Review

COVID-19 and arrhythmia: An overview

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ABSTRACT

Arrhythmias in COVID-19 patients are associated with hypoxia, myocardial ischemia, cytokines, inflammation, electrolyte abnormalities, pro-arrhythmic or QT-prolonging medications, and underlying heart conditions such as severe congestive heart failure, inherited arrhythmia syndromes, or congenital heart conditions. In the pediatric population, multisystem inflammatory syndrome can lead to cardiac injury and arrhythmias. In addition, arrhythmias and cardiac arrests are most prevalent in the critically ill intensive care unit COVID-19 patient population. This review presents an overview of the association between COVID-19 and arrhythmias by detailing possible pathophysiological mechanisms, existing knowledge of pro-arrhythmic factors, and results from studies in adult and pediatric COVID-19 populations, and the clinical implications.

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Introduction

Arrhythmias are a potentially life-threatening complication of coronavirus 2019 (COVID-19) infection, with one study showing arrhythmias in 17% of non-intensive care unit (ICU) hospitalized patients and upwards of 44% of ICU patients [1]. Currently, the mechanisms behind COVID-19′s impact on the heart are not well established. COVID-19 is thought to induce the upregulation of angiotensin-converting enzyme (ACE)−2 receptors in various organs which the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can use as an entry point. Upregulation in the heart may allow the SARS-CoV-2 to infect the conduction pathways more

easily, which can lead to arrhythmia. QT-prolonging medications, induced proinflammatory state, demand ischemia, myocarditis, or underlying heart conditions can also induce arrhythmias in COVID-19 patients. Patients with pre-existing heart conditions and other comorbidities may be more likely to develop arrhythmias and have unfavorable clinical outcomes. This review presents an overview of the relationship between arrhythmias and COVID-19, as elucidated by possible pathophysiological mechanisms, existing knowledge of pro-arrhythmic factors, results from studies in adult and pediatric COVID-19 populations, and implications on management.

SARS-CoV-2 and ACE-2 in the heart

The SARS-CoV-2 virus uses the ACE-2 receptor as an entry receptor when it infects cells. In an experiment conducted using HeLa cells, the SARS-CoV-2 was only able to enter the cells that expressed the ACE-2 receptor [2]. These receptors are found abun-

dantly in human cardiac tissue. ACE-2 mRNA expression is higher in the heart than in the lung. Also, cardiac tissue obtained from 39 consecutive autopsy cases detected SARS-CoV-2 in heart tissue in 24 of the 39 patients. This suggests that SARS-CoV-2 can directly infect cardiac tissue [3].

Firstly, SARS-CoV2's outer spike proteins generate S1 and S2 subunits using the furin enzyme that is found abundantly in the host blood and lungs. Then, the S1 subunit binds to the ACE-2 receptor and facilitates attachment to the host cell. The S2 sub-unit facilitates viral fusion with the host membrane after interaction with transmembrane protease serine 2 [4]. Although the receptor is mainly expressed in type 1 and type 2 pneumocytes in the lungs, it may also be expressed in other organs, including the heart, kidneys, and intestines [5].

Upon entry to the host cell, SARS-CoV2 down-regulates ACE-2 expression [6]. ACE-2 converts the pro-inflammatory and pro-oxidant angiotensin II to angiotensin 1–7 [6]. This down-regulation, especially at the heart, is theorized to promote a pro-inflammatory environment that can lead to arrhythmias [6].

Previously, since the virus uses ACE-2 receptors for host cell entry, there was a concern that taking renin-angiotensin-aldosterone system (RAAS) inhibitors may upregulate the ACE-2 receptor and increase mortality risk [4]. A recent case-control study in Korea found 1644 patients with hypertension or heart failure who had COVID-19 and compared COVID-19 disease severity and mortality between those exposed to RAAS inhibitors and those not exposed. The study found no link between the use of RAAS inhibitors and the severity of COVID-19 [7].

Types of arrhythmias encountered in COVID-19 patients

Tachyarrhythmias and bradyarrhythmias are both encountered in the context of COVID-19. In a global survey of 1197 electrophysiology professionals, the tachyarrhythmia most reported was atrial fibrillation ($n = 179$), followed by premature ventricular contractions/non-sustained ventricular tachycardia ($n = 103$), paroxysmal supraventricular tachycardias ($n = 39$), cardiac arrest secondary to pulseless electrical activity ($n = 38$), cardiac arrest secondary to ventricular tachycardia/fibrillation ($n = 33$), sustained monomorphic ventricular tachycardia ($n = 26$), polymorphic ventricular tachycardia/Torsade de Pointes ($n = 24$), and finally sustained atrial tachycardia ($n = 24$) [8]. For bradyarrhythmias, severe sinus bradycardia ($n = 51$) and complete heart block ($n = 51$) were the most frequently answered, followed by bundle branch block/intraventricular conduction delay ($n = 26$), second degree atrioventricular (AV) block ($n = 21$), and finally first-degree AV block ($n = 18$) [8]. Most professionals did not encounter tachyarrhythmia or bradyarrhythmia in this survey: 550 out of 663 electrophysiology professionals (82.96%) who answered about bradyarrhythmia, did not see bradyarrhythmia, and 449 out 683 who answered about tachyarrhythmias (65.74%), did not see tachyarrhythmias. However, the encounter rate of bradyarrhythmia in this survey is still 17.04%, and tachyarrhythmia is 34.26%, which makes it quite common [8]. Therefore, it is important to anticipate tachyarrhythmia or bradyarrhythmia in hospitalized COVID-19 patients.

Cardiac injury and troponin levels in COVID-19-positive patients

In a recent cohort study, 19.7% of 416 COVID-19 patients had significantly raised levels of high-sensitivity cardiac troponin, indicating cardiac injury [9]. Patients with cardiac injury usually were older and had comorbidities [9]. Another study showed elevated troponin levels in 27.8% of hospitalized COVID-19 patients, and 35.3% of these patients also had underlying cardiovascular disease

[10]. Both studies showed that elevated troponins are associated with higher mortality [9,10]. Elevated troponin I levels were also linked to a higher risk of complications such as acute respiratory distress syndrome (ARDS), acute renal injury, acute coagulopathy, malignant arrhythmias, and a higher mortality rate than patients with normal cardiac biomarkers [9,10].

Mechanisms and factors for arrhythmias in COVID-19 patients

Some risk factors may predispose COVID-19 patients to arrhythmias: hypoxia that can be brought on by pneumonia, electrolyte imbalances from renal failure, diuretics, and renal failure, acute myocardial injury which can be caused by infarction, myocarditis, sepsis, ARDS, acute renal failure, pulmonary embolism, and cardiotoxicity, and finally heart failure [11]. Underlying health conditions such as hypertension, diabetes, congenital heart problems, and thyroid problems may also increase this risk.

Direct viral infection

A study of autopsy cases detected SARS-CoV-2 directly from heart tissue, showing that direct cardiac infection with the virus is possible [3]. Increased troponin levels in these patients also are linked with an elevated risk of cardiac arrhythmia [3]. SARS-CoV-2 virus enters heart cells through the ACE-2 receptors [2].

The pathophysiology of this process can be visualized in Fig. 1 and a close-up between the binding of SARS-CoV-2 and the ACE-2 receptor can be seen in Fig. 2. The binding of the SARS-CoV-2 virus to ACE-2 receptors allows entry into the cell for viral replication. Because ACE-2 receptors are bound by SARS-CoV-2, angiotensin II is unable to bind to ACE-2. This can then down-regulate the expression of ACE-2 receptors thus resulting in a build-up of angiotensin II. Angiotensin II can then act on ACE type 1 receptors leading to a proinflammatory state in the myocardium [12]. The S1 protein is also a major structural component of SARS-CoV-2 involved in binding. The S protein is the combination of an S1 subunit that is distant from the viral membrane and an S2 subunit that is more proximal to the viral membrane. Both S1 and S2 subunits are present on the surface of the virus envelope as a homotrimer involved in the binding to ACE-2 receptors and eventual viral entry. The S1 subunit is a spike protein that is specifically involved in the binding process to ACE-2 receptors. S1 determines receptor recognition through its receptor-binding domain (RBD). S2 subunit is mainly involved in membrane fusion and assists in allowing the virus to enter cells. Both the S1 and S2 have been researched as potential treatments that can interfere with viral receptor binding. By blocking the binding of RBD to ACE-2 receptors the virus is unable to enter cells and replicate [13].

The ACE-2 receptor is an important potential therapeutic target, as this displays the most potent neutralizing activity in vitro. One study found that it conferred strong protection against SARS-CoV-2 infection in Ad5-hACE2-sensitized mice [14]. The study provided a functional basis for neutralizing entry of the SARS-CoV-2 virus into cells. Future perspectives into novel treatments for SARS-CoV-2 have utilized sophisticated artificial intelligence algorithms to predict potential treatments. Baricitinib was identified through this process due to its ability to impair SARS-CoV-2 cellular entry and infectivity. One study found that the combination of baricitinib plus remdesivir was superior to remdesivir alone in the treatment of COVID-19 in patients not on mechanical ventilation. Future perspectives will focus on the role of immunomodulators in the treatment of COVID-19 [15].

Myocarditis and pericarditis

Myocarditis and pericarditis, potential manifestations of direct infection, can precipitate arrhythmias. There are several suggested
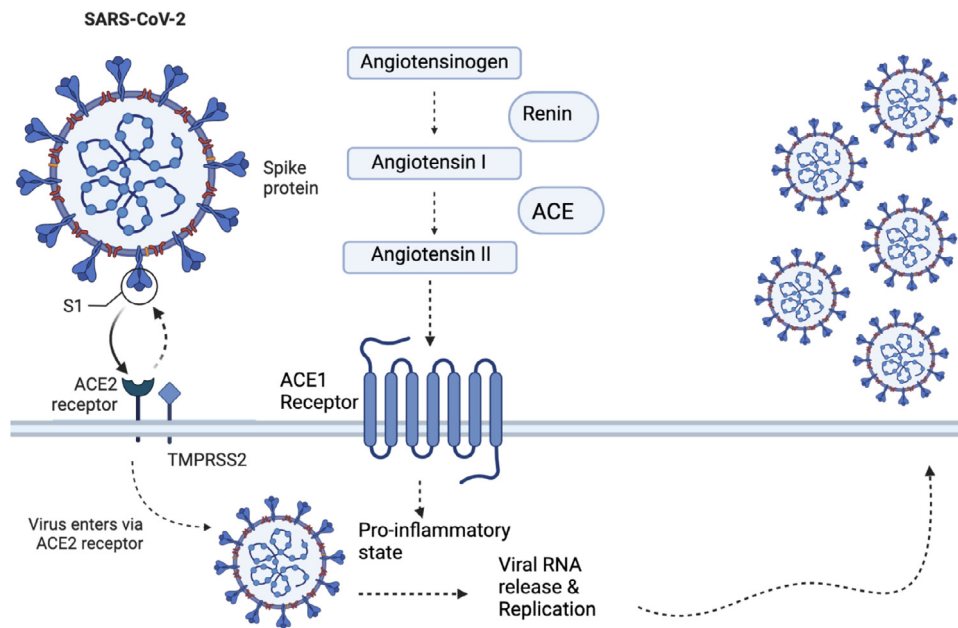
Fig. 1. SARS-CoV-2 mechanism of infection and pathophysiology. ACE, angiotensin-converting enzyme; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TM-PRSS2, transmembrane protease serine 2.
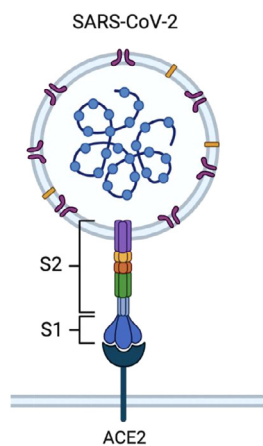

Fig. 2. SARS-CoV-2 receptor with ACE-2 receptor. ACE, angiotensin-converting enzyme; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

mechanisms of arrhythmias in viral myocarditis, including an electrical imbalance in myocytes caused by membrane lysis, ischemia caused by endothelial dysfunction, reduced expression of gap junction proteins in the myocardium, alteration in calcium levels, and channelopathies, and post-inflammatory myocardial scarring.

Reentrant arrhythmias that occur in myocarditis can also be traced back to angiotensin II which enhances cardiac fibrosis and remodeling exacerbated inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin (IL)−6 which are responsible for modifying the function of the cardiac ion channels. The expression and function of the rapid rectifier potassium channels (IKR) and calcium channels were altered secondary to inflammatory cytokines. IL-6 is responsible for arrhythmia generation through cell membrane damage. IL-6 causes displacement of plakoglobin (a desmosomal protein) causing cell membrane damage and inflammatory edema leading to electrical conduction disturbances, causing arrhythmias. IL-6 can also worsen drug-drug interactions by increasing the bioavailability of medication secondary to inhibiting cytochrome P450 [16].

Pericarditis can predispose patients with COVID-19 to electrocardiographic (ECG) abnormalities such as atrial fibrillation development. A study showed that 26% of the COVID-19 patients with pericarditis developed acute onset ECG abnormalities. These abnormalities included atrial fibrillation, ST-T changes, tachycardia-bradycardia syndrome, along with acute pericarditis-related changes. It is difficult to assess COVID-19-related or drug-related ECG changes in patients with pre-existing ST-T changes associated with acute pericarditis [19]. Importantly, the relationship between the onset of COVID-19 symptoms and ECG abnormalities appeared late from the onset of hospitalization [17]. In the study, the timeframe from the onset of symptoms and hospital admission to showing ECG abnormalities was 20–30 days [17].

Myocarditis and COVID-19 vaccine

Myocarditis has been recognized as one of the rare adverse effects of the COVID-19 vaccine, particularly that of mRNA type COVID-19 vaccines. The mechanism of myocardial injury is not yet determined but thought to be due to molecular mimicry at this time. Several theories have been proposed regarding the mechanism for the development of myocarditis. Molecular mimicry between the spike protein of SARS-CoV2 and self-antigens may cause dysregulated cytokine expression, and immune response to mRNA, which leads to activation and dysregulation of immune pathways in certain individuals [18].

According to the Advisory Committee of Immunization practices of approximately 300 million mRNA COVID-19 vaccines administered through June 2021, 1226 reports of possible myocarditis/pericarditis were filed with VAERS (Vaccine Adverse Event Reporting System). Out of these 1226 cases, nearly 67% were reported after the second dose, with 79% being reported in males mostly below the age of 24 years. Seemingly, there is a clear predilection to males when it comes to mRNA vaccine-associated myocarditis, but the mechanism is unknown currently.

The US Centers for Disease Control and Prevention reviewed and characterized 484 possible myocarditis cases in people below 29 years. Most cases had chest pain with the presentation with ST and T wave changes in ECG. Only 17% of these cases had abnormal cardiac imaging [19]. Per VAERS myocarditis cases reported a week

after 2nd dose of mRNA vaccine was administered, crude reporting rates were calculated using national COVID vaccine administration data as of June 11, 2021. For every million second dose of mRNA COVID vaccine administered in males of 12–29 years there were 40.6 cases of myocarditis reported. In males above the age of 30 years, there were 2.4 cases reported per million of second doses of mRNA vaccine. Reporting rates among females in the same age rooms were 4.2 and 1.0 per million, second doses respectively [19].

Hypoxia and myocardial ischemia

Low levels of oxygen can promote anaerobic respiration which decreases cellular pH, which increases cytosolic calcium levels, and increases extracellular potassium levels [20]. This could lead to early and late depolarizations and changes in action potential duration [20]. An increase in extracellular potassium levels can decrease the action potential threshold which can cause faster conduction between cardiac cells [20]. Finally, the gap junctional protein connexin-43 might be susceptible to dephosphorylation in hypoxia, which can decrease electrical coupling and tissue anisotropy [20]. Additionally, scarring after myocardial ischemia can also disrupt conduction pathways and lead to arrhythmias.

Cytokines and systemic inflammation

An overactive inflammatory response, resulting in disseminated intravascular coagulation or cytokine storm of IL-6 and TNF-α, can promote coagulation by disrupting the balance between the coagulation and fibrinolytic pathways [21]. This coagulopathy can lead to complications such as pulmonary embolism, which can lead to right-sided myocardial strain, right atrial overload, and subsequent arrhythmia. Additionally, IL-6, TNF-α, and IL-1 can affect the function of K^+ and Ca^{2+} ion channels on ventricular cardiomyocytes and prolong ventricular action potential duration. This can increase the risk of Torsade de Pointes and subsequent ventricular fibrillation. Both demand ischemia and cytokine-storm-induced disruption of atherosclerotic plaques have been theorized as possible causes of myocardial ischemia in COVID-19 patients, which can lead to arrhythmias. In addition, an increase in the sympathetic drive after myocardial infarction may promote lipolysis of surrounding adipose tissue, which is associated with ventricular arrhythmias [22]. Increased sympathetic drive can also enhance automaticity, prolonging action potential duration and delaying repolarization which can lead to increased risk of atrial tachyarrhythmias [23].

Inflammation is also thought to increase the risk of thromboembolic complications associated with atrial fibrillation. The cytokine response due to SARS-CoV-2 infection has been shown to cause endothelial damage and activation of the clotting cascade [24,25]. Due to the delay in receiving primary percutaneous coronary interventions in some overburdened COVID-19 hospitals, fibrinolytic therapy has been administered instead [26]. The use of therapeutic anticoagulation in COVID-19 patients was high [8]. The relationship between COVID-19-related inflammation and atrial fibrillation reinforces the need to carefully monitor patients for thromboembolic events [17,26].

Electrolyte and volume imbalances

Electrolyte and volume imbalances could be a potential manifestation of COVID-19 itself. Diarrhea, sepsis, acute kidney injury, and dehydration in COVID-19 can lead to electrolyte abnormalities [27]. Imbalances of potassium, calcium, sodium, and magnesium can play a role in increasing patients' susceptibility to arrhythmias [27]. Abnormal potassium levels are the most commonly associated cause of arrhythmias due to their key role in cardiac electro-physiology [27]. More specifically, hypocalcemia, hypomagnesemia, and hypokalemia can cause prolonged QT interval, which can cause premature ventricular contractions (PVCs), ventricular tachycardia, Torsades de Pointes, and ventricular fibrillation [27].

Drug side effects

Certain drugs commonly used in the treatment of COVID-19 patients, such as hydroxychloroquine, azithromycin, and lopinavir/ritonavir, cause arrhythmias like PVCs, Torsades de Pointes, ventricular tachycardias, and ventricular fibrillation [28]. A more detailed list of drugs used in COVID-19 treatment and their potential effect on the QT interval can be found in *Table 1*. Other common drugs that can cause QT prolongation, which also should be cautiously used in patients undergoing certain treatments for COVID-19, are found in *Table 2*. See the "Arrhythmias related to COVID-19 medications" section below for more on drugs and arrhythmia. Other drugs may also alter drug metabolism, by inhibiting cytochrome P450 3A4 (CYP3A4), which may exacerbate the effects of QT-prolonging drugs and arrhythmia risk.

Underlying heart conditions

Patients with underlying heart conditions such as inherited arrhythmia syndromes, including long QT syndrome (LQTS) and Brugada syndrome, chronic congestive heart failure, or congenital heart diseases, are more susceptible to developing arrhythmias [29]. Patients with LQTS commonly have normal QTc intervals but are at higher risk of QT-prolongation and malignant arrhythmias when provoked by sepsis or use of one or more QT-prolonging drugs such as hydroxychloroquine (*Table 1*, *Table 2*) [30]. The managing teams of patients with LQTS with COVID-19 patients should refer to guidelines for help to interpret QTc intervals [29].

Brugada syndrome increases the risk of ventricular arrhythmias and sudden cardiac death [29]. Fever seems to increase the risk of cardiac arrests in patients with Brugada syndrome [29]. COVID-19 patients with Brugada syndrome should be treated with fever reducers and close monitoring in those with persistent fevers [29].

Patients with serious chronic congestive heart failure with symptoms at rest have high mortality of about 50% at 1 year [30]. Malignant arrhythmias and sudden cardiac death is the direct cause of death in about 40% of patients with serious heart failure [30]. Factors that promote arrhythmias in these patients include ventricular remodeling, scarring from myocardial ischemia, high circulating catecholamines, electrolyte abnormalities, and proarrhythmic drugs used in heart failure treatment [30]. Careful considerations around care should be made in patients with concurrent congestive heart failure and COVID-19 infection [31].

Patients with congenital heart conditions, such as tetralogy of Fallot, Epstein's anomaly, valvular disease, septal defects, are likely to develop arrhythmias by early adulthood [32]. These arrhythmias can be due to inherent conduction abnormalities from the structural cardiac malformation, scarring from corrective surgery, hypoxia or cyanosis, or cardiac remodeling from abnormal volumes and pressures [32].

COVID-19 arrhythmia in the pediatric population

COVID-19 infection is less common in childhood and tends to present with milder symptoms in children than in adults although it does not come free of the risk of cardiac involvement. This is increasingly seen in children who suffer from congenital heart disease (CHD) [33]. Several reports have been published describing cardiac involvement in COVID-19 pediatric patients, although the evidence is limited to support this claim. In these children, a potential predisposing factor for COVID-19 cardiac man-

Table 1
Pro-arrhythmic side effects and contraindicated drugs for COVID-19 drugs.

	Pro-arrhythmic side effects	Contraindicated drugs	Drugs to avoid
Hydroxychloroquine	QT prolongation, Torsades de pointes, Ventricular arrhythmia	Eliglustat, Pimozide, Thiodazine	QT-prolonging drugs (Table 2)
Dexamethasone	–	Mifepristone	–
Remdesivir	–	–	–
Lopinavir-ritonavir	QT prolongation, Torsades de pointes, PR prolongation, AV block	Alfuzosin, Apalutamide, Cisapride, Colchicine, Conivaptan, Dihydroergotamine, Disulfiram, Dronedarone, Elagolix, Eliglustat, Eplerenone, Ergotamine, Flibanserin, Grazoprevir, Ivabradine, Lomitapide, Lovastatin, Lurasidone, Methylergonovine, Metronidazole, Midazolam, Naloxegol, Pimozide, Ranolazine, Rifampin, Sildenafil, Silodosin, Simvastatin, Thioridazine, Tinidazole, Tolvaptan, Triazolam, Ubrogepant, Venetoclax	QT-prolonging drugs (Table 2)
Favipiravir	–	–	–
Interferon beta	–	Cladribine, Deferiprone, Ganciclovir, Penicillamine, Primaquine, Thiotepa, Tizanidine, Valganciclovir	
Anakinra	–	–	
Sarilumab	–	–	
Tocilizumab	–	–	
Azithromycin	QT prolongation, Torsades de pointes	Cisapride, Dronedarone, Pimozide, Thioridazine	QT-prolonging drugs (Table 2)

Table 2
Drugs that cause QT-prolongation.

Antipsychotics	Antiarrhythmics	Tricyclic antidepressants	Other antidepressants	Antihistamines	Antibiotics	Other
Chlorpromazine, Haloperidol, Droperidol, Quetiapine, Olanzapine, Amisulpride, Thioridazine	Quinidine, Procainamide, Disopyramide, Flecainide, Encainide, Sotalol, Amiodarone	Amitriptyline, Doxepin, Imipramine, Nortriptyline, Desipramine	Mianserin, Citalopram, Escitalopram, Venlafaxine, Bupropion, Moclobemide	Diphenhydramine, Astemizole, Loratidine, Terfanadine	Erythromycin, Clarithromycin, Azithromycin, Roxithromycin, Moxifloxacin	Chloroquine, Mefloquine, Hydroxychloroquine, Quinine, Methadone, Ondansetron, Sumitriptan, Cisapride, Probucol

ifestations is the past medical history of surgical correction of CHD. In addition to CHD, other conditions that were reported to be associated with predisposition to COVID-19 cardiac manifestations were bronchopulmonary hypoplasia, respiratory tract abnormalities, hemoglobinopathies, and severe malnutrition [33]. Compared to arrhythmias in adult patients, children with COVID-19 tend to have less life-threatening arrhythmias, including premature ventricular complexes, supraventricular tachycardias, first-degree atrioventricular heart blocks, and incomplete right bundle branch blocks [34].

Case-series studies on the potential hyper-inflammatory state, similar to Kawasaki disease, seen in the children COVID-19 patient population spiked concerns and was named SARS-Cov-2-associated multisystem inflammatory syndrome [33]. This population may also suffer from heart failure, coronary artery abnormalities, and even shock along with the non-specific symptoms of a viral illness [35]. The mechanism by which SARS-CoV-2 activates the abnormal immune response is still unknown, the multisystem inflammatory syndrome is hypothesized to be due to immune dysregulation that happens one-two weeks after the acute infection has occurred and leads to Kawasaki-like illnesses [35]. This post-viral immunological reaction and second surge in cytokines can result in myocardial injury leading to a variety of cardiovascular issues such as myocarditis, coronary dilation, ventricular dysfunctions, and consequently, arrhythmia [36]. In Paris, 6 weeks after the first outbreak, there was an increase in the number of children that presented with a phenotype of Kawasaki disease [37]. They reported a series of 16 patients (median age 10 years) that fit criteria of complete Kawasaki disease or incomplete Kawasaki disease, associated with a proven (69%) or highly suspected (19%) SARS-CoV-2 infection. The onset of the disease has been shown to manifest 2–4 weeks post-acute SARS-CoV-2 infection or exposure [37]. A review of cardiac manifestations in SARS-Cov-2-associated multisystem inflammatory syndrome reports myocarditis in 44%, coronary artery dilation or aneurysms in 6–24%, and arrhythmias in 7–60% [36]. Heightened awareness and medical due diligence are vital for combating the cardiovascular complications associated with COVID-19 infection.

Arrhythmias in critically ill ICU patients with COVID-19

Arrhythmias in the ICU department seem to encompass most of the cases of COVID-19-induced arrhythmias [38]. Early pandemic reports from China have suggested an overall occurrence of cardiac arrhythmia of 17% in the hospitalized COVID-19 patient population. Even more elevated arrhythmia rates were reportedly observed in the ICU COVID-19 patient population with an occurrence of 44% [39]. Another study found that every one of the 19 out of 115 admitted COVID-19 patients, who did not have an atrial arrhythmia at the time of admission and developed one in the hospital, was in the ICU [40]. In another study, while controlling for variables such as age, sex, race, body mass index, presence of cardiovascular disease and chronic kidney disease, and ICU status on admission, ICU status was the only factor that was significantly associated with a 10-fold greater chance of getting atrial fibrillation, non-sustained ventricular tachycardia, and bradyarrhythmia [41].

While there is no direct evidence that ARDS may lead to arrhythmias, few studies show that there is an increased risk of developing arrhythmias in COVID-19 patients on mechanical ventilation. A study from New York in April 2020 found that 130 out of 393 COVID-19 patients had invasive mechanical ventilation [42]. Of these patients who received mechanical ventilation, 23 patients (17.7%) developed atrial arrhythmia proving that there is an increased risk (17% more versus 1.9%) [42]. Reports also show that there is a strong correlation between mechanical ventilation, high

troponin levels, and an increase in C-reactive protein when ventricular arrhythmias are present [43].

According to a study looking at 54 severe or critically ill patients with COVID-19, sinus tachycardia was the most common and seen in 23 patients [44]. Additionally, mild pericardial effusion was observed in approximately 10% of arrhythmia cases with most patients being critically ill [44]. Approximately two-thirds of the patients were males in either severe or critical cases with an average age of 57.6 years old [44]. This age and gender distribution suggests that elderly adult male patients are at a higher risk of developing critical conditions.

Cardiac arrests in patients with COVID-19

Studies showed a cardiac arrest rate of 11% and 13% in the COVID-19 patients in the ICU [41,45]. All 9 of the patients who experienced a cardiac arrest in one of the studies were in the ICU [41]. Cardiac arrest was associated with 44% in-hospital mortality [32]. In one of the studies, almost every cardiac arrest from COVID-19 was due to a non-shockable rhythm (i.e. asystolic patients) [41]. After controlling for factors such as the patient's age, sex, race, cardiovascular disease, ICU status, and hydroxychloroquine treatment, the incidence of cardiac arrest was still found to be significantly associated with in-hospital mortality [41]. Moreover, there were zero cardiac arrest events in any of the 621 COVID-19 patients that were not in the ICU in this study [41]. The study's findings suggest that cardiac arrest was associated with COVID-19 not due to the mere presence of SARS-CoV-2 but due to the inflammation and systemic illness that distinguished ICU COVID-19 patients from non-ICU ones [41].

Arrhythmias related to COVID-19 medications

Certain drugs may prolong the QT interval which can cause arrhythmias like PVCs, Torsades de Pointes, ventricular tachycardias, and ventricular fibrillation. Hydroxychloroquine, azithromycin, and lopinavir-ritonavir have been used in the treatment of COVID-19. Hydroxychloroquine is indicated for use for malaria and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine can be arrhythmogenic which may be due to inhibition of ion channels in the SA node, causing bradyarrhythmia and subsequent prolongation of QT interval or Torsades de Pointes [46]. Azithromycin is an antimicrobial agent that increases the risk of arrhythmia and cardiac death (*Table 1*). A study in 490 patients noticed 12% of patients manifested critical QTc prolongation, especially when combining hydroxychloroquine and azithromycin [46]. Lopinavir-ritonavir combination has been used as an antiviral agent and may have a bradyarrhythmia side effect.

During hospitalization, tachycardia could have been due to ribavirin and corticosteroids administration. The use of QT-prolonging medications such as hydroxychloroquine can increase the risk of fatal arrhythmias, especially in high-risk patients [47]. In addition, the use of hydroxychloroquine, even in small doses, can also cause hypoglycemia, neuropsychiatric effects, and idiosyncratic hypersensitivity reactions [48]. Therefore, the possibility of fatal arrhythmias underscores the importance of monitoring the QTc interval with serial ECGs in patients on these QT-prolonging medications [49].

A lower dose of chloroquine led to fewer patients with QTc >500 ms, compared to a higher dose. The use of both hydroxychloroquine and azithromycin together can result in a QT-prolongation arrhythmia and increases the risk of cardiac arrest (*Table 1*) [51]. In a retrospective study of 84 patients given both hydroxychloroquine and azithromycin, 11% had a QTc >500 ms [49]. A total 2.7% of COVID-19 patients taking both hydroxychloroquine

and azithromycin had ventricular tachycardia due to the induced QTc prolongation [48]. In a survey with 1197 respondents, cardiac arrest incidence was found to be 4.8% in patients with ventricular tachycardia or ventricular fibrillation, with pulseless electrical activity in 5.6% [8]. Out of patients taking both hydroxychloroquine and azithromycin, 4.1% developed Torsade de Pointes due to the significant QTc prolongation [8]. Also, electrolyte disturbances, like hypokalemia, and adverse effects of QT-prolonging medications like hydroxychloroquine increase the risk of ventricular tachycardia [50].

Increased levels of IL-6 with inflammation fever and in COVID-19 patients has been suggested to cause QT-prolongation [38]. Fever amplifies blockade of potassium repolarization channels caused by QT-prolonging drugs, increasing QT-interval and risk of arrhythmias [48]. A recent case report described a COVID-19 positive patient who was administered lidocaine, a late sodium channel blocking agent, which decreased the QTc interval and allowed them to be treated with azithromycin and hydroxychloroquine [51].

Management for arrhythmias in COVID-19 patients

If there is a baseline QTc of >500 msec, patients are at risk of developing significant QT prolongation and Torsades de Pointes [52]. There is also an increased risk with the use of more than one QT-prolonging drug, acquired long QT syndrome, pre-existing heart disease, or if QTc increases >60 msec after adding a QT-prolonging drug [53]. In these patients, the team should aim to correct all electrolyte abnormalities, aim for potassium of 5.0, and review and discontinue other nonessential QT-prolonging medications, such as amitriptyline or diphenhydramine (*Table 1*) [53]**.** Various protocols also recommend continuous telemetry, cardiology consultation, and QT-prolongation risk score [52,53].

Complete heart block has also been reported in patients with a COVID-19 infection [54,55]. In these bradycardic patients, isoproterenol, an analog of epinephrine, or dopamine infusion is shown to increase heart rate [47,51]. Monitoring electrolyte levels and reviewing medications can also help prevent arrhythmic complications or cardiac arrest in patients with bradycardia.

Different studies show that 40% of patients who die from COVID-19 disease have cardiac involvement [56]. Monitoring patients with SARS-CoV-2 for arrhythmias or myocardial injury can be done with serial ECGs. The ECG features of SARS-CoV-2 are not well defined especially during the initial stages of the disease. ECG changes seen are late-onset and not in parallel with pulmonary abnormalities with occurrence after negative nasopharyngeal swabs [17]. Echocardiography could be useful to distinguish COVID-19–related myocardial damage and primary cardiac disease and also to monitor and assess COVID-19 cardiovascular complications such as arrhythmias [56].

Prevention of COVID-19 infection spread is also key. COVID-19-positive patients who are recommended for electrophysiology ablation procedures, such as atrial and ventricular arrhythmia ablations, should wait until they are no longer COVID-19-positive to do the procedure to prevent virus transmission. If ablation therapy is for a hemodynamically unstable patient or deemed lifesaving, then it is recommended to proceed by the CSANZ Heart Rhythm Council COVID-19 Pandemic group [43,57].

Conclusion

As this pandemic continues, it is important to recognize that COVID-19 patients, especially those who are critically ill and, in the ICU, may develop life-threatening arrhythmias that can be prevented or detected as early as possible for the appropriate management and optimal outcomes. Arrhythmias may manifest due to

various factors such as electrolyte imbalances, QT-prolonging medications, and virus-induced inflammation. New data continue to emerge about the pathophysiology of arrhythmia in the setting of COVID-19 which can shed light on optimizing management steps. At this time, emphasis should be placed on primary prevention along with careful monitoring of infected patients that are deemed high risk for the development of life-threatening arrhythmias.

Search strategy

We began by manually searching PubMed and EMBASE for clinically confirmed COVID-19 cases associated with arrhythmias. To obtain these data, we conducted a search using pre-specified search terms and keywords in March 2020, including: "COVID-19(MESH) AND Arrhythmia(MESH)", and customized to each database to find the most accurate results, and the last time we updated these searches was in July 2020. We also did a manual search to retrieve additional articles. We searched the citations of included papers, references of relevant papers in PubMed, and relevant citations in EMBASE.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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