Unimagined a few short months ago, SARS-CoV-2 has spread rapidly across the globe to cause a worldwide pandemic, unparalleled since the 1918 H1N1 influenza pandemic. Deaths in the United States due to COVID-19 surpassed 500,000 in February 2021. The extraordinary efficiency in person-to-person transmission and the relatively high level of morbidity and mortality represent the perfect storm of an emerging infectious disease. New York City was among the original US epicenters of the COVID-19 pandemic. Thus, it is fitting that the article by Rubin et al featured elsewhere in JAMA Network Open originates from this epicenter. Uniquely and because of early contact with this virus, the authors were able to compare a population of hospitalized adult patients who tested positive for COVID-19 with those who ultimately tested negative. This is a large and important study that assessed the association of COVID-19 infection with the QT interval. Importantly, Rubin et al found that a COVID-19 infection was independently associated with a significant increase in the QTc, with a greater likelihood of a QTc greater than 500 milliseconds among patients with COVID-19 than among their counterparts, who were ill but ultimately tested negative for COVID-19. The authors are uniquely suited based on location and infection timing to report these important data. Because the data reflect the early days of the pandemic, hydroxychloroquine and azithromycin were still being used. However, these data provide information about the association of the virus with the QT interval even in the absence of these medications as well as in a small cohort of patients empirically treated with hydroxychloroquine and azithromycin who ultimately tested negative for COVID-19. Interestingly, there was 1 patient with COVID-19 who developed torsade de points. She had multiple additional risk factors for QTc prolongation: nonischemic cardiomyopathy and QTc greater than 500 milliseconds on presentation, hypomagnesemia, administration of azithromycin, and elevated inflammatory markers and troponin levels, indicating systemic inflammation and myocardial injury.

Coronavirus outbreaks have become a global public health threat due to their exceptional zoonotic potential, the ability to spillover and infect a diverse range of species with a high capacity for mutation and recombination. As viruses host-switch from their animal reservoir and infect humans, they find a species genetically similar but without immunity from previous infections. Major determinants of host-switching include the evolutionary closeness of the different hosts as well as pathogen opportunity. SARS-CoV-1 in 2003 and Middle East Respiratory Syndrome (MERS)–CoV in 2012, combined with the current COVID-19 pandemic, have put us in the midst of the third deadly international coronavirus outbreak. In the 20 years of these epidemics, what have we uncovered about viruses and their effects on the host?

Arrhythmias, including ventricular tachycardia, are known to be associated with COVID-19 infection and are a major complication of COVID-19 infection. This is thought to be a manifestation of myocarditis, but is it that simple? Are the arrhythmia potential and the QT prolongation entirely from myocyte inflammation? Many viruses result in myocarditis and inflammation. The proposed mechanisms for arrhythmogenicity in viral infections are an interplay between host factors and viral characteristics. These include altered intercellular coupling, interstitial edema, and cardiac fibrosis. Recent data suggest additional abnormal Ca²⁺ handling and downregulation of K⁺ channels that result in repolarization abnormalities and action potential conduction abnormalities, important when considering QTc prolongation and arrhythmia potential.
Ion channels selectively and rapidly transport ions across biological membranes in response to specific stimuli. Ion channels are highly conserved among bilaterian metazoans (animals with bilateral symmetry), play a central role in the regulation of cardiac excitation, and are determinants of the action potential and, as a consequence, the QT interval. Viruses can encode their own ion channels, termed viroporins, and recent data suggest that viruses can also regulate and/or depend on the ion channels expressed by host cells. Among others, K⁺ and Ca²⁺ channels are important in the host viral entry process. The term viral channelopathies has emerged, referring to the link between viral infection and dysregulation of ion channel function. Given the importance of ion channels in cardiac physiology, it is not a surprise that their dysfunction results in disease. We know that disorders of or mutations in ion channels result in the clinical entities of acquired or congenital long QT syndrome, manifesting as QT prolongation on the electrocardiogram and a risk of ventricular arrhythmias and sudden death.

Ion channels play key roles in almost all facets of cellular physiology and have emerged as key host cell factors for a multitude of viral infections. For example, Coxsackie virus B3 is associated with cardiomyopathy and sudden cardiac death. Studies demonstrated that although the surface expression of KCNQ1 is increased in cells infected with Coxsackie virus B3, KCNH2 and Cav1.2 expression are substantially decreased. Data suggest that Coxsackie virus B3 reprograms ion channel expression in cardiac tissue, leading to an increased risk of arrhythmia. Inherited mutations in these, among other ion channels, are associated with QTc prolongation and arrhythmias. Altered KCNH2 expression increases the risk of drug-induced arrhythmias by depleting repolarization reserve.

Similarly, there are emerging data that SARS-CoV-2 genes encode K⁺ channels and may dysregulate the action potential and Ca²⁺ handling in cardiomyocytes, resulting in decreased cardiac contractility and increased susceptibility to arrhythmias. Excessive inflammation (interleukin 6, tumor necrosis factor α, and interleukin 1) can further modulate the function of several ion channels, specifically K⁺ and Ca²⁺ channels, leading to inflammatory cardiac channelopathies, QT prolongation, and arrhythmias. The emergence of ion channel–virus interactions has revealed the intriguing possibility that virally acquired ion channelopathies may explain some commonly observed virus-induced pathologies, including arrhythmias. This collateral damage from COVID-19 infections highlights the importance of monitoring the QT interval during acute illness, correcting all possible contributing factors, such as fever and electrolyte disturbances, and avoiding medications known to lengthen repolarization. Changes in the QT may be an early predictor of myocyte viral damage, a viral channelopathy, and may herald the development of arrhythmias. There are a great number of medications that are known to lengthen repolarization and hence the QT interval, but few that can correct it. Thus, the discovery of a prolonging QT interval in the setting of a COVID-19 infection, like so much to do with this disease, leaves us frustrated about what to do next. The arrhythmias that occur as a consequence of disordered ventricular repolarization—torsade de pointes, polymorphic ventricular tachycardia, and ventricular fibrillation—are treatable, yet a mechanism for avoiding them would be ideal. There are data indicating that increasing the serum K⁺ level and certainly avoiding a low K⁺ might shorten the QTc. Sodium channel–blocking agents, such as mexiletine, can shorten the QT interval even in patients without a sodium channelopathy. How these strategies can be used in a patient with COVID-19 remains uncharted territory.

ARTICLE INFORMATION
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