

Cardiovascular disease, heart failure and COVID-19

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Journal of the Renin-Angiotensin-Aldosterone System
April-June 2020: 1–3
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DOI: 10.1177/1470320320926903
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A viral infection can acutely affect the cardiovascular system, causing an increased risk of acute coronary syndromes, myocardial depression leading to heart failure (HF) or arrhythmias and myocarditis/pericarditis.¹ These complications can be the result of direct invasion of the heart or they can be mediated by the systemic response, including an increase in pulmonary or systemic vascular resistance, systemic inflammation, immune reaction or reduced oxygen delivery.

Patients with cardiovascular disease (CVD) including HF are particularly vulnerable to influenza and other infective diseases of the upper and lower respiratory tract and are at greater risk of poor outcomes.^{2,3} However, the impact of the recent outbreak of coronavirus disease 2019 (COVID-19) caused by the virus SARS-CoV-2 in patients with pre-existing cardiovascular morbidity or the risk of cardiovascular complications has not been extensively evaluated.

Early data from 1590 subjects with COVID-19 admitted to hospitals in 31 provinces across China show that CVD and/or risk factors for CVD, likely to be associated with increased predisposition to HF, was the third most common co-morbidity in the population. Co-morbidities (including hypertension or diabetes) were seen more commonly in severe cases compared to non-severe cases (33.9% vs. 15.3%, respectively in the case of CVD).⁴

To what extent the predisposition of subjects with CVD/risk factors to COVID-19 and adverse outcomes is confounded by age and/or other factors has not been fully elucidated. It is well recognised that age is a major factor in determining outcomes,⁵ but the concomitant presence of a cardiovascular co-morbidity may increase age-specific risk. Case fatality rates for COVID-19 subjects with co-morbidities in China were substantially higher than those for the average population, particularly in cases of established CVD (10.5% vs. 2.3%),⁶ with similar data in Italy, the worst affected country in Europe up to March 2020.

Common complications of COVID-19 include sepsis, respiratory failure, acute respiratory distress syndrome and HF. The prevalence of HF is higher in non-survivors compared to survivors (52% vs. 12%, respectively).⁷ These data are in line with previous observations made with other coronavirus outbreaks (particularly severe

acute respiratory syndrome coronavirus) in which left ventricular performance was affected during the course of infection, and the impairment appeared to be worse in more critically ill patients.⁸

The presence of CVD could be implicated in greater susceptibility to COVID-19 and/or severity of complications in a number of ways. Pre-existing HF or risk factors for HF will predispose subjects to HF as a complication of any viral infection. More specifically, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2), expressed by epithelial cells of the lung, as the receptor-binding domain for its spike protein to gain entry to the epithelium.⁹ ACE2 (and ACE) gene expression is up-regulated in HF.¹⁰ This could theoretically increase susceptibility to infection. It has also been speculated that drugs widely used for hypertension, diabetes and HF – such as ACE inhibitors and angiotensin receptor blockers (ARB) – can lead to up-regulation of ACE2 (including at the cardiac level^{11,12}) which could in theory increase susceptibility to the infection.¹³ However, at present, there is no evidence for this, and there have been very clear statements from the American College of Cardiology, American Heart Association, Heart Failure Society of America and the British Cardiovascular Society that these drugs should not be discontinued.^{14,15}

Whilst up-regulation of ACE2 could lead to increased susceptibility to infection, it might have a protective effect on the injury caused by the virus. Binding of SARS-CoV-2 to ACE2 results in down-regulation of ACE2, leading to greater production of angiotensin II (which may already be high in patients with HF), since the function of ACE2 is a negative regulator of the renin–angiotensin–aldosterone

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system (RAAS) through the inactivation of angiotensin II to angiotensin (1–7), a potent vasodilator acting through the Mas receptor.¹⁶ Increased angiotensin II may contribute to increased lung permeability¹⁷ and may have adverse effects on the myocardium¹⁸ (although these would usually be expected to be long term). Thus, up-regulation of ACE2 and blockade of ACE and/or angiotensin II receptors could be protective. Again, it must be stressed that such effects are entirely speculative. Clinical trials of recombinant soluble ACE2 are planned and will provide more definitive evidence for the role of ACE2 and the interactions with RAAS-interfering drugs.

Some coronaviruses are known to invade and injure the myocardium directly, and the same may be true for SARS-CoV-2. In a series of 138 hospitalized COVID-19 patients with pneumonia, 14.5% had pre-existing CVD, and of the infected subjects, 16.7% developed arrhythmia and 7.2% experienced acute cardiac injury (as evidenced by a rise in troponin) in addition to other COVID-19-related complications.¹⁹ However, with the exception of case reports of fulminant myocarditis, the rise in troponin is in line with the non-specific cardiac injury seen in systemic infections.²⁰ Alternatively, myocarditis may be related to an acute cytokine storm that appears to occur in the most severely ill patients rather than being primarily infective. More data on the incidence and aetiology of possible direct myocardial injury are required.

In conclusion, the presence of HF/CVD or risk factors for these conditions may increase susceptibility to the infection with SARS-CoV-2 and is probably associated with worse outcomes. Whether this results from the systemic response to the infection or to a specific effect of SARS-CoV-2 on the cardiovascular system remains to be established. The role of the RAAS in COVID-19 is an important factor to be addressed, given its prevalence in the population with CVD and CVD risk factors.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the British Heart Foundation (CH/1999001/11735 to A.M.S.), the Department of Health via a National Institute for Health Research (NIHR) Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London (IS-BRC-1215-20006) and by the AIM HY (Ancestry and biological Informative Markers in stratification of Hypertension) stratified medicines programme in hypertension funded by the Medical Research Council and The British Heart Foundation (MR/M016560/1).

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