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Short communication

COVID-19 and cardiovascular disease: What we know, what we think we know, and what we need to know

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The global coronavirus disease 2019 (COVID-19) pandemic has highlighted inherent susceptibility to specific age–group and cardiovascular co-morbidities. While individuals of any age can be infected, and viral load is important, those who are 70 years or older have a notably increased risk. In addition, patients with obesity, heart failure, coronary artery disease, diabetes mellitus and hypertension are also at increased risk and more likely to deteriorate to serious or critical condition when infected. It is not yet clear why these diseases predispose patients to a more severe response to infection. In this letter, we lend insight and perspective to these observations.

Many have raised the potential issue that use of angiotensin converting enzyme (ACE) inhibitors (ACEi) and angiotensin receptor blockers (ARBs) may lead to higher susceptibility to COVID-19 infection due to their ability to increase angiotensin converting enzyme 2 (ACE2) mRNA expression; however, others have suggested that ACEi and ARB use may be protective against COVID-19. To understand why there are conflicting theories, it is important to recognize that ACE2 plays multiple roles in the context of COVID-19.

ACE2 is a principal receptor for virus entry into cells and is highly expressed in vascular tissue, as well as the heart and lungs [1]. SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry, and the serine protease TMPRSS2 for S protein priming [2]. Of interest, TMPRSS2 is the drug target of Camostat [Foipan®], and it is starting to attract some interest for COVID-19, though rigorous evaluation for that use remains to be done. Because we do not fully know all of the mechanisms involved in viral entry or virus concentrations across tissue and cell types, distribution of viral infection within the cardiovascular system remains speculative.

In addition, ACE2 negatively regulates angiotensin II by cleaving it to Ang1–7. Animal model studies in genetically modified mice showed that angiotensin and its type 1a receptor levels play a role in the pathogenesis of acute respiratory distress syndrome (ARDS), with ACE2 serving a protective effect [3]. For these reasons, the consequences of inhibiting ACE (*e.g.* with ACEi/ARB) within the context of COVID-19 are mechanistically convoluted. The use of ACEi or ARB increased gene expression of ACE2 in cardiac cells in a rat model by 5-fold and 3-fold respectively [4]. At the same time, a human study showed no significant change in plasma activity of ACE2 with these medications [5]. The presence or type of heart disease mattered more than whether or not someone was taking an ACEi/ ARB when determining angiotensin II levels or plasma activity of ACE2 [5]. Additional studies are needed to determine if the variation in findings is related to differences in

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medications or cells used in these experiments. If ACE2 expression is increased by these drugs, it raises the question of increased infectivity and rapid clinical progression of COVID-19 in patients on ACEi/ARB. Currently, there is a paucity of clinical data to support the hypothesis of increased susceptibility to infection in these patients.

ACEi and ARBs may actually confer a benefit later in the immunologic response to infection. The mechanism of action proposed is to limit the excess angiotensin II binding to its receptors during fulminant viral inflammation. Excess angiotensin II binding to its receptor results in increased vascular permeability in the lungs which is a proposed mechanism for ARDS, which has similar presentations to COVID-19 induced lung injury [3,6]. This is important when one considers that the binding of COVID-19 to its receptor ACE2 results in inactivation and downregulation of ACE2 to further increase levels of angiotensin [3]. This could promote cellular injury in the lungs, leading to pulmonary edema and ARDS. In support of this hypothesis, recombinant human ACE2 insertion in mice deficient in ACE2 led to a lower risk of developing ARDS when these animals were exposed to acid-induced lung injury [3]. Thus, in a patient, administration of an agent which is specific for blocking virus binding to ACE2 yet does not affect ACE2 functionality, could neutralize the virus and might have the net effect of decreasing infectivity while maintaining angiotensin II conversion to Ang1–7, potentially mitigating lung inflammation and damage.

Myocardial injury associated with the SARS-CoV-2 was a common condition in patients diagnosed with COVID-19 in Wuhan and associated with a higher risk of in-hospital mortality [7].

In the US there have been early unpublished reports about elevated troponin, bradycardia and sudden cardiac death in these patients. There are also early verbal reports of secondary septic-like cardiomyopathy and cardiogenic shock that develops rather late, usually during the preterminal phases of the disease. Unpublished observations also suggest troponin positive patients have vascular inflammation, microthrombosis, microvascular hypo-perfusion, and resultant myocardial damage. These mechanisms may also be participating in pulmonary complications and other non-cardiac systemic vascular manifestations of COVID-19. The predisposing biology of acute viral, thrombotic and inflammatory mechanisms that underpin these cardiovascular observations are novel presentations of this infection and need to be further elucidated.

While there might be a hypothetical argument for discontinuing ACEi and ARBs prior to COVID-19 infection to avoid early excessive ACE2 gene upregulation (*i.e.* increase potential for viral susceptibility), the administration of ACEi or ARBs could mitigate the impact of cellular injury and ARDS in COVID-19 infection and increased pulmonary vascular permeability due to an excessive impact of angiotensin II. While a dual strategy of stopping ACEi/ARB early and then restarting later in COVID-19 patients may appear reasonable, no data to support such a strategy has been established. This dual role in pathogenicity is expected to confound the impact of data interpretation of these medications on clinical outcomes. Furthermore, if patients were to be guided to discontinue these medications during the pandemic, this would likely put them at risk of decompensated heart failure and uncontrolled hypertension. It is imperative that such decisions be made between clinicians and patients to ensure that risks of discontinuing the drugs are understood and weighed against the uncertain benefit. If patients are cardio-dependent on these medications, the prevailing approach is that the benefit of continuation outweighs the risk, and the focus should be on all possible precautions to reduce exposure to COVID-19.

Another issue with this pathogen is that generally, the immune response appears to be inappropriate in some cases leading to severe immunopathology [8]. Most notably, coronaviruses initiate a robust innate immune response, which causes generalized inflammation with little specificity to the virus. As such, the inflammatory response is predominantly mediated through cytokines and the strategy to dampen this response is challenging due to the lack of specific inhibitors of the adaptive immune response to the virus. At this time, it is understood that there is a very specific and robust T helper (CD4+) cell response, but a less than impressive antibody response to those with asymptomatic to mild disease. Indeed, in a limited serological study of COVID-19 it was reported that one patient showed peak specific IgM at day 9 after disease onset and switching to IgG by week 2. In addition, combined sera from a few patients were able to neutralize COVID-19 in an *in vitro* plaque assay, suggesting they are possibly mounting a neutralizing antibody response [9]. Whether the kinetics and titer of specific antibody correlates with disease severity remains to be investigated.

Table 1
Gaps in our understanding of the connections between COVID-19 and cardiovascular implications.

1. Exploration of the effects of TMPRSS2 inhibition on infectivity
2. Explanation for variation in response to different ACEi/ARBs in ACE2 expression
3. Elucidation of whether patients on ACEi/ARB are at greater risk for higher infectivity
4. Clarification of whether ACEi/ARB has a dual role: Is detrimental early (increasing infectivity) and beneficial later (mitigating pulmonary complications)
5. Understanding of how infection induces myocardial damage
6. Determination of whether other components of the renin-angiotensin-aldosterone system are in play
7. Identification of how immune response variation translates to differences in pathology

Since little is known about the pathogenesis of COVID-19, there is an urgent need for prospective data to address questions expeditiously. As summarized in Table 1, there are a number of gaps that remain to be filled. Timely initiation of high-quality COVID-19 and cardiovascular research is warranted, given clear scientific aims and readily available research infrastructure [10]. Moving forward, widespread use of these important drug classes for hypertension, cardiac, and renal disease management may confound interpretation of their impact in the setting of COVID-19 in population studies. These data must therefore be evaluated and interpreted carefully. Ultimately, answering these questions will promote our ability to mitigate the global impact of this pandemic and improve individual COVID-19 patient outcomes. This will be critical, as there are currently no therapies for COVID-19 that have been shown effective to date [11].

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