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Review article

COVID-19 and risk of cardiomyocyte injury: The prevailing scenario

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ABSTRACT

The novel coronavirus which is also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for COVID-19 (coronavirus disease 2019). SARS-CoV-2 is known to cause substantial pulmonary disease, including pneumonia and acute respiratory distress syndrome (ARDS), clinicians have observed many extra-pulmonary manifestations of COVID-19. SARS-CoV-2 infection is associated with a variety of pro-inflammatory mediators that may play important roles in the pathophysiology of cardiac and arrhythmic complications. Systemic inflammatory response syndrome (cytokine storm) is another putative mechanism of myocardial injury. In addition to lung damage, there may be significant cardiac involvement in patients with COVID-19, which is responsible for worsening the clinical condition of the host. The main cardiac manifestations can be oedema, pericarditis, cardiac fibrosis, myocarditis, impairment of contractile function and cardiac electrophysiology. The cardiac status of patients with ongoing SARS-CoV-2 infection of surviving patients in convalescence period should be carefully monitored.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 43 million people and has caused more than one million deaths globally, as of 25 October 2020 (Al-Kuraishy et al., 2020a). While SARS-CoV-2 is known to cause substantial pulmonary disease, including pneumonia and acute respiratory distress syndrome (ARDS), clinicians have observed many extra-pulmonary manifestations of COVID-19. Different emerging literature suggests that the hematologic, cardiovascular, renal, gastrointestinal, hepatobiliary, endocrinologic, neurologic, ophthalmologic and dermatologic systems can be affected by COVID-19 (Al-Kuraishy et al., 2020b). This pathology may reflect either extra-pulmonary dissemination or replication of SARS-CoV-2, as has been observed for other zoonotic coronaviruses or widespread immunopathological squeal of the disease (Al-Kuraishy et al., 2020c).

PATHOPHYSIOLOGY

SARS-CoV-2 seems to employ mechanisms for receptor recognition similar to those used by prior virulent coronaviruses such as SARS-CoV, the pathogen responsible for the SARS epidemic of 2003 (Semwal et al., 2020). The coronavirus spike protein facilitates entry of the virus into target cells. The spike subunit of SARS-CoV and that of SARS-CoV-2 involve angiotensin-converting enzyme 2 (ACE2) as an entry receptor (Fig. 1). In addition, cell entry requires priming of the spike protein by the cellular serine protease (TMPRSS2) or other proteases (Al-Kuraishy et al., 2020d).

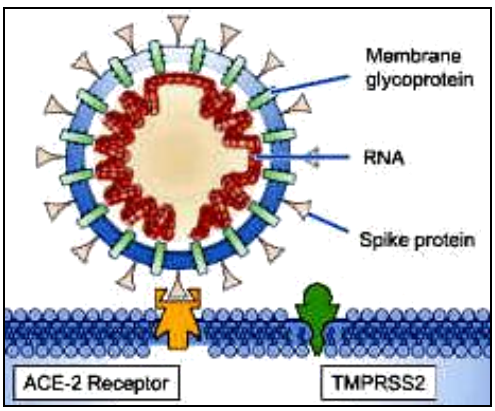

Fig. 1. SARS-CoV-2 and ACE2

Co-expression on the cell surface of ACE2 and TMPRSS2 is required for the completion of this entry process. In addition, the efficiency with which the virus binds to ACE2 is a key determinant of transmissibility, as shown in studies of SARS-CoV (Al-Kuraishy et al., 2020e). Recent studies have demonstrated higher affinity of binding of SARS-CoV-2 to ACE2 than of SARS-CoV to ACE2, which may partially explain the increased transmissibility of SARS-CoV-2 (Al-Kuraishy et al., 2020c). Key mechanisms that may have a role in the pathophysiology of multi-organ injury secondary to infection with SARS-CoV-2 include direct viral toxicity, endothelial cell damage and thrombo-inflammation, dysregulation of the immune response, and dysregulation of the renin-angiotensin-aldosterone system (RAAS) (Al-Kuraishy et al., 2020b). The relative importance of these mechanisms in the pathophysiology of COVID-19 is currently not fully understood. While some of these mechanisms, including ACE2-mediated viral entry and tissue damage, and dysregulation of the RAAS, may be unique to COVID-19, the immune pathogenesis caused by the systemic release of cytokines and the microcirculation dysfunctions may also occur secondary to sepsis (Fig. 2) (Kadhim et al., 2019).

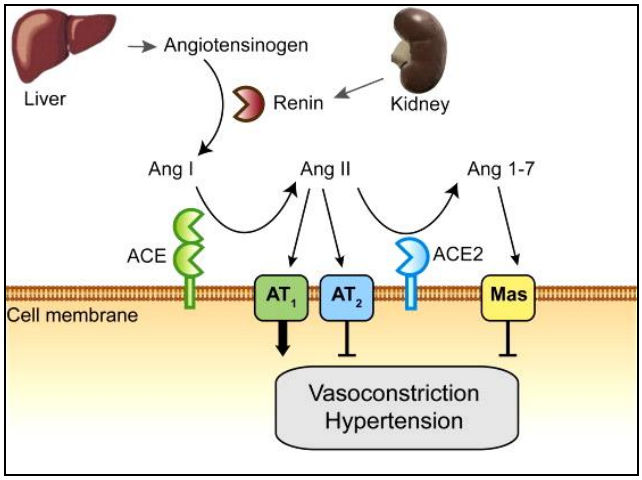

Fig. 2. SARS-CoV-2 and RAAS

COVID-19 AND CARDIAC INJURY

SARS-CoV-2 infection is associated with a variety of pro-inflammatory mediators that may play important roles in the pathophysiology of cardiac and arrhythmic complications. In a single-centre study cardiac injury was observed in 19% of hospitalized patients with COVID-19, and it was associated with a higher risk of in-hospital mortality. Therefore, it is plausible that these patients have an even higher risk of cardiac arrhythmia SARS-CoV-2 infection is associated with a variety of pro-inflammatory mediators that may play important roles in the pathophysiology of cardiac and arrhythmic complications (Al-Kuraishy and Al-Gareeb, 2020).

In a single-centre study cardiac injury was observed in 19% of hospitalized patients with COVID-19, and it was associated with a higher risk of in-hospital mortality. Consequently, it is reasonable that these patients have an even higher risk of cardiac arrhythmias (Recovery Collaborative Group, 2020).

Abundant of our present knowledge of SARS-CoV-2 comes from previous historical epidemics that preceded the current outbreak, as SARS-CoV, MERS-CoV, and H1N1 influenza syndromes. It was observed, during these outbreaks, a significant association between underlying cardiovascular disease, myocardial injury, and worse outcomes (Jang et al., 2020). The first human infection by a new strain of coronavirus, the SARS-CoV, was reported in 2002. At that time it was known that, at least in rabbits, coronavirus infections could induce cardiomyopathy resulting in cardiac chambers dilatation and systolic function impairment, simulating other dilated cardiomyopathies (Liu et al., 2020).

In humans, hypotension, cardiac arrhythmias, and even sudden cardiac death (SCD) were described as possible SARS-CoV manifestations. It has been demonstrated that sinus tachycardia was the commonest cardiovascular SARS-CoV finding with an overall incidence of 72%. Persistent tachycardia mean duration was 12.7 days with a mean heart rate of 117 beats/min (range: 102-150 beats/min) and the tachycardia remained persistent in nearly 40% of patients within 30 days after hospital discharge (Lai et al., 2020). The incidence of tachycardia during the third hospitalization week, when most patients were afebrile, could be related to drug treatment, such as corticosteroid and ribavirin. However, corticosteroid therapy was not associated with persistent tachycardia during follow-up. Hence, longstanding tachycardia could eventually be due to autonomic tone changing. Alternatively, sinus tachycardia secondary to cardiopulmonary or peripheral deconditioning since this disease resulted in prolonged bed rest. Dissimilar, tachycardia, which was persistent, bradycardia was somewhat transient with a mean heart rate of 43 beats/min (range: 38-49 beats/min) and a mean duration of 2.6 days (Yang and Jin, 2020).

Reversible cardiomegaly was also reported in 13 patients (10.7%), with no clinical evidence of heart failure (HF). Transient atrial fibrillation was observed in one patient (Yang et al., 2020). Trying to explain the occurrence of cardiac arrest in patients with SARS, some possible mechanisms (Guzik et al, 2020) are given below.

1. Lung injury caused by SARS virus is leading to hypoxemia and an unsteady state in myocardial electricity.
2. SARS is direct causing new myocardial cells and/or conduction system damage.

3. SARS infection is aggravating pre-existing myocardial conditions or conduction disturbances
4. Extreme anxiety is leading to further endogenous catecholamine release, causing myocardial electrical instability.

In MERS-CoV syndrome, despite some similarities with SARS-CoV, the early mortality rate for the former achieved 60%, during the overall outbreak period, while for SARS-CoV the mortality rate was about 10% (Saad et al., 2014). A meta-analysis suggested that MERS-CoV infection was more likely to occur in patients with underlying cardiovascular diseases (Badawi and Ryoo, 2016). In terms of overall complications, renal failure (40.9%), cardiac arrhythmias (15.7%), hepatic dysfunction (31.4%), besides, pericarditis and hypotension were the most commonly reported (Yang et al., 2020).

Echocardiogram demonstrated severe left ventricular function impairment, cardiac magnetic resonance showed typical findings of acute myocarditis, and sputum was positive for MERS-CoV. The patient was intubated and required hemodialysis. After 6 weeks of intensive care unit (ICU) and 1 month of ward hospitalization, he was discharged in stable condition (Li et al., 2020). As well, influenza virus infection is well-known to exacerbate sufficiently of cardiovascular disorders, is associated with myocarditis, myocardial infarction, and HF exacerbation (La Gruta et al., 2007).

Various mechanisms have been planned to elucidate influenza triggering arrhythmias, among them severe systemic, arterial, and myocardial inflammatory reaction seems to be one of the most plausible. Moreover, influenza is known to exacerbate congestive heart failure (CHF) and increase CHF-related hospital admissions. Decompensated CHF, besides leading to hospitalization, is related to electrical myocardial homeostasis damage, causing ventricular tachycardias (VTs) treated with shock or ATP therapy (Kytömaa et al., 2019). In patients with underlying ischemic cardiomyopathy, the worsening of ischemia by increased oxygen demand and potential acute coronary syndromes led by influenza can also have a role in the increase of arrhythmic events. These concepts were strengthened by a nationwide Denmark studied, which showed a strong relationship between yearly influenza vaccination and mortality in patients with HF. In this study, annual influenza vaccination was associated with 18% reduction in the adjusted risk of all-cause death and 18% reduction in the adjusted risk of cardiovascular death (Modin et al., 2019). Remarkably, influenza infection may result in increased metabolic demand, hypoxia, and adrenergic surges, which may lead to acute exacerbation of HF. Additionally, the infection may induce a hypercoagulable state and trigger acute coronary syndromes, resulting in further left ventricular function deterioration, or it could cause direct myocardial depression (Al-Kuraishy et al., 2020f).

Based on these results, in SARS-CoV-2 myocardial injury biomarkers levels were significantly higher in patients requiring ICU admission than in those not treated in the ICU and high-sensitivity cardiac troponin I suggesting that patients with severe symptoms often have complications involving acute myocardial injury. Overall, arrhythmia rate was also more frequent in ICU patients (Al-Kuraishy, 2021).

It has been demonstrated that SARS-CoV-2 associated myocardial injury occurred on 5 out of 41 patients and was manifested as an increase in hs-cTnI levels (>28 pg/mL). Among these five patients, ICU management was required in four, indicating the severe nature of the myocardial injury in patients with COVID-19. Besides, SARS-CoV-2 positive patients stratified by the level of troponin, which was elevated in 27.8%, developed more frequently complications as acute respiratory distress syndrome, malignant VAs, acute coagulopathy, and acute kidney injury, compared with those with normal troponin T (TnT) levels (Al-Kuraishy et al., 2015). Contrary to the above-mentioned studies, Zhang and Holmes (2020) compared survivors and non-survivors in a cohort of 191 patients from two hospitals in Wuhan, found that despite more frequent in non-survivors (46% vs 1%; $P < 0.001$), hs-cTnI >28 pg/mL was not associated with mortality in multivariate analysis. Even though, it is remarkable that this study was unpowered to conclude this analysis due to the excess of the variable for only 54 events.

Acute myocarditis, as well as VAs might represent the first clinical manifestation of SARS-CoV-2 infection. In the epicentre of the current Italian epidemic, SCD likely occurred in many non-hospitalized patients with mild symptoms who were found a dead home while in quarantine. Myocardial biomarkers should be evaluated in all patients with COVID-19 for risk stratification and prompt intervention. Even after hospital discharge, we should consider that myocardial injury might result in atrial or ventricular fibrosis, the substrate for subsequent cardiac arrhythmias. The extent of myocardial scar, as assessed with cardiac magnetic resonance, might be a powerful tool to better stratify the arrhythmic risk in patients recovered from COVID-19 who had evidence of myocardial injury at the time of infection. Another relevant aspect of COVID-19 infection is that early diagnosis can be confounded in patients with chronic cardiac conditions, once the most frequent symptoms, like fatigue (51%, 95% CI: 34%-68%), dyspnea (30%, 95% CI: 21%-40%), and cough (67%, 95% CI: 59%-76%) can also be manifestations of decompensated HF or arrhythmic syndrome (Farrokhran et al., 2020).

Corroborating this concern, the National Health Commission of China (NHC) reported that among SARS-CoV-2 infection confirmed cases, cardio-vascular symptoms were the first presentation in some patients. The problem behind these atypical presentations is that patients suffering from heart palpitations and chest tightness, rather than respiratory symptoms like fever and cough, had a delayed COVID-19 diagnosis (Zheng et al., 2020).

According to the NHC, among the people who died from COVID-19, 11.8% had substantial heart damage, with elevated troponin I levels or cardiac arrest during hospitalization. Explanatory theories regarding COVID-19, cardiovascular affection postulate that chronic cardiovascular diseases may become unstable in the setting of viral infection as a consequence of the imbalance between the infection-induced increases in metabolic demand and reduced cardiac reserve. This imbalance, concurrent with an accentuated inflammatory response and myocardial damage, could raise the risk of acute coronary syndromes, HF, and arrhythmias (Stephanie et al., 2020).

The deleterious SARS-CoV-2 infection myocardial effects could also be continued by the prompt and severe downregulation of myocardial and pulmonary ACE2 pathways, thereby mediating myocardial inflammation, lung oedema, and acute respiratory failure (Hendren et al., 2020). ACE2 is widely expressed not only in the lungs but also in the cardiovascular system and, therefore, ACE2-related signalling pathways might even have a role in heart injury. Other proposed mechanisms of myocardial injury include a cytokine storm triggered by an imbalanced response by type 1 and 2 T-helper cells, strong interferon-mediated immunopathological events, and respiratory dysfunction and hypoxemia caused by COVID-19, resulting in damage to myocardial cells (Rali et al., 2020). Therapeutic use of corticosteroids, in this context, would further augment the possibility of adverse cardiovascular events. Regarding hypoxemia caused by COVID-19, it is relevant to highlight that this condition can trigger atrial fibrillation, which is the most common arrhythmia among elderly individuals, and that atrial fibrillation can become persistent even before pulmonary improvement. Furthermore, the systemic inflammatory response would make anticoagulation therapy for atrial fibrillation very complex (Atri et al., 2020).

Another essential aspect to be discussed is about chloroquine cardiovascular side effects since this is one of the promising drugs that have been tested in patients with COVID-19. It is well-reported that long-term chloroquine use may increase depolarization length duration and Purkinje fibre refractory period, ultimately leading to atrioventricular nodal and/or His system malfunction (Gevers et al., 2020).

Both chloroquine and hydroxychloroquine are accumulated in lysosomes, directly inhibiting phospholipase activity, inducing cytoplasmic inclusion body formation, increasing lysosomal pH, and causing protein inactivity (Mehra et al., 2020). Due to these properties, drug-induced atrial and VAs have been associated with their use. The most usual electrocardiographic alteration is the fascicular block, which can lead to advanced types of the atrioventricular block generally associated with syncope (Kochi et al., 2020). HCQ can also induce QT interval prolongation, an extremely rare but potentially fatal side effect, due to the risk of induced polymorphic VT and SCD. Inhibitory effects on pacemaker cells were shown to cause delayed rates in depolarization leading to decreased heart rates. These findings may correlate with a proposed mechanism by which refractory action potentials in cardiac myocytes may lead to prolongation of QT interval due to delayed depolarization and repolarization from abnormal ion currents (Cortegiani et al., 2020). QT prolongation in individual medical therapy is not always predictable, dose adjustments and/or additional monitoring with electrocardiograms may be appropriate in some cases. Hydroxychloroquine proarrhythmic risk must be monitored in patients with underlying cardiovascular or renal disorders, and high caution should be posed in the case of electrolyte imbalance, dysrhythmias or concurrent use of QTc-prolonging drugs (White et al., 2020).

PATHOPHYSIOLOGY OF SARS-COV-2 INDUCED CARDIAC INJURY

The pathophysiology underlying cardiovascular manifestations is perhaps multifactorial. Myocarditis is a presumed aetiology of cardiac dysfunction, and the development of myocarditis may relate to viral load. While isolation of the virus from myocardial tissue has been reported in a few autopsy studies, other pathological reports have described inflammatory infiltrates without myocardial evidence of SARS-CoV-2 (Lippi et al., 2020). Moreover, the finding of direct viral infection of the endothelium and associated inflammation, as reported in a patient with circulatory failure and MI, lends credence to the possibility of virus-mediated endothelial-cell damage as an underlying mechanism (Lindner et al., 2020).

Systemic inflammatory response syndrome (cytokine storm) is another putative mechanism of myocardial injury (Mehta et al., 2020). Furthermore, patients with pre-existing cardiovascular disease may have higher levels of ACE2, which would potentially predispose them to more-severe COVID-19. Furthermore, isolated right ventricular dysfunction may occur as a result of elevated pulmonary vascular pressures secondary to ARDS, pulmonary thromboembolism or potentially virus-mediated injury to vascular endothelial and smooth muscle tissue (Rotzinger et al., 2020). Other potential etiologies of myocardial damage not specific to COVID-19 include severe

ischemia or MI in patients with pre-existing coronary artery disease, stress-mediated myocardial dysfunction, tachycardia-induced cardiomyopathy, and myocardial stunning after resuscitation or prolonged hypotension. While patients with viral infections are at risk for MI in general, this risk may be exaggerated in patients with COVID-19, given reports of disproportionately increased hypercoagulability in affected people, which would lead to a possible increase in thrombotically mediated MI (Al-Kuraishy et al., 2014).

Likewise, unique the presentation of atherosclerotic plaque-rupture MI from myonecrosis due to supply-demand mismatch (type 2 MI) in the setting of severe hypoxia and hemodynamic instability and myocarditis can be interesting. This was especially evident in a recent case series of 18 patients with COVID-19 who developed ST-segment elevation on electro-cardiogram, 10 of whom were diagnosed with non-coronary myocardial injury (Al-Kuraishy et al., 2016). As well, upregulation of ACE2 by ACE inhibitors or angiotensin-receptor blockers (ARBs) is lung protective or increases susceptibility to infection with SARS-CoV-2123 has been intensely debated within the cardiovascular community. This has implications for patients with hypertension, heart failure, and/or diabetes, who are overrepresented among critically ill patients with COVID-19 (Al-Kuraishy et al., 2020g).

There is no evidence to support an association between the use of ACE inhibitors and ARBs and more-severe disease; some large studies indicate no relationship between the use of these agents and the severity of COVID-19, whereas other data suggest that they may attenuate the severity of disease (Al-Kuraishy et al., 2020h). The patient's baseline QTc interval should be obtained before the administration of any drugs that may lead to prolongation of this interval1. Diagnostic workup of myocardial dysfunction in patients with COVID-19 is challenging, given the sparing use of cardiac imaging, invasive angiography and hemodynamic assessments, and endomyocardial biopsies in consideration of the serious risk of viral infection of patients and healthcare workers and contamination of facilities (Al-Kuraishy and Al-Gareeb, 2016). Pathophysiology of SARS-CoV-2 induced cardiac injuries are summarized in Fig. 3 and 4.

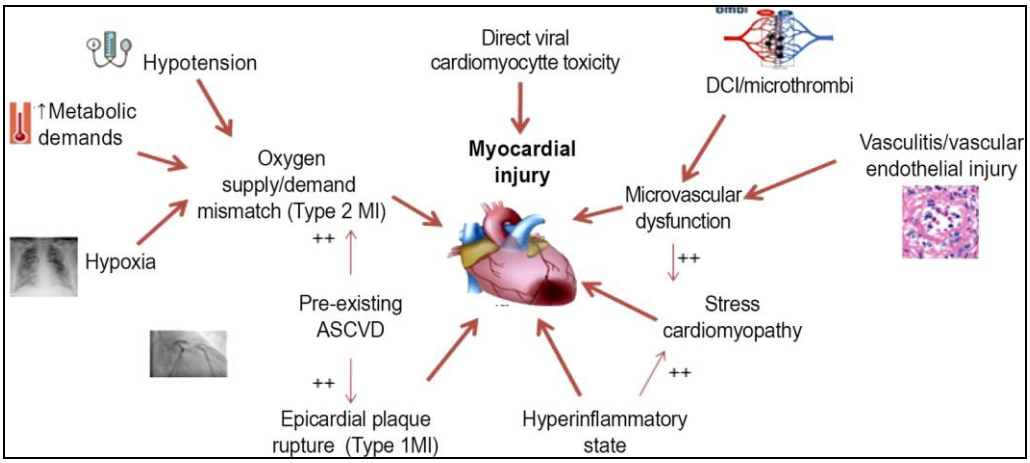

Fig. 3. SARS-CoV-2 induced-cardiac injuries

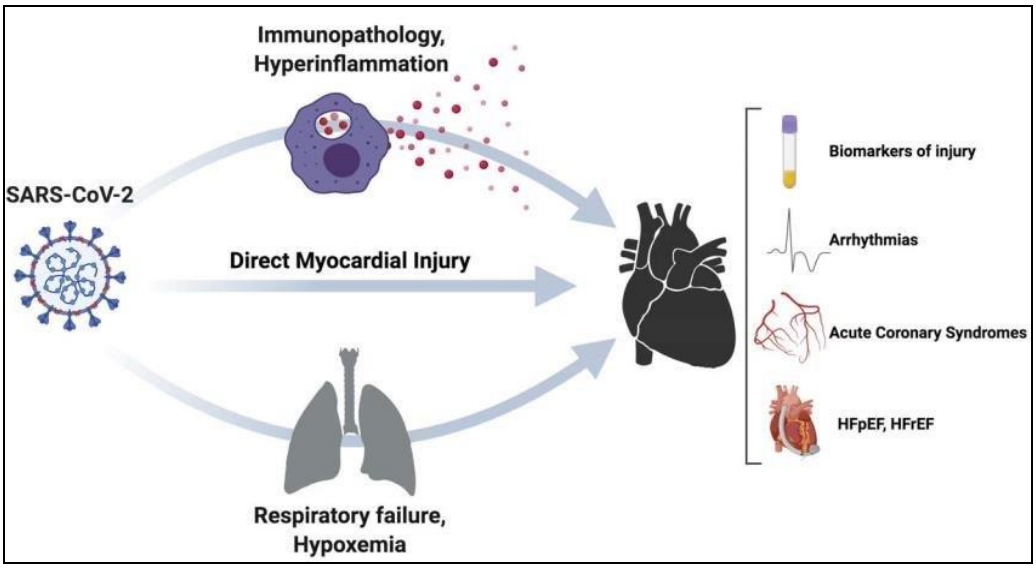

Fig. 4. Direct and indirect effects of SARS-CoV-2 on the heart

MANAGEMENT OF SARS-COV-2 INDUCED CARDIAC INJURIES

In light of the above, it is also essential to adopt a therapeutic strategy aimed at preserving and protecting cardiovascular homeostasis and avoiding cardiac damage, especially in patients with more severe COVID-19. Because of the above, cardiac complications such as cardiac ischemia, cardiac arrhythmia, heart failure or venous thromboembolism caused by COVID-19 can be treated with common pharmacological therapeutic solutions. Finding added values to current therapeutic solutions may be important to preserve and eventually treat cardiac damage from COVID-19. Specifically, an interesting therapeutic strategy could be represented hypothetically by acting on the renin-angiotensin system (RAS); in fact, a decrease in ACE-2 concentrations could decrease the probability of SARS-CoV-2 penetration into cardiac cells. In this direction, one could act with antibodies directed against ACE-2 or alternatively by decreasing the expression of ACE-2 with renin-angiotensin system modifiers (RAS), such as direct renin inhibitors (Al-Kuraishy et al., 2020i).

However, it should be considered that in the most severe stages of infection ACE-2 could play a protective role for both the respiratory and cardiac systems, In this case, the use of ACE inhibitors or AT1-r receptor blockers (ARB), which have been shown to have in vitro modifying effects on ACE-2 concentrations, may have an added value. These scenarios are the subject of scientific discussion and at the moment there is no epidemiological evidence. In addition, with the use of RAS modifying agents such as AT1-r receptor blockers (ARB), it may be increased stimulation of AT2-r receptor with antifibrotic, anti-inflammatory and vaso-dilatory properties. Besides, the vasoconstrictive, profibrotic, hyperproliferative and pro-inflammatory effects mediated by AT1r stimulation are also blocked. After ARB administration the response to hypertrophic and inflammatory growth induced by TNF-α is significantly attenuated. Other drugs that can be used to influence the fibrotic response to cardiac lesions are β-blockers, endothelin antagonists and eplerenone which were introduced as a drug that suppresses the formation of fibrosis by blocking the aldosterone pathway (Kahdim et al., 2019).

Another pharmacological hypothesis to avoid cardiac lesions is the use of neprilysin inhibitors (NEPi) such as Sacubitril. The beneficial effects of neprilysin inhibitor (NEPi) are attributable to the decrease in degradation of natriuretic peptides. Natriuretic peptides cause vasodilation by stimulating the guanylate cyclase receptor to produce cGMP. Besides, sacubitril administration is known to decrease NT-proBNP, which in severe cases COVID-19 is increased. Also, natriuretic peptides act to suppress the renin-angiotensin (RAS) and sympathetic systems and decrease endothelin secretion. Besides, natriuretic peptides also exert anti-inflammatory and antifibrotic effects. In particular, some evidence shows direct mediated anti-inflammatory effects (Al-Kuraishy et al., 2020h). The use of sacubitril especially in severe cases could be of therapeutic benefit, with cardioprotective, anti-inflammatory and antifibrotic effects. The hyperactive and generalized inflammatory state caused by COVID 19 may be responsible for the above mentioned cardiac lesions. The use of immunomodulatory agents such as IL-6 Inhibitors, or steroids in this direction may be of clinical benefit (Al-Kuraishy, 2020). Pericarditis as described above may be another complication caused by COVID-19. In this direction, the use of colchicine, a low cost drug used for many years for the treatment of diseases such as Bechet's disease, prevention and treatment of pericarditis and family Mediterranean fever, could be a valid therapeutic option. Colchicine's multiple effects with the reduction of IL-1, IL-6 and IL-18 that interfere with the NLRP3 inflammatory protein complex, a factor increasingly recognized for its role especially in recurrent idiopathic pericarditis and Mediterranean fever could be of great benefit in patients with COVID-19 (Al-Kuraishy et al., 2019).

CONCLUSION

In addition to lung damage, there may be significant cardiac involvement in patients with COVID-19, which is responsible for worsening the clinical condition of the host. The main cardiac manifestations can be oedema, pericarditis, cardiac fibrosis, myocarditis and impairment of contractile function and cardiac electrophysiology. The cardiac status of patients with ongoing SARS-CoV-2 infection or of surviving patients in convalescence period should be carefully monitored. There are many pharmacological agents' therapeutic choices available to the clinician that, if used appropriately, and within the right timeframe, can be very useful to preserve cardiac homeostasis or reduce cardiac damage and lowered COVID-19 mortality. Finally, several pharmacological scientific hypotheses are to be demonstrated and well-structured clinical studies are necessary in this direction.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATION

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