EDITORIAL

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# Evolving concepts of myocardial phenotypes, myocardial injury, cardiovascular consequences and management in patients with SARS-CoV-2 infection

**"… forsan et haec olim meminisse iuvabit**
**[… and perhaps it will be pleasing to have remembered these things one day]"**
**Virgil, Eclogues. Georgics. Aeneid: Books 1 - 6**

The COVID-19 pandemic is undoubtedly the greatest public health crisis, the most crucial global health calamity of the century, and the most profound biopsychosocial dilemma for humankind since the Second World War. In December 2019, a novel coronavirus strain causing an interstitial pneumonia and acute respiratory distress syndrome (ARDS) emerged from Wuhan, Hubei Province, China; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for occurrence of this disease. The World Health Organization named the clinical syndrome caused by SARS-CoV-2 the coronavirus disease 2019 (COVID-19).[1]

To date, in its first 9 months, SARS-CoV-2 has caused inestimable devastation in all countries and has accounted for over a million deaths. Aided by ease of international travel, it has rapidly spread around the world, posing enormous health, economic, environmental and social devastation to the global human population. In its first year, almost all nations are struggling to slow down the transmission of the disease, despite public health interventions like hand hygiene, physical distancing, screening, testing and treating infected patients, quarantining suspected persons through contact tracing, restricting large gatherings, and maintaining complete or partial national lock-down. Of interest, African countries seem to have much lower mortality rates compared to their American and European counterparts.[2]

While the pneumocyte is the primary site of infection for SARS-CoV-2, where it causes characteristic pneumonia, ARDS and diffuse alveolar damage, there are multiple extra-pulmonary

sites of infection. The heart has emerged as an important target for infection, with evidence of viral replication within the cardiomyocytes, cardiac fibroblasts, interstitial and endothelial cells.[3,4]

Our understanding of cardiovascular risk and the consequences of COVID-19 is evolving continuously. There is clearly a bidirectional interaction between COVID-19 and cardiovascular disease (CVD) – Figure 1. Underlying cardiometabolic risk factors and comorbidities like hypertension, diabetes, heart failure and coronary artery disease increase both susceptibility to COVID-19 as well as disease severity and mortality in those with COVID-19.[5-8] Commonly used cardioprotective agents, particularly inhibitors of the renin-angiotensin-aldosterone system (RAAS), reduce susceptibility, disease severity and mortality in COVID-19.[9,10] Either through direct viral cytopathic effects, endothelial shedding, or systemic inflammation and immune-related injury, COVID-19 promotes development of chronic myocardial injury, acute non-ischaemic myocardial injury, acute myocardial infarction, arrhythmia, pulmonary embolism, Takotsubo, *de novo* heart failure, hypertension and myocarditis.[9-11] In addition, putative therapies for COVID-19 cause acute cardiotoxicity resulting in QT prolongation, drug-induced myocarditis, and activation of channelopathies.[12] Furthermore, there is a growing link between COVID-19 and a Kawasaki disease-like syndrome in children.[13]

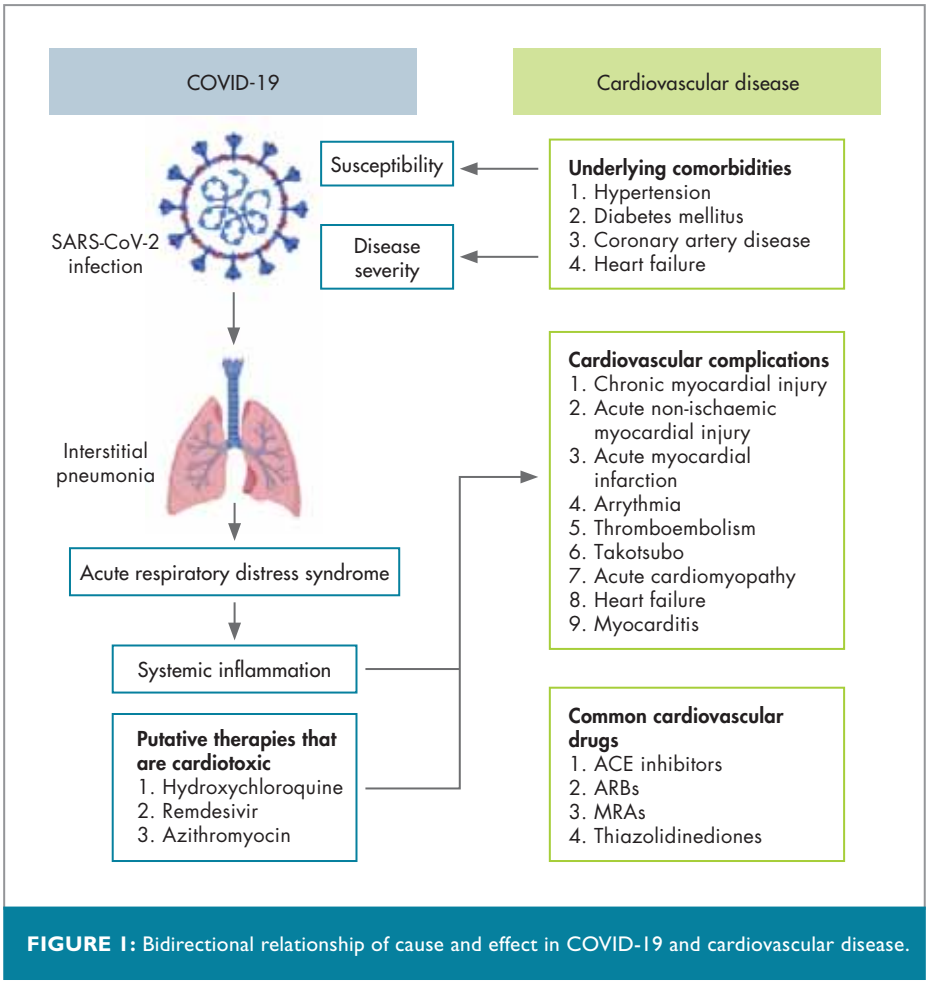


**FIGURE 1:** Bidirectional relationship of cause and effect in COVID-19 and cardiovascular disease.

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Our rapidly evolving comprehension of the pathophysiology of cardiovascular injury in COVID-19 warrants consideration – Figure 2. There is evidence that drivers of oxygen supply/demand mismatch – hypotension, increased metabolic demands, arrhythmia, hypoxia and new-onset hypertension – play a central role in ischaemic myocardial injury.[1,2,14] Direct viral cardiomyocyte toxicity is supported by autopsy studies.[2,15] The cytokine storm, microangiopathy, hypercoagulability, vascular dysfunction and the complex interaction of dysregulated host immune response with pre-existing CVD, epicardial coronary plaque rupture and Takotsubo are important mechanisms of myocardial injury and are reported in the literature.[16-20]

There remain many knowledge gaps in our understanding of the relationship between COVID-19 and CVD – Table 1. First, determinants of CVD severity in COVID-19 are poorly understood. Second, the factors influencing individual variability in phenotype and outcome are unknown. Third, mechanisms by which CVD worsens prognosis in COVID-19 are unclear. Fourth, the exact contribution of the angiotensin converting enzyme receptor 2 in SARS-CoV-2 biology, disease severity and prognosis is incompletely understood. Fifth, the long-term effects of COVID-19 on cardiovascular health are unknown.[6] These and many other important questions remain the subject of ongoing scientific enquiry.

Therefore, we thought it timely to provide a review of these and many other questions and important topics related to COVID-19 and cardiovascular health. We have invited cardiovascular experts from South Africa and beyond to contribute articles to this issue of the Journal. We feature an Opinion Statement from SA Heart® on COVID-19.[21] Delport and colleagues report on a reduced number of patients with acute coronary syndrome presentations in South Africa during the initial COVID-19 surge.[22] This special issue of the Journal is notable for 13 comprehensive reviews providing updated evidence on thrombosis and COVID-19,[23] radiological manifestations of COVID-19,[24] COVID-19 and psychological stress impacting on cardiovascular disease,[25] COVID-19 and pregnancy,[26] COVID-19 and interventional cardiology,[27] COVID-19 and cardiovascular imaging,[28] and COVID-19 and heart failure.[29] In addition, the role of high-flow nasal oxygen in the management of COVID-19,[30] COVID-19 and myocardial injury,[31] COVID-19 and paediatric cardiology,[32] COVID-19 and cardiothoracic surgery,[33] COVID-19 and RAAS inhibitors,[34] and COVID-19 and arrhythmias[35] are considered in this issue of the Journal.

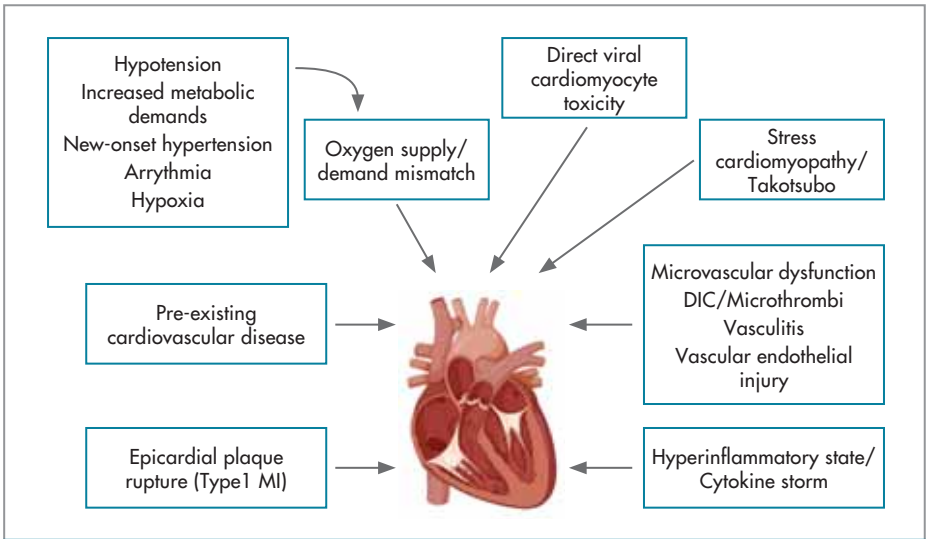


**FIGURE 2:** Putative pathophysiology of cardiovascular disease and myocardial injury in COVID-19.

**TABLE I:** Important knowledge gaps in COVID-19 and cardiovascular disease.

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|---|
| Determinants of CVD severity in COVID-19 are poorly understood. |
| Factors influencing individual variability in phenotype and outcome are unknown. |
| Mechanisms by which CVD worsens prognosis in COVID-19 are unclear. |
| Exact contribution of ACE2 in SARS-CoV-2 biology, disease severity and prognosis are incompletely understood. |
| Long-term effects of COVID-19 on cardiovascular health are unknown. |
| Pathways by which COVID-19 exacerbates CVD are not delineated. |
| Randomised evidence on efficacy of RAAS inhibition in prevention and improving outcomes in COVID-19 are awaited. |
| Therapeutic agents for definitive prevention and management of COVID-19 are not fully clarified. |
| Role of prior immunity for protecting from future cardiovascular complications with subsequent exposure are unknown. |
| Determinants of clinical and immunological response are unknown. |

There are many lessons for humanity in the current pandemic, and many that will be gleaned by posterity. Indeed, there will be many more infectious disease outbreaks in the future. As Virgil reminds us, perhaps sometime in the future, it may be important to remember the important learnings from COVID-19. Similarly, the 1918 influenza pandemic was the most severe pandemic in global history before COVID-19. Lasting from February 1918 - April 1920, it infected over 500 million people, a third of the world's population then, and killed over 50 million people in 4 successive waves. Consequently, tenets of outbreak preparedness were developed after the 1918 influenza pandemic. In addition, important steps were taken towards global cooperation in health with the formation of the United Nations (UN) and the World Bank Group in 1945, following the Second World War. In 1948, UN member states formed the World Health Organization, which has played a central role in coordinating the global response to the current crisis.

There is always opportunity in crisis. Human resilience and ingenuity have been evident in local and national responses to the pandemic. There have been wonderful examples of global solidarity and collaboration, most notably in science. While South Africa is past its first peak, many countries are finding themselves amid a second, and yet others have already weathered the latter. It is now accepted that this virus is here to stay for the foreseeable future, and while we mourn the loved ones lost to COVID-19, we should not lose sight of the many opportunities arising from this crisis. One such opportunity is the sheer incomprehensible amount of new knowledge that has been accumulated in such a short period of time. At the time of writing, there are just under 60 thousand publications on the subject of COVID-19 on PubMed, and nearly 3 thousand when adding the word "cardiac" to the search, all accessible free of charge, indicating that once again the world is moving a step closer together to join forces in fighting a pandemic that threatens the lives and livelihoods of the global population.

This issue of SA Heart® reads like an executive summary of the current knowledge on cardiac involvement with COVID-19, and it is our hope that general practitioners, physicians and cardiologists will find the contents to be of interest.

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## REFERENCES


1. Ntusi NAB. COVID-19 and cardiovascular disease. S Afr Heart J 2020; 17:10-13.
2. Chakafana G, Mutithu D, Hoevelmann J, et al. Interplay of COVID-19 and cardiovascular diseases in Africa: An observational snapshot. Clin Res Cardiol 2020; Epub ahead of print. doi: 10.1007/s00392-020-01720-y.
3. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020;116:1666-1687.
4. Lindner D, Fitzek A, Bräuninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19: Autopsy cases. JAMA Cardiol 2020; Epub ahead of print. doi:10.1001/jamacardio.2020.3551.
5. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811-818
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-1062.
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
8. Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19. Circulation 2020;141:1930-1936.
9. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. Circulation 2020;141:1648-1655.
10. Siripanthong B, Nazarian S, Muser D, et al. Recognising COVID-19 related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020;17:1463-1471.
11. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259-260.
12. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science 2020;3 68:489-493.
13. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;1607-1608.
14. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol 2020;75:2352-2371.
15. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:819-824.
16. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection – a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect 2020;0:1-14.
17. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 2600(20):19-21.
18. Babapoor-Farrokhran S, Gill D, Walker J, et al. Myocardial injury and COVID-19. Possible mechanisms. Life Sci 2020;253:117723.
19. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-848.
20. Bonow RO, Fonarow GC, O'Gara PT, et al. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol 2020;5:751-753.
21. Jankelow D, Manga P, Ntsekhe M, Khan S, Blanche Cupido B, Ntsinjana H, et al. COVID-19 and cardiovascular disease. S Afr Heart J 2020;3:258-262.
22. Delport R, Vachiat A, Snyders A, Kettles D, Weich H. Decline in acute coronary syndrome hospitalisation rates during COVID-19 lockdown in private hospitals in South Africa. S Afr Heart J 2020;3:264-265.
23. Wessels P. Hypercoagulability in COVID-19. S Afr Heart J 2020;3:266-274.
24. Said-Hartley Q, Moosa S. Radiology of COVID-19 pneumonia. S Afr Heart J 2020;3:276-281.
25. Bana T, Hoare J, Letuka P, Ntusi NAB. COVID-19 and impact of psychological stress on cardiovascular disease. S Afr Heart J 2020;3:282-286.
26. Herrey AS, Osman A, Soma-Pillay P, Sliwa K, Ntusi NAB. COVID-19 and the cardiovascular system in pregnancy. S Afr Heart J 2020;3:288-295.
27. Weich H, Hitzeroth J, Khan S, Kettles D, Vachiat A, Ntsekhe M. Interventional cardiology during the COVID-19 epidemic. S Afr Heart J 2020;3:296-304.
28. Meel R, Cupido B, Pecoraro A, Doubell A, Lubbe W, Ntusi NAB. COVID-19 and cardiovascular imaging: A guide for the practising clinician. S Afr Heart J 2020;3:306-312.
29. Tsabedze T, Kraus S, Hitzeroth J, Ntsekhe M, Mpe M, Makotoko M. COVID-19 and heart failure. S Afr Heart J 2020;3:314-322.
30. Smit FE, Oelofse AN, Linegar AL, Hanekom HA, Botes L, Turton EW. Supplemental oxygen therapy in COVID-19. S Afr Heart J 2020;3:324-328.
31. Herrey AS, Mohiddin SA, Letuka P, Ntusi NAB. COVID-19 and myocardial injury. S Afr Heart J 2020;3:330-337.
32. Zühlke L, Brown S, Cilliers A, Hoosen E, Lawrenson J, Ntsinjana H. Direct and indirect effects of the COVID-19 pandemic on children with cardiovascular disease. S Afr Heart J 2020;3:338-345.
33. Reddy D, Kleinloog R, Janson J, Manganyi R, Brink J, Zilla P. COVID-19 and cardiothoracic surgery: A risk-adjusted approach in the context of a global pandemic. S Afr Heart J 2020;3:346-350.
34. Valera P, Letuka P, Mathenjwa N, Ntusi NAB. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists and SARS-CoV-2 infection. S Afr Heart J 2020;3:352-361.
35. Chin A, Moses J, Thornton A. Arrhythmias and COVID-19 infection. S Afr Heart J 2020;3:362-369.