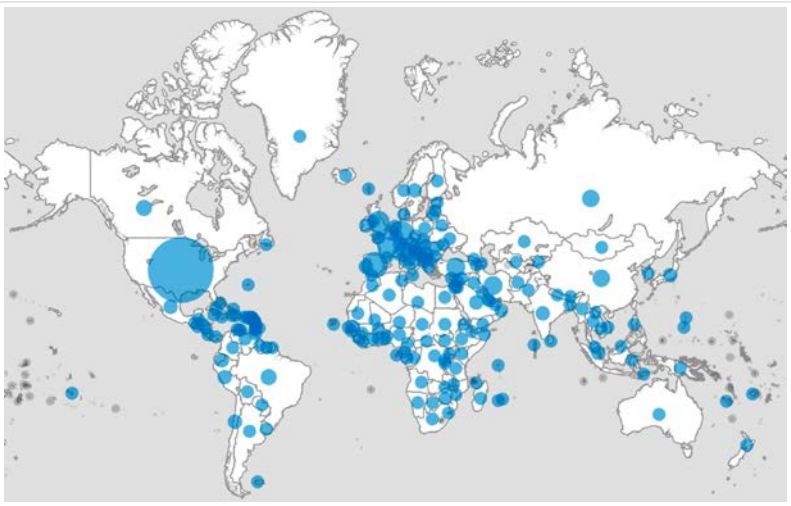

Figure 1. World Health Organization map showing confirmed cases. Taken from World Health Organization. Coronavirus (COVID-19) – WHO Health Emergency Dashboard[7].

Phylogenetic origin

Seven species of these beta-coronaviruses are known to be responsible for causing infections in humans. Four of them mainly cause mild flu-like symptoms and the remaining three produce potentially fatal diseases (SARS [severe acute respiratory syndrome], MERS [Middle East Respiratory Syndrome] and COVID-19)[8].

Evolutionary analysis and genetic sequencing of SARS-CoV-2 show more than 80% identity with SARS-CoV and 50% with MERS-CoV. Therefore, evidence from phylogenetic analysis indicates that SARS-CoV-2 from COVID-19 belongs to the beta-coronavirus genus[1,9,10]. Bats are known to be reservoirs of a wide variety of coronaviruses and so they are in this particular case. The virus could easily be transmitted to humans through unknown intermediate hosts; domestic animals may be among them [8,11,12]. Direct contact with these intermediate hosts or consumption of wild animals could have been the main route through which SARS-CoV-2 was transmitted between species; but its true origin and transmission mechanisms remain to be elucidated[12].

Transmission

Regardless of the high probability that SARS-CoV-2 may be of zoonotic origin, the virus has been shown to have effective human-to-human transmission, primarily through respiratory secretions, yet it can also be aerosolized (Flügge droplets) or detected in feces[13]. Huang *et al*[14], in 16 patients with COVID-19 admitted to intensive care, detected RNA (ribonucleic acid) of the virus in lower respiratory tract samples (sputum or endotracheal aspiration) in 100% of cases, nasal mucosa (81%), feces (69%), oropharynx (63%), gastric content (46%), anal mucosa (25%), conjunctiva (6.7%) and urine (6.2%). It follows that the virus is transmitted beyond the airway.

SARS-CoV-2 can remain viable up to 3 hours (h) as an aerosol (spray), and up to 72h on certain surfaces: copper coins (4h), latex gloves (8h), cardboard (24h), clothing –including nasobuccal mask– (48h) and stainless steel or plastic –such as electronic device screens– (48-72h)[13].

Transmission may happen in symptomatic and asymptomatic patients, with varying secondary infection rates; the mean incubation time, also variable, ranges from 2-5 days (up to 14) to 97.5% of cases experiencing symptoms within 11-12 days of exposure[15,16].

Recent studies in pregnant women infected with COVID-19 reveal that pregnancy does not imply an increased risk of complications or poor prognosis compared to the general population. There is no evidence so far of vertical virus transmission from mother to fetus or newborn during delivery or breastfeeding; neither has it been possible to define the optimum time of delivery, nor its safety via the uterus, or whether vertical transmission is prevented by cesarean section. Therefore, the route and time of delivery should be individualized according to obstetric indications and maternal-fetal status[17-20]. However, after birth, mother-to-child transmission may take place through the usual routes; therefore, the most appropriate measures, including isolation, should be taken[21].

Symptoms

The typical symptoms, found in several studies, included fever (88.7%), predominantly dry cough (67.8%), fatigue/asthenia (38.1%), cough with expectoration (33.4%), dyspnea (18.6%), odynophagia (13.9%) and headache (13.6%). Furthermore, some of the patients have shown gastrointestinal symptoms, such as diarrhea (3.8%) and vomiting (5.0%), as well as rhinorrhea (4.8%), muscular pain, lightheadedness, anosmia and ageusia[1,12,15,22]. Fever and cough are the main symptoms. Anosmia often appears alongside other well-known symptoms of COVID-19,

but it occurs isolated in 10-20% of patients, which would help to identify previously asymptomatic individuals[23]. The elderly and patients with comorbidities are more vulnerable[1,22,23].

According to Clerkin *et al*[15], reports from China reveal that the vast majority of patients (81%) experience mild symptoms, without pneumonia or with benign parenchymal involvement. Among the remaining patients, 14% presented severe symptoms (dyspnea, polypnea≥30 breaths per minute, oxygen saturation ≤93%, PaO_2/FiO_2 ratio <300, with or without pulmonary infiltrates >50% in 24-48 hours), and 5% were considered critical (acute respiratory distress syndrome [ARDS], septic shock and multiple organ dysfunction or failure).

Clinical manifestations

In principle, three main clinical manifestations of the disease have been recognized (A, B and C)[4,5,24], to which another four (D-G) as a result of the greater severity of the disease, have been subsequently added[15,25-27]:

A. Upper respiratory disease with mild symptoms.
B. Uncomplicated lower respiratory disease (pneumonia).
C. Severe pneumonia beginning with mild symptoms for 7-8 days and then progressing to rapid deterioration with the onset of severe acute respiratory distress syndrome (ARDS) requiring advanced life support.
D. Systemic inflammatory response syndrome: cytokine storm and macrophage activation syndrome.
E. Coagulopathy/thrombogenicity.
F. Septic/cardiogenic shock.
G. Multiple organ failure.

Siddiqi and Mehra[26] have proposed three distinct phases of COVID-19 (**Table 1**), which briefly outline the contributions of several other authors[28-30], who provide guidance for diagnosis and treatment management.

Table 1. COVID-19 phases or stages, proposed by Siddiqi and Mehra[26].

Stages	Symptoms	Diagnosis	Treatment
Stage I (mild): early infection	Mild, often nonspecific symptoms such as malaise, fever, and dry cough	Includes PCR of respiratory sample, IgG and IgM serological SARS-CoV-2 tests, along with radiographic studies of the chest, liver function tests and complete hemogram that may reveal lymphopenia and neutrophilia, with no other significant alterations	Aimed at symptom relief. If antiviral therapy (such as remdesivir) is shown to be beneficial, it should be targeted at selected patients to reduce symptom duration, minimize transmission, and prevent disease progression.
Stage II (moderate): - **IIa: With pulmonary involvement, without hypoxia** - **IIb: With pulmonary involvement and hypoxia**	Patients develop viral pneumonia, with cough, fever, and possibly hypoxia (defined as PaO_2/FiO_2 <300 mmHg)	Chest X-ray or CT scan will show bilateral infiltrates or ground-glass opacities. Blood tests show increased lymphopenia and elevated transaminases. There may be non-significant elevation of systemic inflammation markers. In addition, serum procalcitonin is normal or low in most cases of pneumonia.	In the early stages (without significant hypoxia) the use of corticosteroids should be avoided; but if hypoxia is present, patients are likely to require mechanical ventilation and in that context they may indeed be useful, although should be used with caution.
Stage III (Severe): Systemic Inflammatory Response Syndrome	It is the most severe stage of the disease and, in addition to respiratory failure, it presents as an extrapulmonary systemic hyperinflation syndrome. Systemic organs are affected and myocarditis, shock, vasoplegia and cardio-pulmonary collapse may appear.	Decrease of helper, suppressive and regulatory T-cells, with elevation of systemic inflammation markers: IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C-reactive protein, ferritin, and D-dimer. In addition, elevated troponins and NT-proBNP is present, and a syndrome similar to hemophagocytic lymphohistiocytosis may occur	It is individualized and relies on the use of immunomodulators to reduce systemic inflammation before it leads to multiorgan dysfunction. Corticosteroids could be used along with cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist), and intravenous Ig to modulate an immune system that remains in a hyperinflammatory state.

FiO_2, inspired oxygen fraction; Ig, immunoglobulin; IL, interleukin; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PaO_2, partial pressure of arterial oxygen; PCR, polymerase chain reaction; CT, computed tomography.

CARDIOVASCULAR MANIFESTATIONS OF COVID-19

An overview

Angiotensin-converting enzyme 2 (ACE-2), a crucial receptor for SARS-CoV-2, is also expressed in the heart, thus providing the link between coronaviruses and the cardiovascular system[27]. Just as seasonal influenza COVID-19 causes mild, self-limiting illness in most infected people; but can be severe, most likely in older patients or individuals with comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease and chronic kidney disease, among other conditions, including cardiovascular disease[5]. These may become unstable in the context of viral infection owing to an imbalance between the infection-induced increase in metabolic demand and decreased cardiac output[27].

Patients with underlying cardiovascular disease, which is more prevalent in older adults, are at greater risk of complications and death during the intense inflammatory response to COVID-19 than younger, healthier people[31].

Pathophysiology

Pérez[22] provides a very illustrative graph on the pathophysiology of acute cardiac injury in COVID-19, published by Fernando de la Guía[32] –summarizing the information from various publications, including those of Chen *et al*[33] and Zheng *et al*[34]– which we have modified to give a more comprehensive view (**Figure 2**)[8,15,27,28,31,35-39].

Although the exact pathophysiological mechanism of myocardial injury caused by COVID-19 is not fully elucidated, previous reports have shown that in 35% of patients with severe SARS-CoV infection, the virus' RNA was detected in the heart; and as these two coronaviruses have been shown to have highly similar genomes (over 80% identity)[8], they could share exactly the same infection mechanisms [40], so a high possibility of direct damage to myocytes from SARS-CoV-2 is evident[8,22,35].

In the Guo *et al*[35] study, troponin T plasma levels were significantly correlated linearly with plasma levels of high-sensitivity C-reactive protein, indicating that myocardial injury may be closely associated with inflammatory pathogenesis during disease progression.

Certainly, in its pathophysiology, a wide variety of factors are thought to be part of the mechanism that produces acute myocardial injury. Notable among them are direct myocardial and vascular damage, hypoxia, systemic inflammatory response syndrome, endothelial dysfunction and thrombogenicity. All these factors are summarized in **Figure 2**.

Pre-existing heart failure

Breathlessness and fatigue, two key symptoms of heart failure, are very common in patients with COVID-19, especially in its more advanced stages; therefore, diagnosis becomes particularly difficult in patients with chronic heart failure. In addition, both COVID-19 and heart failure cause hypoxemia, which is the basic pathophysiological mechanism leading to death[28,29].

Similarly, heart failure patients are also prone to hemodynamic decompensation during the severe infectious disease stress[31].

Myocarditis

Inciardi *et al*[25] reported the case of a patient with no history of cardiovascular disease, admitted for COVID-19 with significant left ventricular dysfunction, suffering from severe acute myopericarditis. Among their main findings are that cardiac involvement in COVID-19 may occur even without signs and symptoms of respiratory infection.

Viral myocarditis has a remarkably broad spectrum of clinical presentation, ranging from undetected to potentially fatal arrhythmias or advanced heart failure[41]. It produces focal or global myocardial inflammation, with areas of necrosis, which produce electrocardiographic and echocardiographic alterations, and elevated markers of myocardial injury that could be interpreted as an acute coronary syndrome. Cardiac pathogenesis associated with SARS-CoV-2 may express a process of virus replication and spread through the blood or lymphatic system from the respiratory tract[25,31]. However, although the ultrastructural mechanisms are not fully known, possible binding to a viral myocyte receptor may favor the internalization and subsequent replication of capsid proteins and viral genome[25,42].

Acute heart failure

Acute viral myocarditis, in this case from SARS-CoV-2, is not the only cause of acute heart failure –which may eventually be severe–. The massive interplay of molecular and cellular mechanisms involved in the physiopathology of COVID-19, in its most advanced stages, explains why ventricular dysfunction takes place, apart from the direct involvement of the myocardium by the virus. Hypoxia, produced by respira-

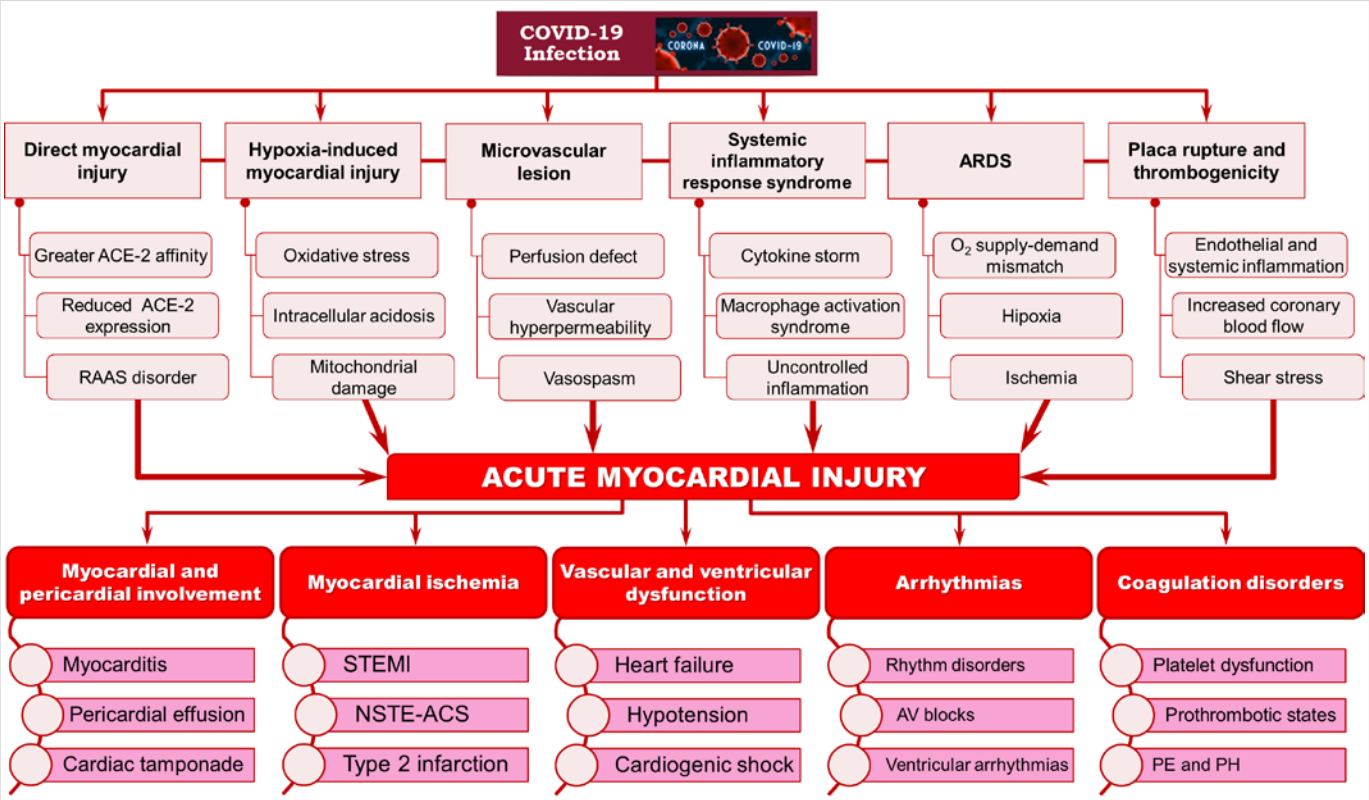

Figure 2. Pathophysiological mechanisms of acute cardiac injury in COVID-19 and its main clinical manifestations[8,15,27,28,31,35-39]. Modified from @Cardio_delaGuia (Fernando de la Guía)[32]. ARDS, acute respiratory distress síndrome; AV, atrioventricular; ACE-2, angiotensin-converting enzyme 2; PH, pulmonary hypertension; STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; RAAS, renin-angiotensin-aldosterone system; PE, pulmonary embolism.

tory distress decreases oxygen supply to the myocardium, which in turn requires large amounts of this gas by sympathetic stimulation secondary to infection[8,15,27]. On the other hand, the systemic inflammatory response syndrome favors increased cytosines with a well-known myocardial depressant effect. In addition, inflammation and sympathetic stimulation increase the risk of arrhythmias and the possibility of acute myocardial ischemia[28,31,35,36,43].

Arrhythmias

Hypoxemia may trigger atrial fibrillation, which is the most typical arrhythmia among the elderly[28,43], which may be refractory to treatment before pulmonary function improves; on the other hand, the systemic inflammatory response and coagulation disorders found in COVID-19 make its anticoagulant treatment extremely challenging[28-30].

Sinus tachycardia is frequent in severe patients, even without cardiac involvement, due to increased peripheral demands and sympathetic stimulation. The appearance of malignant arrhythmias is more associated with the presence of myocarditis, acute coronary syndrome and heart failure.

Acute coronary syndrome

Patients with previous ischemic heart disease and heart failure are at increased risk as the systemic inflammatory response may trigger atheroma plaque erosion or rupture in patients with or without underlying coronary disease[28-30,43]. Since non-significant plaques, which do not produce symptoms, may be especially vulnerable because of their high lipid content and weak capsule.

The systemic inflammation has a procoagulant effect that may increase the likelihood of stent thrombosis, so platelet function assessment and appropriate antiaggregation therapy should be considered in individuals with a history of percutaneous coronary intervention[27].

According to Bonow *et al*[31], in their JAMA (Journal of the American Medical Association) editorial,

these acute coronary events may result from increased myocardial demands triggered by the infection, leading on to injury or myocardial infarction, as it does in type 2 infarction[44]. In addition, circulating cytokines, released by a severe systemic inflammatory response, may lead to atherosclerotic plaque instability and rupture.

Coagulation disorders and cytokine storm

The response to the viral infection leads to a state of hypercoagulability. This, coupled with endothelial cell inflammation, may lead to platelet dysfunction and some predisposition to thrombus formation which, although venous in most cases, may also appear in the arterial system and produce infarctions at any level in addition to pulmonary embolism and hypertension. The ultimate expression of this disorder is the presence of a coagulopathy resembling that of the antiphospholipid syndrome or formation of disseminated intravascular coagulation[24,27].

Zhang *et al*[45], report on a 69-year-old man with a history of hypertension, diabetes and stroke who was admitted to intensive care for worsening symptoms (ARDS requiring mechanical ventilation). They found signs of bilateral ischemia in the lower limbs and in two fingers of the left hand, as well as a number of bilateral cerebral infarctions on the CT scan. The patient had leukocytosis, thrombocytopenia, prolonged prothrombin time, elevated fibrinogen and D-dimer; moreover, the presence of IgA anticardiolipin antibodies and anti-β2-glucoprotein I, IgA and IgG antibodies was subsequently demonstrated.

Gauna and Bernava[46], in a paper published in this issue of CorSalud, suggest the existence of a thrombotic immune response associated with COVID-19 (RITAC, acronym in Spanish) where, rather than appearing in immunosuppressed individuals, it occurs in those who are immunocompetent, due to the appearance of a macrophage activation syndrome combined with a pathological thrombin activation, with the subsequent production of multiple thrombotic events. This is why ferritin and D-dimer determinations are so useful. The diagnostic criteria for RITAC are shown in **Box 1**.

Macrophage activation syndrome, a frequently fatal systemic inflammatory pathological reaction –which can be triggered by infectious, rheumatic and neoplastic diseases (**Figure 3**)[47,48]– is part of the so-called cytokine storm that occurs in patients with COVID-19. This is a hyperinflammatory state resembling secondary hemophagocytic lymphohistiocytosis (HLH), characterized by an excessive release of cytokines that may lead to multiple organ failure[24,49,50]. According to Mehta *et al*[24], HLH is commonly triggered by viral infections. It occurs in 3.7-4.3% of patients with sepsis and clinically produces persistent fever, cytopenias and hyperferritinemia. It also causes pulmonary involvement, including ARDS, in half of the patients.

Box 1. RITAC diagnostic criteria[46].

Patients with confirmed COVID-19 infection with respiratory symptoms presenting one or more of the following criteria:
1. D-dimer > 1000 ng/mL
2. Ferritin > 500 ng/mL
3. Rapidly progressive dyspnea
4. Refractory hypoxemia
5. Thrombotic disorders
6. Shock

This cytokine storm, together with clotting disorders related to thrombogenicity[45], mainly at the level of the small vessels, obviously has cardiovascular implications affecting the prognosis of patients with COVID-19 (**Figure 2**).

Diastolic function

Yang and Jin[29] claim that the transient diastolic function deterioration, detected by echocardiography, can be ascribed to the systemic inflammatory syndrome response to viral infection, as several cytokines such as tumor necrosis factor and the interleukin-6 family have been shown to have a clinically significant negative inotropic influence. This may also be a contributing factor to the development of heart failure or the deterioration of pre-existing heart failure.

Congenital heart disease

Although there are no publications on patients with congenital heart diseases affected by COVID-19 and it cannot be assured that they are at greater risk of infection, there is consensus on the fact that those with complex congenital heart disease should be considered as patients at high risk of complications and mortality, due to their known decrease in functional reserve[51]. Therefore, prevention is paramount, and in the presence of symptoms or suspected infection, diagnostic tests should be prioritized to ensure

the most appropriate therapeutic strategies[52].

Interventional Cardiology procedures

The different scientific societies (Spanish[53,54] and European Societies of Cardiology, American College of Cardiology's Interventional Council[55] and the Society of Cardiovascular Angiography and Intervention[55]) agreed to suspend all elective procedures (**Box 2**) during the COVID-19 pandemic and perform only emergency cases, always under strict protection and control conditions[56].

Cuba is a very special case as it has few medical facilities where this type of procedure is performed. There is a rather small number of trained specialists; hence, these professionals (cardiologists and nurses) currently working in our country's Hemodynamics and Interventional Cardiology Units, should be kept out of outpatient care for patients suspected or confirmed to have COVID-19. Since, if infected, they could put at risk the rest of the trained personnel and, consequently, all the appropriate care of those who −with or without this viral infection− present an acute coronary syndrome with indication for urgent cardiac catheterization.

Welt *et al*[55] clearly state that, in order to avoid infection, two interventional cardiologists or two teams with the same skills should not be operating in the same area. Many hospitals have therefore set up special shifts with different schedules. This way if one of them gets infected the service will not be suspended.

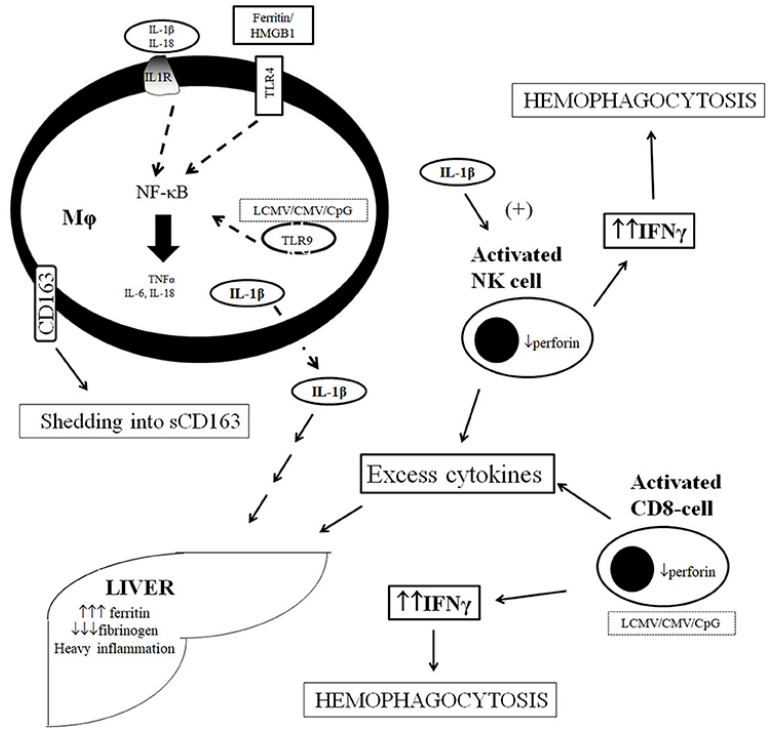

Figure 3. Current concept of pathogenesis of macrophage activation syndrome in sepsis. Over-production of IL-1β is effected through the stimulation of TLRs by ferritin and HMGB1 and by the per se autocrine effect of IL-1β on IL-1R at the macrophage level. Stimulation leads to cytokine storm and shedding of CD163 from macrophage cell membrane. Over-produced cytokines stimulate further ferritin production by the liver and liver dysfunction whereas IL-1β leads to over-production of IFNγ by NK cells leading to hemophagocytosis. Excess cytokine production may result independently by disturbances in NK cell and CD-cell function leading to their over-activation.
CMV, cytomegalovirus; CpG, bacterial oligonucleotides; IL, interleukin; IL-1R, receptor of IL-1; LCMV, lymphocytic choriomeningovirus; Mϕ, macrophage, NF-κB, nuclear factor kappa B; NK, natural killer; TLR, Toll-like receptor; TNFα, tumor necrosis factor-alpha. Taken from Karakike E, Giamarellos-Bourboulis EJ. Front Immunol. 2019[48] (CC BY-NC-ND 4.0).

All of the heads of Hemodynamics and Interventional Cardiology Units must coordinate adequate training for the work team with the Department of Epidemiology and Infection Control to ensure the availability of any required equipment and their appropriate use for individual and collective protection[54,55]. Moreover, as a precaution, all patients coming into the room should be provided with a surgical (nasobuccal) mask to prevent the spread of potentially infected Flügge droplets.

Strict indications for percutaneous coronary intervention are still maintained for patients with ST-segment elevation myocardial infarction, or non-ST-segment elevation acute coronary syndromes with high and very high risk criteria[25,57-59]. Especially when they are hemodynamically unstable (moderate-severe ventricular dysfunction or cardiogenic shock), presenting recurrent ischemia, high suspicion of left main coronary artery disease or malignant ventricular arrhythmias.

CorSalud is publishing in this same issue a paper by Gómez Guindal[58] setting out the care protocol for patients with acute coronary syndrome in the *Hospital de Fuerteventura*. This protocol can be easily adapted to Cuba as it is that of an island territory with similar characteristics to most of the provinces of our country, which, not having the possibilities of

Box 2. Procedures to be postponed during the COVID-19 alarm phase[53-55,58,59].

Percutaneous coronary intervention in:
- Patients with stable angina
- Patients with STEMI and effective fibrinolysis with clinical and electrical signs of reperfusion
- Patients with stable, low-risk NSTE-ACS (GRACE < 110)
Endovascular intervention for lower limb peripheral artery disease
Percutaneous structural heart interventions:
- Patent foramen ovale (PFO), patent ductus arteriosus (PDA), and atrial (ASD) and ventricular (VSD) septal defect closures
- Left atrial appendage closure
- Heart valve disease, including transcatheter aortic valve implantation (TAVI) and MitraClip
Embolectomy in stable patients with pulmonary embolism
Diagnostic and therapeutic electrophysiological studies in stable patients
Non-urgent implantation of programmed electrical stimulation devices

NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

performing hemodynamic studies and interventional cardiology procedures, have to refer their cases to a reference center.

It is very important to know that acute myocardial injury (type 2 infarction or myocarditis) may be found in about 7% of patients with COVID-19[44,55,58]. Hence, differential diagnosis to "primary" or type 1 acute coronary syndromes is essential to define the behavior to be followed: in type 2 infarction, if the patient has hemodynamic stability, any invasive procedure must be postponed or deferred.

TREATMENT

Drugs for COVID-19

As with most diseases, it is important to stress that treatment should be personalized and in accordance with the severity (stages) of the infection (**Table 1**); since in the advanced stages the prognosis is gloomy and recovery is scarce. Hence, rapid detection, before the occurrence of multi-organic dysfunction, coupled with early initiation of appropriate treatment will achieve better results. The use of immunomodulators to reduce systemic inflammation[26] and anticoagulants (low molecular weight heparin) in the case of thromboembolic manifestations is indicated in these cases[24,45,46].

The use of hydroxychloroquine and azithromycin for the initial stages has become widespread. This issue of CorSalud features an in-depth article by Barja *et al*[60], addressing the risk of sudden death related to these drugs, due to the effect they have on the QTc interval. The authors explain in great detail when to withdraw or maintain these medications, based on electrocardiographic criteria. Their instructions, therefore, should be of obligatory consultation for those who are responsible for the treatment of patients with COVID-19.

Cardiovascular drugs

COVID-19 strongly affects patients with cardiovascular disease. They happen to have a higher risk of adverse events because the very infection is associated with cardiovascular complications and its treatment includes drugs that may interact with those of the underlying heart disease[22,61,62] or have direct side effects such as dangerously prolonged QT interval (**Table 2**)[60,62].

SARS-CoV-2 reaches human cells by binding to the angiotensin-converting enzyme 2 (ACE-2), widely found in heart and lung tissue. This enzyme has important functions in neurohumoral regulation, so its binding to the virus can produce alterations in ACE2-related signaling pathways and lead to acute lesions in both organs[8,61].

Perhaps this is what has raised concern about the risk of using their (ACE) inhibitors or angiotensin-receptor blocker (ARB), as the increased expression of ACE-2 induced by these drugs (ACE inhibitors and ARB) −hypothetically− would aggravate lung injury in patients with COVID-19[63]; however, it is quite the opposite. Henry *et al*[64] found these drugs' beneficial effects on patients admitted with viral pneumonia, as ACE and ARB significantly reduced the pulmonary inflammatory response and cytokine release caused

Table 2. Drugs used in COVID-19 according to cardiovascular interactions and adverse effects. Modified from Vetta *et al.* J Cardiol Cardiovasc Res. 2020;1(2):1-12[62].

Drug	Drugs interaction	Adverse effects
Lopinavir/Ritonavir	Antiarrhythimics, Anti-coagulants, Antiplatelet agents, statins	QTc prolongation, Impaired cardiac conduction, high degree AV block, *torsade de pointes*
Remdesivir	Unknown	Hypotension?
Ribavirin	Warfarin	Hypotension/Hypertension, arrhythmias, acute coronary syndrome
Bevacizumab	Unknown	Direct myocardial toxicity, hypertension, thromboembolic events
Chloroquine/ hyroxychloroquine	Antiarrhythmics drugs and other QT-prolonging agents	Direct myocardial toxicity, altered cardiac conduction: AV block, bundle branch block, torsade de pointes, ventricular tachycardia/fibrillation
Fingolimod	Antiarrhythmics Ivabradine	Hypertension, first and second-degree AV block, bradycardia, QTc prolongation Contraindication: Sick sinus syndrome, AV block, QTc ≥ 500 ms, and acute coronary/cerebrovascolar syndromes
Interferon	Unknown	Direct myocardial toxicity, hypotention, arrhythmia, cardiomyopathy, and acute coronary syndrome
Tocilizumab	Unknown	Hypertension, hypercholesterolemia

AV, atrioventricular; QTc, corrected QT interval

by the viral infection; probably related to a compensatory increase in ACE-2[65-67]. In fact, Kuba *et al*[68] propose that downregulation of this enzyme, mediated by SARS-CoV, contributes to the severity of pulmonary pathologies, as ACE-2 is key to reducing the severity of acute pulmonary edema and failure.

For the aforementioned reasons, there is no evidence, so far, supporting ACE and ARB cessation in patients with COVID-19[35,69]; much less to prevent infection or for fearing of getting sick and being at greater risk of complications. Although the study by Guo *et al*[35], also cited by Madjid *et al*[43], showed more patients taking these drugs in the elevated troponin T group, their use was not associated with mortality rates.

PROGNOSIS

Poor prognosis factors

Age over 60 years, male sex and presence of comorbidities (high blood pressure, diabetes mellitus, pre-existing heart and cerebrovascular diseases, as well as chronic kidney and obstructive pulmonary diseases) are the main clinical factors associated with the severity and mortality of COVID-19 (**Box 3**)[8,9,22,24-27,31-36,43,61]. Even if there is previous heart disease, patients who do not have acute myocardial involvement (normal or slightly elevated troponins) have a better prognosis. Elevated NT-proBNP, presence of myocardial injury (elevation of troponins > 99 percentile), respiratory distress (ARDS) and the appearance of malignant arrhythmias have been shown to be independent factors strongly associated with mortality[8,31,35,36,43,70].

Pending issues

Many clinical assumptions regarding patient outcome have been made in relation to the better-known previous coronavirus infections (SARS-CoV and MERS-CoV)[27,34,38], all with a strong scientific basis relying on the genomic similarity of these with the new SARS-CoV-2. Some have been indeed demonstrated in those affected by COVID-19, yet it is not less true that concerning this pandemic, many aspects still remain to be elucidated. Immunity is one of them, since antibody tests can determine whether a person has had the viral infection. If they are positive, two things can be assured: that the individual has been infected with the disease and therefore has a certain degree of immunity. What is impossible to specify is "how much" immunity is there and just for how long.

For their part, Huang *et al*[14], as we previously

mentioned, in patients with confirmed COVID-19, admitted to intensive care, found that lower respiratory tract samples had higher viral loads and slower virus clearance, compared to those in the upper respiratory tract. Besides, only in 13 (81%) patients the nasopharyngeal samples proved positive for SARS-CoV-2 and the oropharyngeal samples in 10 (63%); while in all patients (100%) the lower airway samples (sputum or endotracheal aspiration) were positive.

The most striking aspect of these findings is that, despite being seriously ill COVID-19 patients, the presence of the virus was only confirmed in all cases when samples were taken from the lower respiratory tract. These findings bear crucial implications and are sobering: if this has occurred in patients with a recognized high viral load, what would then happen to those whose viral load is lower? Evidently, many patients who are actually infected and able to spread the disease escape the diagnosis; and this is one of the most important factors why COVID-19 has reached such proportions.

Long-term cardiovascular outcomes

Previous experience has shown that patients with pneumonia show increased systemic and procoagulant inflammatory activity that may persist long after

Box 3. Poor prognostic factors in patients with COVID-19[8,9,22,24-27,31-36,43,61,70].

Minor
- Age > 60 years
- Male
- Comorbidities: High blood pressure, diabetes mellitus
Major
- **Clinical**
• Comorbidities: Ischemic heart disease, cardiomyopathies, complex congenital heart diseases, cerebrovascular disease, chronic renal failure, chronic obstructive pulmonary disease
• Cancer treatment with possible cardiotoxicity
• Decreased level of consciousness
• Persistent fever
• Acute kidney or liver dysfunction
• Coagulopathies
• Hypotension/Vasoplegia
• Established acute heart dysfunction: heart failure, infarction, myocarditis, atrioventricular conduction disorders
• Average virus removal time greater than 3 weeks
- **Humoral**
• Significant elevation of D-dimer on admission
• Significant elevation of NT-proBNP (N-terminal pro-B-type natriuretic peptide)
• Significant elevation of markers of myocardial injury (troponins and myoglobin), evidence of acute myocardial injury (hazard ratio: 4.26)
• Leukocytosis/leukopenia, lymphopenia, pancytopenia
• Significant elevation of inflammatory markers: interleukin (IL)-6, IL-2, IL-7, tumor necrosis factor-alpha, monocyte chemotactic protein 1, granulocyte colony-stimulating factor, gamma-interferon-induced protein 10, serum ferritin, C-reactive protein, and procalcitonin
• Thrombotic immune response associated to COVID-19 (RITAC, acronym in Spanish)
Severe (with very high mortality demonstrated in multivariate models)
• Acute respiratory distress syndrome (ARDS) (hazard ratio: 7.89)
• Malignant ventricular arrhythmias
• Shock
• Multiple organ failure

the infection has resolved. Its clinical effects have been associated with an increased risk of cardiovascular disease up to 10 years later[27,34,61]. This is why Corrales-Medina *et al*[38] raise the possibility that the cases currently infected by COVID-19 will experience similar results.

Corticosteroid treatment increases the likelihood of adverse cardiovascular events. However, long-term follow-up data on respiratory virus outbreak survivors are scarce[8,34]. In contrast, Wang *et al*[71], in a study enrolling 25 SARS survivors, found that lipid metabolism remained altered for up to 12 years after clinical recovery, while the cardiovascular disorders, observed during hospitalization, in 8 patients with H7N9 influenza were fully resolved within 1 year.

Certainly, it is impossible to make any long-term considerations when we know that this is a newly known disease as it was declared an international public health emergency on 30 January 2020[2]. Current assumptions are based on previous infections with viruses of similar characteristics[27,38,71]. Further prolonged follow-up studies will highlight the real long-term cardiovascular impact of COVID-19.

As stated by Bansal[8], the great expansion and virulence of COVID-19 means that a large number of affected patients have pre-existing heart disease or develop it during the course of the infection. But the true long-term impact caused by the coexistence of both diseases is not yet well articulated, as the expression of the virus in humans is quite recent. Undoubtedly, more research is required to specifically know their incidence, the whole spectrum of their clinical presentation and the prognosis of different cardiovascular manifestations. We experience the heavy impact on our patients on a daily basis. But that, in the long run, is a pending issue.

CONFLICT OF INTERESTS

None declared.

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