COVID-19 and heart failure

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ABSTRACT

Acute and chronic heart failure patients have a 2- to 3-fold increased risk of complicating with severe COVID-19, and these patients tend to have multiple co-morbidities which are the primary aetiologies for the heart failure clinical syndrome. Furthermore, the incidence and prevalence of heart failure increases with advanced age, and advanced age is an independent risk factor for poor prognosis and mortality. The SARS-CoV-2 infection also has multiple mechanisms that cause acute heart failure and precipitate acutely decompensated chronic heart failure. Additionally, the optimal management of these patients has been marred with the controversy around the use of the renin-angiotensin-aldosterone system blockers. This review provides an update on how heart failure patients should be managed during COVID-19 and summarises the existing evidence, focusing on heart failure.

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INTRODUCTION

On 11 March 2020, the World Health Organisation (WHO) declared the novel beta coronavirus disease 2019 (COVID-19), caused by the coronavirus SARS-CoV-2, as a global pandemic.[1] As of 1 June 2020, this pandemic has infected more than 6 million people and killed a sobering 370 000 patients globally. On the same date in South Africa, more than 31 000 had been infected, with 650 reported deaths.[2]

With no available cure or viable vaccine in sight for at least another 12 months, it is evident that all clinicians need to learn how to manage this disease optimally and to timeously share knowledge and novel therapeutic insights as they develop. Furthermore, available evidence indicates that COVID-19 is associated with increased morbidity and mortality in patients with existing cardiovascular disease and other co-morbidities.[3-5] These patients have been reported to frequently require intensive care therapies and monitoring.[6] Common co-morbidities such as hypertension, diabetes, lung disease and obesity have also been implicated.[7] Moreover, all of these are also important aetiologies for heart failure.

Heart failure is a common clinical syndrome whereby the heart is no longer able to pump an adequate cardiac output to meet the body's physiological and metabolic needs. Patients present with typical signs and symptoms such as exertional dyspnoea, pedal oedema, a raised jugular venous pressure and a third heart sound.[8] In sub-Saharan Africa, the common causes of heart failure are hypertension, ischaemic heart disease and idiopathic dilated cardiomyopathy.[9] The first two aetiologies tend to be associated with advanced age and the metabolic syndrome, of which all have been reported to confer poor outcomes in SARS-CoV-2 infected patients.[3,5,6] In this narrative review, we discuss currently available data on the pathobiology of COVID-19 and heart failure, with a focus on the clinical presentation and multidisciplinary principles of management.

THE PATHOBIOLOGY OF COVID-19 AND HEART FAILURE

The novel beta coronavirus, SARS-CoV-2, is a positive strand RNA virus belonging to the family Coronaviridae.[10] This family

of viruses has been responsible for 2 previous epidemics, the middle east respiratory syndrome (MERS) and the severe acute respiratory syndrome (SARS), which occurred in the years 2012 and 2002 - 2003 respectively.[11] Furthermore, SAR-CoV-2 has a high nucleotide sequence similarity with SARS-CoV, the virus responsible for the SARS epidemic.[10] Therefore, a fair amount of our understanding of the current virus has been extrapolated from existing data on the SARS virus.

THE ROLE OF ANGIOTENSIN CONVERTING ENZYME 2 (ACE2)

Corona viruses infect human cells through the aid of their "spike proteins" which give them their characteristic "crown"-like resemblance. These proteins interact with the transmembrane angiotensin-converting enzyme 2 (ACE 2) protein to enter type 2 alveolar epithelial cells, pericytes, macrophages and other cells in the human body expressing these membrane proteins. This step is key to the viral transmission, and it is facilitated by the cellular serine protease TMPRSS2.[12] Therefore, infection with SARS-CoV-2 requires the co-expression of ACE2 and TMPRSS2 in the same cell type. Some studies have suggested that SARS-CoV-2 has a higher affinity for ACE2 than SARS-CoV, and hypothesise that this feature explains its higher basic reproduction rate (R0 = 2 - 2.5).[13] This SARS-CoV-2 feature is key to its virulence as higher viral loads and prolonged virus shedding periods are directly proportional to COVID-19 severity and prognosis.[14]

In contrast, patients with heart failure have an initially appropriate compensatory neurohormonal response aimed at improving cardiac output to meet the body's metabolic needs. Among other actions, the neurohormonal response involves activation of the renin angiotensin aldosterone system (RAAS), which ultimately causes vasoconstriction, a raised sympathetic tone, hyperaldosteronism, cardiac hypertrophy and fibrosis.[15] As part of an endogenous negative feedback mechanism, ACE2 is naturally upregulated in patients with RAAS activation, which is seen in heart failure. In the RAAS, ACE2 mediates the conversion of angiotensin II to angiotensin I-VII, which has vasodilatory and other protective properties for the cardiovascular system.[16] Furthermore, the blockage of RAAS with the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) improves heart failure morbidity and mortality.[17-19] However, the use of these therapies is also suggested to cause an increase in the levels of ACE2.[16, 20-22]

Since heart failure and other cardiovascular conditions such as hypertension, where RAAS blockers are used, are suggested to be associated with elevated ACE2 levels, these co-morbidities have been hypothesised to facilitate increased viral transmission and poor outcomes.[16] However, there are currently no data supporting a causal relationship between ACE2 activity and the severity of COVID-19. Contrary to this hypothesis, SARS-CoV-infected animal models have been used to demonstrate the protective effects of ACE2 on the cardiovascular system. Viral spike proteins led to down-regulation of ACE2, which was associated with worse pulmonary disease in mice. These detrimental effects were attenuated by treatment with RAAS blockers.[23]

MECHANISMS OF MYOCARDIAL INJURY LEADING TO HEART FAILURE

Several publications indicate that myocardial injury is the most common cardiovascular manifestation of COVID-19. The myocardial injury typically manifests as a troponin leak above the upper reference limit, which may or may not be associated with left ventricular regional wall motion abnormalities or global hypokinesia.[3,4] Despite a relatively mild elevation of cardiac troponin, the presence of myocardial injury has been associated with a worse prognosis.[4]

Early case series of critically ill patients treated in China and the United States of America have reported a significant proportion of patients presenting with overt clinical heart failure syndrome,[24,25] and this was associated with a very high mortality rate in these cohorts, ranging from 40% - 50%.[24,25] A significant limitation of these reports is the small sample size and the high probability of selection bias. Importantly, recent larger case series from China and Italy have not reported a high incidence of heart failure.[26, 27] These differences highlight the variation in the study methodologies and the high probability of selection bias. Table I is a summary of published studies where the prevalence and outcomes of heart failure in COVID-19 patients have been reported.

Potential mechanisms for the myocardial injury, which may precipitate acute heart failure or acute decompensated chronic heart failure, include direct viral infection and the indirect injury of cardiac myocytes. The effects of SARS-CoV-2 cause direct cardiac injury mediated by ACE2 downregulation.[16,28] As discussed above, ACE2 plays a protective role in neurohormonal modulation of the cardiovascular system. Hence, when ACE2 levels are reduced, this leads to direct and indirect myocardial injury.[16]

A significant number of patients with severe COVID-19 have been reported to suffer from the systemic inflammatory response syndrome (SIRS).[5,24] This deranged immunological state is mediated by the virally triggered cytokine storm, which causes widespread organ damage and affected patients have the potential to further degenerate into multiorgan failure. This clinical state is marked by the presence of high levels of circulating pro-inflammatory cytokines associated with microvascular and endothelial dysfunction.[5,24]

TABLE I: Summary of studies reporting the prevalence of heart failure in COVID-19 patients.

Region	No. of patients	Heart failure %	Age years*	Male %	High blood pressure	Diabetes %	Authors
China	274	0.4	62 (44 - 77)	62	34	17	Chen, et al.[51]
Italy	99	21	67 ± 12	81			Inciardi, et al.[34]
Italy	6 272	5.1	66 ± 14	55	54.2	15.8	Mancia, et al.[52]
Asia, Europe, North America	8 910	2.1	49 ± 16	60	26.3	14.3	Mehra, et al.[50]
USA	12 594	6.2	49 (34 - 63)	42	34.6	18	Reynolds, et al.[53]
China	416	4.1	64 (21 - 95)	49	30.5	14.4	Shi, et al.[4]

**Median (interquartile range) or mean ± standard deviation. USA = United States of America.*

TABLE II: Cardiovascular effects of COVID-19 therapies.

Class	Drug	Side effects	Toxicities	Use with caution or avoid
Antimalarials	Chloroquine	QT interval prolongation	Heart failure, cardiomyopathy	Cardiomyopathy
	Hydroxychloroquine			
Biologics	Tocilizumab	Hypertension		
	Interferon alpha 2B		Cardiomyopathy	
Antiviral	Lopinivir Ritonivir		2nd and 3rd degree AV block	Cardiomyopathy or structural heart disease
			QT and PR interval prolongation	

Modified from Guzik, et al.[54]

The SARS-CoV-2 infection has also been implicated in causing a myocardial oxygen supply-demand mismatch. This state exists when there is an increased cardiometabolic demand caused by the systemic infection occurring simultaneously with worsening hypoxia driven by the viral acute respiratory syndrome. Ultimately, this leads to myocardial injury via a type 2 myocardial infarction mechanism.[29] The virus has also been reported to potentially destabilise atherosclerotic plaques through the deranged systemic inflammatory response and the cytokine storm.[30] Both these mechanisms of clinical and subclinical myocardial injury may be responsible for the acute deterioration of heart failure patients.

Also, COVID-19 causes coagulation abnormalities. These manifest as a disseminated intravascular coagulation (DIC) phenotype or overt pulmonary embolism.[31] These states may further complicate with microvascular dysfunction impairing myocardial perfusion or precipitate acute right heart failure from a massive pulmonary embolism.[24,32] Elevated fibrin degradation products and increased D-dimer levels are associated with these clinical scenarios and indicate a poor clinical prognosis.[24]

Myocardial injury leading to heart failure may also occur from the potential therapies for COVID-19 (Table II). Knowledge of the cardiovascular effects of these molecules has been gathered over time, where these drugs have been used as immunosuppressant therapies (chloroquine/hydroxychloroquine and tocilizumab) and Human Immunodeficiency Virus (HIV) infection therapies (lopinavir/ritonavir). Of note, the antimalarial therapies have been reported to cause heart failure in 26.8% of patients on chronic treatment.[33] Figure 1 summarises the mechanisms of myocardial injury leading to acute heart failure.

CLINICAL PROFILES

The clinical presentation of heart failure in COVID-19 infected patients may vary depending on the mechanism of cardiac injury (described above) and the presence of underlying cardiovascular disease. Due to an overlap in presenting symptoms and signs, it may be difficult to clinically distinguish between heart failure and respiratory disease in these patients. Potential clinical scenarios that may be encountered are described in Table III and include the following:

- Acute "de novo" heart failure as a result of direct (acute myocarditis) or indirect (cytokine-mediated cardiomyopathy) myocardial injury from COVID-19 infection.

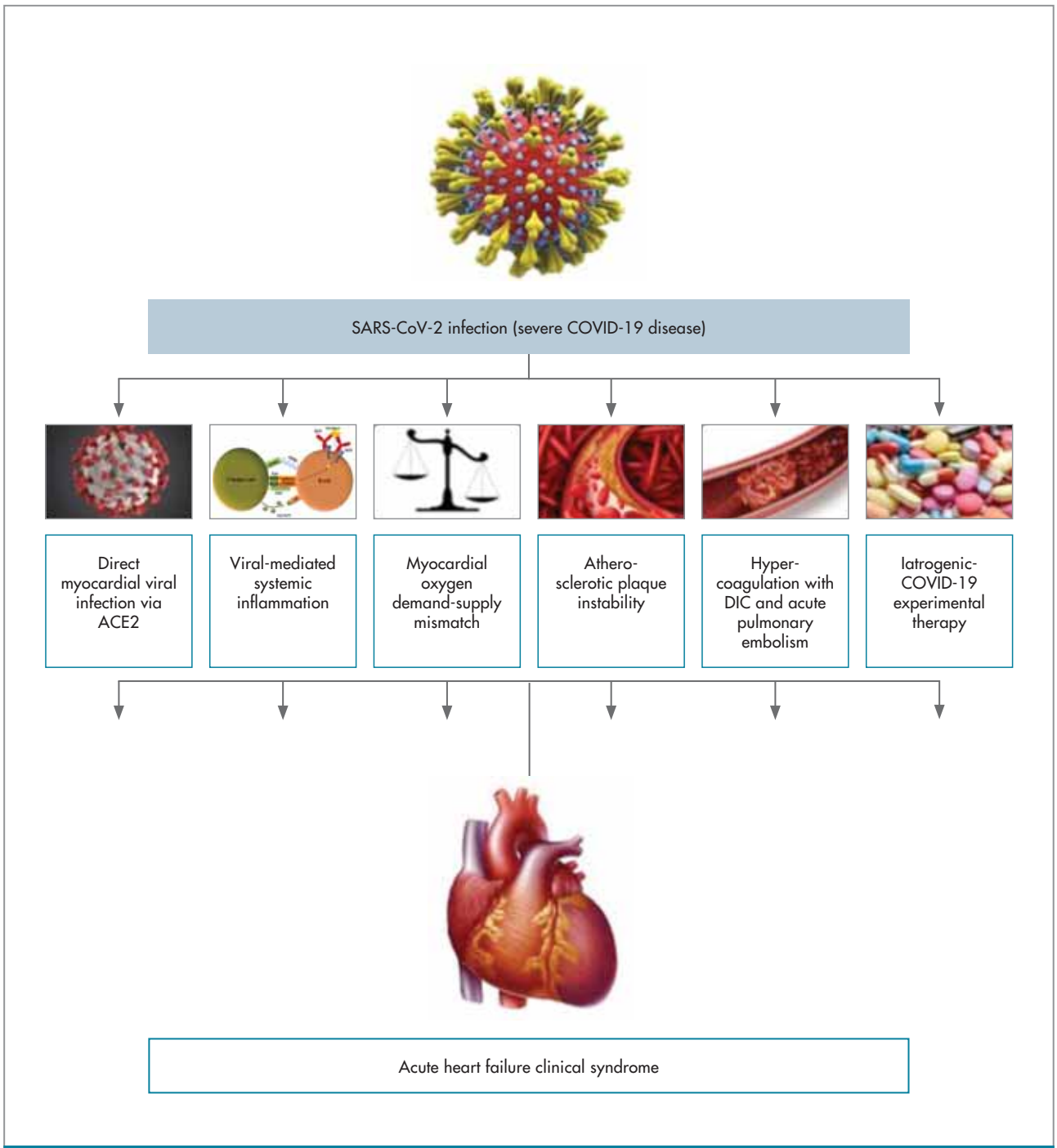

FIGURE 1: Mechanisms of myocardial injury leading to heart failure.

- Acute heart failure secondary to a cardiac event (e.g. acute coronary syndrome, stress-induced cardiomyopathy, atrial or ventricular arrhythmia) precipitated by COVID-19 infection.
- Acute decompensated chronic heart failure precipitated by COVID-19 infection, or other factors associated with COVID-19 infection (e.g. acute kidney injury), in patients with underlying structural heart disease (hypertensive heart disease with heart failure, ischaemic left ventricular dysfunction, cardiomyopathy, valvular heart disease, congenital heart disease, pericardial disease and cor-pulmonale).
- Acute right-sided heart failure secondary to pulmonary embolism in COVID-19 infected patients.

TABLE III: Clinical presentations of heart failure in COVID-19 patients.

	AHF secondary to myocardial injury from COVID-19 infection	AHF secondary to a cardiac event	Acute decompensated chronic heart failure	Right-sided heart failure secondary to acute PE	COVID-19 pneumonia in the absence of myocardial injury
Underlying pathology	Myocarditis or myopericarditis; cytokine-mediated cardiomyopathy	ACS; stress-induced cardiomyopathy; atrial/ventricular arrhythmias	Pre-existing structural and/or functional cardiac disease	Pulmonary embolism with acute right-sided heart failure	COVID-19 viral pneumonia
Clinical presentation	Acute pulmonary oedema associated with viral symptoms (± cytokine storm); fulminant heart failure ± cardiogenic shock; ± chest pain	Chest pain syndrome with AHF ± cardiogenic shock; Tachyarrhythmias may present with AHF and new onset palpitations, and/or syncope	Worsening HF symptoms such as progressive effort intolerance, orthopnea, PND and peripheral oedema; new-onset arrhythmias	Acute dyspnoea; chest pain; ± collapse with hypotension or cardiogenic shock; right-sided HF; hypoxia; absence of pulmonary oedema	Viral symptoms such as fever, cough, shortness of breath, myalgia; hypoxia
Biomarkers[55]					
Troponin	Mild-moderate troponin elevation (hs-TnT >50pg/ml); normal troponin does not exclude myocarditis	ACS - marked troponin elevation; Arrhythmias may be associated with a mild troponin leak	Mild troponin elevation; or normal troponin level	May be elevated (mild)	Troponin levels should not be elevated if renal function is normal
Natriuretic Peptides	Borderline or elevated*	Borderline or elevated*	Elevated* (Relative to baseline levels in chronic HF patients)	May be elevated*	Usually not elevated* (may be elevated in severe respiratory disease)
Chest radiograph[56-58]					
Typical features	**Acute HF**; including central, peri-hilar bilateral GGO with peripheral sparing ("batwing distribution"); interlobular septal thickening (Kerley B lines); pleural effusions; peri-bronchial cuffing	**Acute HF**; including central, peri-hilar bilateral GGO with peripheral sparing ("batwing distribution"); interlobular septal thickening (Kerley B lines); pleural effusions; peri-bronchial cuffing	**Typical features of acute HF** (central, peri-hilar bilateral GGO with peripheral sparing, interlobular septal thickening, pleural effusions, peri-bronchial cuffing); **Additional features seen in chronic HF** including upper lobe blood diversion; azygos vein distension; cardiomegaly	**Acute PE**; enlarged pulmonary artery (Fleischer sign); regional oligaemia (Westermark sign); peripherally located wedge-shaped opacity (Hampton hump); and non-specific signs including pleural effusion, elevated diaphragm, vascular redistribution; chest radiograph may be normal	**Typical:** Peripheral bilateral GGO ± consolidation; multifocal GGO with rounded morphology **Intermediate:** Absence of typical features AND the presence of: multifocal, diffuse, peri-hilar or unilateral GGO with or without consolidation
Atypical features	**Atypical features in HF:** Unilateral GGO, with or without pleural effusions; pseudotumor	**Atypical features in HF:** Unilateral GGO, with or without pleural effusions; pseudotumor	**Atypical features in HF:** Unilateral GGO, with or without pleural effusions; pseudotumor		Isolated lobar or segmental consolidation without GGO; smooth interlobular septal thickening with pleural effusions
Additional investigations					
ECG	Non-localising ST changes (typically concave in shape) and/or non-specific T wave changes	ACS - ST elevation or depression, T wave changes, Q waves; Atrial or ventricular arrhythmias	Changes in keeping with underlying cardiac diagnosis	May be normal; sinus tachycardia; ± RV strain with "S1Q3T3" pattern (McGinn-White Sign)	Not routinely indicated; ± sinus tachycardia
Additional Imaging	**Echocardiogram:** ventricular dysfunction with or without dilatation of the ventricles; ± regional wall motion abnormalities, ± pericardial effusion; **CMR** if myocarditis is suspected, demonstrating acute myocardial oedema	**Echocardiogram:** regional wall motion abnormalities, ± ventricular dysfunction; coronary angiogram to confirm obstructive CAD (performed according to ACS guidelines in COVID-19 patients)	**Echocardiogram:** structural or functional abnormality in keeping with underlying diagnosis	**CTPA** confirming pulmonary embolism; V/Q scan should only be considered if the chest radiograph is completely normal	**CT chest** may be indicated

TABLE III continued: Clinical presentations of heart failure in COVID-19 patients.

*Natriuretic peptide cut-off values for heart failure in the acute setting:				
	NT-proBNP (pg/ml)			Brain natriuretic peptide - BNP (pg/ml)
Age (years)	<50	50 - 75	>75	All ages
HF unlikely	<300	<300	<300	<100 ICU patients - BNP of <150 pg/ml; Obese patients (BMI >35kg/m^2) – BNP of <50 pg/ml; Renal failure (eGFR <60ml/min) – cut-off values for diagnosing HF need to be raised
HF possible (borderline)	300 - 450	300 - 900	300 - 1 800	100 - 400
HF likely	>450	>900	>1 800	>400

ACS = acute coronary syndrome, AHF = acute heart failure, BMI = Body Mass Index, BNP = brain natriuretic peptide, CAD = coronary artery disease, CMR = cardiovascular magnetic resonance, CT = computed tomography, CTPA = computed tomography of the pulmonary arteries, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, GGO = ground glass opacities, HF = heart failure, hs-TnT = high sensitivity troponin T, ICU = intensive care unit, PE = pulmonary embolism, RV = right ventricle, VQ = ventilation-perfusion.

PRINCIPLES FOR CLINICAL MANAGEMENT

Patients infected with COVID-19 primarily present with a respiratory disease to healthcare facilities, with a broad spectrum of respiratory symptoms which may range from a mild flu-like illness associated with fever and malaise, to a more severe acute respiratory distress syndrome associated with hypoxia.[10,34] Much of these clinical signs and symptoms overlap with those seen in the acute heart failure clinical syndrome and therefore necessitate the use of available laboratory and imaging investigations to diagnose and optimally manage evident myocardial dysfunction or overt heart failure. Currently, there are no specific treatments for COVID-19, and the backbone of hospital care is mainly supportive, and to treat any emerging complications. Patients with cardiovascular co-morbidities also require these conditions to be optimally managed to prevent acute deterioration.

INVESTIGATIONS

COVID-19 mediated myocardial injury, which may lead to acute heart failure or decompensated chronic heart failure, may be asymptomatic and is usually only detected by cardiac biomarkers. The most sensitive and readily available cardiac biomarkers are the highly sensitive cardiac troponins. These markers identify myocardial injury once the troponin levels have increased above the upper reference limit (URL).[24,35] The higher the troponin leak, the worse the clinical outcomes. This association has been especially noted in those with severe COVID-19 and those with accompanying cardiovascular co-morbidities, which has led to an increase in hospital mortality.[4,24,34-36]

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a useful cardiac biomarker to rule out heart failure when plasma levels are below the heart failure reference limit. However, this biomarker is not specific to heart failure only. Therefore, elevated NT-proBNP levels may be present in other cardiac and non-cardiac conditions (see Table IV).[37] Furthermore, cut-off levels for NT-proBNP vary according to age and gender, and caution must be taken when interpreting natriuretic peptide levels in obese patients and those in intensive care with septic shock.[38] Concerning COVID-19, a few retrospective observational studies have demonstrated an association between an elevated NT-proBNP and myocardial injury. However, an ele-

TABLE IV: Causes of elevated concentrations of natriuretic peptides.

Cardiac	Heart failure Acute coronary syndromes Myocarditis Left ventricular hypertrophy Hypertrophic or restrictive cardiomyopathy Valvular heart disease Atrial and ventricular tachyarrhythmias Heart contusion Cardioversion Implantable cardioverter defibrillator (ICD) shock Surgical procedures Congenital heart disease
Pulmonary	Pulmonary embolism Pulmonary hypertension Pneumonia Chronic obstructive pulmonary disease (COPD)
Central nervous system	Ischaemic stroke Subarachnoid haemorrhage
Metabolic and hormonal abnormalities	Thyrotoxicosis Diabetic ketosis
Other	Advanced age Anaemia Liver dysfunction (liver cirrhosis with ascites) Severe infections Sepsis Severe burns Paraneoplastic syndrome

vated NT-proBNP was not independently associated with morbidity and mortality.[4,36,39]

Another important myocardial manifestation of COVID-19 is acute fulminant myocarditis. This entity is not as common as myocardial injury; however, infected patients may present with cardiogenic shock and require intensive care therapies.[40-42] To make a definitive diagnosis one needs to perform an endomyocardial biopsy demonstrating myocardial inflammation with varying degrees of myocardial necrosis. A less invasive investigative strategy is to perform cardiac magnetic resonance imaging, which may reveal ventricular wall thickening associated with oedema.[40-42] Acute myocarditis associated with COVID-19 infection is discussed in more detail in another manuscript in this journal issue, and is beyond the scope of this paper.

Other routine heart failure clinical investigations that may add value include the electrocardiogram, which is mostly normal or has non-specific changes. Its importance is realised when unsuspected electrolyte abnormalities, prolonged QT syndromes and new-onset tachyarrhythmias are revealed. The chest X-ray is another readily available clinical test that may aid in excluding pulmonary disease and may reveal cardiomegaly and/or bilateral pleural effusions in keeping with heart failure. The transthoracic echocardiogram adds value to confirm regional wall motion abnormalities and to determine left ventricular systolic function. It is not necessary for every COVID-19 patient with respiratory symptoms to receive an echocardiogram, but this investigation should rather be reserved for cases where it may alter the management strategy. Furthermore, every precaution should be taken to prevent equipment contamination from the patient and infection of the clinical staff. Ideally, a dedicated echocardiogram machine should be reserved for those with COVID-19, in order to minimise the risk of equipment contamination.

MEDICATIONS

As a general rule, the same guideline-recommended treatment strategies for acute and chronic heart failure apply in the treatment of patients with and without COVID-19.[43] As per clinical guidelines, patients living with heart failure should ideally have an annual influenza vaccine and take every precaution to follow current recommended protective measures to prevent SARS-Cov-2 infection.[44,45] Standard protective measures aimed at preventing COVID-19 transmission include wearing a facemask in public spaces, social distancing, regular handwashing with soap and water or the use of alcohol based hand sanitisers.

Those who are in the New York Heart Association (NYHA) functional class I-II, and are ambulatory, should ideally minimise their routine hospital visits to reduce their risk of contracting the virus. Where available, the use of telemedicine may be an appropriate substitute to facilitate the follow-up and review of stable ambulatory heart failure patients. However, unstable and acutely decompensated patients should present themselves for medical review at their local health facility, as infection with SARS-CoV-2 may precipitate the acute decompensated heart failure state.

Guideline-directed medical therapy should be continued in chronic heart failure patients.[43] Foundational therapies, namely beta blockers, ACE inhibitors or ARBs, mineralocorticoid receptor antagonists, sacubitril/valsartan and recently the SGLT2 inhibitors, should all be continued and up-titrated to target dosage. As briefly discussed above, despite the controversy around the RAAS blockers, there are still no data to support the discontinuation of ACEi or ARBs. Yet some observational studies have demonstrated the protective effects of ACEi and ARBs in severe COVID-19.[46-50] Clinicians and patients must also consider that all principal heart failure therapies have compelling randomised controlled trial data showing significantly improved morbidity and mortality outcomes in heart failure with reduced ejection fraction. The use of these therapies should not be withdrawn, as this may precipitate acute decompensation.

CONCLUSION

The SARS-CoV-2 virus infection has worse outcomes in elderly patients with multiple co-morbidities. Heart failure is one of the co-morbidities with poorer outcomes and therefore the care of these patients should be optimised to minimise the risk of infection with the virus and to anticipate potential complications in those infected – to manage them timeously before deterioration. The use of ACEi and ARBs is still recommended, and all heart failure patients should be initiated, up-titrated, and continue taking these lifesaving therapies. Once patients have been diagnosed with de novo myocardial involvement, they should ideally be followed up to ensure that they do not deteriorate to overt global hypokinesia and the heart failure clinical syndrome.

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