

EP News: Basic and Translational

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SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been shown to be associated with a high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias. The current study by Hoffmann et al (Cell 2020;doi:10.1016/j.cell.2020.02.052; PMID 32142651) investigates the mechanisms of SARS-CoV-2 entry into mammalian cells. The spike (S) protein of coronaviruses facilitates viral entry into target cells by binding of the surface unit (S1) of the S protein to a cellular receptor, angiotensin-converting enzyme 2 (ACE2), as the entry receptor. Priming of coronavirus S proteins by host cell serine proteases, TMPRSS2, is essential for viral entry into cells, with S protein cleavage at the S1/S2 and the S20 sites. The S1/S2 cleavage site of SARS-2-S harbors several arginine residues, which indicates high cleavability. Finally, a serine protease inhibitor blocks SARS-CoV-2 infection of lung cells. *The authors conclude that the study provides key insights into the first step of SARS-CoV-2 entry into cells and potential targets for antiviral intervention.*

Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19

The current article by Vaduganathan et al (N Engl J Med 2020;doi:10.1056/NEJMsr2005760; PMID 32227760) provides literature review on the use of renin–angiotensin–aldosterone system (RAAS) inhibitors in patients with coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronaviruses interact with angiotensin-converting enzyme 2 (ACE2) to gain the initial entry into cells, followed by endocytosis of the viral complex. There are safety concerns regarding the use of RAAS inhibitors, which may alter ACE2 expression in patients with COVID-19. ACE2 is an enzyme that physiologically counters RAAS activation. Preclinical studies have suggested that RAAS inhibitors may increase ACE2 expression. However, there are insufficient data to determine whether these observations can translate to humans. Clinical trials are ongoing to test the safety and efficacy of RAAS modulators in COVID-19. *The authors conclude that RAAS inhibitors should be continued in patients in otherwise*

stable condition who are at risk for, being evaluated for, or with COVID-19.

Potential effects of coronaviruses on the cardiovascular system

The current article by Madjid et al (JAMA Cardiol 2020;doi:10.1001/jamacardio.2020.1286; PMID 32219363) provides a timely review of the literature on the potential effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), on the cardiovascular system. COVID-19 can cause a viral pneumonia with additional extrapulmonary manifestations, including vascular inflammation, myocarditis, and cardiac arrhythmias. A significant proportion of patients have comorbidities, including hypertension, diabetes, cardiovascular disease, and malignant neoplasms. Myocardial injury is associated with infection-related myocarditis and/or ischemia and is an important prognostic factor. A high troponin level is seen associated with a higher incidence of complications, including acute respiratory distress syndrome (ARDS), malignant arrhythmias, and acute renal injury. Finally, the cytokine storm likely plays a role in the development of ARDS and myocarditis. *The authors conclude that cardiovascular risk factors and complications should be thoroughly evaluated and treated per evidence-based guidelines in patients with COVID-19.*

The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2

The current study by Chen et al (Cardiovasc Res 2020;doi:10.1093/cvr/cvaa078; PMID 32227090) investigates possible underlying mechanisms for cardiac injury in patients with coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Specifically, the study tests angiotensin-converting enzyme 2 (ACE2) expression, the key host cellular receptor of SARS-CoV-2, in human heart using single nucleus RNA sequencing based on the 10× Genomics chromium platform. Pericytes show high expression of ACE2 and may serve as the target cardiac cells of SARS-CoV-2. Patients with heart failure show a significant increase in ACE2 expression at both mRNA and protein levels, which may contribute to an increased risk of cardiovascular complications in COVID-19. *The authors conclude that the findings may provide insights into the increased severity among COVID-19 patients with underlying cardiovascular disease and have implications in the treatment of cardiac injury in patients infected with SARS-CoV-2.*

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