SPECIAL FEATURE REVIEW

Cardiovascular disease in SARS-CoV-2 infection

Kei Sato^{1,2}, Jane E Sinclair³, Habib Sadeghirad⁴, John F Fraser^{1,2}, Kirsty R Short^{3,5†} & Arutha Kulasinghe^{2,6†}

¹Critical Care Research Group, The Prince Charles Hospital, Brisbane, QLD, Australia

²Faculty of Medicine, University of Queensland, Saint Lucia, QLD, Australia

³School of Chemistry and Molecular Biosciences, The University of Queensland, Saint Lucia, QLD, Australia

⁴Centre for Genomics and Personalised Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia

⁵Australian Infectious Diseases Research Centre, The University of Queensland, Saint Lucia, QLD, Australia

⁶The University of Queensland Diamantina Institute, The University of Queensland, Brisbane, QLD, Australia

Correspondence

A Kulasinghe, The University of Queensland
Diamantina Institute, Translational Research
Institute, The University of Queensland,
37 Kent Street, Woolloongabba,
QLD 4102, Australia.
E-mail: arutha.kulasinghe@uq.edu.au

†Co-senior authors.

Received 14 June 2021;
Revised 21 August 2021;
Accepted 23 August 2021

doi: 10.1002/cti2.1343

Clinical & Translational Immunology
2021; 10: e1343

Abstract

Pre-existing cardiovascular disease (CVD) increases the morbidity and mortality of COVID-19 and is strongly associated with poor disease outcomes. However, SARS-CoV-2 infection can also trigger *de novo* acute and chronic cardiovascular disease. Acute cardiac complications include arrhythmia, myocarditis and heart failure, which are significantly associated with higher in-hospital mortality. The possible mechanisms by which SARS-CoV-2 causes this acute cardiac disease include direct damage caused by viral invasion of cardiomyocytes as well as indirect damage through systemic inflammation. The long-term cardiac complications associated with COVID-19 are incompletely characterised and thought to include hypertension, arrhythmia, coronary atherosclerosis and heart failure. Although some cardiac-related symptoms can last over 6 months, the effect of these complications on long-term patient health remains unclear. The risk factors associated with long-term cardiovascular disease remain poorly defined. Determining which patients are most at-risk of long-term cardiovascular disease is vital so that targeted follow-up and patient care can be provided. The aim of this review was to summarise the current evidence of the acute and long-term cardiovascular consequences of SARS-CoV-2 infection and the mechanisms by which SARS-CoV-2 may cause cardiovascular disease.

Keywords: cardiovascular disease, COVID-19, SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 and has caused the ongoing coronavirus disease 2019 (COVID-19) pandemic, infecting > 170 million people worldwide. SARS-CoV-2 causes a broad range of respiratory symptoms, ranging from

subclinical disease to viral pneumonia.¹ Despite the recent availability of vaccines, approximately 500 000 individuals are still infected daily with SARS-CoV-2. It is increasingly apparent that like other severe respiratory virus infections, SARS-CoV-2 causes a variety of extra-respiratory complications.^{1,2} Specifically, SARS-CoV-2 infection has been associated with acute myocardial injury,

myocarditis, arrhythmias, venous thromboembolism and other *de novo* cardiovascular complications.^{3–7} There is also now a growing body of evidence of increased cardiovascular disease in convalescent COVID-19 patients.⁸ Here, we review the current evidence of the acute and long-term cardiovascular consequences of SARS-CoV-2 infection and the mechanisms by which it may cause cardiovascular disease.

SARS-CoV-2 pathogenesis

The primary cellular receptor for SARS-CoV-2 is the membrane-bound aminopeptidase angiotensin-converting enzyme-2 (ACE-2). In addition to binding to ACE-2, the spike protein of SARS-CoV-2 must be cleaved at the S1/S2 boundary.⁹ This cleavage can be effected by host cell surface proteases, transmembrane protease, serine 2 (TMPRSS2) and endosomal cysteine proteases cathepsin B/L, which then primes the SARS-CoV-2 spike protein for entry.¹⁰ Additional cleavage by furin produces a sequence motif that binds to cell surface neuropilin-1, which enhances SARS-CoV-2 infection *in vitro*.¹¹ *In vivo* SARS-CoV-2 primarily targets epithelial cells within the respiratory tract, including type 2 pneumocytes in the lower respiratory tract. Whilst initial studies suggested that SARS-CoV-2 could also infect endothelial cells,¹² this has recently been called into question.¹³ Central to the pathogenesis of SARS-CoV-2 infection is the induction of a dysregulated pro-inflammatory response referred to as a cytokine storm. It is thought that this cytokine storm, and associated immunopathology, plays a significant role in both primary viral pneumonia and acute respiratory distress syndrome that is characteristic of severe COVID-19.¹⁴

Cardiovascular disease in acute COVID-19

The prevalence of myocardial injury and cardiovascular disease in the acute phase of COVID-19 varies dramatically between studies. This likely reflects the differing cardiovascular complications of SARS-CoV-2 infection, as well as hospital and laboratory facilities available across different countries.

Myocardial injury is defined as electrocardiogram abnormalities or an increase in cardiac enzyme and biomarker serum levels, such as troponin (cTnT), induced by ischaemia or non-

ischaemic causes.¹⁵ Myocardial injury, as defined by elevated cTnT, is found in 19.7–27.8% of COVID-19 patients requiring hospital admission.⁴ Abnormal findings in echocardiography are also found with 55% of COVID-19 patients during their initial hospital admission, including 39% of left ventricle (LV) and 33% of right ventricle (RV) abnormalities.¹⁶ In contrast, data from China suggest that approximately 7% of patients infected with SARS-CoV-2 develop cardiac injury, defined as elevated high-sensitivity cardiac troponin I or new echocardiographic, ECG abnormalities.¹⁷ This prevalence increases to 25% in those hospitalised with COVID-19¹⁸ and 22% in patients who required ICU admission.¹⁷ Following these myocardial injuries, various cardiac complications, such as cardiac arrhythmias, heart failure and myocarditis, may follow.

Cardiac arrhythmias are abnormal heartbeat rhythms that can manifest as tachycardia (an abnormally fast heartbeat), bradycardia (an abnormally slow heartbeat) or irregular heartbeat.¹⁹ Heart palpitations were the most common presenting symptom of arrhythmias in COVID-19 patients who did not have a fever or cough.²⁰ In a study of 137 patients infected with SARS-CoV-2, heart palpitations were reported in 10 (7.3%) cases.²¹ Amongst 138 hospitalised COVID-19 patients, cardiac arrhythmias were seen in 16.7% of all patients and were more prevalent in ICU admitted cases.¹⁷ In a study of 85 fatal cases with COVID-19, cardiac arrhythmias were found in 51 (60%) cases.²² Life-threatening arrhythmias were also reported in 11 (5.9%) of 187 COVID-19 patients.⁴

Myocarditis is a complication of COVID-19 that refers to inflammation of the heart muscle.²³ Segmental wall motion abnormalities or a reduced LV ejection fraction has been reported, although it is not specific for COVID-19, and also found in acute coronary syndrome. Amongst 68 fatal COVID-19 cases, 5 patients (7%) with myocarditis and circulatory failure were identified, whilst 22 patients (33%) had myocarditis and respiratory failure.²⁴ A systematic review of 14 cases of COVID-19-related myocarditis included 58% of male with the median age of 50.4 years and showed that the most prevalent comorbidity associated with myocarditis was hypertension (33%).²⁵ ECG findings varied from case to case, but troponin elevation was seen in 91% of cases. Of the patients who underwent echocardiography, 60% had a reduced ejection fraction. The overall

survival rate was 81%, and survival rate in those who received steroids was 85%.

Heart failure is a condition where cardiac output is insufficient to meet the oxygen demand for the body. Heart failure can be caused by SARS-CoV-2 as a result of acute coronary syndrome (following plaque rupture) or the mismatch between oxygen supply and demand because of hypoxic respiratory failure or viral cardiomyopathy.²⁶ This complication is characterised by an increase in serum NT-proBNP and a decrease in left ventricular ejection fraction.²⁷ In a study of 799 patients with COVID-19, heart failure was reported in 24% of all patients and in 49% of those who died.²² Amongst 191 COVID-19 patients, heart failure affected 23% of all patients and 52% of those who died.²⁸

Clinical consequences of cardiovascular disease in acute COVID-19

For the most part, the acute onset of cardiovascular injury because of COVID-19 is associated with a poor overall prognosis.^{17,18} For example, COVID-19 patients with cardiac injury had a higher mortality than those without cardiac injury during hospitalisation: 51.2% vs. 4.5%²⁹ or 59.6% vs. 8.9% respectively.⁴ Similarly, elevated cardiac biomarkers were associated with a poor COVID-19 prognosis. Amongst 41 COVID-19 patients, 5 (12%) had acute cardiac injury, of whom 4 were admitted to the intensive care unit (ICU).⁵ A study of 138 hospitalised patients infected with SARS-CoV-2 found cardiac injury in 10 patients (7.2%), almost all of whom required ICU care.¹⁷ A study of 191 COVID-19 patients reported that 33 (17%) cases developed acute myocardial injury, of which 32 patients died.²⁸ In another cohort of 416 COVID-19 patients, cardiac injury occurred in 19.7% of patients during hospitalisation, and cardiac injury was identified as an independent risk factor for in-hospital mortality.²⁹ These findings suggest that acute myocardial injury could be associated with severity and mortality for in-hospital COVID-19 patients.

At present, no specific treatment is available for COVID-19-induced cardiovascular disease. However, in the early stages of the COVID-19 pandemic there was significant concern that the use of ACE inhibitors (ACEi) and angiotensin

receptor blockers (ARB) for either *de novo* or pre-existing cardiovascular disease would increase COVID-19 severity. This was based on the suggestion that ACEi/ARB can increase the level of ACE-2 and thereby facilitate increased SARS-CoV-2 replication. However, when limited to a hypertensive subgroup, a recent meta-analysis showed a significant association between renin-angiotensin-aldosterone system (RAAS) inhibition and *reduced* risk of death.³⁰ This most likely reflects the vasodilation and anti-inflammatory effects associated with increased ACE-2 expression, which acts to counterbalance the renin-angiotensin system by degrading angiotensin II.^{31,32} However, this mechanism of action remains speculative and the exact role of RAAS inhibition in the pathogenesis of SARS-CoV-2 remains to be defined.

Mechanisms of cardiovascular disease in acute COVID-19

During acute COVID-19, cardiovascular disease may arise as the direct consequence of viral infection or as an indirect result of inflammation and respiratory distress (Figure 1). In terms of direct viral infection, *in vitro* studies have shown that SARS-CoV-2 can efficiently infect and replicate in human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) by binding to ACE-2.^{33–36} In contrast, human pluripotent stem cell-derived smooth muscle cells are refractory to infection.³⁴ SARS-CoV-2 infection of hPSC-CMs results in cessation of beating,³³ cell death,^{34,36} impaired electrophysiological function,³⁴ transcriptional and morphological signatures of damage³⁵ and impaired contractile function,^{34,36} all of which may contribute to cardiovascular disease *in vivo*. However, the *in vivo* evidence of SARS-CoV-2 infection in the heart remains equivocal. In autopsy and endomyocardial biopsy specimens from 4 COVID-19 patients, viral protein was detected by immunostaining in cardiomyocytes but not cardiac macrophages, fibroblasts or endothelial cells.³⁶ Similarly, in autopsies of 39 patients with COVID-19, SARS-CoV-2 RNA was detected in the myocardium of 24 patients, whilst negative sense RNA (indicative of active viral replication) was only detected in the myocardium of the 5 patients with the highest virus load.³⁷ An autopsy study of a further 41 patients showed that whilst SARS-CoV-2 RNA

could be detected in the hearts of a large number of patients ($n = 30$), SARS-CoV-2⁺ cells in the myocardium were rare.³⁸ In contrast to these findings, amongst autopsy specimens from five COVID-19 patients no viral antigens could be detected in the heart, although all patients displayed severe myofibrillar anomalies.³⁵ Similarly, in 8 COVID-19 autopsies SARS-CoV-2 could not be detected in the heart of any patient by *in situ* hybridisation, immunohistochemistry or qRT-PCR.³⁹ Therefore, the contribution of direct

viral infection of cardiomyocytes to *in vivo* pathogenesis remains unclear.

When considering the consequences of direct viral infection of the heart, it is important to recognise that the cellular receptor for SARS-CoV-2, ACE-2, plays an integral role in the renin-angiotensin system (RAS). In the RAS signalling pathway, ACE and ACE-2 play opposing roles. On the one hand, ACE converts Ang I to Ang II in order to induce vasoconstrictive, pro-oxidative and pro-inflammatory effects.^{31,32,40} On the other hand,

Figure 1. Schematic representation of the putative mechanisms by which SARS-CoV-2 causes cardiovascular disease. SARS-CoV-2 binds to ACE-2 in myocardium (1) to enter the target cell. This causes downregulation of ACE-2, which converts vasoconstricting/inflammatory angiotensin II into vasodilating/anti-inflammatory protein angiotensin 1–7. The concentration of angiotensin 1–7 decreases and that of angiotensin II increases, contributing to reduced coronary artery flow, myocardial ischaemia (2) and inflammation. Increased angiotensin II also cause vasoconstriction at the alveolar-capillary bed, leading specific increased strain on a right heart that is already struggling because of the hypoxic pulmonary vasoconstriction and micro vascular thromboses.⁵² Cell injury such as myocardial fibrosis (3) and apoptosis (4) is caused by both direct viral involvement and systemic inflammation from an imbalance of T helper 1 and 2 responses, denoted by elevated serum cytokines (5),⁵ facilitating long-term disease including arrhythmias (6) and hypercoagulability. Increased cardiometabolic demand leads to a reduced cardiac reserve, denoted by compensative left ventricular hypertrophy (7), further contributing to angiotensin-aldosterone system dysregulation. Therapies used during the acute phase of infection, such as high-dose steroid treatment, may increase plaque formation (8) and hypertension and decrease cardiac function. High-dose steroid also could work as a stress hormone, inducing excess catecholamine, leading to excess oxygen consumption of myocardium and decrease cardiac function.⁵³ Cardiac injury results in elevated cardiac troponin (CTN) and NT-pro BNP levels (5). All mechanisms promote plaque destabilisation and increase wall shear stress (10).⁵⁴ The image was created with Biorender.com.

ACE-2 degrades Ang II to Ang (1–7) resulting in the prevention of hypertension, fibrosis, inflammation, diabetes and cardiovascular disease.⁴¹ SARS-CoV-2 binds and internalises ACE-2 upon infection contributing to an increase in Ang II levels and, as a result, an increase in Ang II-induced biological effects, making COVID-19 patients more susceptible to cardiovascular diseases.²⁷ This dysregulation of the RAS may occur in conjunction with virus-induced cardiovascular damage and systemic inflammation, the combination of which may increase the development of *de novo* cardiovascular complications. Indeed, the role of ACE-2 in both viral replication and RAS may explain why SARS-CoV-2 induces a higher rate of cardiac complications than other pneumonia-inducing viral infections (which do not bind to ACE-2) such as seasonal influenza virus.^{42,43}

SARS-CoV-2 infection also induces a systemic inflammatory response, which may contribute to myocardial injury.⁵ Detection of SARS-CoV-2 pathogen association molecular patterns (PAMPS) and danger-associated molecular patterns (DAMPS) in the lung results in the induction of pro-inflammatory cytokines and interferons (IFNs) and induces the expression of IFN-stimulated genes (ISGs). Whilst serving to reduce viral replication and spread, a dysregulated pro-inflammatory response or 'cytokine storm' will itself culminate in tissue damage by attracting more cytokine-secreting cells to the lung and triggering epithelial cell apoptosis/necrosis. This pulmonary inflammatory response is further perpetuated in the vasculature where endothelial cells, although not directly infected with SARS-CoV-2, sense the viral infection in the adjacent epithelial cells and mount an inflammatory response.¹³ The local and systemic cytokine profile during COVID-19 includes IL-6, IL-10, IL-1 β , IL-18, tumor necrosis factor α (TNF- α), IFNs (IFN- α/β , IFN- γ) and C-X-C motif chemokine ligand 10 (CXCL10).^{5,44} This cytokine storm can cause acute cardiac injury through a variety of different mechanisms. Pro-inflammatory cytokines such as TNF- α , IL-1 and IL-6 have a negative inotropic effect on cardiac contractility.²³ Furthermore, TNF- α -induced continuous activation of inflammatory signalling can cause widespread cardiomyocyte apoptosis, leading to pathological remodelling of the left ventricle and, ultimately, acute heart failure.²³ Alternatively, in particular amongst patients with underlying comorbidities, inflammation may trigger cardiovascular disease

by triggering the rupture of the coronary atherosclerotic plaques.⁴⁵ Finally, this inflammatory response may not be independent of viral infection of the heart. SARS-CoV-2 infection of the heart would not only augment cardiovascular inflammation, but the resultant downregulation of ACE-2 would also serve to further perpetuate the inflammatory response.^{27,46,47}

In addition to systemic inflammation, it is possible that SARS-CoV-2 indirectly contributes to cardiovascular disease via the induction of respiratory distress, acute respiratory distress syndrome (ARDS) and systemic hypoxia, with resultant hypoxic pulmonary vasoconstriction.⁴⁸ Long-term hypoxia causes myocardial cell injuries and necrosis, as well as cardiac arrhythmias.^{4,49,50} Specifically, cardiomyocytes undergo cell membrane destruction as a result of intracellular acidosis and reactive oxygen species (ROS) production caused by decreased blood oxygen and energy supply (hypoxemia).⁵¹ Hypoxemia also induces an influx of calcium ions, which contributes to cardiomyocyte injury and apoptosis.⁵¹ Alternatively, it is possible that viral pneumonia and the often-associated pulmonary thromboembolisms result in RV abnormalities.

Long-term cardiovascular complications in COVID-19 patients

At present, it remains unclear how long the cardiovascular complications of COVID-19 can persist in convalescent individuals (Figure 2). Hospitalisation for bacterial pneumonia is associated with an increased long-term risk of cardiovascular disease.⁵⁵ In contrast, the cardiovascular complications associated with acute avian influenza (including tachycardia, atrial fibrillation and ST changes) resolve within 1 year of infection.⁵⁶ The limited number of studies performed on the long-term complications of COVID-19 suggests that the prevalence of cardiovascular disease may vary depending upon the patient population in question. Studies such as the long-term impact in intensive care survivors of coronavirus disease-19 (AFTERCOR study – ACTRN12620000799954p)⁵⁷ may shed light upon this.

Amongst individuals who experienced severe COVID-19 (i.e. hospitalised during the acute phase of disease), signs of persistent cardiovascular disease appear to be relatively common. For

Long-term Cardiovascular Complications in COVID-19 Patients

Figure 2. Schematic representation of the long-term cardiovascular complications of COVID-19. Amongst studies of patients initially hospitalised with severe COVID-19, signs of persistent cardiovascular disease appear to be relatively common, with patients continuing to suffer from chest pain, late gadolinium enhancement (LGE), LV dysfunction, myocardial infarction and palpitations 6 months post-infection. Cardiovascular complication incidence amongst convalescent COVID-19 patients who experienced mild illness is less well defined, with patients suffering from cardiac involvement, myocarditis and LGE earlier post-infection but seeming to recover by 6 months post-infection. Considering that some cases with mild illness still have cardiovascular complications at 6 months post-infection,⁶⁶ it cannot be concluded that mild cases of COVID-19 never cause chronic cardiac complications. The image was created with Biorender.com.

example, 21% of previously hospitalised COVID-19 patients still experienced chest pain 60 days post-symptom onset.⁵⁸ At 6 months post-infection, 9% of previously hospitalised COVID-19 patients continue to experience heart palpitations, whilst a further 5% experienced chest pain.⁵⁹ Cardiovascular magnetic resonance (CMR) showed that amongst 148 patients recovering from severe COVID-19 (median follow-up time post-symptom onset = 68 days), 11% of patients had abnormal left ventricular function, whilst 19% of patients had myocardial infarction and 54% of patients had late gadolinium enhancement (LGE) or ischaemia.⁶⁰ LGE indicates myocardial fibrosis, which is important because LGE may play a role in the pathophysiology of dilated cardiomyopathy,^{61,62} eventually leading to impaired cardiac contraction.⁶³ Of patients with ischaemic injury pattern, 66% (27/41) had no history of coronary disease. CMR of another COVID-19 patient cohort (where the average duration from hospital discharge was 102 days)

showed LGE in approximately 30% of convalescent COVID-19 patients.⁶⁴ These findings are consistent with smaller studies ($n = 26$) where 31% of patients with a history of COVID-19 hospitalisation displayed LGE.⁶⁵ The prevalence of LGE is of particular concern given that LGE is an independent predictor of all-cause mortality and cardiac mortality in myocarditis.⁶⁴

The incidence of cardiovascular complications amongst convalescent COVID-19 patients who experienced a mild illness is less well defined. Recently, the long-term complications of COVID-19 were investigated amongst 73 435 users of the Veteran Health Administration (VHA).⁶⁶ All convalescent COVID-19 patients experienced a mild, acute disease (i.e. patients were not hospitalised) with a median follow-up time of 126 days post-symptom onset.⁶⁶ Compared to approximately 4 million COVID-19-negative VHA users, a history of COVID-19 diagnosis was associated with an excess burden of hypertension, cardiac dysrhythmias, circulatory signs and

symptoms, chest pain, coronary atherosclerosis and heart failure.⁶⁶ Amongst COVID-19 convalescent patients, there was also evidence of excess use of beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics and antiarrhythmics.⁶⁶ These data suggest that (1) the cardiac risk and associated burden of post-acute sequelae are evident even among individuals who did not require hospitalisation at acute phase (representing the majority of people with COVID-19) and (2) the cardiac risk and associated burden increase across the severity spectrum of acute COVID-19 infection (from non-hospitalised to hospitalised individuals, to those admitted to intensive care).⁶⁶ These findings have been echoed in several smaller scale studies. Amongst 100 convalescent COVID-19 patients (follow-up time > 2 weeks post-symptom onset), cardiac magnetic resonance imaging showed that 78% of patients had cardiac involvement and 60% had ongoing myocardial inflammation.⁶⁷ Strikingly, the presence of cardiovascular disease was independent of time from the original diagnosis, pre-existing conditions and the severity and course of the acute illness, raising concerns that cardiovascular disease may emerge in patients who only experienced mild or even asymptomatic COVID-19.⁶⁷ Consistent with this notion, amongst 26 competitive college athletes who had recovered from mild COVID-19 (11–53 days post-symptom onset) four athletes had CMR findings consistent with myocarditis, whilst 12 athletes had LGE.⁶⁸ In contrast to these findings, no significant long-term cardiovascular complications were recorded in healthcare workers ($n = 74$) 6 months following a mild COVID-19 infection.⁶⁹ Specifically, compared with seronegative healthcare workers there was no significant changes in cardiac structure, function, tissue characterisation or biomarkers of individuals with a history of COVID-19 infection.

At present, the mechanisms by which COVID-19 may cause long-term cardiovascular disease remains purely speculative. Elevated cytokine levels have been detected in the sera of convalescent COVID-19 patients, including elevated levels of pro-angiogenic MIP-1b, BDNF and VEGF.^{70,71} Whether this is sufficient to drive cardiovascular dysfunction, or is indicative of other underlying inflammation that then plays a causative role in cardiovascular disease, remains to be determined. Alternatively, it is possible that therapies used during the acute phase of illness

(such as high-dose steroid treatment) have long-term consequences, as was previously observed with SARS-CoV-1.^{72,73} However, such a hypothesis would fail to explain the incidence of cardiovascular disease in convalescent individuals who had mild COVID-19. Recovered COVID-19 patients may have increased cardiometabolic demand, as previously described in SARS-CoV-1 survivors, resulting in reduced cardiac reserve and dysregulation of the angiotensin-aldosterone system.⁸ Myocardial fibrosis or scarring (resulting from the acute inflammatory response or viral infection) may also facilitate long-term disease, including re-entrant arrhythmias.⁸

The current clinical consensus is not to advise the routine use of advanced cardiac imaging in convalescent COVID-19 patients. It is vital that research in this field continues to define which patients are most at-risk of long-term cardiovascular disease so that targeted cardiovascular follow-up can be performed.

CONCLUSION

During SARS-CoV-2 infection, myocardial injury and cardiovascular complications are more common than other pneumonia-inducing viral infections and this often leads to poor outcomes. Acute cardiac complications include arrhythmia, myocarditis and heart failure. Direct myocardial injuries can be caused by the invasion of the virus itself in patients with underlying comorbidities. Indirect myocardial injuries can be caused by systemic inflammation because of the cytokine storm, causing a negative inotropic effect on cardiac contractility, cardiomyocyte apoptosis and acute heart failure. Long-term cardiac complications include hypertension, arrhythmia, coronary atherosclerosis and heart failure. As the mechanism of long-term complications, hypoxia, cytokines, increased cardiac metabolism and myocardial fibrosis might be related. Whilst the incidence of the long-term complications is independent of the severity of the acute illness, studies to determine which patients are most at-risk of long-term cardiovascular disease are vital so that targeted cardiovascular follow-up can be performed.

ACKNOWLEDGMENTS

AK is supported by a fellowship from the NHMRC (APP1157741).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Kei Sato: Conceptualization; Writing-original draft; Writing-review & editing. **Jane E Sinclair:** Writing-original draft; Writing-review & editing. **John F Fraser:** Conceptualization; Writing-review & editing. **Arutha Kulasinghe:** Conceptualization; Resources; Supervision; Writing-original draft; Writing-review & editing.

REFERENCES

- Clerkin KJ, Fried JA, Raikhelkar J et al. COVID-19 and cardiovascular disease. *Circulation* 2020; **141**: 1648–1655.
- Short KR, Veeris R, Leijten LM et al. Proinflammatory cytokine responses in extra-respiratory tissues during severe influenza. *J Infect Dis* 2017; **216**: 829–833.
- 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.
- 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.
- 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.
- Sala S, Peretto G, Gramegna M et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. *Eur Heart J* 2020; **41**: 1861–1862.
- Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020; **17**: 259–260.
- Nalbandian A, Sehgal K, Gupta A et al. Post-acute COVID-19 syndrome. *Nat Med* 2021; **27**: 601–615.
- Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses* 2012; **4**: 1011–1033.
- Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; **181**: 271–280 e278.
- Cantuti-Castelvetri L, Ojha R, Pedro LD et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* 2020; **370**: 856–860.
- Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417–1418.
- Schimmel L, Chew KY, Stocks C et al. Endothelial cells elicit a pro-inflammatory response to SARS-CoV-2 without productive viral infection. *bioRxiv* 2021. <https://doi.org/10.1101/2021.02.14.431177>
- Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol* 2020; **11**: 1708.
- Sarkisian L, Saaby L, Poulsen TS et al. Clinical characteristics and outcomes of patients with myocardial infarction, myocardial injury, and nonelevated troponins. *Am J Med* 2016; **129**: 446 e5–e21.
- Dweck MR, Bularga A, Hahn RT et al. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging* 2020; **21**: 949–958.
- Wang D, Hu BO, Hu C et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061–1069.
- Giustino G, Croft LB, Stefanini GG et al. Characterization of myocardial injury in patients with COVID-19. *J Am Coll Cardiol* 2020; **76**: 2043–2055.
- Chung MK, Zidar DA, Bristow MR et al. COVID-19 and cardiovascular disease: from bench to bedside. *Circ Res* 2021; **128**: 1214–1236.
- Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 2020; **17**: 543–558.
- Liu K, Fang Y-Y, Deng Y et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)* 2020; **133**: 1025–1031.
- Du Y, Tu L, Zhu P et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. *Am J Respir Crit Care Med* 2020; **201**: 1372–1379.
- Li N, Zhu L, Sun L, Shao G. The effects of novel coronavirus (SARS-CoV-2) infection on cardiovascular diseases and cardiopulmonary injuries. *Stem Cell Res* 2021; **51**: 102168.
- Ruan Q, Yang K, Wang W, Jiang L, Song J. 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.
- Sawalha K, Abozenah M, Kadado AJ et al. Systematic review of COVID-19 related myocarditis: insights on management and outcome. *Cardiovasc Revasc Med* 2021; **23**: 107–113.
- Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. *J Card Fail* 2020; **26**: 470–475.
- Wu L, O’Kane AM, Peng H, Bi Y, Motriuk-Smith D, Ren J. SARS-CoV-2 and cardiovascular complications: from molecular mechanisms to pharmaceutical management. *Biochem Pharmacol* 2020; **178**: 114114.
- 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.
- Shi S, Qin MU, Shen BO et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802–810.
- Baral R, White M, Vassiliou VS. Effect of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. *Curr Atheroscler Rep* 2020; **22**: 1–9.
- Donoghue M, Hsieh F, Baronas E et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. *Circ Res* 2000; **87**: E1–E9.
- Crackower MA, Sarao R, Oudit GY et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature* 2002; **417**: 822–828.

33. Sharma A, Garcia G, Wang Y et al. Human iPSC-derived cardiomyocytes are susceptible to SARS-CoV-2 infection. *Cell Rep Med* 2020; **1**: 100052.
34. Marchiano S, Hsiang T-Y, Khanna A et al. SARS-CoV-2 infects human pluripotent stem cell-derived cardiomyocytes, impairing electrical and mechanical function. *Stem Cell Rep* 2021; **16**: 478–492.
35. Perez-Bermejo JA, Kang S, Rockwood SJ et al. SARS-CoV-2 infection of human iPSC-derived cardiac cells reflects cytopathic features in hearts of patients with COVID-19. *Sci Transl Med* 2021; **13**: eabf7872.
36. Bailey AL, Dmytrenko O, Greenberg L et al. SARS-CoV-2 infects human engineered heart tissues and models COVID-19 myocarditis. *JACC Basic Transl Sci* 2021; **6**: 331–345.
37. 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; **5**: 1281–1285.
38. Bearse M, Hung YP, Krauson AJ et al. Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. *Mod Pathol* 2021; **34**: 1345–1357.
39. Massoth LR, Desai N, Szabolcs A et al. Comparison of RNA *in situ* hybridization and immunohistochemistry techniques for the detection and localization of SARS-CoV-2 in human tissues. *Am J Surg Pathol* 2021; **45**: 14–24.
40. Dushpanova A, Agostini S, Ciofini E et al. Gene silencing of endothelial von Willebrand Factor attenuates angiotensin II-induced endothelin-1 expression in porcine aortic endothelial cells. *Sci Rep* 2016; **6**: 30048.
41. Tikellis C, Bernardi S, Burns WC. Angiotensin-converting enzyme 2 is a key modulator of the renin-angiotensin system in cardiovascular and renal disease. *Curr Opin Nephrol Hypertens* 2011; **20**: 62–68.
42. Xie Y, Bowe B, Maddukuri G, Al-Aly Z. Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. *BMJ* 2020; **371**: m4677.
43. Cheng MP, Cau A, Lee TC et al. Acute cardiac injury in coronavirus disease 2019 and other viral infections – a systematic review and meta-analysis. *Crit Care Med* 2021; **49**: 1558–1566.
44. Zhao Z, Wei Y, Tao C. An enlightening role for cytokine storm in coronavirus infection. *Clin Immunol* 2021; **222**: 108615.
45. Knowlton KU. Pathogenesis of SARS-CoV-2 induced cardiac injury from the perspective of the virus. *J Mol Cell Cardiol* 2020; **147**: 12–17.
46. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. *EMBO Mol Med* 2010; **2**: 247–257.
47. Pacurari M, Kafoury R, Tchounwou PB, Ndebele K. The renin-angiotensin-aldosterone system in vascular inflammation and remodeling. *Int J Inflam* 2014; **2014**: 689360.
48. Serebrovska ZO, Chong EY, Serebrovska TV, Tumanovska LV, Xi L. Hypoxia, HIF-1 α , and COVID-19: from pathogenic factors to potential therapeutic targets. *Acta Pharmacol Sin* 2020; **41**: 1539–1546.
49. Lakkireddy DR, Chung MK, Gopinathannair R et al. Guidance for cardiac electrophysiology during the COVID-19 pandemic from the Heart Rhythm Society COVID-19 Task Force; electrophysiology section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. *Circulation* 2020; **141**: e823–e831.
50. Nasi A, McArdle S, Gaudernack G et al. Reactive oxygen species as an initiator of toxic innate immune responses in retort to SARS-CoV-2 in an ageing population, consider N-acetylcysteine as early therapeutic intervention. *Toxicol Rep* 2020; **7**: 768–771.
51. Li BO, Yang J, Zhao F et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; **109**: 531–538.
52. Farha S, Heresi GA. COVID-19 and pulmonary arterial hypertension: early data and many questions. *Ann Am Thorac Soc* 2020; **17**: 1528–1530.
53. Gubbi S, Nazari MA, Taieb D, Klubo-Gwiedzinska J, Pacak K. Catecholamine physiology and its implications in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8**: 978–986.
54. Sokolowska M, Lukasik ZM, Agache I et al. Immunology of COVID-19: Mechanisms, clinical outcome, diagnostics, and perspectives – a report of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy* 2020; **75**: 2445–2476.
55. Corrales-Medina VF, Alvarez KN, Weissfeld LA et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA* 2015; **313**: 264–274.
56. Wang J, Xu H, Yang X et al. Cardiac complications associated with the influenza viruses A subtype H7N9 or pandemic H1N1 in critically ill patients under intensive care. *Braz J Infect Dis* 2017; **21**: 12–18.
57. Wildi K, LiBassi G, Barnett A et al. Design and rationale of a prospective international follow-up study on Intensive Care survivors of COVID-19: the long-term impact in intensive care survivors of coronavirus disease-19-AFTERCOR. *Front Med* 2021.
58. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; **324**: 603–605.
59. Huang C, Huang L, Wang Y et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; **397**: 220–232.
60. Kotecha T, Knight DS, Razvi Y et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021; **42**: 1866–1878.
61. Verdonschot JAJ, Merlo M, Dominguez F et al. Phenotypic clustering of dilated cardiomyopathy patients highlights important pathophysiological differences. *Eur Heart J* 2020; **42**: 162–174.
62. Becker MAJ, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *JACC Cardiovasc Imaging* 2018; **11**: 1274–1284.
63. Schultheiss HP, Fairweather D, Caforio ALP et al. Dilated cardiomyopathy. *Nat Rev Dis Primers* 2019; **5**: 32.
64. Wang H, Li R, Zhou Z et al. Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2021; **23**: 14.

65. Huang L, Zhao P, Tang D et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging* 2020; **13**: 2330–2339.
66. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021; **594**: 259–264.
67. Puntmann VO, Carerj ML, Wieters I et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265–1273.
68. Rajpal S, Tong MS, Borchers J et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. *JAMA Cardiol* 2021; **6**: 116–118.
69. Joy G, Artico J, Kurdi H et al. Prospective case-control study of cardiovascular abnormalities 6 months following mild COVID-19 in healthcare workers. *JACC Cardiovasc Imaging* 2021. Online ahead of print. <https://doi.org/10.1016/j.jcmg.2021.04.011>
70. Ong SWX, Fong S-W, Young BE et al. Persistent symptoms and association with inflammatory cytokine signatures in recovered COVID-19 patients. *Open Forum Infect Dis* 2021; **8**: ofab156.
71. Lawler NG, Gray N, Kimhofer T et al. Systemic perturbations in amine and kynurenine metabolism associated with acute SARS-CoV-2 infection and inflammatory cytokine responses. *J Proteome Res* 2021; **20**: 2796–2811.
72. Wu QI, Zhou L, Sun X et al. Altered lipid metabolism in recovered SARS patients twelve years after infection. *Sci Rep* 2017; **7**: 9110.
73. Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. *Eur Heart J* 2020; **41**: 1798–1800.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.