Arrhythmogenesis and COVID-19

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Abstract: The ongoing coronavirus infection-2019 (COVID-19) global pandemic has had devastating impacts on the global population since 2019. Cardiac complications are a well-documented sequela of COVID-19, with exposed patients experiencing complications such as myocardial infarction, myocarditis, and arrhythmias. This article aims to review prominent literature regarding COVID-19 and its link with arrhythmias, as well as to discuss some of the possible mechanisms by which arrhythmogenesis may occur in patients with COVID-19.

Key Words: Coronavirus disease 2019, arrhythmia, ventricular fibrillation, atrial fibrillation, QT prolongation, Torsades de pointes, cardiovascular, hydroxychloroquine

(Heart rhythms, arrhythmogenicity, COVID-19, cardiovascular system, electrolyte abnormalities, QT prolongation, comorbid conditions, pathogens, infection)

MECHANISMS OF ARRHYTHMOGENESIS

The proposed mechanism by which arrhythmias develop in patients with COVID-19 is likely to be multifactorial, yet research is needed to help delineate which factors are the most influential in the pathogenesis of arrhythmias. Currently, proposed mechanisms of arrhythmogenicity in patients with COVID-19 include acute myocardial injury due to direct viral infection, hypoxia, systemic inflammation, side effects of medications used for the management of COVID-19, drug interactions, and electrolyte abnormalities (Fig. 1).

Certain assumptions can be drawn from existing data. Strikingly, the severity of illness is strongly correlated with the development of arrhythmias. In the previously mentioned cohort study of 700 patients, after adjustment for multiple variables (sex, age, body mass index, history of heart failure, chronic heart disease, diabetes, hypertension, and even hydroxychloroquine treatment), admission to the intensive care unit (ICU) was the only variable associated with an increased odds of developing AF (odds ratio, 4.69; 95% confidence interval, 1.66–13.18) or developing NSVT (odds ratio, 8.92; 95% confidence interval, 1.73–46.06) when compared with patients not needing ICU admission. Another cohort study of 393 patients in New York also reported higher rates of arrhythmias, specifically of atrial arrhythmias, in patients requiring mechanical ventilation (17.7%) versus noninvasive ventilation groups (1.9%). These data are further supported in the Wuhan cohort study of 138 patients in which a higher rate of arrhythmias was also seen in more severely ill patients, as defined by patients necessitating ICU level treatment. Of the 36 patients in this study who were transferred to the ICU, 44.4% (16 patients) experienced an arrhythmia, as opposed to the 6.9% (7 patients) of non-ICU patients. It should be noted, however, that there was also a higher instance of comorbid conditions in the patients who needed ICU admission, and a large percentage of these patients had been managed with antibiotics known to have possible QT prolongation side effects, such as moxifloxacin and azithromycin.

The other Wuhan cohort of 85 fatal cases further supports the rationale for disease severity being linked with arrhythmogenicity since 60% of the patients in this study experienced arrhythmias. Outside factors, such as antibiotic therapy, were noted to be more similar among patients in this study; however, the researchers do not clarify which antibiotics were given to each patient. The study also suggests that overall systemic inflammation may be heavily involved in arrhythmogenesis, as the laboratory findings on admission showed a patient population with elevated patient mean levels of D-dimer, fibrinogen, and C reactive protein (CRP), all of which are relevant serum markers for inflammation. These further indicate an increased relationship between disease severity, a systemic inflammatory response, and the development of arrhythmias in patients with COVID-19.

In the Wuhan retrospective case series of 187 total patients, 11 patients developed malignant arrhythmias of ventricular tachycardia (VT) or ventricular fibrillation. Patients with elevated serum troponins, a common measure of myocardial injury, had more frequent
occurrences of these ventricular arrhythmias compared with patients with normal troponins (11.5% vs 5.2%; \( P < 0.001 \)). The elevated troponins were also positively correlated with increased serum levels of CRP. The paper reported no significant differences in treatment therapies among patients with normal or elevated troponins, aside from increased rates of steroid therapy and mechanical ventilation in patients with elevated troponins. Although the study displays evidence that disease severity and inflammation increase the prevalence of arrhythmias, the authors acknowledge that direct myocardial injury must also be considered as a possible cause of any arrhythmogenesis that follows.

**DRUG MECHANISMS**

A wide variety of both atrial and ventricular arrhythmias have been documented in patients with COVID-19, including sinus tachycardia, sinus bradycardia, bundle branch blocks, AF, supraventricular tachycardia (SVT), ventricular fibrillation, NSVT, torsades des pointes, and asystole.\(^5\) Therefore, while disease severity and inflammation may explain some of the observed arrhythmias seen in patients with COVID-19, they are unlikely to provide an explanation for the wide variety of arrhythmias.

This gap may be partially explained by the use of treatment modalities in the initial management of COVID-19. Earlier in the pandemic, hydroxychloroquine and azithromycin were some of the main medications used in the management of COVID-19, while they have since fallen out of favor with our increased understanding of the virus, their usage might explain some of the arrhythmias seen earlier in the disease spread. Hydroxychloroquine is well known for its side effects of QT elongation, presumably from its effects on altering cardiac conductivity and even possibly through direct myocardial damage. Aside from QT elongation, the known side effects of hydroxychloroquine include bundle branch blocks and ventricular arrhythmias, such as torsades de pointes. Furthermore, hydroxychloroquine is also known to have multiple interactions with medications, such as antiarrhythmics and beta blockers.\(^7\) Azithromycin, an antibiotic, which was also commonly used in the management of COVID-19, is also known to have possible side effects of QT prolongation.\(^7\)

Studies have shown this side effect of QT prolongation among the COVID-19 patient population. In Saleh et al,\(^8\) a group of 201 patients were treated with either monotherapy of hydroxychloroquine/chloroquine or combination therapy of hydroxychloroquine and azithromycin. Throughout hospitalization, the maximum corrected QT interval (QTc) was significantly longer in the combination group than the group receiving monotherapy (470.4 ms vs. 453.3 ms). Also, new arrhythmic events were noted in the patient population, including 17 cases of new AF, 7 new cases of NSVT, and 1 case of stable VT. Another 7 patients discontinued their combination therapy due to QTc prolongation; however, no cases of torsades de pointes or changes in risk of death were noted.\(^8\)

Additionally, in a double-blind study, Borba et al\(^9\) showed similar side effects of hydroxychloroquine in COVID-19 patients but demonstrated the effects to be more dose dependent. In this study, hydroxychloroquine given to higher dosage groups (600mg twice daily) showed increased mortality and more instances of QTc

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**FIGURE 1.** The schema illustrates the various arrhythmias encountered in patients with COVID-19 infection as a consequence of the virus infection affecting the heart and lung or producing systemic inflammation, the adverse (proarrhythmic) effects of COVID therapies and the drug-drug interactions that may occur. AF, atrial fibrillation; AVB, atrioventricular block; LQT, long QT interval; PEA, pulseless electrical activity; SB, sinus bradycardia; SCD, sudden cardiac death; SNS, sympathetic nervous system; STach, sinus tachycardia; TdP, torsade des pointes; VAs, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia.\(^5\)
intervals over 500 ms compared with the low-dose group (450 mg QD). A severe prolongation of QTc greater than 500 ms is commonly associated with a higher risk of malignant arrhythmias and sudden cardiac death.

Aside from dosage, data have also been released suggesting the synergistic effects of hydroxychloroquine and azithromycin. Another study of 85 COVID-19 patients treated with a combination of hydroxychloroquine and azithromycin showed that 30% of patients had their QTc increase significantly by greater than 40 ms, and a further 11% had QTc intervals greater than 500 ms. In total, there is evidence that hydroxychloroquine, if not properly dosed or if improperly added with azithromycin, may be at play in causing some of the arrhythmias seen in patients with COVID-19.

**CONCLUSIONS**

The purpose of this article is to discuss some of the research related to COVID-19 and the arrhythmogenesis that occurs as a result of the disease. Although our understanding of this virus is constantly evolving and data are still needed, early evidence suggests a correlation between disease severity and the development of arrhythmias in patients with COVID-19, possibly linked to the systemic inflammation that occurs as a result of infection. A smaller but still significant portion of arrhythmias, mostly QT prolongation, can also be attributed to the medications used in the early management of COVID-19. There are several constraints of this study, including the lack of data analyzing the impact of comorbidities, hypoxia, and electrolyte disturbances, which can have a role in the pathogenesis of arrhythmias. Also, as management of COVID-19 evolves, more research is needed regarding the side effects of more favorable current treatments, such as remdesivir, which also has been reported to have correlations with arrhythmias like AF.

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