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Review

Can COVID 2019 induce a specific cardiovascular damage or it exacerbates pre-existing cardiovascular diseases?

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ABSTRACT

A novel coronavirus SARS-CoV-2 causes acute respiratory distress syndrome (ARDS) with cardiovascular and multiple organ failure till death. The main mechanisms of virus internalization and interaction with the host are down-regulation or upregulation of the ACE2 receptor, the surface glycoprotein competition mechanism for the binding of porphyrin to iron in heme formation as well as interference with the immune system. The interference on renin–angiotensin–aldosterone system (RAAS) activation, heme formation, and the immune response is responsible for infection diffusion, endothelial dysfunction, vasoconstriction, oxidative damage and releasing of inflammatory mediators. The main pathological findings are bilateral interstitial pneumonia with diffuse alveolar damage (DAD). Because ACE receptor is also present in the endothelium of other districts as well as in different cell types, and as porphyrins are transporters in the blood and other biological liquids of iron forming heme, which is important in the assembly of the hemoglobin, myoglobin and the cytochromes, multiorgan damage occurs both primitive and secondary to lung damage. More relevantly, myocarditis, acute myocardial infarction, thromboembolism, and disseminated intravasal coagulation (DIC) are described as complications in patients with poor outcome. Here, we investigated the role of SARSCoV-2 on the cardiovascular system and in patients with cardiovascular comorbidities, and possible drug interference on the heart.

1. Introduction

Between the December 31, 2019 and the beginning of February 2020, a novel coronavirus SARSCoV-2 spreads from China all over the world. SARS-CoV-2 induced a disease called COVID-19 by the World Health Organization (WHO) which declared the pandemic status (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen).

The SARS-CoV-2 is an RNA virus (family Coronaviridiae), similar to SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) [1,2]. The 3 main symptoms of COVID-19 are fever, cough, and shortness of breath. Less common symptoms are muscle pain, anorexia, malaise, sore throat, nasal congestion, dyspnoea, and headache with an onset between 2 and 14 days. The clinical severity ranges widely from asymptomatic infection to fatal disease. The involvement of the upper respiratory district and lung is typical and primary. Radiological features include interstitial thickening, lung opacities, lower lobe predominance, and bronchiectasis; multifocal peripheral subpleural ground-glass opacification or consolidation has been commonly observed CT feature up to pleural and pericardial effusion, with symptoms ranging from flu syndrome to acute respiratory distress syndrome (ARDS), caused by diffuse alveolar damage (DAD), with cardiovascular and multiple organ failure till death [3–5].

A multicenter study evaluated pulmonary and extrapulmonary manifestations such as hepatic and renal dysfunction, lymphopenia, thrombocytopenia, and elevated inflammatory biomarkers on a large series of hospitalized patients. The study shows that the main risk factors of clinical behavior are diabetes hypertension and coronary heart disease [6]. The mortality rate of COVID-19 is estimated at 3.7 %, according to the national official statistics in China [7]. Preliminary reports in the United States indicate that the highest mortality is found in people aged 85 and over (10 %–27 %), followed by people aged 65–84 (3 %–11%), people aged 55–64 (1 %–3 %) and people aged 20–54 (< 1 %), with no few deaths among people aged 19 or under. However, contrary to previous reports from China, 20 % of deaths

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occurred among adults aged 20–64, and 20 % of those hospitalized were between 20 and 44 years of age [8,9].

According to PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), in less than two months, over 12,000 papers have been published on SARS-CoV-2 including its virology, epidemiology, pathogenesis, diagnosis, and treatment. From the literature, it emerges that many deceased patients are old, with oncological, immunological, or dysfunctional systemic diseases linked to the cardiovascular system; it also emerges that multi-organ complications take place in the lung infection, including cardiovascular complications especially that often constitute the real cause of death. This scenario is a survival challenge for patients and a challenge for all those who work to find the right therapy and prevent the unfortunate event of death. Here, we examine pathophysiological effects of SARS-CoV-2, on the cardiovascular system as well as drug mechanisms with side effects on cardiovascular complications.

2. Pathogenesis

It is important to focus that coronaviruses mainly infect epithelial cells of the upper respiratory tract and pulmonary pneumocytes but also other types of epithelial cells such as endothelial cells of arteries and veins, smooth muscle cells, intestinal epithelium cells and immune cells [10,11] (1112). The RNA genome is released into the cytoplasm of the cells through the fusion of the capsid with the cell plasma membrane. After interaction with its proposed receptors angiotensin-converting enzyme 2 (ACE2), genomic RNA accompanied by envelope glycoproteins and nucleocapsid proteins forms virion-containing vesicles, which then fuse with the plasma membrane to release the virus [12]. Physiologically, ACE2 counters renin–angiotensin–aldosterone system (RAAS) activation by the degradation of angiotensin II to angiotensin which attenuates its effects on vasoconstriction, sodium retention, and fibrosis. ACE2 also cleaves angiotensin I to angiotensin and participates in the hydrolysis of other peptides and may be up-regulated in certain clinical states [13–15] The interaction between SARS viruses and ACE which is localized above all on the endothelium of the pulmonary capillaries, causes alterations of the circulation with the variation of the pressure levels (Fig. 1). On the other hand, SARS-Cov-2 also generates interference in the native immune response (Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs), which trigger the expression of interferon (IFN) and activation of anti-viral effectors such as Natural Killer cells, T CD8 + cells, and macrophages); generates interference in the recruitment of inflammatory cells, in the regulation of host DNA replication with transcription anomalies and with triggering of the apoptotic pathways, and in dysregulation of the renin-angiotensin system [8] (Fig. 1).

2.1. Pulmonary infection and pathological findings

Mainly, the SARS-CoV-2 is responsible for bilateral interstitial pneumonia with DAD and primary pulmonary hypertension from direct alveolar and endothelial damage. The morphological changes are represented in the first phase by an interstitial inflammatory infiltrate, diffuse vascular congestion, edema, and subsequently from proteinaceous edema with or without hyaline membranes lining alveolar walls, inflammatory mononuclear infiltrate with multinucleated giant cells, exfoliation to also intra-alveolar granulocyte inflammation and position of fibrinoid material which are the true signs of direct damage. The foci of reactive alveolar epithelial hyperplasia, fibroblastic proliferation with fibrosis, and of alveolar rupture are present as a consequence [16]. These changes in the parenchyma induce primary pulmonary hypertension due to an increase in lung resistance and overload of the right and left circulation. The clinical manifestation is characterized by systemic hypertension and ventricular hypertrophy, as it happens in all lung diseases from direct damage with increased of resistance.

2.2. Cardiovascular system

Cardiovascular mortality is known to be higher in all influenza pandemics than in all other causes. Acute respiratory viral infections, such as coronaviruses are well known to trigger factors for cardiovascular disease (CVD) [17]. During COVID-19 pandemic, the literature produced in a few months report that the increase in morbidity and mortality is found in particular in the elderly and in those who present comorbidities. The most prevalent comorbidity were hypertension, diabetes, and cardiovascular diseases [18,19]. Compared to lung, data concerning cardiovascular involvement are less described [20]. This makes it difficult to draw a line between complications of comorbidity and possible direct cardiovascular damage by COVID-19. There are autopsy data relating to the infection produced by SARS CoV in 2003 and by MERS-CoV in 2012 that can help better understand the involvement of the cardiovascular system. However, these data are affected by the difficulty of autopsy diagnosis made in a particular background. For example, an autopsy study reported post-mortem examinations in 8 patients who died of SARS in which 4 patients had pulmonary thromboembolism and 3 patients with deep vein thrombosis. One patient had a subendocardial infarction with occlusive coronary artery disease. One patient had valve vegetations along with heart attack, kidney, spleen, and brain [21]. The reported presence of increased D-Dimer and alteration of coagulation parameters highlights the need to understand whether positive CoV-2 patients have a greater risk of hypercoagulability than negative patients with comorbidity and the need to understand the correct use of the antiplatelet therapy. Some clinical trials have compared the clinical characteristics, coagulation parameters, and mortality between the COVID and non − COVID groups both with underlying chronic diseases including hypertension, diabetes, heart disease, and lung disease, and antiplatelet therapy and D-Dimer evaluation. In the COVID group, significantly lower mortality was found in users of heparin with markedly high D-dimer compared to non-users, while no difference in mortality among heparin users compared to non-users was found in the non − COVID group. No significant improvement in clinical symptoms. However, further studies on the role of anticoagulants are still needed [22].

Some authors have paid attention to surface structural proteins and non-structural proteins of CoV-19 not only in the mechanism of integration into the host cell but also indicated inhibition of the normal metabolic pathway of heme with competition mechanism for the binding of porphyrin to iron. Heme is the degradation product of hemoglobin through the link with porphyrin [23]. This mechanism is not yet clear, but it explains the finding of the virus also in biological liquids such as urine, saliva, feces, and blood. The reported data requires clinical and experimental demonstration. ACE2 is the putative receptor of SARS viruses which is present mainly in the epithelial cells of the upper respiratory district, in pulmonary endothelium and pulmonary alveolar pneumocytes, but also present in other cell types in different organs as heart and kidneys [12]. It is possible to hypothesize direct cardiac damage mediated by the interaction of the virus with ACE2 or much more reasonably mediated by the imbalance caused by the alteration of the functioning of the RAAS. Based on these considerations, it is difficult to distinguish between death from direct cardiac or systemic vascular damage induced by SARS-CoV-2 in patients without comorbidity and death in patients with previous cardiovascular disease. Because the pandemic infection broke out in a very short time, there are no large autopsy studies able to shed light on the real damage to the cardiovascular system in subjects who died from COVID-19 [24,25]. Can SARS-CoV-2 induce new heart conditions or can it only exacerbate pre-existing cardiovascular diseases? We believe that attention must be paid to three fundamental entities that can cause sudden death in patients infected by SARS-CoV-2: myocarditis, coronary syndrome, thromboembolism.

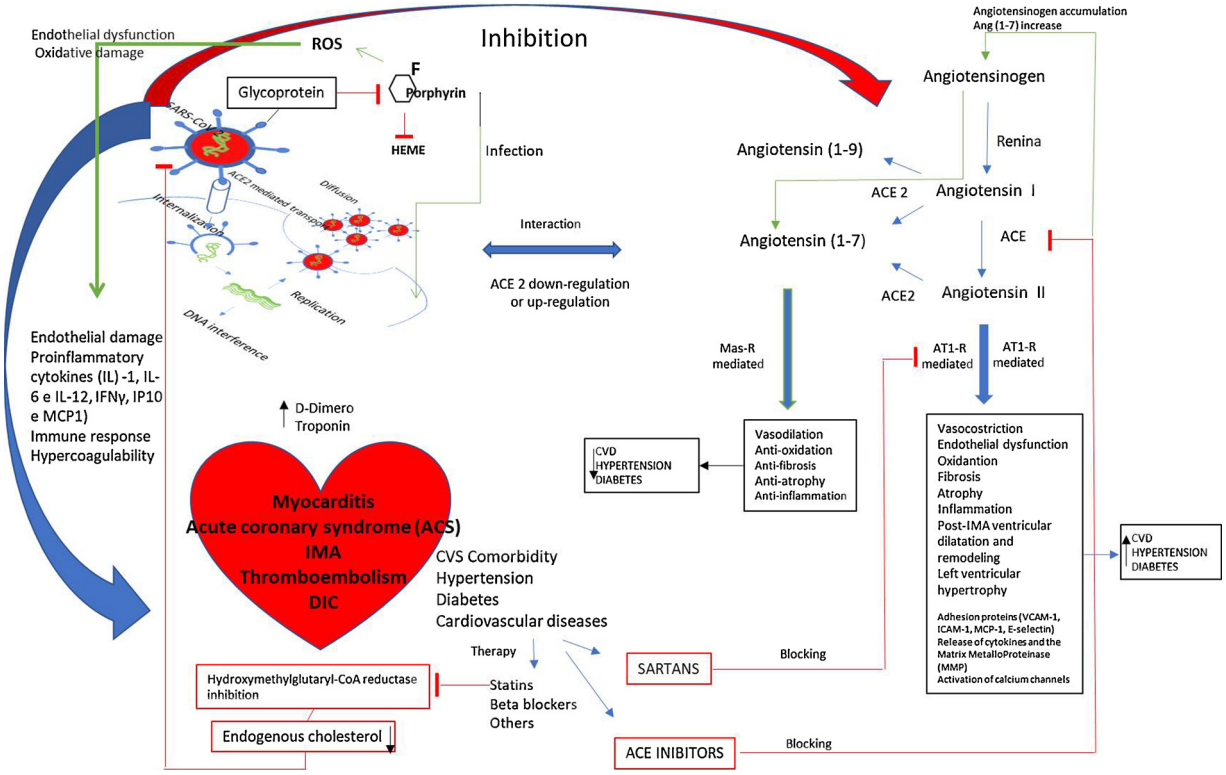

Fig. 1. SARS-CoV-2 infects host cells through ACE2 receptors. The virus can act on the cardiovascular system increases the risk of damage and sudden death in people with comorbidities.

The figure shows the main hypothesized mechanisms of interaction between the virus and the cardiovascular system with the causes of damage most reported in the literature. Damage mediated by the release of inflammation mediators, by direct action on the vascular endothelium that acts on the determinism of hypercoagulability and hypoxic damage by alterations of perfusion (acute coronary syndrome, IMA, thromboembolism, DIC), and by the immune response responsible in the first instance of myocarditis with myocardial damage. The damage mediated by the proposed downregulation or up-regulation of the ACE2 Receptor with a consequent imbalance of the normal circulatory and inflammatory homeostasis. The surface glycoprotein competition mechanism for the binding of porphyrin to iron in HEMA formation. In red the inhibition pathways, and green the main activation pathways both of the virus infection modality, of the pathogenetic mechanisms of the damage, and when taking the drugs used in people with hypertension, diabetes, and vascular disease.

2.2.1. *Myocarditis*

Only a few cases with myocarditis and pericarditis involvement were reported, without consistent histological evidence [26,27]. It is clear that in a condition of myocarditis during COVID-19, with inflammatory infiltrate and myocardial necrosis according to Dallas criteria [28], ventricular dysfunction, arrhythmias, and sudden cardiac death can occur as occurs in enterovirus or adenovirus myocarditis due to an exuberant inflammatory response in subjects without pre-existing diseases. Only one case of cardiac tamponade in a 47-year-old man SARS-CoV-2 infected without cardiovascular risk is reported in the literature as a complication of myocarditis and pericarditis [29]. The causes of hydropericardium and cardiac tamponade also include infectious and inflammatory causes (15 %) and mechanical complications of myocardial infarction (12 %) [30]. Our autoptic experience leads us to some considerations. Myocarditis is a cause of sudden death in children and in young adults with undiagnosed or underestimated viral infections [31]. Patients who died for complications of COVID-19 are old and have often comorbidity due to cardiovascular diseases. We can, therefore, hypothesize that myocarditis with the presence of inflammatory infiltrates in the myocardial interstitium and with the structural damage validated by the laboratory markers of damage and cardiac necrosis, can be a secondary complication of the immune response and not of the direct action of the virus on cardiomyocytes. To date is not evidence of RNA coronaviruses in the heart. Considering the reported presence of ACE2 in different cell types and also in the heart [12], we can only hypothesize a hematogenous diffusion of the pathogen and a similar interaction as happens in the lung; the hypothesis remains that the SARS-CoV-2 action on the heart in old people is mediated by systemic imbalance caused by the alteration of the functioning of the RAAS on comorbidity background.

2.2.2. *Acute myocardial infarction and myocardial structural damage*

The hypothesis that influenza viruses can trigger myocardial infarction has long been known [32,33]. Large and more recent studies have reported that previous myocardial infarction, diabetes, dyslipidaemias, hypertension, and other cardiovascular risk factors can predispose to an acute ischemic event in respiratory virus infections such as recently reported during the pandemic COVID-19 [34–36]. A cohort study compared patients with and without heart damage and analyzed the association between heart damage and mortality. The results of the study showed that out of 416 hospitalized patients, 19.7 % had heart damage, and, compared to patients without heart damage, these patients were older with comorbidity, leukocytosis, high sensitivity troponin I increase regardless of abnormalities in electrocardiography and echocardiography. The study demonstrated that cardiac injury and mortality in patients with COVID-19 were significantly associated [37].

Heart damage patients had higher mortality than those without heart damage. Another study evaluated the association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19. The study showed that of 187 patients with SARS-CoV-2, 27.8 % of patients had a myocardial injury, resulting in cardiac dysfunction and arrhythmias and an unfavorable prognosis while the prognosis of CVD patients without myocardial damage was relatively favorable. A percentage of 35.3 had underlying CVD including hypertension, coronary artery disease, and cardiomyopathy, and 27.8 % showed myocardial damage as indicated by elevated

TnT levels. The study showed that myocardial damage and mortality was markedly higher

in patients with high TnT levels than in patients with normal TnT levels and that the patients with underlying CVDs had the highest mortality (69.44 %) and the shortest survival period [38]. This data favor the role of the pre-existence of disease as a risk factor and of high mortality in adults and old people. Since Covid-19 binds to ACE2 which is expressed in different cell types and the kidney and heart, a mechanism of direct damage to cardiomyocytes is conceivable but the systemic inflammatory responses, destabilized coronary plaque and aggravated hypoxia constitute now the only obvious modes of heart damage (Fig. 1). The induction of an abnormal inflammatory state is the first cardinal point implicated in cardiovascular complications and acute myocardial infarct responsible for the death. Already in previous SARS-CoV epidemics, the studies have shown that an increase of proinflammatory cytokines in serum (e.g. (IL) -1, IL-6 e IL-12, IFNγ, IP10 e MCP1), associated with lung inflammation and extensive lung damage as well as in patients SARS-CoV-2 positive probably leading to activated T-helper-1 (Th1) cell responses [39,40], and increased of T-helper-2 (Th2) cytokines (eg, IL4 and IL10) that suppress inflammation [40]. The inflammatory state can aggravate acute coronary syndrome with myocardial infarction until sudden death.

It is crucial to emphasize that in this context, only biopsy and autopsy studies could provide information to understand the disease. Acute myocardial infarction has been indicated as a complication, as well as laboratory parameters reported as the increase in cardiac troponin. The clinical data do not explain the type of heart damage. The increase in cardiac troponin is a marker of myocardial damage without distinguishing between necrosis and apoptosis. The identification of histological features could certainly be useful. We believe that it is fundamental to be able to distinguish in the heart between necrosis from hypoxic, ischemic damage, myocarditis and direct virus damage, or other cardiomyopathies responsible for heart failure and sudden death. There is currently no evidence of the presence of CoV-19 in human myocardiocytes with the PCR method. Some autopsies were performed on old subjects (> 60 years old) and the morphological data highlighted the presence of cardiomyocyte hypertrophy, degeneration, and necrosis of some cardiomyocytes, mild hyperemia and edema of the interstitial cells and infiltration of a small amount of lymphocytes CD4+, macrophages neutrophils but no evidence of SARS-CoV-2 in tissue [41]. These aspects do not allow to make a correct differential diagnosis because they lack a conspicuous consistency of the data also in light of the same histological diagnostic criteria.

2.2.3. Thromboembolism

It is known that patients with cardiovascular disease have a higher risk of a thrombo-embolic event as it is known that all viral infections have a potential role in disseminated intravascular coagulation (DIC) The endothelial damage, the blood flow turbulence, and hypercoagulability are the basis of the mechanism. Some clinical studies have highlighted that SARS-CoV-2 positive and symptomatic patients have more thrombus-embolic and DIC risk. There is evidence for abnormal coagulation parameters with significantly higher levels of D-dimer and fibrin degradation, longer prothrombin times, and activated partial thromboplastin time in hospitalized patients with severe COVID-19 and non-survivors; DIC diagnosis was performed according to clinical and laboratory criteria [42–44]. The greatest incidence of an adverse event is however detected in patients with underlying diseases including cardiovascular disease. Vascular inflammation and hemodynamic instability can contribute to the hypercoagulable state and endothelial dysfunction resulting in thromboembolism or DIC in patients with underlying cardiovascular diseases. Also, in this case the literature is deficient in the morphological data that could be taken from an autopsy case study.

3. Cardiovascular comorbidities and peculiarities in elderly individuals

Some clinical studies have shown that one-third of patients with COVID-19, aged 40–60 years, have comorbidities such as CVD, hypertension and atherosclerotic cardiovascular disease and have shown that a predisposition to acute cardiac complications related to comorbidities already in this age group [45] Although clinical studies are limited by the short time and the absence of an autoptic finding, some meta-analyses have identified a movement towards intensive care and increase the mortality risk with the increase in average age and patients whit cardiovascular comorbidities such as diabetes, hypertension and coronary disease [18]. A high proportion of severe to critical cases and high fatality rates were observed in the elderly patients (aged 71 ± 8 years), with hypertension (40.8 %), diabetes (16.0 %), and cardiovascular disease (15.7 %) [46]. Hemodynamic heart failure by severe respiratory syndrome, hypercoagulability by sepsis and endothelial dysfunction, inflammatory state, oxidative stress, and heme dysfunction are trigger factors that in patients over 60 years with cardiovascular comorbidities induce a greater risk of heart damage, thromboembolism and disseminated intravascular coagulation (DIC) with inauspicious prognosis and death.

4. Immunocompromised subjects

Many patients may be immunocompromised due to the underlying malignancy or anticancer therapy or primitive immunodeficiencies and are at higher risk of developing infections. As with other infections, the risk of COVID-19 is increased in these patients. Clinical studies in cancer patients report a higher risk of infection than in a non-cancerous population (median age 66 years) ([47]). However, some data suggest that there is no greater multiorgan compromise from SARS-CoV-2 in immunocompromised individuals as a consequence of chemotherapy ([48])

5. Cardiovascular effects of current therapy against COVID-19

To date, there are no specific effective therapies for COVID-19, but pharmacologic agents are under active investigation. Old antiviral drugs of which the pharmacokinetics and side effects are already known to have been re-evaluated in the treatment [49–60]. The real dilemma is the role of the basic drugs used in cardiological comorbidities and their possible interference in worsening the prognosis.

Lopinavir/Ritonavir (Kaletra) inhibits the replication of the RNA virus and has evidence of a synergistic in vitro effect with ribavirin [57–59]; has been used for years as components of treatment for HIV [55,60] it may interfere with the dosage of anticoagulants such as ribavirin [56].

Moreover, it may also interact with HMG-CoA reductase inhibitors (statins) due to the risk of rhabdomyolysis [61].

Favipiravir (Avigan) is an anti-influenza virus that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses [49]. The preliminary results indicated that favipiravir had more potent antiviral action and not significant adverse reactions [50].

Remdesivir is an antiviral agent that binds to the active site on RdRp has broad-spectrum activities against viruses including EBOLAV, MERS-CoV, and SARS-CoV with controversial results and in the absence of reported cardiovascular toxicity. It was the first drug used in SARS-CoV2. Clinical trials have shown no cytotoxicity or adverse reactions related [51–54].

Ribavirin that binds to the active site on RdRp has been used for years as components of treatment for hepatitis C [55], has broad-spectrum activities against viruses including MERS-CoV, SARS-CoV-2 [51,52]; it can influence the dosage of anticoagulants and can also influence the activity of P2Y12 inhibitors through the inhibition of CYP3A4, which results in a reduction of the serum concentrations of the

active metabolites of and increased serum concentrations [56].

Hydroxychloroquine (HCQ) was originally developed and used for the treatment of malaria and it is increasingly used in the management of a variety of autoimmune disorders, with well-established roles in dermatology and rheumatology and emerging roles in oncology [62,63]. HCQ is a modulator of the immune response through several mechanisms. HCQ inhibits the toll-like receptors 7 and 9 in dendritic cells, inhibiting the production of interferon-alpha, counteracts the effect of extracellular oxidants, and stops the signaling of T cell receptor-dependent calcium within T cells and hence antigen processing. It also induces apoptosis and interferes with lysosomal function, influencing the processing of antigenic peptides necessary to trigger autoimmune responses [64,65]; and has to interfere with heme which is essential for the parasite [66]. Retinopathy and some cardiac effects such as bundle-branch block, ventricular tachycardia, and cardiomyopathy often with hypertrophy, restrictive physiology, and congestive heart failure are known [67].

Recently these drugs have attracted intense attention as a possible solver of COVID-19. Based on Chinese clinical trials [68–70], a French study evaluated 26 patients treated with hydroxychloroquine and 16 control patients, all positive for the virus at baseline. Despite the small sample size, it showed a reduction or disappearance of the viral load in COVID -19 patients. It also showed that the effect of the drug was enhanced by azithromycin [71]. The experimental protocol included 200 mg of oral hydroxychloroquine sulfate, three times a day for ten days in combination with an antibiotic based on clinical judgment. The authors documented the efficacy of hydroxychloroquine in reducing the viral load at day 7. Although the use of HCQ is now approved in many autoimmune and inflammatory systemic diseases, and in oncology, and although it has also been shown that the use of HQC reduces the level of low-density lipoproteins with antithrombotic effect [72], cardiac complications are described and related to the accumulation of granular deposits in the cytoplasm, a consequence of lysosomal dysfunction, are described [73,74].

Cardiotoxicity with potential conduction or structural abnormalities on electrocardiogram (ECG) has been reported. An association between cumulative HCQ dose above the median and structural ECG abnormalities (left ventricular hypertrophy or atrial enlargement) was reported; however, it is not shown a statistically significant association with ECG structural abnormalities. The cumulative AM decreases the odds of ECG conduction abnormalities (prolonged corrected QT interval, short PR interval, left bundle branch block (LBBB), right bundle branch block (RBBB) and atrioventricular block (AVB), premature atrial complex, tachycardia, bradycardia, atrial fibrillation, ectopic atrial rhythm, premature ventricular complex and ventricular bigeminy [75,76].

Since the dose of HQC used in COVID-19 therapy is lower, and its use is not chronic, we can rule out a cardiotoxic effect.

Recent studies have shown that azithromycin (AZM), and the closely related drug roxithromycin, both act as drugs that can target and selectively remove senescent cells, with an efficiency of nearly 97 % [77]. Used in cystic fibrosis, is has an anti-fibrotic effect by targeting myofibroblast cells and functionally acts as an anti-inflammatory drug and reduces mediators, such as IL-1beta and IL-6 [78,79]. It also inhibits the replication of other viruses, such as Ebola and HIV-1 [69,80,81]. Azithromycin has been linked to an increased risk of ventricular arrhythmia, prolonged QT interval such as rifampicin. Clinical trials indicate that the risk of ventricular arrhythmia with the use of azithromycin is likely to be due to the patient's health rather than due to the drug itself. The QT interval prolongation is not observed in the association between chronic AZM therapy [81–85]. ACE2 is essential in the mechanism by which anti-RAAS inhibitor drugs work to reduce the risk of cardiovascular disease due to hypertension and diabetes. Concerning cardiovascular risk in positive SARS-CoV-2 subjects taking antihypertensive and hypoglycaemic therapy, the literature produced so far is confusing. Contrary, some authors indicate overexpression of ACE2 in SARS-CoV-2 infection [86,87], which we could explain as a rebound effect [88]. ACE2 is expressed in different cell types and also in the kidney and heart, but mainly in the lung as well as ACE (angiotensin-converting enzyme) (11,12). Considering the pathogenesis and the effects produced by SARS-CoV-2 in the lung, it is more reasonable to believe that there is a down-regulation. In both cases, there is no scientific evidence that patients using anti-RAAS or ACE inhibitors have a higher risk of SARS-CoV-2 infection or that they have a higher cardiovascular risk. Furthermore, an up-regulation would favor greater treatment efficacy and protection rather than risk. Some authors suggest the protective role of ace inhibitors against SARS-CoV-2 infection as opposed to others. However, we still have doubts about how to truly interpret the role of ACE inhibitors which, unlike anti-RAAS [86–88], act on the angiotensin-converting enzyme. Instead, Sartan antagonizes the angiotensin II receptor, which acts by blocking the activation of the angiotensin 2 AT1 receptors.

The scenario is very confusing regarding anti-RAS and ACE inhibitors, but even more so regarding the use of statins. As the mechanisms of the inflammatory and immune response are still unclear and even less so if blood sugar can alter virulence or if the virus interferes with insulin secretion, there is little data on the development of acute diabetes complications in patients with Sars-CoV-2 disease. Statins inhibit the synthesis of endogenous cholesterol by acting on the enzyme hydroxymethylglutaryl-CoA reductase. Cholesterol plays important role in the entry of viruses into cells and statins are reported to block the infection of many enveloped viruses by inhibiting the cholesterol pathway [89,90]. The use of statins in EBOLA virus infection is described as a protective factor [91,92]. Besides, for anti-inflammatory effects, statins have been proposed as adjunctive therapy in influenza although extensive clinical studies in patients with ARDS have shown no clinical benefit [93,94]. This data suggest the protective effect of statins in SARS-CoV infections although few [89,92,95].

6. Conclusions

The main mechanisms of virus internalization and interaction with the host are regulated by ACE2 receptor and porphyrin binding. Because ACE receptor is also present in the endothelium as well as in different cell types, and as porphyrins are transporters in the blood and other biological liquids of iron forming heme, which is important in the assembly of the hemoglobin, myoglobin and the cytochromes, multi-organ damage occurs both primitive and secondary to lung damage.

The absence of important predisposing factors in COVID-19 pneumonia seems to confirm the role of serious infections as a precipitating factor for acute thromboembolism and heart failure through the inflammatory state and dysregulation of the immune response. The presence of cardiovascular comorbidities seems to aggravate the prognosis until death by myocarditis, coronary syndromes, and diffuse thromboembolism or DIC. No large autopsy studies able to shed light on the real damage to the cardiovascular system in subjects who died from COVID-19 and our autoptic experience suggests that the autopsy exam is very important [25,96–98]. There is no substantial data to say that anti-RAAS, ACE inhibitors, statins increase the risk of cardiovascular damage in COVID patients. The role of anticoagulants can be useful especially in people with cardiovascular disease. HQC therapy appears to be effective and the risks for cardiovascular complications are related to the long-term cumulative dose.

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Disclosures

None declared.

Author's contributions

G.M. and C.N. the concept and design of the study. G.B., M.N. and C.N. gave the final approval.

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