REVIEW ARTICLE

COVID-19. Review on Its Cardiovascular Impact

COVID-19. Su repercusión cardiovascular. Una revisión

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INTRODUCTION

For more than six months, the world has suffered a pandemic called COVID-19 (coronavirus disease 19), which, originating in Wuhan, China, quickly spread to the rest of the planet. Its causal agent, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), has become a serious threat worldwide, with a distinctive feature, the speed of its transmission with concomitant exponential growth of the illness. Although its lethality is less than that of other family members, the rapid increase in cases and its impact on the health systems, leading to an early exhaustion of resources, means that this virus has clearly surpassed its predecessors. (1, 2).

The disease has geographically disseminated in stages. After its presentation in China, with an approximate three-month duration of the most serious period of its evolution (from December 2019 to the beginning of March 2020), the epidemic moved to Europe, with an epicenter in the Mediterranean countries (Italy, Spain, France), but also reaching Belgium and Great Britain. In the last month and a half, the focus has been on America, with the US and Brazil as the countries with the highest number of infected and fatal cases, but also with a high proportion of affected persons in Mexico, Chile and Peru. (3)

With more than 8 million people infected and 440,000 deaths, questions continue to arise in the quest to find an explanation for the current situation. A multiplicity of factors favored massive contagion in many Western countries, including the surprise or lack of adequate initial information in China, the late understanding by many governments about the opportunity that lay in early diagnosis and social isolation as active behaviors that slowed the spread, the high rate of contagion, poor public health systems, advanced age of the population in many European countries, with conditions that favor infection, added to the early collapse of the hospital chain, socioeconomic fragility and lack of adequate protection of a population with serious inequalities in the Americas, plus, of course, the absence of effective treatment or vaccines.

Isolation measures were implemented early in our country. This resulted in a flattening of the contagion curve, which enabled the hospital system to be prepared for the most critical moments and to define adequate control measures. Currently we are witnessing a significant increase in the number of cases, probably due to greater testing and to the arrival of the peak of infection. At the time of writing this article, there are more than 35,500 confirmed cases (40% of them of community circulation and almost the same number of close-contact confirmed cases) and more than 900 deaths; the case fatality rate is 2.6% and the highest risk is found in the age group ≥60 years. (4)

Although the target organ of this disease is the lung and history of lung disease is a very important risk factor, clearly associated with a negative evolution for COVID-19, the presence of cardiovascular diseases or cardiovascular risk factors comprises a significant proportion of patients and is basically associated with a worse prognosis. The prevalence of different cardiovascular conditions differs according to the source, the country and whether it is estimated on the total number of patients or on those admitted to intensive care units. (5)

Different cardiovascular conditions are among the most frequent complications of COVID-19: acute coronary events, conditions of decompensated chronic heart failure or onset of de novo heart failure, and arterial and venous thrombotic conditions. This places cardiologists before a great challenge regarding the accurate diagnosis of these conditions and their treatment, in a situation where the optimal treatment

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must be balanced with the biosecurity of the intervening staff to avoid the spread of infection in the health centers. (6, 7)

A serious developing problem, not related to a pathophysiological mechanism of COVID-19, but clearly an emerging one, is the fall of the usual consultation for cardiovascular disease. Different factors play a fundamental role: the limitation of many routine healthcare activities, the advice to stay at home, the fear of contagion or the postponement of diagnostic and therapeutic procedures considered non-urgent among others. This fact is repeated in the care of cancer patients and in those with other chronic diseases, and the possibility of an increase in morbidity and mortality from these conditions during and after the peak of the pandemic raises deep concern. (8, 9) Also, the proper care of health personnel and the measures that must be taken to preserve their physical (10) and emotional health is not a minor issue. (11)

COVID-19 is a multi-system condition. Day to day, new evidence of organs involved motivate the attention of the entire medical community. And it is increasingly necessary that, given the avalanche of published information and the speed with which it is generated, very serious information is available; the possibility of uncertain data, not adequately checked, places all the scientific journals in the world before an enormous responsibility. (12)

The objective of this review assumed by the RAC initiative is to offer the cardiology community with an update of the cardiovascular involvement of SARS-CoV-2, its treatment and its impact on cardiovascular therapy, as well as to provide a brief review of the measures recommended in its daily management.

THE VIRUS

Coronaviruses (CoV) owe their name to the presence of spikes on their crown-shaped surface. They belong to the Coronavirinae subfamily and are classified into four groups: CoV α, ß, γ and δ, of which the α and ß groups cause infection in humans. (7) They are RNA viruses, with the largest known size, and contain 4 main structural proteins: protein S (for spike), which mediates the binding to the host receptor and subsequent fusion of the virus to the cell membrane; protein N (for nucleocapsid); protein M (for membrane) and protein E (for envelope). (13) Until 2003, only 2 species capable of infecting humans had been recognized. Currently 7 different strains of CoV are known to infect humans, 4 of these (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) generally cause mild infection of the upper airways or gastrointestinal tract and the other 3 are responsible for severe symptoms. (14) The latter correspond to the severe acute respiratory syndrome coronavirus (SARS-CoV) (15), the Middle East respiratory syndrome coronavirus (MERS-CoV) (16) and the newly identified SARS-CoV-2, responsible for the COVID-19 condition. (1) These three viruses stand out for their high infectivity and attack rate, generating high mortality, despite not being so lethal.

Transmission of SARS-CoV-2 infection is primarily by aerosolized saliva droplets, but also by contact with contaminated hands and fomites. (17) The virus can remain stable for up to 3 hours in aerosolized solution, 1 day in cardboard and 3 days in stainless steel or plastic. (18) Incubation has a median duration of 4.5 days and 97% of those affected have symptoms within 11 days. (19) There is uncertainty about the true mortality rate associated with the infection, since, due to lack of universal testing, the total number of infected and, therefore, the real proportion of asymptomatic patients, is unknown. Person-to-person transmission is now well established for COVID-19, with an estimated R0 (expected number of secondary cases produced by a single typical infection) currently close to 2.5. (20, 21) In comparison, seasonal influenza has a reported median R0 of 1.28, while measles R0 is 12–18. However, R0 is calculated from imperfect data and across different populations, and estimates are influenced by local variations in susceptibility, case detection efficiency, and infection control responses.

THE GATEWAY: THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The gateway for SARS-CoV-2 into the body is the angiotensin 2-converting enzyme (ACE2). (Figure 1) The infection is caused by the binding of the virus protein S, activated by a transmembrane serine protease 2 (TMPRSS2), with the ACE2 receptor. (22)

Angiotensin-converting enzyme is a dipeptidyl carboxypeptidase that acts on angiotensin I, converting it to angiotensin II. ACE2 (a zinc-containing metalloproteinase, 42% homologous to ACE) is a monocarboxypeptidase 400 times more related to angiotensin II than to angiotensin I. (23) ACE2 activity, not inhibited by ACE inhibitors (ACEI) (24), resides in counterregulating the effect of the renin-angiotensin system by different mechanisms: a) breaking down angiotensin I to angiotensin-(1-9), which acts on the AT2R receptor, promoting vasodilation and antihypertrophic effect; b) breaking down angiotensin AII to angiotensin-(1-7), which acts on the Mas receptor and generates the activation of phosphatidyl inositol kinase, with increased formation of nitric oxide and inhibition of protein kinase C and collagen expression. ACE2, due to its vasodilator and antifibrotic effect, has been considered an endogenous ACEI. (25) ACE2 is expressed in a wide variety of tissues and organs. The sites of highest expression are the small intestine and the testicles; then, in decreasing order, adipose tissue, thyroid gland, kidney, heart, colon, breasts, ovaries, and, only after other organs, finally the lung. Within the heart and vessel cells, those with the highest expression of ACE2 are the pericytes, then the cardiomyocytes, and even less, fibroblasts and endothelial cells. (26)

Binding of the virus protein S with the ACE2 re-

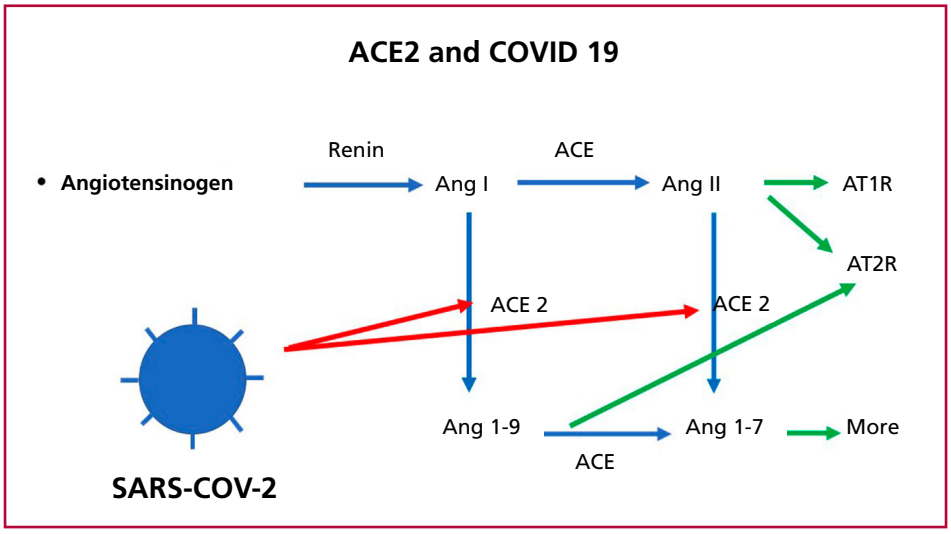


Fig. 1. ACE2 and COVID 19. Ang I: Angiotensin I. Ang II: Angiotensin II. Ang 1-9: Angiotensin 1-9. Ang 1-7: Angiotensin 1-7. ACE: Angiotensin-converting enzyme. ACE2: Angiotensin-converting enzyme 2. AT1R: Angiotensin I receptor. AT2R: Angiotension II receptor.

ceptor generates its down-regulation, with an increase in angiotensin II levels and a reduction in angiotensin-(1-7), increasing pulmonary vascular permeability and favoring vasoconstriction. Chronic therapy with ACEI inhibitors or angiotensin receptor blockers (ARB) increases ACE2 expression. This increase in ACE2 can be seen in a dual way: on the one hand, it exerts a cardioprotective, vasodilator and antagonistic effect on acute lung injury, by breaking down angiotensin II and favoring the formation of angiotensin-(1-7) and angiotensin-(1 -9) and, on the other, it theoretically increases the entrance door to SARS-CoV-2. (27, 28) This has given rise to controversy about the use of these drugs in the context of the pandemic.

Different observational studies have been presented in relation to this topic. Although a study suggested that in patients hospitalized for COVID-19 there would be a possible harm with these drugs (mortality rates for hypertensive patients who did not take an ACEI or ARB, who took an ACE inhibitor or who took an ARB were 26.7 %; 32.7% and 30.6%, respectively), the results were not adjusted for known confounders, including age, sex, race, and comorbidities. (29) Most of the published studies do not demonstrate an increased risk in patients treated with these drugs. In an Italian study with 6,272 patients hospitalized for COVID-19 and 30,759 controls, the use of ACEI and ARB was higher in the former, due to a higher prevalence of cardiovascular disease, but was not associated with an increased risk of contracting the infection. (30) The same was evidenced in a study carried out in Florida (USA), in which among 18,472 patients tested for COVID-19, 9.4% was positive. In a propensity score matching, there was no evidence that the use of ACEI or ARB predisposed to SARS-infection. (31) Identical result was obtained in the analysis of 12,594 patients in New York (USA), almost half of which were COVID-19 positive, and a third, hypertensive. The use of ACEI or ARB did not increase the probability of infection. (32) A similar publication, with 8,910 patients hospitalized by COVID-19 in 169 hospitals in Europe, Asia and the United States, also did not demonstrate excess risk in those treated with these drugs, and even suggested, cautiously due to the risk of residual confusion, a protective effect of ACEI, with a reduction in the risk of mortality of 67% (95% CI: 46% to 80%). (33) The conclusions of this last study have been questioned after the quality of the data was disputed. (34) Different reviews performed throughout these months (35-38) have suggested the non-suspension of the medication. This has been supported by the main cardiology societies in the world (39-41), as well as by the SAC (42), who have advised to continue using it during the pandemic.

THE PULMONOLOGIST'S VIEW

The lung is the organ preferably affected by SARS-CoV-2, since its entry into the body is mainly by inhalation. After binding to ACE2 receptors of the capillary endothelium and type 2 pneumocytes, it affects the alveolocapillary barrier, resulting in highly permeable edema. This edema is responsible for different conditions, ranging from a simple pneumonic image on chest x-rays or chest computed tomography (CT) scan to extensive bilateral involvement, associated with the development of acute respiratory distress syndrome (ARDS), according with the definitions accepted by the Berlin consensus. (43)

Typically, ARDS is characterized by the presence of non-cardiogenic pulmonary edema, hypoxemia related to atelectasis, and reduced aerated lung size ("baby lung"), which explains the serious disturbances of gas exchange. (44) In that condition, increasing lung size by recruiting previously collapsed lung units is often by the use of high levels of positive end-expiratory pressure (PEEP), recruitment maneuvers, and adequate recumbency. Since high transpulmonary pressure induces stress in the entire lung, relatively low tidal volumes, along with tolerance to modest (permissive) hypercapnia, facilitate the goal of minimizing

ventilator-induced lung injury (VILI). Furthermore, in the early stages of ARDS, before the patient has become fatigued or sedated, high transpulmonary pressures associated with spontaneous vigorous inspiratory effort may also contribute to the damage (the so-called patient self-induced lung injury). (45)

After respiratory distress appears, COVID patients initially maintain fairly good ventilation, despite very poor oxygenation. Respiratory rate is relatively high, infiltrates are often limited in extent, and are initially characterized by a ground glass pattern on CT, meaning interstitial rather than alveolar edema. Many patients do not appear to have exaggerated respiratory distress and, even though they are deeply hypoxic, their respiratory mechanics is good. These patients with high ventilation-perfusion ratio (V / Q) would have a "L-type" ARDS (as stated by Gatinoni) (46), characterized by low lung elastance (high compliance), lower lung weight, as estimated by CT scan, and low response to PEEP. For many patients, the disease can stabilize at this stage without further deterioration, while others, either due to disease severity and host response or suboptimal management, may progress to a more typical clinical condition of the syndrome. They are defined by Gatinoni as "type H", with wide CT scan consolidations, high elastance (low compliance), higher lung weight, and high response to PEEP. Clearly, types L and H are the extremes of a spectrum that includes intermediate stages, in which their characteristics can overlap. Another reported constant is an intensely activated coagulation cascade, with generalized micro- and macrothrombosis in the lung and other organs, in addition to very high serum levels of the D-dimer. (47)

These observations indicate the critical role played by disproportionate endothelial damage, disrupting pulmonary vasoregulation, promoting ventilation-perfusion mismatch (the leading cause of initial hypoxemia), and favoring thrombogenesis. Added to this is the lack of a clear understanding of the mechanisms involved, which could lead to counterproductive and wrong conducts, such as lack of attention to the cardiovascular aspect (for example, volume overload) and the generation of adverse conditions (as, for example, edema) and iatrogenic damage.

Patients with L-type ARDS, with adequate or high V/Q ratio, accept higher tidal volumes (7-8 m/kg of ideal body weight) than those usually indicated for traditional ARDS, without worsening VILI risk. Actually, in a 70 kg man, with a system compliance of 50 ml/cm H2O and PEEP of 10 cm H2O, a tidal volume of 8 ml/kg produces a plateau pressure of 21 cm H2O and a managing pressure of 11 cm H2O, both well below the currently accepted thresholds for VILI protection (30 and 15 cm H2O, respectively). A higher tidal volume helps to prevent the production of atelectasis and hypercapnia due to hypoventilation at lower tidal volumes.

The key at this early stage is interrupted vasoregulation, since pulmonary vasoconstriction that normally occurs in response to hypoxia does not occur due to endothelial injury, disconnecting perfusion from ventilation which can lead to profound hypoxemia. The doctor's first response, increasing the fraction of inspired O2, can be effective from the start. Non-invasive support (for example, high-flow nasal O2, CPAP and Bi-PAP, which can be administered with some care) can stabilize the clinical course in mild cases, provided that the patient does not exert excessive inspiratory efforts. If these are not reduced by oxygen administration and noninvasive support, persistently intense spontaneous inspiratory efforts simultaneously increase tissue tensions and pulmonary transvascular pressures, vascular flows, and fluid leak. (48, 49) Progressive deterioration of lung function can then occur rapidly. Early intubation, effective sedation, and/or paralysis can interrupt this cycle. Aiming for a lower PEEP (8-10 cm H2O) would be appropriate. Increasing mean transpulmonary pressures due to increased PEEP or inversion of the inspiratory-expiratory relationship redirects blood flow away from oversized open airspaces, accentuating tensions in the microvasculature, increasing permeability and compromising gas exchange, without the benefit of widespread recruitment of functional lung units.

If the pulmonary edema increases in the L-type patient, due to disease progression, the H-type phenotype develops progressively. Over time, overlapping VILI and uncontrolled viral disease induce inflammation and edema, promoting localized and widespread thrombogenesis, intense cytokine release, right ventricular overload and multiple-organ failure. In this advanced state, it is advisable to apply a more conventional lung protection strategy: higher PEEP (15 cm H2O), lower tidal volume (6 ml/kg), and, perhaps, prone position, minimizing oxygen consumption. Whatever the type of involvement, in case of improvement, weaning should be carried out with caution.

RISK FACTORS AND CARDIOVASCULAR DISEASE

Although SARS-CoV-2 can affect humans almost universally, its most threatening progression puts the elderly, especially those with cardiovascular disease (CVD), diabetes, or high blood pressure (HT) at risk. (33) Initial studies reported risk at a median age of 42 to 64 years, with older ages among severely ill patients admitted to the intensive care unit (ICU) (64 vs. 51 years). (47, 50-53) In general, COVID-19 affects men and women equally, but mortality rates are higher in men.

In China, the case fatality rate was 0.32% in patients below 60 years; 3.6% in patients aged 60 to 69 years; 8% in patients between 70 and 79 years and 14.8% in those over 80 years. (54, 55) In Italy, mortality ranged from 0% in patients below 30 years to 3.5% in those between 60 and 69 years, and reached 20% in cases above 80 years, especially in those with CVD. (56, 57) Specifically, it has been suggested that the fact that the mortality rate of people with COVID-19 was higher in the Italian population would be, in part, related to

the demographic characteristics of its population, with a high proportion of senior patients. (9) The age of patients in the United States was also higher than in China. Among patients hospitalized in New York, mean age was 63 years, with a lower proportion of women (40%). Mortality was 0% for patients younger than 20 years, but it was higher for men than women in each 10-year age range older than 20 years. (29)

In Argentina, the average age of those affected by coronavirus is 36 years and the distribution by gender is 1: 1. However, among deceased patients, the average age is 75 years and with predominance of male sex (60% vs. 40%). (58)

Risk factors and CVD correlate with increasing age. Pre-existing CVD has been common in patients with diseases of other precursor coronaviruses. In SARS, the prevalence of diabetes and CVD had been 11% and 8%, respectively, and their presence increased the risk of death (7) In MERS, diabetes and HT were associated diseases in almost half of the patients and CVD in about a third. (7) Approximately in 80% of patients a comorbidity has been reported in the severe form of COVID-19 (50)

Patients with cardiovascular risk factors (advanced age, HT, and diabetes), as well as those with CVD (coronary artery disease, heart failure, and stroke), are more likely to suffer from the severe form of COVID-19 and specially present cardiovascular complications. Shi et al. found that in 416 patients, 30.5% were hypertensive; 14.4% had diabetes; 10.6% had coronary heart disease and 5.3% stroke. (52) A meta-analysis of 6 studies that included 1,527 patients with COVID-19 evaluated the prevalence of CVD and reported HT in 17.1%; stroke in 16.4% and diabetes in 9.7%. (59) A large meta-analysis of eight studies from Wuhan, China, which included 46,248 infected patients, showed that the most prevalent comorbidities were HT (18%), diabetes (8%), and CVD (5%). Also, this study reported an overall mortality of 2.3%, but which amounted to 6.0% in hypertensive patients, 7.3% in diabetics and 10.5% in those with CVD. (5) Another meta-analysis of 10 Chinese studies in 79,993 patients found similar results: HT in 16% (95% CI: 10%-23%), diabetes in 8% (95% CI: 6%-9%) and CVD in 12 % (95% CI: 4%-22%). (60) Similar results stand out in Europe and, mainly, in Italy, one of the most affected countries. (61) Initial data from Brazil shows that 90% of deaths occur among individuals over 60 years of age and 84% of these deaths in those with at least one comorbidity, 51% with CVD and 38% in diabetic subjects. (62)

However, it is difficult to know if the presence of comorbid cardiovascular conditions represents an independent risk factor or if it is mediated by age or other factors. (7, 47) The mechanism of these associations remains unclear. Possible explanations include CVD as more common in older people, and presence of a functionally impaired immune system, elevated levels of ACE2, or increased predisposition to COVID-19 as more frequent in people with CVD.

Not only an association has been found with higher mortality, but also with progression to severe disease. A report of 1,099 patients with COVID-19 infection confirmed these data and highlighted that the presence of HT, diabetes, ischemic heart disease and CVD was more common in the subgroup of patients with a more severe form of the disease (39% vs. 21 %). (62)

Studies evaluating only the hospitalized population report a higher prevalence of hypertension (31.2%), CVD (19.6%), and diabetes (10.1%). (51) In the population hospitalized for COVID-19 in New York, mean Charlson comorbidity score was 4 (IQR, 2-6), which corresponds to an estimated survival rate of 53% at 10 years. Older people, men, and those with pre-existing HT or diabetes were highly prevalent in this case series, and the pattern was similar to the data reported in China, although with higher mortality. (29)

Pre-existing CVD may also increase the predisposition to COVID-19-induced myocardial injury, which is associated with increased mortality. (52) Guo et al. reported that 27.8% of patients with COVID-19 presented acute myocardial injury. (19) These patients were older (71.4 vs. 53.5 years), predominantly male (65%) and had more comorbidities: CVD (54.5% vs. 13.2%), HT (63,5% vs. 20.7%), coronary heart disease (32.7% vs. 3.0%), cardiomyopathy (15.4% vs. 0%), diabetes (30.8% vs. 8.9%) , chronic obstructive pulmonary disease (7.7% vs. 0%) and chronic kidney disease (9.6% vs. 0.7%). In-hospital mortality was almost 10 times higher in patients with underlying CVD and elevated troponin T (TnT) compared with patients without underlying CVD and normal TnT levels (69.4% vs. 7.6%). (63)

The prevalence of HT appears to be higher in patients with COVID-19 who develop severe disease. (47) Initial reports from China noted that HT is frequently associated with the need for respiratory assistance. (5, 50, 51, 62) Hypertensive patients accounted for 13% of COVID-19 cases, but comprised 32% of deaths. (5) These data have not been adjusted for age, which is a major limitation because the prevalence of HT increases in older populations. In two meta-analyses, patients with COVID-19 and HT had a 2 to 2.5 relative risk ratio of developing severe disease, require ICU care, or die. (59, 64) A meta-regression analysis suggested that HT may be a clinical predictor of COVID-19 severity in people older than 60 years.

The mechanisms underlying possible relationships between HT and COVID-19 are unknown, but it has been speculated that the ability of the coronavirus to enter cells through ACE2 may play an important role. The controversy regarding the use of ACEI and ARB has already been mentioned. However, there is currently no evidence demonstrating benefits or risks of continuing such antihypertensive medications during infection with respect to COVID-19 progression. (65)

People with diabetes are at increased risk for respiratory infections due to a compromised immune system, especially innate immunity. It is not yet known

whether people with diabetes are more likely to have COVID-19, but several studies have reported an increased risk of developing severe disease or acute kidney injury, as well as requiring ICU or invasive mechanical ventilation. (29) A systematic meta-analysis of 30 studies with 6,452 patients with COVID-19 showed an association of diabetes with higher mortality, respiratory distress and disease progression. An additional meta-regression analysis showed that the magnitude of risk linked to diabetes as sole factor was greater in studies with younger, non-hypertensive patients. (66)

Obesity is a CV risk factor, frequently associated with dyslipidemia and insulin resistance, and it is also related with an increased risk of pneumonia. Beyond the cardiometabolic and thrombotic consequences, obesity has detrimental effects on lung function. Obesity and excess ectopic fat could be a unifying risk factor for severe SARS-CoV-2 infection, both by reducing cardiorespiratory reserve as enhancing immune deregulation that appears to mediate progression to multiple organ failure. This would explain the results of a French study where the risk of mechanical ventilation in patients with SARS-CoV-2 infection admitted to ICU was 7 times higher for those with body mass index (BMI) >35, compared with those who had BMI <25. (67)

In the Western hemisphere, especially in the United States, obesity is a growing issue. Among patients hospitalized for COVID-19 in New York, 41.7% had BMI ≥30 and 19% had morbid obesity (BMI ≥35). (29) Another study reported that among individuals younger than 60 years with COVID-19, those with BMI >35 were 3.6 times more likely to be admitted to ICU and require respiratory assistance than those with BMI <30. (68) According to these data, obesity seems to be a risk factor in young, hospitalized patients who need critical care. More research is required to determine if this is an independent risk factor for sensitivity to infection.

Smoking is recognized as a CV risk factor, but it is also associated with acute and chronic respiratory diseases. In a systematic review of five studies conducted in China, smokers were 2.4 times more likely to be admitted to ICU, need mechanical ventilation, or die compared with nonsmokers (RR = 2.4; 95% CI: 1.43–4.04). (62, 69) In a meta-analysis that included a total of 9,025 patients with COVID-19, 495 (5.5%) had a history of smoking and greater progression of COVID-19 (OR: 2.25; IC95 %: 1.49-3.39; p = 0.001). (70) In a single study among the 12 studies reporting adjusted OR by multivariate analysis, the effect of smoking on disease severity was much greater (OR: 14.29; 95% CI: 1.58-25.0; p=0.018). (71)

In conclusion, risk factors and pre-existing CVD are widely represented in patients with COVID-19 and are associated with a worse prognosis. Currently, there is no firm evidence ensuring that HT and other risk factors constitute per se an independent risk factor for serious complications or death in COVID-19. As with other common pathological conditions in elderly patients, the mortality rate is directly related with the age, frailty and comorbidities of patients.

There is geographic variation in reported mortality. Case mortality rates of 0.8%, 2.3%, 5.9% and 7.2% are reported in South Korea, China, the United States and Italy, respectively. Regional risk factors have been cited to explain it, such as the prevalence of smoking, pollution, obesity or population aging. (72, 73) We do not yet have conclusive data in Latin America, but it is expected that social inequality will prove to be an important risk marker for contracting the disease and dying from it.

MYOCARDIAL ISCHEMIA AND INJURY

In 20-30% of hospitalized COVID-19 cases, myocardial injury can be verified, evidenced by elevated troponin levels. Acute COVID-19 cardiovascular syndrome (ACovCS) (74) has been defined as the condition of acute myocardial injury associated with ventricular dysfunction in the absence of coronary heart disease, similar to myocarditis; although in other cases it may be due to an acute coronary syndrome, increased oxygen demand, ischemic microvascular damage, or cytokine release-mediated injury.

Patients with the highest risk of myocardial injury are those with pre-existing diseases or cardiovascular risk factors, and generally present with evidence of more severe systemic inflammation, higher white blood cell count, C-reactive protein and procalcitonin levels, as well as high levels of other biomarkers of injury and myocardial stress such as CPK, myoglobin, and NT-proBNP.

However, the mechanisms of injury remain unknown and it is very likely that they may vary according to the individual, in addition to overlapping causes. The following are among the postulated mechanisms:

a) Acute cell injury, probably due to SARS-CoV-2 infection of cardiomyocytes, pericytes, or fibroblasts through ACE2-mediated entry and subsequent viral replication. (75)
b) Another untested hypothesis focuses on an inflammatory storm with excess cytokines, such as interleukin-6 (IL-6), as well as D-dimer, alpha interferon, ferritin and C-reactive protein. The elevation of cytokines can generate instability of the atherosclerotic plaque and rupture, with the consequent myocardial injury and troponin elevation. (76)
c) Plaque rupture or vasospasm are other possible mechanisms in this context. Given the hemodynamic stress and exaggerated inflammatory response observed in patients with COVID-19, the risk of acute coronary syndrome is higher. This has already been observed in epidemiological and clinical studies on influenza and other acute inflammatory conditions. Such coronary events could result from the marked increase in myocardial demand triggered by infections, which precipitate myocar-

dial injury or infarction (AMI), similar to type-2 AMI. (77-79)

d) Stress cardiomyopathy and myocarditis are other symptoms that can occur with elevated troponin; these are described in more detail in the "Heart failure" section.

What can we do to better understand myocardial injury?

Biomarkers, echocardiography, and cardiac nuclear magnetic resonance imaging (MRI) are the non-invasive modalities available to characterize the type of injury and try to differentiate etiologies. However, in the case of MRI, we are faced with the difficulty of infected patient transfer, staff exposure and device contamination. There are similar limitations with respect to echocardiography, but they can be solved with portable devices in critical care units. This allows to quickly assess the presence or absence of segmental wall motion abnormalities, which, added to the systematic use of cardiac and inflammatory biomarkers and clinical symptoms, can provide information on different phenotypes, without increasing the risk of staff exposure.

In any case, we must consider a series of limitations regarding the available information:

- The true number of people with COVID-19 is unknown, biasing the estimates on the disease prevalence, risk factors, and cardiovascular events. (47, 51, 52, 64, 80, 81)
- There is heterogeneity in the definition of myocardial injury between studies, in addition to demographic differences between regions.
- There is variability in care and, on the other hand, data collection has not been systematic. However, the availability of some data is, in itself, a success and an acknowledgment of the intention of the treating physicians to communicate the observations by the patient's bed, in order to inform the scientific community.

Currently, the treatment of acute myocardial injury in patients with COVID-19 is intuitive. Despite our best efforts, there will be cases when the wrong clinical decision will be made. We need to better understand the mechanisms of injury; the case-by-case analysis will guide us in making the most appropriate decisions to achieve myocardial recovery.

Regarding acute coronary syndromes in the COVID-19 era, first of all we must make it clear to the population that the "stay home" message does not apply to those patients whose reason for consultation is chest pain. Second, we must take into account some considerations when proposing a systematic approach for the care of patients with AMI during the pandemic.

The ideal scenario would be to promptly determine the diagnosis of COVID-19, which would allow categorizing the patient's risk, define the treatment plan (AMI with or without COVID-19), determine the place of hospitalization within the hospital, if there is or not a specific hemodynamic lab for COVID-19 and the unit where the patient will be admitted after the procedure.

Adequate protection must be guaranteed for all health care workers in the emergency medical service, transfer hospitals, the emergency department of the center with hemodynamics and within the same ward. (10) Upon arrival, all patients requiring emergency activation of the hemodynamic lab should be treated as possible carriers of COVID-19. Given the potential risk of aerosol generation, all personnel should use personal protective equipment (PPE): gown, gloves, full face mask and N95 respiratory mask.

Primary angioplasty is the standard of care for patients presenting in centers with hemodynamic lab within 90 minutes of the first medical contact, even during the COVID-19 pandemic, although there are some important recommendations: (82, 83)

- Each center with primary angioplasty must monitor the ability to provide it in a timely manner depending on the availability of personnel, PPE, exclusive lab or its reconditioning to continue working. In the absence of these resources, a fibrinolysis approach should be considered.
- We must bear in mind that, in selected cases, more time may be required to establish the diagnosis of AMI (for example, the performance of an echocardiogram to evaluate wall motion) or for the specific management of the patient with suspected COVID-19 that requires ventilatory support. For these reasons, during the pandemic, door-to-balloon times may be prolonged.
- The systematic transfer of patients is not recommended without previously ensuring the logistics and availability of resources in the receiving center.
- In patients with diagnostic confirmation of COVID-19, with mechanical ventilation for adult respiratory distress syndrome or pneumonia and ST-segment elevation AMI (STEMI), with or without acute coronary occlusion, compassionate medical care might be considered, given the high mortality rate.
- In cases of non-ST segment elevation acute coronary syndromes (NSTEMI), patients with positive or probable COVID-19 should be treated medically and only urgent coronary angiography and possible angioplasty should be indicated in the presence of high-risk clinical features (GRACE score >140) or hemodynamic instability.

In any case, these aspects must be adapted to each emergency system, hospital center and region. In addition, there should be close communication to optimize patient management. These are challenging and unprecedented times, during which it may not be possible to offer treatments as usual.

HEART FAILURE

Patients with COVID-19 frequently present with heart failure (HF). Whether this is a comorbidity present in the infected patient, or a product of the underlying

infectious condition, it is clearly a worse prognostic factor in all cases (84). In a recent study, an incidence of 23% HF was observed in patients with COVID-19, which was frankly higher in those who had worse evolution (51.9% vs. 11.7%), but it was not possible to define whether the cause was due to decompensation for a preexisting condition or a new cardiomyopathy due to direct viral aggression or other causes. (47). Mehra et al. demonstrated in a cohort of patients from Asia, Europe and the United States an increased risk of in-hospital mortality among those who presented HF vs. those who did not (15.3% vs. 5.6%), with an OR of 2.48 and 95% CI of 1.62-3.79. (33)

Undoubtedly, the chronic HF syndrome acts as the ideal substrate to define a population with worse evolution. Chronic HF is "the perfect storm", where overexpression of ACE2, chronic inflammatory activity, exacerbated with the progression of the disease, endothelial dysfunction and a chronic prothrombotic state are associated, all conditions that predispose to greater aggressiveness of the viral infection.

The development of decompensated HF can be due to different causes.

a) It may be secondary to an ischemic condition generated by an acute thrombotic event, or an imbalance between O2 supply and demand (type-2 AMI) in a patient with or without previous coronary heart disease, due to destabilization of atherosclerotic plaques as a result of the systemic inflammatory condition, with cytokine storm or changes in the polarization of immune cells, generating a more unstable phenotype. (47, 59, 81)
b) Another mechanism involved is the possibility of microvascular inflammation due to high pericyte ACE2 expression, causing severe dysfunction in the small vessels and triggering AMI with non-obstructive coronary arteries (MINOCA). (85)
c) It can also be iatrogenic, as a consequence of aggressive fluid resuscitation in patients with significant hemodynamic deterioration and previous ventricular dysfunction, as well as in those with preserved systolic function with little tolerance to sudden expansion. The generation of ventricular dysfunction or exacerbation of a previous condition has also been observed with the use of some antiviral or systemic corticosteroid drugs. (86-88)
d) The possibility of myocarditis, either due to aggression and direct viral infiltration or secondary to intense reactive inflammation as a trigger for HF, should not be underestimated. Isolated cases of this disease have been observed and some reports have described signs of fulminant myocarditis with histological evidence of a large mononuclear inflammatory infiltration (33-35). In a recent study on 150 patients, it was reported as a direct cause of death in 7% of cases and as a cofactor for death in 34%. (89)
The diagnosis can be made clinically by the presence of chest pain and palpitations, electrocardiographic changes, elevation of necrosis and arrhythmia biomarkers, but in many cases, a severe condition has been observed with sudden hemodynamic decompensation and death. The diagnostic difficulty lies in the few possibilities of carrying out the diagnostic methods that define the presence of this pathology, such as MRI or endomyocardial biopsy (EMB) (90). Viral etiology present in approximately 37.8% and 77.4% of cases has been currently reported in EMB in Europe. (91)
An interesting fact is that most of the time, myocarditis is a late complication of systemic infection, which appears between 10 and 15 days after the onset of the disease, supporting theories of the exacerbated inflammatory response (generated by the cytokine storm or derived from a de novo autoimmune reaction). This would open up the possibility of establishing more specific treatments with immunoglobulins, steroids and, if necessary, circulatory mechanical assistance, when there is pathological diagnostic certainty. (26, 91)
e) Another cause of acute ventricular dysfunction that must be considered is stress cardiomyopathy, or Takotsubo disease, triggered by the intense catecholaminergic activity associated with these conditions. (92, 93)
f) Isolated right ventricular dysfunction or associated with severe pulmonary hypertension should make us think of different differential diagnoses. This may be secondary to previous heart disease, in the context of severe lung disease and concomitant respiratory distress, or it may be part of acute pulmonary thromboembolism, an entity that is becoming increasingly relevant given the growing evidence of both arterial and venous thrombotic events secondary to the underlying inflammatory process, as it emerges from the analysis of the autopsies of patients with COVID-19. (94-96)

The presence of both supraventricular and ventricular arrhythmias is not pathognomonic of cardiogenic conditions, and especially supraventricular arrhythmias may be present in older subjects, secondary to hypoxia and stress. Different series have shown an incidence of 16.7% of cases, more frequently in hospitalized patients in critical care (44.4% vs. 6.9%) (51, 64). The appearance of sudden severe ventricular arrhythmia, accompanied by greater hemodynamic deterioration and a significant increase in troponins, should suggest the probability of acute myocarditis. (91)

The increase of biomarkers, both of cellular injury (troponins T and I) as those indicating the presence of myocardial stress (natriuretic peptides), has been associated with worse prognosis. The increase in troponins, as a marker of microcellular damage, is one of the most frequently reported. Its importance has been clearly shown in different series, with an increase ranging between 7% and 27.8%, associated with an OR for mortality between 12 and 80. (47, 51, 89) It is important to closely monitor the kinetics of troponin concentration. In patients who suffered a continuous

increase in this biomarker, mortality was higher, with an average of 18.5 days until death, whereas when it remained stable, the evolution was more favorable. (97, 98)

In the case of natriuretic peptides in the context of COVID-19, the results have been slightly more controversial. Peptides are frequently increased in patients with severe respiratory failure, even in the absence of elevated filling pressures or decompensated HF. In patients with COVID-19, increased biomarkers have been associated with worse prognosis, though not always due to the presence of acute HF. (97-99)

The extremely high transmission of the virus and the coexistence of acute hemodynamic and respiratory deterioration, the impossibility of evaluating ventricular function, the presence of abnormal segment motion and loading conditions, have led in many cases, even with high concentrations of troponins and/or natriuretic peptides, to erroneous diagnoses and treatments which could have been the associated cause of the increased risk of death in these patients. These issues added to the lack of pathological studies, which could have redefined the etiology of death with greater certainty, have perhaps led to underdiagnose HF in this population.

PRACTICAL MANAGEMENT OF PATIENTS WITH HEART FAILURE

The emergence of the COVID 19 pandemic has led to prioritize the practical management of patients with HF in this scenario. Patients with chronic, respiratory, cardiovascular, diabetic, HT and autoimmune diseases, or cancer, are more likely to suffer the worst consequences of viral infection. (81). Those with HF may have one or more of these diseases, and are therefore at greater risk of hospitalization and serious complications. The clinical vulnerability of this population generates the implementation of preventive measures aimed at avoiding contagion. We know that one of the most effective actions in this regard is social isolation, so this recommendation will be a priority in all patients with HF. (100) One of the decisions that generates the greatest difficulty is the management of the face-to-face consultation, given the greater possibility of contagion when moving both in the means of transportation and in the healthcare centers. On the other hand, the absence of periodic medical controls in patients with HF is one of the most frequent causes of disease worsening.

Different recommendations have been made to address this situation (101). In patients without suspected COVID 19 infection, it is suggested to:

- Minimize hospital visits
- Make consultations via telemedicine, video calls or phone calls
- In-person consultation only in cases considered essential
- Day hospital only as an alternative to hospitalization.

In patients with suspected coronavirus infection, it is suggested to:

- Follow-up by phone to review alarm data
- Minimize hospital visits
- Perform rapid diagnostic unit
- Home hospitalization.

In patients with confirmed coronavirus infection:

- Specific isolation zones will be established
- Use exclusive transfer circuits
- Use of personal protective equipment
- Surveillance of specific treatment interactions.

These recommendations, which try to avoid exposure to an increased risk of infection, must be followed in a balanced way, to prevent patients who need an in-person consultation from suffering decompensation due to lack of care. It should be noted that during the course of this pandemic, there has been a significant reduction in admission to critical care units for patients with cardiovascular disease, stroke, and acute coronary syndrome. (102) This situation can be explained, in part, by patients' fear of contagion when attending a healthcare center, which, in many cases, results in the postponement of consultation in the presence of symptoms, and the lack of an alternative medical response to the face-to-face consultation. For this reason and trying to prioritize the reasons for such visits, these are recommended in the following situations: worsening of HF signs or symptoms that have not responded to the outpatient increase in diuretics, more than one stage increase in functional class, presence of low cardiac output signs or syncope, repeated cardio-defibrillator shocks, severe alarms in the telemetry review, repeated heart rate <40 or >100 beats per minute, chest pain with an ischemic profile and unstable characteristics, and patient's wish consented with the doctor after risk-benefit assessment, among other variables to consider. (103)

As an alternative to face-to-face consultation, virtual consultations appear based on the need to avoid the circulation of patients with HF. Different remote communication systems are actively emerging solving, at least on many occasions, the need for face-to-face consultations. For many years, HF units have made it possible to significantly improve the quality of care in this population, based on their success in active communication with the patient. These operational units consist of secretaries, nurses and HF specialists who work closely in contact with the patient, using different communication channels for their control over time. (104)

Among other strategies, telephone follow-ups are carried out, delivery of written information on prescribed medications, an explanation of what signs and symptoms can alert about disease progression, when to attend a consultation in person, and when to plan short hospital stays in the day hospital, among many other measures. The result of these interventions has demonstrated to significantly reduce hospitalizations due to HF progression, and in the

context of this pandemic, it has become a working model to be reproduced in the different healthcare centers. (105) Different platforms have been developed for this purpose and some of them enable, in addition to the visual contact between doctor and patient, to establish an interface that allows access to parameters such as vital signs, oximetry or weight, and to carry out electrocardiographic monitoring. (106) Communication with the patient will allow, in the first instance, to perform a complete interrogation that will serve as a point of reference from which to develop the consultation. Thus, evaluation of temporo-spatial orientation and clinical stability, control of pharmacological treatment, interconsultation with other specialties and, if necessary, indication of face-to-face consultation, can be carried out. The visualization of the patient will allow obtaining some data from the physical examination: general appearance, skin and mucous membrane coloration, signs of congestion (edema, jugular engorgement) and presence of dyspnea at rest. In turn, the patient will be able to self-monitor vital signs, weight, blood pressure, heart rate, as well as submit the reports of the complementary studies carried out. (107) On the other hand, the system allows to extend medical indications and prescriptions, as well as request complementary practices.

The limitations of telemedicine are difficult access to technology in certain populations, patients with cognitive disorders, advanced age, limited socioeconomic resources, the impossibility of performing a complete physical examination, lack of support from health funders and the legal medical aspect, among others.

The emergence of the pandemic quickly generated the need for another form of response to patients' requirements, with the fundamental objective of avoiding infections. After this crisis in the health system is over, virtual consultations are likely to remain another tool when it comes to conducting medical consultations, and will become a new form of doctor-patient communication (108).

HEART TRANSPLANTATION

The pandemic has exposed the vulnerability of transplant services, which face doubts about how to test donors, the risk of donor to recipient transmission, the impact of infection on recipients, safety issues for the teams involved in the procedure and the changes generated by the lockdown and social isolation measures in the availability of donors.

Just as we understand that a recipient exposed to SARS-CoV-2 will develop the infection, the possibility of transmitting the virus from donor to recipient by tissue, organ or blood transplantation is not defined. Several determinants are considered, such as donor exposure and infectivity during the incubation period and in the asymptomatic period, the degree and duration of viremia, and virus viability in the blood or organs. The estimated incubation period is 2 to 14 days, and viral RNA has been detected in the patients' plasma (15%) and faeces with COVID-19, which shows that other sites, in addition to the respiratory tract, can be affected.

To learn the impact on transplant activity and the variation in the level of activity between centers in the US, a national survey was conducted between March 24 and 31, 2020. The response rate was 80%, which shows interest in knowing the impact of COVID-19. It was found that 18% of heart transplantation programs continue to operate without restrictions, but several programs limit the procedures to the most serious cases, such as emergency recipients. (109)

National data shows that the number of heart transplantations in recipients over 18 years of age performed during the period from March 1 to April 28, 2019 was 24. During the same period this year, the number of heart transplantations was 13, which represents a drop of 46%. (110)

We have little data on the clinical characteristics, management and evolution of COVID-19 after solid organ transplantation during the pandemic. Regarding the recipients, an observational, retrospective, and single-center study showed the initial data of 87 heart transplant recipients from the province of Hubei in the period between December 20, 2019 and February 25, 2020. Four recipients were reported with upper airway infection, 3 of which were COVID-19 negative and the fourth was not tested. All evolved favorably and a very high rate of compliance with protection measures was observed. The authors concluded that heart transplant recipients who complied with prevention measures had a low rate of SARS-CoV-2 infection. (111)

Less favorable data is shown in an experience with 18 solid organ transplant recipients diagnosed with COVID-19 as of March 23, 2020 in a center in Madrid: 44.4% of the cases were kidney, 33.3%, hepatic and 22.2%, cardiac transplants. The time interval between transplantation and infection was 9.3 years (or days?). Fever and pulmonary disorders with unilateral or bilateral multifocal consolidations were the most common form of presentation. A combination of lopinavir/ritonavir was used in 50% of patients and was discontinued in 2 cases. As of April 4, the death rate was 27.8%. After a median follow-up of 18 days from the onset of symptoms, 30% of survivors developed progressive respiratory failure and 61% were discharged. These data suggest a serious involvement of COVID-19 infection in transplanted patients. (112)

Although we do not have a specific treatment, the combination of lopinavir/ritonavir, with or without interferon ζ or an RNA polymerase inhibitor, remdesivir, (not available in our country) is suggested experimentally. The Ministry of Health recommends the use of lopinavir/ritonavir in cases of pneumonia associated with severity parameters. It is important to remember that protease inhibitors interact with cal-

cineurin inhibitors, whose dose is adjusted according to the value measured in plasma and, generally, one or two weekly doses are enough.

The other unresolved issue is how to assess an intrathoracic organ donor during exposure to SARS-CoV-2 and the possible impact of the infection on the ablation and implant teams, and organ recipient. In the past two decades, there have been rare, but well documented donor-derived infections for various viruses, such as hepatitis B and C, lymphocytic choriomeningitis, rabies or HIV.

The profound changes imposed by social isolation, lockdowns and restrictions on geographic mobility, added to the capacity of the health system, today saturated by the demand of COVID-19 patients, can generate changes in the waiting list and increase organ waiting time, and mortality

On March 20 of this year, INCUCAI, together with the Argentine Society of Infectious Diseases (SADI) and the Argentine Society for Transplantation, published a consensus document, "2019-2020 Coronavirus Pandemic". In the COVID-19 considerations regarding "Organ procurement and transplantation", two scenarios regarding the local circulation of the virus are considered. In regions without local circulation, it is recommended not to accept the organ if the donor is a confirmed case of COVID-19, has visited a risk area or has been in contact with a positive case in the previous 21 days and there is no current negative CRP, or has severe pneumonia of unknown etiology. In areas with local circulation, donors are classified as high, intermediate or low-risk donor, based on the presence of epidemiological and clinical data (see Tables A and B). High-risk donor corresponds to the presence of one or more epidemiological criteria and one or more clinical criteria. Intermediate risk corresponds to the donor with one or more epidemiological criteria without clinical criteria, or one or more clinical criteria without another alternative diagnosis and without CPR testing for COVID-19. Low risk occurs when there is no epidemiological or clinical risk criteria.

It is not recommended to consider the donor if he/she has active COVID-19 infection, if there are positive tests for COVID-19 during the donation procedure, or if he/she has been classified as a high-risk donor and there is no possibility of performing the CRP test.

With donors classified as intermediate risk, it is suggested to perform a CRP test for COVID-19. If this is not possible, the lung or intestine should not be used. The risk/benefit of accepting the organ must be carefully analyzed; it is suggested to limit the use of the organ to cases of recipients in an emergency situation. The recipient and his/her family must be informed of the lack of treatment in case of transmission and the donation must be expressly consented.

On April 12, The Organ and Tissue Transplantation and Procurement Committee of the Argentine Society of Intensive Care, developed a tool for the screening of cadaveric donors and decision-making (Figure 2).

In transplantation, several competing conditions meet to establish that a reliable and highly sensitive test with a quick response for the presence of SARS-CoV-2 should be widely available for universal organ donor testing in all regions. All potential recipients should also be tested for COVID-19 prior to transplantation. Finally, the urgency in the need to accept the organ must be resolved in the context of available resources in terms of medical equipment, health care staff, availability of intensive care beds in hospitals and personal protective equipment for all intervening personnel. (113)

PULMONARY HYPERTENSION

Pulmonary arterial hypertension (PAH) is a complex entity, of low incidence and prevalence, with progressive clinical repercussions secondary to vascular obliteration and right ventricular dysfunction, and high morbidity and mortality during its progression. Since it is an entity with low clinical suspicion, the diagnosis is established late, and when the clinical condition is confirmed, the presence of HF, advanced functional class and decreased cardiac index are highly frequent findings in the various published registries.

All publications emphasize the vulnerability presented by patients with a previous diagnosis of respiratory and cardiovascular diseases in the COVID-19 era, and the presence of PAH points to a high-risk population. Let us bear in mind that COVID-19 can generate different processes of lung damage, ranging from pneumonia, injury, adult respiratory distress syndrome, HF, and right ventricular dysfunction. (114, 115) However, recent reports and preliminary reviews emphasize the predominance of mild symptoms in this entity, although more casuistry and follow-up time are required to refute or validate such information. (116)

Some clinical case references have shown mild presentations and multiple pathophysiological hypotheses have been proposed to explain the best prognosis, such as reduction of ACE2 receptors, a protective effect on pulmonary vascular remodeling, accompanied by increased cytokine secretion and inflammatory cascade activity, which would generate less viral damage in its local action. Also, anticoagulation could have protective effects on major and minor circulation.

The recommendations on infection prevention strategies in this entity are similar to those of the general population; there is no information available about a higher propensity for contagion, so the measures should be similar. (117)

Pulmonary hypertension patients must respect the same behaviors as other susceptible individuals, but we must stress that they must continue with their daily activities (respecting the protection regulations) and maintaining specific and general treatment, according to usual recommendations. Consultations

Travel to or residency in an area with local COVID-19 transmission in the last 21 days	
Travel or origin from a high-risk area (CDC level 2-3)	
Direct contact with a suspected or confirmed case of COVID-19 in the last 21 days*	
Confirmed diagnosis of COVID-19 in the last 28 days	
Case of COVID-19 in the Intensive Care Unit **	

*Contact at less than 1.8 m.
*Close contact: take care of, live with, visits, share the waiting room or a room with a case of COVID-19, or having had contact with secretions of an infected patient with COVID-19.
**In case all the recommended measures of Infection Control have not been confirmed or have not been fulfilled.

Table A. Donor epidemiological screening Criteria (yes-no-don't know)

Did the donor have the following symptoms in the last 21 days?	
Fever (≥ 38°C) or subjective fever	
Asthenia or flu symptoms, +/- myalgias	
Cough of recent origin	
Dyspnea	
Pulmonary infiltrates	

Table B. Clinical / imaging screening. Criteria (yes-no-don't know)

with professionals should be optimized on the current symptoms and possible complications; video calls or telephone contact by trained personnel can reduce travel and constitute useful alternatives in this scenario.

We must highlight the relevance of evaluation in patients at high risk or with recent diagnosis or clinical progression (dyspnea, angina and/or syncope), since collateral damage due to care and treatment deficit can greatly exceed the risk of infection. Moreover, specialized pulmonary hypertension units must ensure compliance with the appropriate measures to maximize the protection of this population and the feasibility of carrying out various complementary studies, including right cardiac catheterization, if necessary. (118)

The specific treatment of the infectious process remains controversial; there is little scientific evidence to recommend a particular scheme, although various drugs can be used in patients with PAH, in agreement with the general practitioner. However, the possibility of pharmacological interaction of antivirals with specific drugs for the treatment of PAH should be considered. In this regard, the interaction of lopinavir/ritonavir combined with endothelin receptor antagonists, which increase their plasma concentration, and the incidence of liver toxicity (mainly with bosentan) are noteworthy, which is why it is suggested to suspend them previously. Phosphodiesterase 5 inhibitors (sildenafil or tadalafil) and the guanylate cyclase stimulant (riociguat) should be administered with caution due to the vasodilator and hypotensive effect they generate; therefore, an individualized dose adjustment is recommended. (119) On the other hand, remdesivir is characterized by presenting a better safety profile and a lower level of interaction. Other pharmacological options, such as ribavirin and ß interferon, have so far not shown relevant interactions, and therefore can be used without limitations.

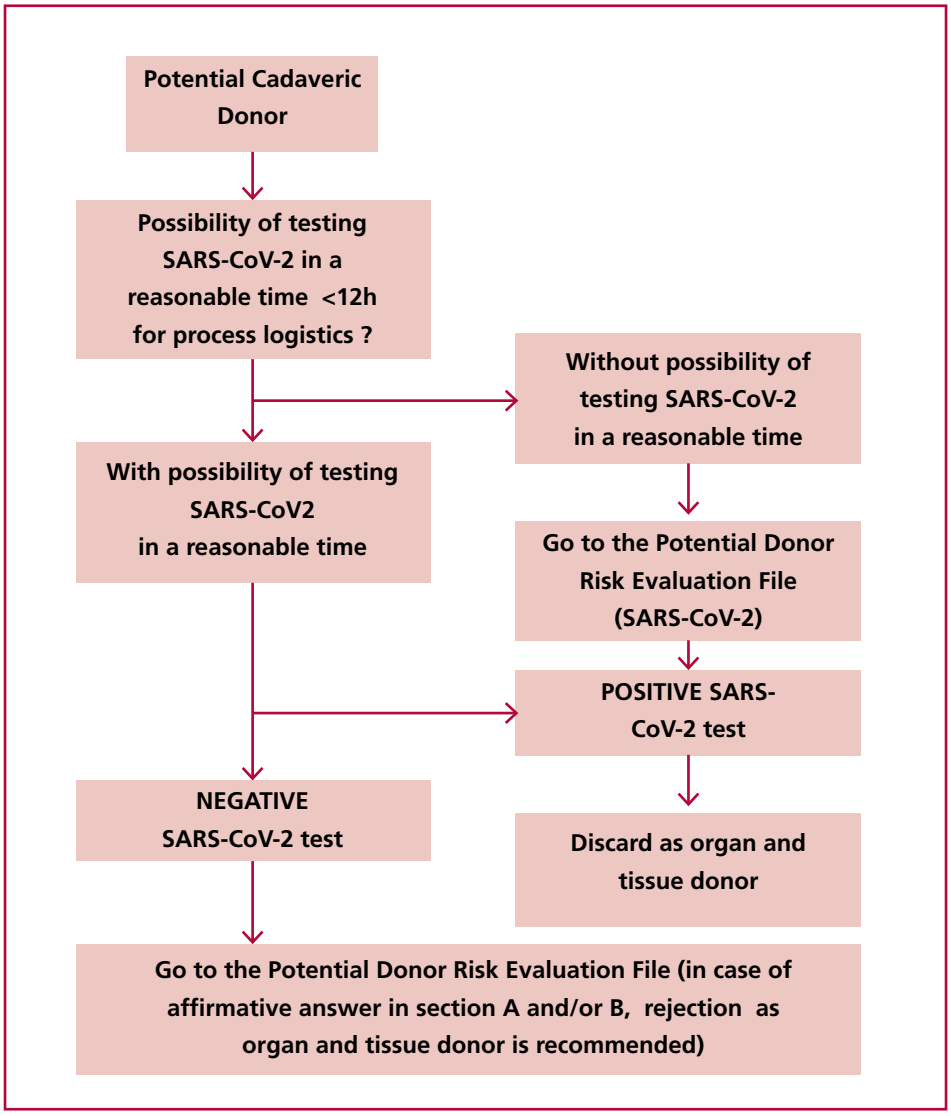
In cases of COVID-19 infection, it is necessary to achieve an adequate level of oxygenation, with high-flow nasal cannula, if required, in order to avoid the use of non-invasive ventilation, due to the risk of viral dispersion. On the other hand, mechanical ventilation should be reserved for those situations in which it is essential, since we can promote a worsening of the clinical condition and greater right ventricular systolic dysfunction, in addition to generating a very complex scenario to achieve weaning.

In cases with systolic right ventricular dysfunction, we must optimize its properties: preload (expansion or diuretics, depending on end-diastole pressure), afterload (specific vasodilator drugs) and inotropic drugs, to improve cardiac output (dobutamine, milrinone or levosimendan). In addition, it is imperative to exclude triggers, such as the presence of pulmonary thromboembolism, sepsis, ARDS, anemia, etc. (120) In certain conditions where hemodynamic decompensation is observed, the use of intravenous epoprostenol (prostanoids) and nitric oxide is recommended for their vasodilator properties, although the need for tight management and by groups of experts should be advocated.

Proper fluid management is a complex challenge for this entity, since harmful effects are observed, both with hypovolemia (decreased preload) and with the increase in right ventricular end-diastole pressure, which decrease the cardiac index and, consequently, blood pressure and tissue perfusion. In the presence of volume overload, loop diuretics should be used as drugs of choice and/or early ultrafiltration, to decrease right atrial pressure and improve right ventricular efficiency and renal function.

Among the general considerations to be high-

Table 1. Comparative table of patients seen between March and April 2020, and those seen at the doctor's office in same period of 2019



lighted, we must prioritize the importance of maintaining daily activities, the indicated routine physical exercise, adequate nutrition and complying with the immunization plan. Psychological support becomes vitally important for the support of the patient and his family group, and symptoms such as anxiety, fear or depression require early interdisciplinary therapy. However, we should highlight a vital concept in this disease: the recommendations we indicate refer to physical isolation, since remote social activities must continue.

Finally, we would like to point out that, to date, the information available on the association between PAH and COVID-19 is scarce, referred to case series, so these observations should be interpreted with caution, since the information presents frequent changes.

CLOTTING DISORDERS

Serious coagulation disturbances have been described in the severe form of COVID-19. Coagulation is a process that requires a balance between the amount and activation of procoagulant and profibrinolytic substances to ensure correct thrombosis at sites of vascular damage, prevent thrombus formation in its absence, and restrict the clot to the indicated sites. Pathologies such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy (TMA) constitute an alteration of this balance and are systemic disorders with the potential of causing thrombosis and bleeding. In the case of DIC, unchecked activation of the coagulation system can occur due to exposure to procoagulant substances, such as tissue factor (TF) and to bacterial, inflammatory or oncological components. In severe intravascular hemolysis, the generation of cytokines, such as tumor necrosis factor (TNF) or interleukin 1 (IL-1) induce an excessive release of TF from monocytes, with the potential to trigger DIC. (121) In sepsis, another pathology capable of producing DIC, endothelial dysfunction caused by infection leads to excess thrombin production and decreased fibrinolysis. An extreme example generated by the massive release of cytokines with the consequent ac-

tivation of the coagulation system is secondary hemophagocytic lymphohistiocytosis, frequently linked to viral infections. (122) Another important activator of the coagulation system is free DNA degradation products (that is, outside the cytoplasm), which can be generated by severe inflammation. A marked activation of coagulation can lead to consumption coagulopathy, thrombocytopenia and deficiency of endogenous anticoagulants such as protein S, C or antithrombin. Disseminated intravascular coagulation can either be acute or chronic. In the acute form, bleeding predominates because the consumption of factors cannot be compensated by their generation and because fibrinogen degradation products compromise fibrin formation and platelet aggregation. The chronic form has greater proprnsity to thromboembolism because the production of clotting factors continues and, therefore, the thrombosis process is continuous.

In TMA, platelets are more compromised than the coagulation system and, in general, it does not present with a marked deficit of coagulation factors or great compromise of the laboratory parameters that involve them.

In the context of an infection, in this case viral, the activation of the coagulation system is essential together with the immune system to counteract the spread of the virus. Although in contrast there is risk that the inflammatory response is massive and the procoagulant stimulus increases the risk of thrombosis, both in the lung and other organs (123-125), it is well known that viruses such as Ebola or cytomegalovirus (CMV) can induce DIC, and it is therefore possible to think that SARS-CoV-2 can do the same.

The altered coagulation parameters that are observed in the laboratory tests of some patients with severe COVID-19 may correspond, in some cases, to DIC or MAT. In others, they do not meet all the diagnostic criteria necessary to determine the presence of one of these pathologies. What does seem to be clear, so far, is that its alteration carries a worse prognosis. (126, 127)

As already developed in the respective section, some patients with COVID-19 have ARDS-type lung involvement. The endothelial injury and vascular alteration were described in ARDS years ago, as well as the correlation between its severity and prognosis. (128) Hypoxia can induce thrombosis, not only through increased blood viscosity (129), but also through the activation of mediators that enhance it. (130)

Numerous publications report that in severe cases, SARS-CoV-2 triggers a cytokine storm that ultimately leads to activation of the coagulation system and causes microvascular thrombosis. (122) In a recently published work, Tang et al. describe that around 71% of deceased patients and 0.6% of survivors present evidence of DIC in laboratory studies. Based on their findings, this group concludes that DIC is a frequent phenomenon that indicates worsening of SARS-CoV-2 pneumonia prognosis and is associated with mortality. (126) The frequency with which this phenomenon occurs is not entirely clear. D-dimer and fibrinogen breakdown products (FBP) could serve as risk markers. (126)

This prothrombotic situation generates venous and arterial thromboembolic disease. For example, higher rates of arterial limb ischemia (131) and neurological or renal involvement have been reported in patients with COVID-19. In fact, in some cases, its clinical manifestations became criteria of clinical suspicion for the World Health Organization (WHO).

Although altered coagulation has been demonstrated, for the most part, in patients with severe disease, there are also reports of abnormal laboratory parameters in patients with ambulatory follow-up, that is, without serious expression of the disease. (95, 132)

In turn, the presence of antiphospholipid antibodies has been described in three critically ill patients in the city of Wuhan at the beginning of the pandemic. (133) It cannot yet be stated that the generation of these antibodies constitutes a frequent condition in this disease. The hypothesis of some phenomenon involving autoimmunity has been recently reinforced by reports of children with COVID-19 and Kawasaki disease. (134)

Numerous pathological studies published to date, all with a small sample size, describe the greater or lesser extent of pulmonary vascular microthrombosis. On a sample of three minimally invasive autopsies Yao et al. found, in addition to exudative alveolar inflammation at the pulmonary level, interstitial involvement and hyaline thrombi in the vessels that course through the interalveolar septa. (135) In turn, a group in São Paulo published a series of 10 ultrasound-guided necropsies, which showed the presence of a variable number of small fibrotic thrombi in the pulmonary arterioles, in addition to exudative-proliferative alveolar damage. These were found in both diseased and preserved lung parenchymal areas. Endothelial swelling and a large number of pulmonary megakaryocytes, indicators of coagulation cascade activation, were also observed. Due to the characteristics of these biopsies, large arteries could not be evaluated to rule out or confirm the presence of pulmonary embolism. (136) In a series of four necropsies in New Orleans, diffuse alveolar damage was observed with marked interstitial infiltrate and presence of microthrombi at the capillary level. A significant megakaryocytic infiltration was also observed, which may justify the absence of thrombocytopenia, despite probable DIC. There is doubt as to whether the virus can infect megakaryocytes, something that has already been observed with SARS-CoV-1. (137)

In a retrospective cohort of 450 patients with severe COVID-19 Tang et al. recognized age, prothrombin time, D-dimer and platelet count as prognostic factors for short-term mortality (28 days). (138) Moreover, as a therapeutic hypothesis, they routinely pro-

moted the use of heparin. Although there was no benefit in the overall number of patients, in those with DIC markers, such as a six-fold increase in D-dimer levels or the presence of a sepsis-induced coagulopathy score greater than 4, anticoagulation was beneficial. It should be emphasized that the dose of heparin used was, for the most part, in the prophylactic range, and this was not a randomized study. (138, 139) Some international societies have proposed the indication of low molecular weight heparin in prophylactic doses in patients hospitalized for COVID-19 without high risk of bleeding. (140) There are doubts regarding the intensity of anticoagulation, since some groups suggest that prophylactic doses may not be sufficient in these patients. (141) However, there are still no recommendations to go further in terms of anticoagulation if there is no defined criterion for doing so.

It is clear that coagulopathy and its laboratory indicators are a prognostic marker, but as yet, there is no generalized line of treatment. Although many groups around the world are raising the need for anticoagulation, and many have applied it with good and promising results, there are still no studies with the necessary methodological quality to support a clear indication.

The possibility that the combination and assistance of anti-inflammatory and anticoagulant drugs may cut the vicious circle of inflammation and coagulation activation, already described by Marongiu et al. (123), should be evaluated in future interventional studies.

CARDIOVASCULAR ADVERSE EFFECTS DERIVED FROM THE PHARMACOLOGICAL TREATMENT OF COVID-19

Different drugs have been evaluated in the treatment of COVID-19. At the moment, the drugs used are not novel, but known drugs applied for other pathologies, so that, in general, their cardiovascular effects are already known. Cardiovascular complications, typical of COVID-19, expose patients to greater vulnerability to the treatments administered and generate uncertainty regarding adverse effects. As in all critically ill patients, chronic cardiac treatment should be reevaluated. Naturally, in the face of hemodynamic compromise, all medications will adjust dynamically to the situation.

Antivirals

They are the drugs upon which the greatest expectation has befallen in these months. Ribavirin is a guanine analog antiviral, which binds to the active site of the viral RNA-dependent RNA polymerase. Its use is indicated in patients with hepatitis C and could be useful against COVID-19. (142) In vitro studies suggest that a high concentration of this drug is necessary to inhibit the virus and also that its effect could be enhanced by combining it with lopinavir or ritonavir. A systematic review of the available evidence showed no benefit. (143) No cardiovascular adverse effects have been reported. The main adverse effects were hematological and hepatic. It is important to keep in mind that ribavirin interacts with warfarin (144), so a very strict control should be carried out in anticoagulated patients with vitamin K antagonists, so as not to expose them to bleeding risk.

Lopinavir-ritonavir is a combination of antiretroviral inhibitors of the human immunodeficiency virus protease, used in HIV positive patients, and is also under evaluation in patients with COVID-19. Digestive intolerance and abnormal liver panel have been reported as frequent adverse effects with a standard dose of 400/100 mg, twice daily. Changes in heart rhythm and QT prolongation are the most widely described cardiovascular effects, so it is essential to consider the patient's baseline risk and the concomitant medication he/she are receiving.

Beyond ECG abnormalities, it is important to consider that lopinavir and ritonavir interact with the new anticoagulants apixaban and rivaroxaban. (10) These antiviral drugs also impact on antiplatelet effects. They can increase the effect of ticagrelor and reduce that of clopidogrel, so prasugrel might be an option. They do not impact on the effect of cangrelor, which is administered intravenously. Their interaction with statins is also known, although the use of rosuvastatin or atorvastatin is possible.

Remdesivir is an antiviral originally developed to fight the Ebola virus. For the moment there is insufficient evidence to confirm its beneficial effect in patients with COVID-19. (145) Despite having been tested in patients in advanced stages of the disease, it has not shown serious cardiovascular adverse effects, the most reported being hypotension.

Although oseltamivir has not been shown to be effective in patients with COVID-19, many patients with suspected influenza also receive it and it should be noted that it also causes QT prolongation. (146)

Chloroquine, hydroxychloroquine, and azithromycin

One of the first alternatives proposed for the treatment of patients has been the use of chloroquine or hydroxychloroquine, often in combination with azithromycin. However, these drugs have so far not shown effectivity. (147, 148) Like other potentially useful drugs for COVID-19, these also cause QT prolongation.

In the short-term use, chloroquine and hydroxychloroquine prolong QTc, especially in the elderly (who are also the highest risk patients for COVID-19) with prior heart disease. Co-administration with azithromycin, which also prolongs QTc, increases risk. Several trials have been carried out in which chloroquine or hydroxychloroquine were tested in patients with COVID-19, although, to date, these studies are of limited scientific quality (small number of patients, publications without peer review, and modification of the study design due to the decrease in the follow-up period or the number of patients to include). (149,

150) The cardiovascular safety of these drugs is not yet established. It is possible that patients with more severe forms of COVID-19 also have direct damage caused by the virus, immune myocarditis or coronary injury, which means that its use is likely to entail a higher cardiac risk than its administration in earlier stages of the disease. A rigorous evaluation of the QT interval is imperative, before administration, and also afterwards, to assess drug effects. It is also necessary to review and reevaluate the rest of the medication that the patient is receiving to reduce risks.

In patients with known diagnosis of congenital long QT, or in those with a history of drug-induced polymorphic ventricular tachycardia, the use of these agents is more unsafe and the benefits and risks must be carefully weighed to define their indication. In case of administration, strict monitoring is essential. In a trial carried out in Brazil, Borla et al. evaluated in 81 patients the safety of chloroquine in two different schemes, high dose: 600 mg twice daily for 10 days, vs. low dose; 450 mg/day for 4 days, with the addition of azithromycin in most of these patients. The incidence of QTc greater than 500 ms was 11% in the low-dose group and 19% in the high-dose group. Mortality was higher in the high-dose group: 39% (16/41) vs. 15% (6/40) with low dose, although the latter was a higher risk group. The authors did not diagnose any polymorphic ventricular tachycardia as a consequence of QT prolongation. This is a study with many methodological limitations, in which probably the most important information from the cardiological point of view is the incidence of QT prolongation, especially when using a high-dose protocol. With similar results, Mercuro et al. observed that in 19% of the patients who received hydroxychloroquine, QTc was prolonged for more than 500 ms and in 3% it was greater than 600 ms. When in addition to hydroxychloroquine, patients received azithromycin, in 21% of patients the incidence of QTc was greater than 500 ms and in 13% it was greater than 600 ms. (151)

Tisdale et al. developed a risk score for QT interval prolongation in order to identify the patients most likely to present this adverse effect. Advanced age, female gender, hydroelectrolytic disorders, myocardial ischemia, or ventricular dysfunction, in addition to treatment with drugs that prolong QT, were associated with increased risk. (152)

Corticosteroids

In June 2020 and as part of the Recovery megatrial, the University of Oxford announced the beneficial effect of dexamethasone in patients with COVID-19 in advanced stages of the disease, with a treatment scheme consisting in the daily administration of 6 mg during 10 days. This study has not been published, so the available information is still scarce. Tolerance and cardiovascular adverse effects may be particularly different in these severely ill patients.

The advantage that dexamethasone has in relation to hydrocortisone is its lower mineralocorticoid effect, so hydrosaline retention, hypertension and hydroelectrolytic disorders would tend to be lower. However, this is an aspect that cannot be ignored, especially in patients vulnerable to the development of heart failure. In healthy individuals, acute administration of dexamethasone was associated with hyperglycemia, but also hyperinsulinemia and weight gain. (153)

Regarding the use of corticosteroids in acute heart failure, the evidence is very limited. Miró et al. compared the evolution of patients with heart failure, with and without administration of corticosteroids in the emergency room, and after adjusting for disease severity and comorbidities, they did not observe differences between both groups. (154)

CONCLUSION

The COVID-19 pandemic has imposed a challenge on mankind which was unthinkable months ago. As a consequence of the action of an invisible enemy, widely disseminated and attacking by mechanisms not yet completely unraveled, millions of people have been affected and hundreds of thousands have died in a short time. Health systems have been overwhelmed, and we have witnessed marches and countermarches, ephemeral theories, and conflicting opinions. Everyday life and our interactions are permeated by the virus, whether we are healthy or sick. There is much that is not yet known, but also much that we have learned. Scientists from all branches of knowledge, from basic to social sciences, have tirelessly tried to get closer to the truth. Difficult task when it comes to a disease that is barely half a year old, with symptoms and signs whose incidence is variable as time passes, with diagnostic methods that are far from being the gold standard, and treatments that are enthroned and ruled out in a matter of weeks.

Cardiovascular disease in its different manifestations is central to understanding the virus mode of action, and the manner of death of many patients. This review presents a comprehensive evaluation of the knowledge available so far, and it is expected that it will contribute to the most appropriate decision-making. In this context, the authors, in any case, understand that, surely, some of their statements, all based on existing references, may be contested, not because they imply an opinion that deserves to be discussed, but because, rapidly, reality and new findings will come to do it. As always, new research and the passage of time will consolidate the definitive knowledge.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

Ethical approval

Not applicable.

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