

## EP News: Basic and Translational

Nipavan Chiamvimonvat, MD

From the Department of Internal Medicine and Pharmacology, University of California, Davis, Davis, California.

**The science underlying COVID-19: Implications for the cardiovascular system**

Liu et al (Circulation April 15, 2020;doi:10.1161/CIRCULATIONAHA.120.047549, PMID 32293910) provided an overview of coronavirus disease 2019 (COVID-19) that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The high infectivity of the SARS-CoV-2 virus is contributed by new mutations in the receptor-binding domain and acquisition of a furin cleavage site in the S spike protein. The virus uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry, which is mediated by the host cell serine protease TMPRSS2. The tissue expression of ACE2 correlates with organ dysfunction in the disease. The cardiovascular system is often involved in COVID-19 with the release of troponin and natriuretic peptides, along with cytokines such as interleukin-6. Inflammation in the myocardium can result in myocarditis, heart failure, cardiac arrhythmias, acute coronary syndrome, and sudden death. *The authors conclude that aggressive support based on early prognostic indicators with expectant management as well as treatment of heart failure, arrhythmias, acute coronary syndrome, and thrombosis is critical in the disease.*

**Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19)**

Mercurio et al (JAMA Cardiol May 1, 2020;doi:10.1001/jamacardio, PMID 32356863) conducted a cohort study of patients hospitalized with coronavirus disease 2019 (COVID-19) and clinical findings of pneumonia, who received at least 1 day of hydroxychloroquine. A total of 90 patients were included in the study who received hydroxychloroquine, while 53 patients received concomitant azithromycin. Patients receiving concomitant azithromycin had a greater median (interquartile range) change in QT interval (23 [10–40] ms) than did those receiving hydroxychloroquine alone (5.5 [–15.5 to 34.25] ms) ( $P = .03$ ). The likelihood of a prolonged corrected QT (QTc) interval was greater in those who received concomitant loop diuretics or had a baseline QTc interval of  $\geq 450$  ms. Ten patients who received hydroxychloroquine discontinued early because of adverse drug

events, including 1 case of torsades de pointes. *The authors conclude that patients who received hydroxychloroquine for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation and that concurrent treatment with azithromycin was associated with greater changes in QTc interval.*

**Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor**

Lan et al (Nature 2020;581:215, PMID 32225176) reported the crystal structure of the receptor-binding domain (RBD) of the spike (S) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) bound to the cell receptor angiotensin-converting enzyme 2 (ACE2). The overall ACE2-binding mode of the SARS-CoV-2 RBD is nearly identical to that of the SARS-CoV RBD, which also uses ACE2 as the cell receptor. Structural analysis identified residues in the SARS-CoV-2 RBD that are essential for ACE2 binding, the majority of which either are highly conserved or share similar side chain properties with those in the SARS-CoV RBD. *The authors conclude that the similarity in structure and sequence suggests convergent evolution between SARS-CoV-2 and SARS-CoV RBDs for improved binding to ACE2.*

**Massively multiplexed nucleic acid detection using Cas13**

Ackerman et al (Nature April 29, 2020;doi:10.1038/s41586-020-2279-8, PMID 32349121) reported the development of high-throughput Combinatorial Arrayed Reactions for Multiplexed Evaluation of Nucleic acids (CARMEN), a platform for scalable, multiplexed pathogen detection with attomolar sensitivity. Nanoliter droplets containing CRISPR-based nucleic acid detection reagents self-organize in a microwell array to pair with droplets of amplified samples, testing each sample against each CRISPR RNA (crRNA). The authors took advantage of the exquisite specificity of Cas13 with CARMEN to identify viral mutations in multiplex. The combination of CARMEN and Cas13 simultaneously differentiates all 169 human-associated viruses with  $\geq 10$  published genome sequences as well as crRNA to detect the causative agent of coronavirus disease 2019. *The authors conclude that scalable, highly multiplexed CRISPR-based nucleic acid detection can provide diagnostic and surveillance efforts by comprehensively testing large sample sets while incorporating a large number of pathogens or their mutations using miniaturization to reduce costs.*

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**Address reprint requests and correspondence:** Dr Nipavan Chiamvimonvat, Department of Internal Medicine and Pharmacology, University of California, Davis, GBSF 6315, 451 Health Science Dr, Davis, CA 95616. E-mail address: [nchiamvimonvat@ucdavis.edu](mailto:nchiamvimonvat@ucdavis.edu).