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CLINICAL REVIEW

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Cardiac arrhythmias in patients with COVID-19

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Abstract

The emergence of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a major global public health concern. Although SARS-CoV-2 causes primarily respiratory problems, concurrent cardiac injury cannot be ignored since it may be an independent predictor for adverse outcomes. Cardiac arrhythmias are often observed in patients with COVID-19, especially in severe cases, and more likely contribute to the high risk of adverse outcomes. Arrhythmias should be regarded as one of the main complications of COVID-19. Mechanistically, a number of ion channels can be adversely affected in COVID-19, leading to alterations in cardiac conduction and/or repolarization properties, as well as calcium handling, which can predispose to cardiac arrhythmogenesis. In addition, several antimicrobials that are currently used as potential therapeutic agents for COVID-19, such as chloroquine, hydroxychloroquine and azithromycin, have uncertain benefit, and yet may induce electrocardiographic QT prolongation with potential ventricular pro-arrhythmic effects. Continuous electrocardiogram monitoring, accurate and prompt recognition of arrhythmias are important. The present review focuses on cardiac arrhythmias in patients with COVID-19, its underlying mechanisms, and proposed preventive and therapeutic strategies.

KEYWORDS
angiotensin-converting enzyme-2, arrhythmia, COVID-19, electrocardiogram, QT interval, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a new infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has reached pandemic status. Although clinical manifestations in patients with COVID-19 are mainly related to the respiratory system, cardiovascular complications have also been identified in the earliest reported cases from Wuhan, the epicenter of the outbreak.[1–3] COVID-19 can significantly affect cardiac function and induce cardiac injury. And the latter is associated with increased disease severity and fatal outcomes.[4–7] A variety of pro-inflammatory mediators play a key role in the pathophysiology of cardiac complications in COVID-19. Previous work has identified that ARDS (20%), arrhythmias (17%), shock (9%), and acute cardiac injury (7%) are common compilations in COVID-19.[1] Therefore, a better understanding of cardiovascular effects in SARS-CoV-2 infection is essential to mitigate poor prognosis in patients with COVID-19. The aim of this study is to conduct a comprehensive review of published studies on the electrophysiological effects of COVID-19. This is followed by a discussion on the underlying mechanisms, with proposals of preventative and therapeutic strategies for treating cardiac arrhythmias in COVID-19 patients.

2 | COVID-19-RELATED CARDIAC INJURY: A POSSIBLE CAUSE FOR ARRHYTHMIA?

The clinical course of SARS-CoV-2 infection is mostly characterized by respiratory tract symptoms, including fever, cough, pharyngodynia, fatigue, and complications related to pneumonia, such as acute respiratory distress syndrome and shock. Nevertheless, a brief case reported by Inciardi et al[8] suggests that cardiac involvement may occur in patients with COVID-19 even without signs and symptoms of respiratory tract infection. Cardiac injury in the setting of COVID-19 has attracted extensive attention and follow-up research in the academic community.

Several studies have proved that SARS-CoV-2 infection can induce cardiac injury. Previous studies defined cardiac injury as the serum levels of cardiac biomarkers (eg, troponin I) were above the 99th percentile upper reference limit.[1,2,9] Huang et al[2] first reported a 12% (5/41) incidence of acute cardiac injury in patients with COVID-19. A series of subsequently published studies confirmed the previous findings, the incidence of cardiac injury ranged from 7.2% to 28%.[1,2,6,7,10,11] Moreover, the incidence of myocardial injury was higher in severe and critical cases, which ranged from 22% to 44%,[1,2,9,12] compared to an incidence of approximately 2% to 4%[1,2] in less severe cases. Death cases (28% to 89%) had a conspicuously higher risk of cardiac damage than survivors (1% to 15%).[5,6,9,10,12–15] Several investigators have reported cardiac function and structural abnormalities in patients with SARS-CoV-2 infection, including acute heart failure (HF),[3,10,16] takotsubo syndrome,[17,18] viral myocarditis,[19] and acute myocardial infarction.[10,20,21] Chen et al[4] showed that elevated cardiac troponin I (TnI) (Odd ratio [OR]: 26.9, 95%CI 4.1-177.2, $P = .001$) was the independent risk factor for COVID-19 severity. Furthermore, Shi et al[6] first demonstrated that cardiac injury was independently associated with an increased risk of mortality in patients with COVID-19 (HR = 3.4, 95%CI 1.6-7.2, $P < .001$). Subsequently, Wang et al[5] has drawn a similar conclusion.[6] (Hazard ratio [HR]: 5.4, 95%CI 2.4-12.1, $P < .001$), with the presence of myocardial injury being significantly associated with higher risk of in-hospital mortality among COVID-19 patients. Guo et al[7] also found that the prognosis of patients with underlying cardiovascular disease (CVD) but without myocardial injury was relatively favorable, mortality during hospitalization was 7.6% (8/105) in patients without underlying CVD and normal troponin T (TnT) levels, 13% (4 of 30) in those with underlying CVD and normal TnT levels, 38% (6/16) for those without underlying CVD but elevated TnT levels, and 69% (25/36) for those with underlying CVD and elevated TnTs. Together, data from these studies illustrate that the SARS-CoV-2 infection results in varying degrees of cardiac damage, which explains adverse outcomes observed.

Cardiac injury is a common condition among hospitalized patients with COVID-19. However, cardiac biomarker levels reflecting myocardial injury in COVID-19 patients are affected by numerous factors, such as infection, hypoxia, and renal function, there may also be false positives. It is therefore incomplete to evaluate the risk of cardiac adverse events in COVID-19 patients simply by cardiac biomarkers alone.

3 | COVID-19-RELATED CARDIAC ARRHYTHMIAS

Full-genome sequencing and phylogenic analysis indicated that SARS-CoV-2 has features typical of the coronavirus family and distinct classified in the beta-coronavirus, belongs to the same genus as human severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).

In patients with SARS, tachycardia was the most common ECG abnormalities but usually self-limiting, the incidence ranged from 72%[22]; bradycardia was relatively less common, ranged from 2% to 15%.[22–24] ST-T changes and cardiac arrhythmias such as branch block, atrial fibrillation (AF), premature beats, QT interval prolongation, or even sudden cardiac death (SCD) were also seen in SARS patients.[22–27] Cardiac arrhythmias, including variable tachyarrhythmias and severe bradycardia requiring temporary pacemaker implantation, occurred in 16% (11/70) MERS cases.[28] More importantly, two MERS patients complicated with tachyarrhythmia were reported in 2014, one had hyperkalemia with associated ventricular tachycardia, and eventual cardiac arrest; the other had supraventricular tachycardia later in the course of illness, both patients ended up with death.[29] Thus, arrhythmias in SARS and MERS patients are not uncommon, and may lead to adverse outcomes.

Cardiac involvement has also been reported in patients with COVID-19, which can manifest as ECG abnormalities. COVID-19-related cardiac arrhythmia was first described by Wang and colleagues,[1] who reported a 17% (23/138) incidence of arrhythmias, 16 of them were admitted to intensive care unit (ICU), accounting for 44% of the total number of ICU patients. A recent study reported a rate of only 26% of the patients showing normal ECGs.[20] Lei et al[30] reported 24% of arrhythmias in COVID-19 patients, and 33% of patients admitted to ICU developed arrhythmias. In fatal cases of COVID-19, 60% had arrhythmia,[14] in addition, cardiac arrhythmias were independently associated with an increased risk of in-hospital death (11.5%, vs 5.6% among those without arrhythmia; odds ratio, 1.95; 95% CI, 1.33-2.86).[31]

Thus, arrhythmia should be regarded as one of the main complications of COVID-19, and proactive arrhythmia monitoring and management is needed.

3.1 | Tachycardia

COVID-19 patients have relatively increased fast heart rates (HR) ranging from 80 to 88 beats per minute (bpm) in sinus rhythm.[1,5,20,32] HR in patients treated in the ICU was faster than whom admitted in the general ward.[1] Nonsurvivors showed significantly faster baseline heart rates on admission compared to survivors.[10] Another study documented heart rate in 17 COVID-19 patients, and tachycardia was found in three patients (17.6%), one of those was a severe case, and two were critical cases.[33] Moreover, two patients in the critical group had AF with elevated ventricular rates between 123 and 160 bpm. One patient had persistent AF whereas the other did not have prior AF. Both passed away from COVID-19. The rising of HR in COVID-19 patients is disproportionate with the increase in the body temperature.[33]

Atrial tachyarrhythmias that had not been present on admission was recorded on a subsequent 12-lead ECG in 19 COVID-19 patients (19/115, 16.5%), all admitted to the MICU (27.5% of MICU patients), among them, atrial fibrillation in 12 patients, atrial flutter in 6 patients, and atrial tachycardia in 1 patient.[34] Atrial tachyarrhythmias were common among patients with COVID-19 who required admission to an intensive care unit and were often followed by hemodynamic deterioration.

In short, we have to pay attention to the tachycardias in the severe and critical COVID-19 patients. In addition to exacerbating the previous cardiomyopathy and conduction disorders, inducing arrhythmia events, SARS-CoV-2 may also induce electrophysiological abnormalities in patients with no previous history of heart disease under a variety of mechanisms.

3.2 | Atrioventricular/intraventricular conduction block

Our recent work reported that the incidence of cardiac arrhythmias in COVID-19 patients ranged from 17% to 30%.[1,20] Among these, atrioventricular/ventricular block (11.8%) was the highest incidence in arrhythmia, and the ratio exceeded sinus tachycardia (7.5%), sinus bradycardia (8%), atrial arrhythmias (7%), and ventricular arrhythmias (4%).[20] Complete heart block and severe left ventricular dysfunction were developed in a Child with COVID-19 Infection.[35] Another case from Iran also reported transient complete heart block in a patient with COVID-19,[36] and a 21-year-old female patient' ECG showed nonspecific intraventricular conduction delay and multiple premature ventricular complexes.[19]

3.3 | ST-T changes

In our report, ST-T changes were the most common ECG abnormality in COVID-19 patients, accounting for about 41% (38/93). Five of these patients were diagnosed with acute myocardial infarction (AMI).[20] A recent case series showed 18 patients with COVID-19 who had ST segment elevation in ECG, 13 (72%) patients died in the hospital (acute ST segment elevation myocardial infarction: n = 4; noncoronary myocardial injury: n = 9).[21] A 61-year-old Hispanic male presented with a Brugada-type pattern ECG in right precordial leads, 2 days later he developed a brief episode of atrioventricular nodal reentrant tachycardia (AVNRT).[37] A patient finally died within 24 hours of the occurrence of multifocal ventricular tachycardia (VT) and ST segment elevation.[38]

3.4 | QT interal prolongation

Our study found a proportion of 13% (12/93) COVID-19 patients had prolonged QT interval, mean QT interval was 431 milliseconds (414-454 milliseconds).[20] QT prolongation has previously been described associated with various conditions (eg, inherited arrhythmia syndromes, myocarditis toxicity, metabolic disorders, certain drugs). Several antimicrobials that are currently used as potential therapeutic agents for COVID-19 have uncertain benefit, and yet may induce electrocardiographic QT prolongation with potential ventricular pro-arrhythmic effects. These agents are chloroquine (CQ), hydroxychloroquine (HCQ), azithromycin, and lopinavir/ritonavir.[39] Recent evidence indicates significant QT prolongation in patients with COVID-19 receiving HCQ.[40]

For example, Borba and colleagues[41] performed a parallel, double-blind, randomized clinical trial designed to assess the safety of CQ in dosages, they found that prolongation of QTc interval was observed in 4 of 36 patients (11.1%) in the low-dose group (ie, 450 mg twice daily on day 1 and once daily for 4 days) and 7 of 37 patients (18.9%) in the high-dose group (ie, 600 mg CQ twice daily for 10 days); in addition, 2 patients in the high-dose group (2.7%) experienced ventricular tachycardia, 60% (3/5) patients in the high-dose group with underlying heart disease died. Moreover, the patients who received HCQ with concurrent treatment of azithromycin were at high risk of greater changes in QTc,[42] 12% of them manifested critical QTc prolongation, and the combination caused greater prolongation than either drug alone.[43] Chorin et al[44] observed QTc prolongation from a baseline average of 435 ± 24 milliseconds to 463 ± 32 milliseconds ($P < .001$), which was observed 3.6 ± 1.6 days after administration of HCQ + azithromycin therapy. In a subset of those patients (9/84, 11%), QTc was severely prolonged to >500 milliseconds, a known ECG marker of high risk of malignant arrhythmia and sudden cardiac death.[44] A greater proportion of patients receiving HCQ+azithromycin experienced cardiac arrest (15.5%) and abnormal ECG findings (27.1%), as did those in the HCQ alone group (13.7% and 27.3%, respectively), compared with azithromycin alone (6.2% and 16.1%, respectively).[45]

Certain antifungal drugs, glucocorticoids and certain antiarrhythmic drugs lead to prolonged QT intervals as well. If these medications are used, clinicians should monitor the patient for side effects, especially prolonged QTc interval by continuous ECG monitoring.

3.5 | Malignant arrhythmias

COVID-19 patients generally have comorbidities that can increase the risk of serious arrhythmias. Malignant arrhythmias in COVID-19 were first described by Guo and colleagues,[7] who reported a 5.9% (11/187) incidence of malignant arrhythmias, including VT/ventricular fibrillation (VF). Also, Du et al[14] reported a large series of patients who died from COVID-19, and found that common cause of death in 7 of the 81 patients was cardiac arrest (8.64%), followed by acute coronary syndrome (4.94%) and malignant arrhythmias (2.47%). In adjusted models with those receiving HCQ or azithromycin as comparison, cardiac arrest was more likely in patients receiving HCQ + azithromycin (adjusted OR, 2.13 [95% CI, 1.12-4.05]; E-value = 1.31).[45] SARS-CoV-2 can cause a variety of ECG changes, similar to SARS-CoV. By contrast, SARS-CoV-2 is more likely to induce atrioventricular/intraventricular conduction block, QT interval prolongation, which may lead to a higher risk of malignant ventricular tachyarrhythmias.

At present, the ECG data of COVID-19 patients are limited, and there are discrepancies in terms of the reported rates of various arrhythmia types among the different studies. This is likely the result of the nonhomogeneous characteristics of selected cases among studies, small sample size, region of origin, and the lack of continuous ECG monitoring data. A single ECG evaluation is not comprehensive. Dynamic ECG monitoring is required to better identify the type of arrhythmias. The available data indicate that the clinical course of COVID-19 develops rapidly, the ECG abnormalities detected during hospital stay may be used as a predictor for the severity of disease. If any critical COVID-19 patient has pathophysiological changes similar to fulminant myocarditis, or ECG abnormalities such as conduction block, QT interval prolongation, and ventricular arrhythmia, they probably have a poor prognosis. It is therefore recommended that clinicians should perform a comprehensive evaluation through combining cardiac injury biomarkers, ECG dynamic changes and cardiac imaging, and be alert to life-threatening ventricular arrhythmia storms.

4 | PUTATIVE MECHANISMS OF ARRHYTHMIAS IN SARS-COV-2

A summary of the potential mechanisms by which cardiac arrhythmias occur in SARS-COV-2 infections is shown in Figure 1.

First, SARS-COV-2 may induce injury to cardiomyocytes directly. SARS-COV-2 virus can be internalized after binding to the ACE2 surface receptor on cell membranes, facilitated by the membrane binding proteases of transmembrane serine protease 2 (TMPRSS2) by cleaving the virus S protein.[46,47] Once inside the cell, coronaviruses replicate using a number of host molecular machinery, such as the NF-κB pathway.[48] Activated NF-κB can affect mRNA expression of pore-forming subunit of fast transient outward potassium current (Ito,f), which can promote arrhythmia by affecting action potential (AP).[49]

Second, SARS-COV-2 may induce cell death. Recent studies have shown that after SARS-COV-2 infection of human bile duct epithelial cells, the expression of genes related to "positive regulation of cell death" and "cell response to external stimulation" such as CD40, caspase recruitment domain family member 8 (CARD8) and serine/thunine kinase 4 (STK4) were significantly up-regulated to induce cell death.[50] We speculate that an analogous mechanism may operate in cardiomyocytes. Previous tissue visualization has revealed irregular shape of the myocardium, darkened cytoplasm, mild fibrosis, and mild hypertrophy of the myocardium.[51] Finally, myocardial damage may reflect ongoing myocarditis and could induce arrhythmias by inducing electrical abnormalities.

Hypoxemia caused by respiratory dysfunction causes a relatively hypoxic environment of the myocardium. Hypoxia can promote cardiomyocyte cell death and affect the function of ion

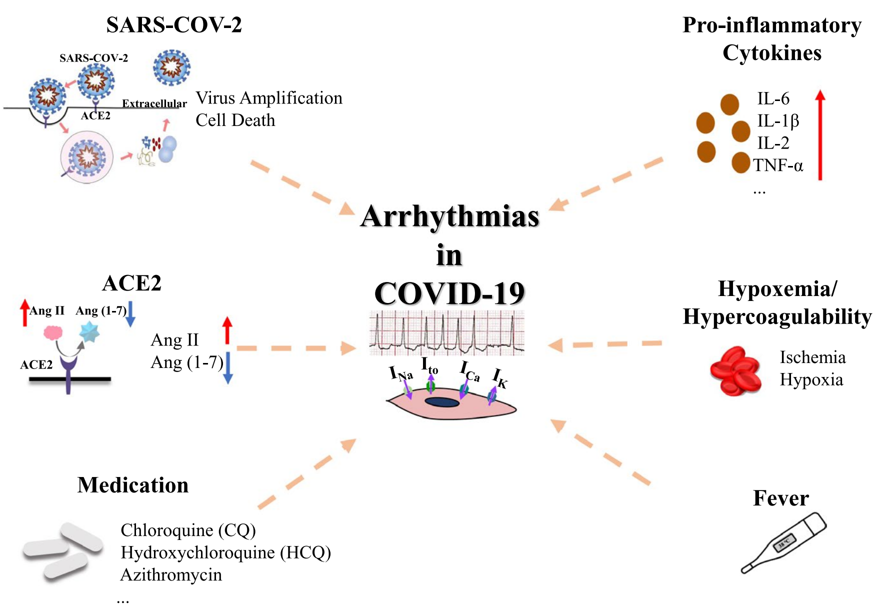

FIGURE 1 Potential Mechanisms of Cardiac Arrhythmias in COVID-19. SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ACE2: Angiotensin-converting enzyme-2; Angiotensin II: Ang II; Angiotensin (1-7): Ang (1-7); I_K: potassium channel; I_{Na}: sodium current; I_{Ca}: Ca^{2+} current; IL: Interleukin

channels, leading to alterations in cardiac AP prolongation and/or repolarization, thereby promoting arrhythmogenesis.[52] Hypoxia degrades the expression of the hERG, encoding pore-forming subunit of the fast-activated delayed rectified potassium channel (I_{Kr}), by secreting calopersin, which reduces the I_{Kr}.[53] Moreover, late sodium current (I_{NaL}) is increased under hypoxia.[54] Together, ventricular repolarization may be prolonged, leading to reentrant arrhythmias. By contrast, a shortening in repolarization time caused by small-conductance Ca^{2+}-activated K^+ (SK) channels may also be pro-arrhythmic, especially where there is accompanying shortening in the effective refractory periods.[55] This would be expected to reduce cardiac excitation wavelength in turn predisposing to reentrant activity.

Pro-inflammatory cytokines usually increased in COVID-19 patients, and cytokine storms have been reported in severe cases. These cytokines include IL-6 and IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, CCL3, and TNF-α.[2,56–58] Acute administration of IL-6 significantly increased L-type Ca^{2+} current (I_{CaL}) density and higher amplitudes/durations of calcium transients in ventricular cardiomyocytes.[59] Long-term exposure to IL-6 significantly down-regulated the expression level of Ca^{2+}-ATPase (SERCA2) gene in neonatal rat ventricular myocytes, which affected intracellular Ca^{2+} level.[49] These studies suggest that IL-6 may affect cardiac AP in multiple ways. In addition, there was a significant correlation between IL-6 level and P wave index. Moreover, IL-6 can down-regulate atrial myocyte junction proteins causing atrial electrical remodeling.[60] Thus, increased IL-6 in COVID-19 patients may affect AP and electrical conduction leading to arrhythmias. IL-1β extends the APD by reducing I_{to} current, increasing CaMKII oxidation/phosphorylation and Ca^{2+} spark frequency, promoting arrhythmia.[61] Also, IL-2 increases the peak I_{Na} density by increasing the transcriptional level of SCN3B, encoding the sodium channel,[49,62] which leads to a decrease in the AP maximum upstroke velocity and ultimately promotes arrhythmia. TNF-α significantly decreased the I_{Kr} density in ventricular myocytes by altering the type of reactive oxygen species, thereby prolonging APD.[49,63] In addition, TNF-α also reduced I_{CaL}, intracellular calcium transients. Moreover, TNF-α may reduce the expression of SERCA2a by inducing the level of DNA methyltransferase.[64] Therefore, TNF-α signaling is also an important inflammatory factor leading to arrhythmia.

Patients with COVID-19 often present with fever. In the patients with some underlying heart diseases, fever can trigger ventricular fibrillation.[65,66] It may be related to ion channel mutations, such as SCN5A in Brugada syndrome.[64] Besides, abnormal sodium current also plays an important role.[67,68] In addition, fever can cause tachyarrhythmias in individuals without inherited heart disease. Its presence may alter the efficacy of sodium channel blockers in terms of their antiarrhythmic effects.[69]

SARS-COV-2 may induce myocardial injury by inhibiting the activity of ACE2. It is thought that ACE2 could be internalized and shed from the membrane surface diminishing function of ACE2 when SARS-COV-2 binding to ACE2 to enter cells.[68] The conversion of angiotensin II (Ang II) to Ang (1-7) may be reduced, which weakens the cardiovascular protection effect of Ang (1-7) through the Mas receptor.[70,71] For example, Ang1-7 could change I_{CaL}, Ito, expression of Kv4.3 potassium channel, and Ca^{2+} channel to prevent AF ionic remodeling.[72] Besides, Ang II induces automatic activities by activating IP_3 receptors and Na^+-Ca^{2+} exchanger in guinea pig pulmonary vein myocardium. In addition, chronic Ang II exposure induces ROS production by NOX2 resulting in oxidative activation of CaMKII, further promotes SR- Ca^{2+} leakage, thus increasing the possibility of delayed after depolarization (DAD).[73] Ang II induces membrane depolarization and activation of I_{CaL}.[74] The accumulation of Ang II promotes myocardial fibrosis and cardiac remodeling. These will promote the occurrence of arrhythmias.

Many patients have disorders of coagulation and fibrinolytic system, showing hypercoagulability of blood, and even disseminated intravascular coagulation (DIC).[75] The effects of hypercoagulation on the myocardium, such as acute coronary syndrome,[76] will be ischemia and hypoxia, leading to cardiac electrophysiological abnormalities. It has been changed that Na^+-Ca^{2+} exchange, I_K current, and phosphorylation of proteins in the sarcoplasmic reticulum.[77,78] Next, early and late depolarization, inducing ectopic beats, and the APD changed. All these will promote the development of reentrant arrhythmias such as malignant ventricular arrhythmia.[64,77] In addition, acute left atrial ischemia led to ATP-sensitive potassium current (IKATP) conductor-dependent shortened APD, as well as spontaneous focal discharges and reentry loops.[79] Chronic atrial ischemia/infarction promoted atrial fibrillation by unprompted ectopy and sustained reentry.[80]

Administration of certain drugs may affect the electrophysiological properties of the myocardium. For example, the recently controversial CQ and HCQ can cause prolongation of QT interval. In sinoatrial node (SAN) myocytes, HCQ decreased spontaneous action potential firing rate and the "funny" current (I_f), and it also affected I_{CaL} and I_{Kr}.[81] These changes caused a delay in the depolarization, thus lowering the heart rate.[76,82] In addition, azithromycin can also affect the occurrence of AP promoting arrhythmias in cardiomyocytes. It is reported that azithromycin can inhibit I_{CaL}, I_{Na}, and I_{Kr} current, causing bradyarrhythmia.[83] However, azithromycin can increase I_{Na} currents in cardiomyocytes with chronic (24 hour) exposure.[84] Moreover, azithromycin promoted the production of reactive oxygen species in cardiomyocytes, mitochondrial damage,[85] inducing cardiac dysfunction and eventually arrhythmia occurs.

Together, a number of ion channels can be adversely affected in COVID-19, leading to alterations in cardiac conduction and/or repolarization properties, as well as calcium handling, which can predispose to cardiac arrhythmogenesis.

5 | MANAGEMENT STRATEGIES OF ARRHYTHMIAS IN SARS-COV-2

5.1 | Clinical manifestations and diagnosis

Clinicians should be vigilant of potential rhythm disturbances in COVID-19. Palpitation has been reported as the initial symptom in

7% (10/137) of COVID-19 patients.[86] Around 4% of COVID-19 patients have a prior history of cardiac arrhythmias and may be particularly susceptible to further rhythm disorders.[87] Therefore, there is a need to determine essential clinical information, such as a history of arrhythmias, unexplained syncope, family history of premature sudden cardiac death, as well as a detailed medication history, especially medications that can induce electrocardiographic QT prolongation, and baseline ECGs. Patients with underlying cardiovascular diseases require attention to their ECG abnormalities and potential risk of cardiac arrhythmias, so as to prevent adverse clinical events.

Baseline examination is necessary to evaluate the hospitalized patients or those who may be at higher risk for cardiac arrhythmias. If the patients with COVID-19 present with palpitation, dizziness, or even unexplained syncope, monitoring for cardiac arrhythmias should be performed. If baseline ECG examination reveals a moderately prolonged QTc, optimization of medications and electrolytes may permit therapy. If the QTc is markedly prolonged, medications which further prolong it should be avoided, or expert consultation may permit administration with mitigating precautions.

ECG should be closely monitored for early warning and intervention. During the pandemic, avoidance from nonessential testing, including serial ECG, reduces exposure of front-line medical workers and other patients to infectious risk. Therefore, continuous ECG monitoring should be applied more in patients with COVID-19, especially in the patients with cardiac comorbidities. Some other experts suggest that it may be feasible to use a handheld ECG device and mobile continuous telemetry monitor (MCOT) as a QT screening tool in patients with COVID-19.[88,89] Experts from National Center for Gerontology[90] suggest that cardiologists and primary care physicians should pay attention to the following ECG indicators: the ST-T changes accompanied by continuously dynamic changes in two or more leads (I, II, aVF, V5) with R waves domination; new-onset sinus, atrioventricular conduction block, complete right or left bundle branch block, sinus arrest; continuous, coupled, pleomorphic, or multifocal premature contractions; atrioventricular reentrant tachycardia; atrial flutter/atrial fibrillation, QRS complex low voltage, abnormal Q waves and wide QRS complex (QRS > 120ms), continuous ECG monitoring if necessary. Attention should also be paid to whether patients have paroxysmal tachycardia or an increase in pulse rate that does not match the disease severity status. Early identification of high-risk ECG and arrhythmia, and timely intervention are quite important. Bedside temporary cardiac pacemaker and defibrillator monitoring can be helpful.

5.2 | Prevention and treatment

Thus far, no specific antiviral drugs or vaccines have been confirmed to benefit COVID-19 except for symptomatic relief and supportive treatments. The treatment guidelines for COVID-19 published by The National Institutes of Health (NIH) determined that no drug(s) has been proven to be safe and effective for treating COVID-19 at present. Although reports have appeared in the medical literature asserting successful treatment of COVID-19 by multiple medications,[41,91,92] additional evidence from ongoing clinical trials will be needed to identify the optimal treatment. Several antiviral agents and immunomodulating therapies are currently under clinical investigation.

Moreover, the COVID-19 Treatment Guidelines Panel recommends against the use of the following drugs for the treatment of COVID-19: the combination of HCQ plus azithromycin (AIII) because of the potential for toxicities, except in the context of a clinical trial; Lopinavir/ritonavir (AI) or other human immunodeficiency virus (HIV) protease inhibitors (AIII) because of unfavorable pharmacodynamics and negative clinical trial data.[93]

Tempered with concerns of increased risks of QT prolongation and development of TdP, which may be life-threatening, our potential therapeutic options are that it is necessary to discontinue unnecessary medications which may also increase the risk of arrhythmias. If this combination proves to be life-saving for COVID-19 patients, monitoring the QT interval to allow patients to receive combination therapies will be critical.

Certainly, the use of combination therapies with azithromycin and CQ or HCQ in high-risk patients must be carefully weighed against the risks. The higher dosage of CQ (ie, 600 mg CQ twice daily for 10 days) should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir.[41] The late sodium channel-blocking drugs like mexiletine have been proposed to be used if the QT interval prolongs.[94] A temporary transvenous pacemaker may be necessary to overdrive pace if the patient is bradycardia with premature ventricular complexes. Careful attention to serum electrolytes, heart rate, and monitoring of QTc intervals may allow administration of a full course of these drugs.

Prevention or treatment of arrhythmias in COVID-19 patients should include optimization of supportive treatments, including bed rest, maintaining water and electrolyte balance, medication or physical cooling in patients with fever, oxygen supplementation in patients with hypoxia or dyspnea, and noninvasive or invasive ventilator support treatment where indicated. For patients with sinus tachycardia, diltiazem or ivabradine may be used for rate management.[90] Diltiazem, propafenone, or verapamil were also considered first in patients with atrial premature beats or tachycardia without cardiac disease.[95] Beta-blockers may promote bronchial smooth muscle spasm and induce asthma adverse reactions, should be used with caution in patients with COVID-19 combined with sinus or atrial tachycardia. If the patient shows sustained VT, intravenous infusion of amiodarone and other antiarrhythmic medications may be given, electrical defibrillation can be used if it necessary. If VF occurs, cardiopulmonary resuscitation should be initiated and defibrillation should be initiated immediately. If patients with severe bradycardia resulting in dizziness, amaurosis, syncope and other symptoms, can be given atropine, isoproterenol, and other drugs to increase the heart rate or a temporary venous pacemaker may be placed. In anticipation of the predicted surge of patients infected with COVID-19 and the need to rationally utilize personal protective equipment (PPE) while continuing to provide urgent and emergency cardiac interventions, adequate provision of PPE is just the first step.

6 | CONCLUSIONS

Outbreaks of COVID-19 threaten public health but the associated extrapulmonary manifestations and their prolonged consequences are often overlooked. Previous reports reveal that cardiac arrhythmias are one of the common complications associated with COVID-19, which may sometimes be life-threatening. We would suggest that front-line clinicians monitor cardiac rhythm as part of the routine care, and the data may shed light on whether COVID-19-related arrhythmic complications is an independent predictor of adverse outcomes. Early diagnosis and timely treatment to reduce mortality is of crucial importance. Herein, we summarize potential pharmacological and interventional strategies for dealing with such problem. Several medications are currently being tested for their antiviral actions, with potential side effects such as QT prolongation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

Not required.

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