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Review Article

COVID-19 and the Cardiovascular System: A Review

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INTRODUCTION

More than 35 million cases and 1 million deaths due to coronavirus disease 2019 (COVID-19) have been reported to date, with case-fatality rates ranging from 2.3% to 7.3%.(1,2) COVID-19 is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is related to SARS-CoV-1 and Middle East Respiratory Syndrome (MERS) coronaviruses, which have both caused pandemics in the last 20 years.(3,4) Similar to SARS-CoV-1 and MERS, SARS-CoV-2 primarily affects the respiratory system. However, it has become evident that COVID-19 is a multisystem infection leading to a variety of symptoms and clinical presentations. Amongst these, COVID-19 has also been associated with a range of cardiovascular system (CVS) manifestations with its attendant morbidity and mortality. Overall, several studies have demonstrated an increased incidence of elevated cardiac troponins, myocardial injury, acute coronary syndromes (ACSs), coagulopathy and cardiac arrhythmia in patients with COVID-19. Furthermore, underlying CVS comorbidities have been found to be important in outcomes among patients infected with SARS-CoV-2. The aim of this review is to summarise the important links between COVID-19 and the CVS, highlighting currently recommended interventions to improve patient outcomes.

SARS-COV-2 BIOLOGY

SARS-CoV-1, SARS-CoV-2 and MERS are members of the *Betacoronavirus*. Genomic sequencing has demonstrated almost 80% homology with SARS-CoV-1, which has led scientists to conclude that there are many similarities in the biology of SARS-CoV-2 compared with SARS-CoV-1.(5) Both viruses use the angiotensin converting enzyme-2 (ACE2) receptor to attach and enter host cells.(6) ACE2 is highly expressed in the lung, kidneys, heart and vasculature, which appear to be the most predominantly affected organs.(7) Once the spike protein of the coronavirus binds to ACE2 on the host cell, the virus enters via membrane fusion or endocytosis (Figure 1).(8) The viral RNA is released into the host cell cytoplasm and translated into polypeptides, which are then cleaved by viral proteases into several smaller proteins, including RNA-dependent RNA polymerase, which is responsible for the replication of the viral genome. Translation of viral proteins results in the production of new viral particles, which are then released from infected cells via exocytosis. Viral particles cause pneumonia in the lungs but also affect the CVS predominantly through systemic inflammation and coagulopathy.

CARDIOVASCULAR COMORBIDITIES AND COVID-19

COVID-19 affects all age groups but seems to be more severe in older patients (over the age of 60 years) and in patients with hypertension, diabetes, obesity, chronic lung disease and underlying cardiovascular comorbidities.

Hypertension is a common disease and therefore it is difficult to determine whether or not it is an independent risk factor for COVID-19. Frequency rates of hypertension

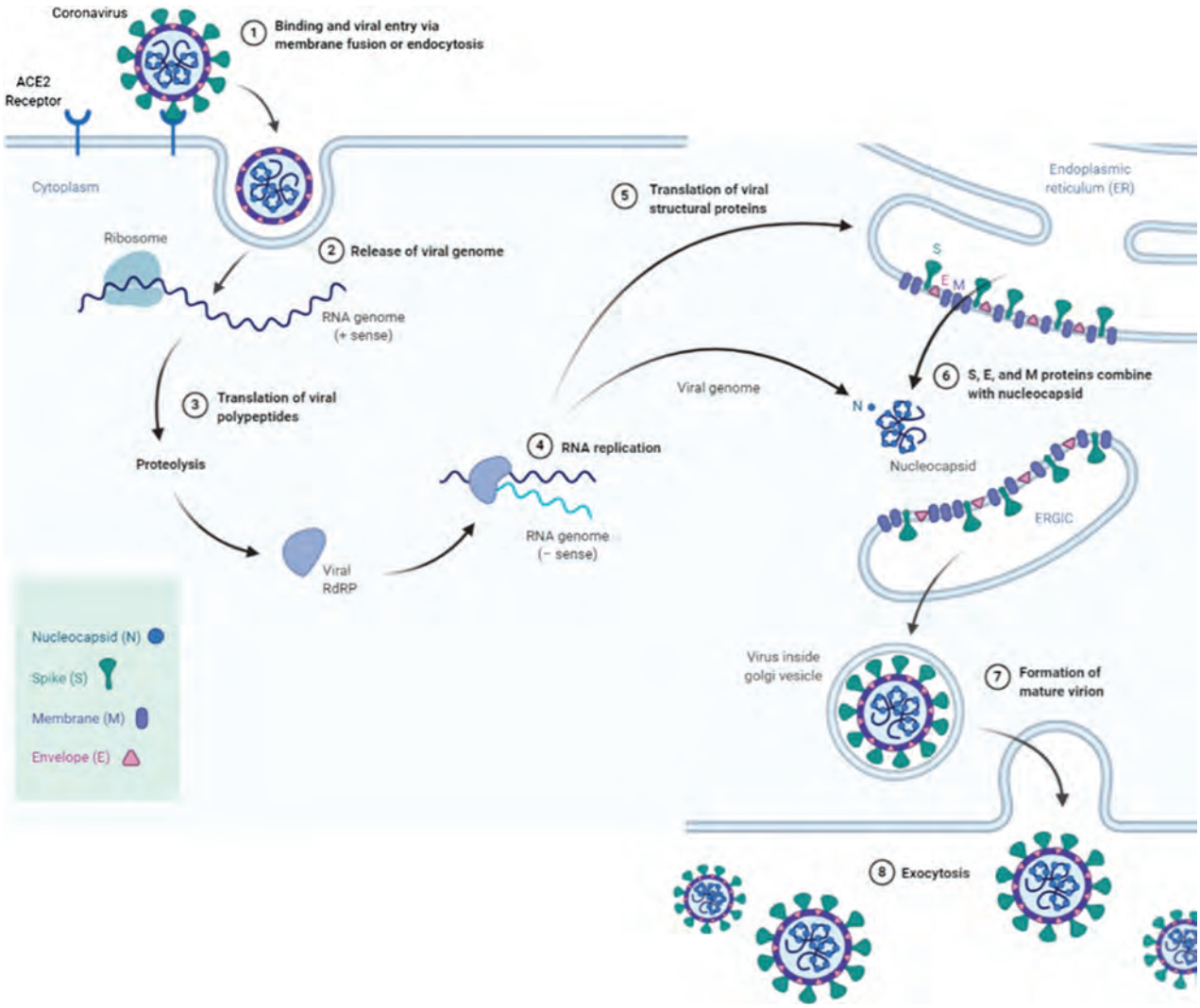

Fig 1: Life cycle of SARS-CoV-2. SARS-CoV-2 infection is triggered by binding of the spike protein to the ACE2 receptor on a host cell. Viral RNA is released from the incorporated viral complex and translated into polypeptides, which are cleaved into non-structural proteins such as RNA-dependent RNA-polymerase (RdRP). RdRP replicates viral genomic RNA. Translated structural proteins are assembled in the endoplasmic reticulum and endoplasmic reticulum-Golgi intermediate compartment (ERGIC). New viral particles are released via exocytosis. Created with BioRender.com.

in COVID-19 patients vary from 20% to 49%.(9,10) However, the national prevalence of hypertension in many countries is above 40% anyway, especially in patients older than 55 years.(11,12) Several reports from China suggested that COVID-19 disease severity was worse in patients with known hypertension compared with those without hypertension.(9,13) This is in contrast to a single-centre French study, where hypertension was not reported to be significantly associated with the progression of COVID-19 (defined by the requirement for invasive mechanical ventilation during hospitalisation).(14) Hypertension is often accompanied by other comorbidities, which may also play a role in severe COVID-19 disease. Overall, there is currently insufficient evidence to support a causal relationship between hypertension and severe COVID-19 disease.

The prevalence of diabetes in COVID-19 varies. A meta-analysis of 12 studies, including 2108 Chinese patients, reported a prevalence of 10.3%, which is similar to the known national prevalence in the general population.(15) There is data to suggest that diabetes is more common in more severe COVID disease manifestation, but similar to hypertension, multivariable adjusted analysis is lacking to link diabetes as an independent risk factor for progression to severe disease.(13,14,16)

In contrast, obesity and male sex appear to be independent risk factors for developing severe COVID-19 disease.(14,16) Being overweight was associated with an 1.84-fold increased risk of developing severe COVID-19, while obesity was reported to increase the risk of severe COVID-19 by 3.4-fold even after adjusting for other comorbidities.(16) The risk

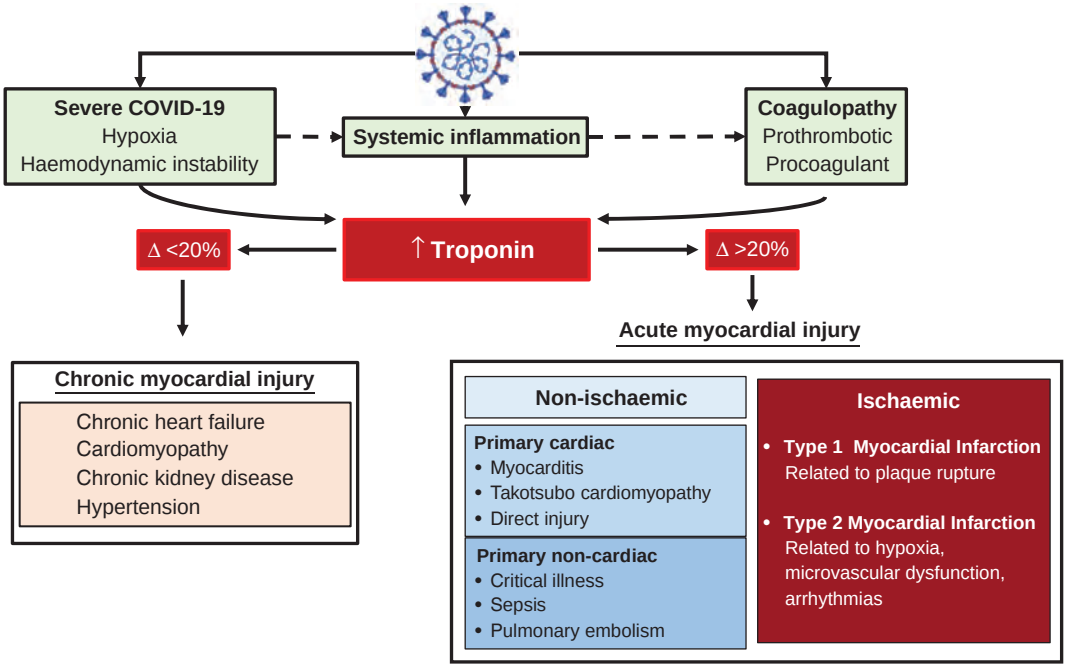

Fig 2: Myocardial injury in COVID-19. SARS-CoV-2 causes severe viral pneumonia leading to hypoxia and haemodynamic instability. This causes systemic inflammation and coagulopathy, which all contribute to an increase in cardiac troponin. Chronic myocardial injury is diagnosed when the dynamic change in troponin is <20% of baseline, whereas acute myocardial injury is diagnosed when there is a >20% dynamic change in baseline troponins. Adapted from Sandoval et al.(19)

for severe COVID-19 in obese patients may be related to decreased expiratory reserve volume and restrictive ventilation. Furthermore, obesity is associated with increased inflammation and oxidative stress, which may contribute to severe COVID-19.(17)

Despite smokers having elevated ACE2 levels, there is no conclusive data to suggest an increased susceptibility of developing COVID-19 infection.

COVID-19-MEDIATED MYOCARDIAL INJURY

Myocardial injury is diagnosed when highly sensitive cardiac troponin (hs-cTn) concentration levels rise above the 99th percentile of the upper reference limit.(18) In COVID-19-infected patients, myocardial injury may be broadly categorised into acute or chronic myocardial injury (Figure 2). Acute myocardial injury is diagnosed when the hs-cTn increases by more than 20% from baseline, and it may be further sub-divided into ischaemic and non-ischaemic aetiologies. The diagnosis of chronic myocardial injury is considered when serial cardiac troponins, repeated within 24–48 h, change by less than 20%. This form of myocardial injury is common in many COVID-19 patients because of the high prevalence of common cardiovascular comorbidities such as chronic heart failure, hypertension and chronic kidney disease.(19) Even though the rise in hs-cTn is less than 20% from baseline, these elevations are clearly indicative of myocardial injury and are associated with a worse prognosis.(20)

Mechanisms of myocardial injury in COVID-19

Despite the many reports of acute myocardial injury with COVID-19 infection, the underlying pathophysiological mechanisms remain incompletely understood. The risk of acute myocardial injury and myocardial infarction with viral or bacterial infections is well known, which has been attributed to an increased inflammatory as well as a prothrombotic state.(21,22) In patients with myocardial injury, the severe COVID-19 clinical state is characterised by an increasingly elevated hs-cTn as well as the presence of elevated markers of inflammation such as C-reactive protein, ferritin, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNFα) and markers of thrombosis such as elevated D-dimers.(19,20) These data support the relationship among myocardial injury, inflammation, heightened prothrombotic state and the severity of the COVID-19 infection.(23)

Endothelial cell activation may be a unique mechanism of COVID-19-mediated microvascular injury, thrombosis and subsequent multiorgan failure. The microvasculature has a relatively high expression of ACE2 receptors and this may explain why SARS-CoV-2 has been shown to cause endothelial cell injury, which can contribute to coronary microvascular dysfunction and resultant myocardial ischemia.(24) There has been a definite increase in the incidence of stress-induced (Takotsubo) cardiomyopathy during the COVID-19 pandemic as compared to the pre-pandemic era, for which the reasons are multifactorial.(25)

One proposed mechanism is the development of acute coronary microvascular dysfunction due to severe COVID-19.(25)

Acute non-ischaemic myocardial injury

An increasing body of literature indicates that acute non-ischaemic myocardial injury is one of the most common clinical manifestations of COVID-19.(26,27) This group of disorders may be caused by primary cardiac disorders such as myocarditis, acute heart failure related to systolic or diastolic dysfunction and stress cardiomyopathy or non-cardiac diseases such as those related to sepsis and pulmonary embolism.(19) The prevalence of non-ischaemic acute myocardial injury has been reported to range from 8% to 41%, which is most likely related to differences in in definition of hs-cTn cut-off values in different populations.(20,28,29) However, hs-cTn elevation has prognostic value, and higher levels are proportionally associated both with severe COVID-19 disease requiring intensive care unit (ICU) admission and mortality.(19,20)

COVID-19 myocarditis

Myocarditis refers to any inflammatory disease involving the myocardium, characterised by a focal myocardial inflammatory infiltrate and evidence of non-ischaemic myocardial injury.(30) Therefore, a diagnosis of COVID-19 myocarditis is considered when there is elevation of cardiac biomarkers, typical electrocardiogram abnormalities and evidence of impaired cardiac function.(30) A number of case reports have described typical features of myocarditis in patients with severe COVID-19. These cases reported on patients with marked myocardial injury accompanied by significant left ventricular dysfunction diagnosed on cardiac magnetic resonance imaging (MRI) or echocardiography.(31,32) The cardiac MRI findings included biventricular interstitial oedema, diffuse late gadolinium enhancement and circumferential pericardial effusion in keeping with acute viral myocarditis. Several autopsy studies have also investigated for evidence confirming direct SARS-CoV-2-mediated myocardial injury resulting in viral myocarditis. In one study, there was evidence of viral replication within the myocardial tissue in 5 of 39 autopsies. However, although cardiac infection with SARS-CoV-2 was found in 62% of the cases, there was no characteristic myocarditis-like inflammatory cell accumulation in the myocardium.(33)To date there is no universal consensus on the pathogenic mechanism for COVID-19-related myocarditis.(31,34,35) It is also unclear whether these patients truly had myocarditis or their symptoms were due to systemic inflammation, which has also been suggested as a plausible pathogenic cause.(35) The cross-sectional nature of many of these studies makes it difficult to confirm a direct causal link between SARS-CoV-2 and myocarditis.(36)

Acute ischaemic myocardial injury

Acute coronary syndromes

Previous studies have shown an elevated risk of acute myocardial infarction (AMI) with influenza and other viral infections. One study suggested that the incidence of AMI was six-fold higher during the week after a laboratory confirmed influenza infection.(21) Therefore, it is likely that COVID-19 infection also predisposes high-risk patients to an increased risk of AMI. Possible mechanisms include coronary plaque rupture, endothelial dysfunction, coronary spasm, microthrombi due to systemic inflammation and the presence of a prothrombotic state.(8,24,37) COVID-19-induced ACSs may present as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and stress cardiomyopathy. Interestingly, there have been fewer ACS events reported globally during the pandemic. This is possibly related to fear of the contagious disease, inappropriately higher perceived risk related to hospital admission and atypical presentations with an overlap of respiratory symptoms.(38,39) Nevertheless, there have been observational studies where STEMI was the first clinical presentation of COVID-19 supporting the hypothesis that substantial inflammation with COVID-19 can provoke an ACS event.(40)

Several guidelines for the management of the COVID-19 patient with an ACS have already been published.(41) With the availability of more rapid diagnostic tests, the European Association of Percutaneous Cardiovascular Interventions recommends further optimisation of the treatment plan for STEMI.(42) Currently, it is recommended that patients presenting to the emergency department with STEMI should be managed as potentially COVID-19 positive and all staff should use personal protective equipment (PPE). In low-risk patients and in patients where there might be a delay to primary percutaneous coronary intervention (PCI), thrombolysis can be considered. However, for the remainder, primary PCI should be the treatment of choice.(41)

Although there is benefit for early (within 24 h) coronary angiography in patients with NSTEMI, it is reasonable to extend that period until the results of a COVID-19 screening test are available. If there is a clear indication for early angiography in the appropriate high-risk patient, and there is no possibility of delay for confirmation of COVID-19 status, then balancing of the risks should be undertaken. Consideration should be given to catheterisation laboratory turnaround and disinfection time, and the availability of adequate PPE for all staff. In certain contexts, an optimal medical therapy strategy should be the preferred management for NSTEMI patients during the pandemic.

COAGULOPATHY

COVID-19-associated coagulopathy is characterised by profound inflammation with high levels of IL-1, IL-6,

TNFα and other inflammatory cytokines. Inflammation promotes thrombosis through an activation of endothelial cells, platelets, monocytes and tissue factor VIIa.(19,20) The most common haematological abnormalities associated with severe COVID-19 and coagulopathy include mild thrombocytopaenia, increased D-dimer levels, increased fibrin degradation products and increased prothrombin time. The COVID-19 coagulopathy that develops is characterised by venous and pulmonary thromboembolism, acute arterial thrombosis, myocardial infarction and disseminated intravascular coagulation.(43) These complications have been described in approximately one third of COVID-19 ICU admissions despite thromboprophylaxis,(44) and the haematological abnormalities that develop have been associated with an increased risk of ventilation, ICU admissions and death.(43) Since standard prophylactic doses may be insufficient to prevent venous thromboembolism in high-risk patients (D-dimer >3 μg/mL), full anticoagulation is recommended if there are no contraindications.(45)

COVID-19 AND HEART FAILURE

Early observational studies from China, Italy and the United States have reported acute heart failure in a significant number of patients with severe COVID-19.(28,46,47) Heart failure prevalence rates have ranged from 0.4% to 6.2% due to variations in the definition of heart failure diagnosis, the relatively small study sample sizes and the high probability for selection bias.(29,47) Similar to other cardiovascular comorbidities, acute and chronic heart failure patients have a two- to three-fold increased risk of developing severe COVID-19.(48–50) Furthermore, these patients have multiple comorbidities and tend to be of advanced age, which are all associated with a poor prognosis.

There are multiple pathophysiological mechanisms mediated by SARS-CoV-2 for the development of acute ("de novo") heart failure and these include pulmonary embolism, myocardial injury, ACS, tachyarrhythmia or stress-induced cardiomyopathy. Stable patients with chronic heart failure may also acutely decompensate due to the massive demand placed on the myocardium in critically ill patients.(48)

The clinical presentation of heart failure in COVID-19 is variable depending on prior existing cardiovascular disease and the extent of COVID-19-mediated cardiac injury. Furthermore, the heart failure clinical syndrome may be challenging to distinguish from the respiratory distress syndrome associated with SARS-CoV-2 viral pneumonia. Echocardiography is helpful to evaluate systolic and diastolic function and the natriuretic peptide levels have an excellent negative predictive value in heart failure.(51)

COVID-19 AND HEART TRANSPLANT PATIENTS

Heart transplant recipients are at a higher risk of acquiring bacterial and viral infections due to the presence of comorbidities, frequent contact with medical personnel and immunosuppression. However, it is currently uncertain whether transplant-related immunosuppression increases susceptibility to infection with SARS-CoV-2 since the anti-inflammatory effects of immunosuppression might diminish the clinical expression of COVID-19 in heart transplant recipients.(52)

The majority of published studies on the management of SARS-CoV-2 infection in heart transplant recipients are in the form of case series with no randomised trial data.(53) In the acute phase of the SARS-CoV-2 infection, immunosuppression may be reduced or withheld. During that time, close monitoring of graft function is mandatory. In-hospital management should ideally take place in a transplant facility, as a careful reintroduction of immunosuppressive therapy will be required at a later stage. A multi-centre survey conducted in Germany found a high mortality rate of 87.5% in heart transplant recipients who had a severe course of COVID-19 infection, but there were no deaths in those who had a non-severe course.(53) This underscores the importance of preventing SARS-CoV-2 infection in these patients.

ARRHYTHMIAS

Generally, viral infections lead to a higher incidence of arrhythmias. A retrospective survey of 163,831 patients with implantable defibrillators showed that more shocks were delivered during influenza months compared with other seasons, with a significant correlation between higher viral loads and implantable defibrillator therapy.(54) Although arrhythmias have frequently been reported during the COVID-19 pandemic, the actual incidence of arrhythmias still needs to be determined. It has been difficult to determine whether arrhythmias are a direct result of COVID-19 infection itself, the systemic illness or side effect of drug therapy.(55) Arrhythmias in COVID-19 can be caused by hypoxia, leading to alterations in pH and related abnormalities, but also from various other mechanisms causing cardiovascular injury such as myocardial inflammation and myocardial ischaemia.

A Chinese study of 138 patients with COVID-19 infection reported a prevalence of cardiac arrhythmias of 17%. The frequency was much higher in those admitted to ICU (44%) compared with those not requiring ICU management (6.9%).(56) In a study of evaluating atrial tachyarrhythmia in COVID-19-infected patients, of the 16.5% who developed atrial tachycardia, the majority (63%) were in atrial fibrillation.(57) Another study in 187 COVID-19 patients documented ventricular tachycardia/ventricular fibrillation (VT/VF) in 5.9% of patients, and these patients had higher troponin levels as compared with patients without VT/VF.(58) Vagal-related bradycardia due to tracheal suctioning or patient proning can also occur. These arrhythmias should be managed according to standard guidelines for the general population.

Drug–disease interactions may also be responsible for some of the reported cardiac arrhythmias. Certain drugs, which have been trialled during the pandemic, such as lopinavir–ritonavir, azithromycin and hydroxychloroquine, inhibit cytochrome p450 isoenzymes. These increase serum levels of certain antiarrhythmic agents (such as amiodarone, disopyramide, flecainide and sotalol) potentially increasing the risk for developing cardiac arrhythmias.(59) Furthermore, hydroxychloroquine and azithromycin can prolong the QT interval with the risk of developing polymorphic VT/VF. It is recommended that QT-prolonging drugs such as hydroxychloroquine and azithromycin should not be prescribed in patients with COVID-19 if the baseline-corrected QT interval is ≥500 ms. In addition, if prescribed, there should be daily monitoring of the QT interval as well as adequate monitoring of potassium, calcium and magnesium levels.(60)

RENIN ANGIOTENSIN BLOCKERS IN THE SETTING OF COVID-19

The SARS-CoV-2 virus gains entry into human hosts when its spike protein binds to the ACE2 receptor, expressed in alveolar cells in the lungs.(61) ACE2 receptors are important in maintaining homeostatic balance through the activation of Angiotensin I and II to Angiotensin 1–7, which is a powerful vasodilator through Mas receptors (Figure 3). Lack of ACE2 receptor activity promotes vasoconstriction, inflammation and fibrosis through an increased activity of AT1 receptor.

There have been suggestions that because ACE-inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) upregulate ACE2 receptor expression, they could either facilitate COVID-19 infection or contribute to increased severity of infection.(62) On the basis of this theoretical risk of RAAS inhibition, and upregulation of ACE2 receptor in COVID-19 patients, there are some clinicians who recommend discontinuing ACEI/ARB agents. However, there is no published evidence to support this belief, and currently there is no compelling evidence that withdrawal of ACEIs or ARBs prevents infection or impacts clinical outcomes.(63) The only randomised study to date on the subject (BRACE CORONA trial, NCT04364893, European Society of Cardiology Scientific Late Breaking Trials Session, 1 September 2020) showed no difference in outcome in those patients hospitalised with COVID-19 infection who were on ACEI/ARB combination versus those not on RAAS inhibitors. The BRACE CORONA trial, which was conducted in patients who had been taking an ACEI or an ARB on a long-term basis and who were subsequently hospitalised with COVID-19, showed no difference in the primary endpoint of number of days alive and out of hospital among those whose medication was suspended for 30 days and those who continued undergoing treatment with these agents. Based on current evidence, all major medical societies, including the South African Heart Association, have recommended the continuation of RAAS inhibitors in those patients already on RAAS inhibitors. Until more evidence becomes available, it is important for clinicians to treat all hypertensive patients to target based on current practice guidelines.

CONCLUSION

Cardiovascular complications related to myocardial injury are emerging as a key threat in patients with COVID-19 infection, especially in those with severe infection and those requiring intensive care treatments. The underlying pathophysiological mechanisms remain poorly understood.

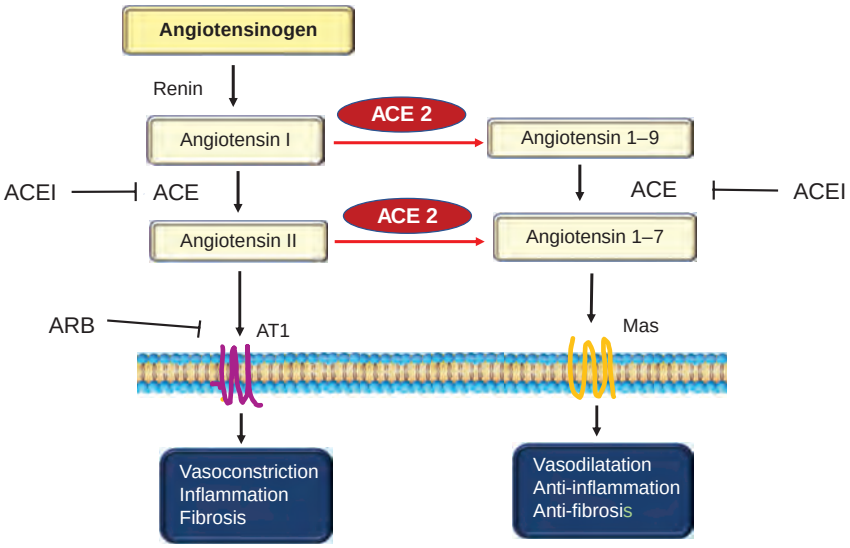

Fig 3: The renin–angiotensin–aldosterone system. With COVID-19 infection there is downregulation of the ACE2 receptor, leading to the promotion of Angiotensin II related vasoconstriction and inflammation.

It is important for physicians who manage these patients to be aware of potential cardiovascular complications and manage them appropriately. Clinical judgement together with serial monitoring of hs-cTn in patients hospitalised may aid in diagnosing myocardial injury as well in risk stratifying patients with severe COVID-19.

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