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Cardiac Arrhythmias in Critically Ill Patients With COVID-19: A Brief Review

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Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2, is now a global pandemic affecting more than 12 million patients across 188 countries. A significant proportion of these patients require admission to intensive care units for acute hypoxic respiratory failure and are at an increased risk of developing cardiac arrhythmias. The presence of underlying comorbidities, pathophysiologic changes imposed by the disease, and concomitant polypharmacy, increase the likelihood of life-threatening arrhythmias in these patients. Supraventricular, as well as ventricular arrhythmias, are common and are associated with significant morbidity and mortality. It is important to understand the interplay of various causal factors while instituting strategies to mitigate the impact of modifiable risk factors. Furthermore, avoidance and early recognition of drug interactions, along with prompt treatment, might help improve outcomes in this vulnerable patient population.

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Coronavirus disease 2019 (COVID-19) is now a global pandemic, affecting more than 17 million patients worldwide, and has caused more than 700,000 deaths worldwide, and the number continues to grow. COVID-19 is caused by a novel strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which invades host cells through the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is expressed in the lung (principally type II alveolar cells) and appears to be the most predominant portal of entry. In addition to lungs, ACE2 is highly expressed in the heart, with increasing evidence linking COVID-19 to increased morbidity and mortality from cardiovascular disease resulting from the disease itself. Also, it is reported that pre-existing cardiovascular disease is associated with worse outcomes and increased risk of death in patients with COVID-19. The disease severity in SARS-CoV-2 infection ranges from asymptomatic or mild illness to acute, sometimes severe hypoxemic respiratory failure and multi-system organ failure, necessitating hospitalization or intensive care unit (ICU) admission. The combination of severe infection, hypoxia, sepsis, and/or hemodynamic instability predisposes patients with COVID-19 to myocardial injury and potentially dangerous arrhythmias. In this brief narrative review, the authors highlight the incidence, risk factors, and pathophysiology of development of arrhythmias in patients with COVID-19, and provide a pragmatic approach for risk mitigation and management of these arrhythmias.
Incidence

In 138 hospitalized COVID-19 patients, arrhythmias represented a leading complication (19.6%), with a prevalence as high as 44.4% in those admitted to the ICU. Specifi- cally, malignant ventricular arrhythmias, that is, ventricular tachycardia/fibrillation, were found in 5.9% of patients. In another cohort of critically ill patients with COVID-19, the incidence of atrial arrhythmias was found to be 17.7%. Bhatla et al. reported a 7.5% overall incidence of arrhythmias, of which 43% occurred in the patients who were admitted to the ICU.

The higher likelihood of serious disease and ICU admissions among older patients with comorbidities, the hyperinflammatory response, and myocardial injury associated with SARS-CoV-2 infection, as well as the use of arrhythmogenic agents to target COVID-19, such as anti-malarial or antiviral medications, all contribute to a heightened risk of arrhythmias, which creates unique challenges for critical care providers.

Risk Factors

It is the conglomeration and interplay of various insults that are part of COVID-19-induced critical illness, which contributes to the development of life-threatening arrhythmias in this patient population. Although some of these factors are modifiable, for most, the optimal preventive and treatment modalities remain unclear. Figure 1 depicts the various insults and the associated pathophysiology that contribute to the development of arrhythmias in critically ill patients with COVID-19. A brief description of the individual risk factors is discussed below.

Pre-Existing Patient-Specific Factors

COVID-19 seems to cause more serious disease in older patients and those with comorbidities, a population that is already at enhanced risk for development of arrhythmias. Increased age is one of the most important risk factors for supraventricular arrhythmias and atrial fibrillation, more common in the aging heart, which forms a substrate for the development of atrial fibrillation (AF). Although this is likely due to a combination of multiple cultural and socioeconomic factors, an underlying genetic susceptibility to SARS-CoV-2 infection, its sequelae (such as hypoxia and inflammation), or the potentially lethal side effects of COVID-19-directed therapies, cannot entirely be ruled out. The role of Nav1.5 sodium channel variant p. Ser1103Tyr-SCN5A, which confers an increased risk of drug-induced cardiac arrhythmias, in exacerbating outcome-related health disparities, has been reviewed recently. p.Ser1103Tyr-SCN5A is seen almost exclusively in individuals of African descent. The modest increase in late/persistent sodium current generated by p.Ser1103Tyr-SCN5A is accentuated markedly by hypoxia/acidoses, potentially leading to an increased risk of ventricular arrhythmia and sudden cardiac death in African Americans. Other comorbidities, such as...
hypertension, diabetes, obesity, and coronary artery disease that have been described as the most prevalent comorbidities in COVID-19 patients, further heighten the risk of development of arrhythmias. Patients with inherited arrhythmia syndromes, such as long QT syndrome (LQTS), Brugada syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia, may be further susceptible to the proarrhythmic milieu seen in patients with COVID-19.

Critical Illness

Approximately 14%-to-16% of patients hospitalized with COVID-19 require admission to the ICU. These patients have high disease severity, frequently need mechanical ventilation, and often require vasopressor support, with prolonged ICU stays. Although supraventricular arrhythmias are more common in critically ill patients, ventricular arrhythmias are more likely to occur in patients with pre-existing cardiovascular disease and are associated with worse outcomes. A multitude of triggers can lead to the development of arrhythmias in the ICU. Some inciting factors are modifiable or treatable, while others are associated with the patient’s diagnosis, severity of illness, and life-sustaining ICU therapies. Recent evidence suggests that AF might be a marker of disease severity in critically ill patients as a consequence of increased release of catecholamines and progressive autonomic dysfunction. Factors associated with increased sympathetic activity, such as anemia, pain, agitation, ventilator dyssynchrony, hypoxia, hypercarbia, acidosis, and hypovolemia, all can be potent triggers for development of supraventricular arrhythmias in these patients.

SARS-CoV-2 Infection

Myocardial damage might represent a major cause of enhanced arrhythmic risk in patients with COVID-19. Cardiac myocyte injury, reflected by increased troponin levels, has been demonstrated in many individuals, particularly in those with severe disease. Although the exact mechanisms of myocardial involvement in this disease are still being investigated, direct viral infection, hypoxia-induced apoptosis, and cytokine storm–related cell damage are probable causes. However, factors other than myocardial damage also may be involved. The downregulation of affected ACE2 receptors may contribute to myocarditis and cardiomyopathy, with inflammation and fibrosis likely to provide a substrate for arrhythmia. Myocarditis itself is a heterogeneous condition associated with a number of arrhythmic states, including bradyarrhythmia and atrial or ventricular tachyarrhythmia.

Critically ill patients with COVID-19 also have been observed to have a hyperinflammatory state associated with overproduction of early response proinflammatory cytokines (tumor necrosis factor, IL-6, and IL-1β) resulting in a “cytokine storm.” This hypercytokinemia (in particular elevated levels of IL-6) serves as a significant pro-arrhythmic risk factor via hERG blockade, QT prolongation, and direct inflammatory cell infiltration and oxidative damage to atrial myocytes. Inflammation is also an important risk factor for LQTS and Torsades de Pointes (TdP), primarily via direct electrophysiologic effects of cytokines on the myocardium. It has been demonstrated that IL-6, tumor necrosis factor α, and IL-1 can prolong ventricular action potential by modulating the expression and function of several cardiomyocyte ion channels, specifically K+ and Ca++ channels. Specifically, IL-6 directly inhibits the hERG-K+ channel and prolongs action potential in ventricular myocytes. Besides the direct cardiac effects, systemic inflammation might additionally predispose to LQTS and TdP as a result of indirect mechanisms. Inflammatory cytokines can induce cardiac sympathetic system hyperactivation, via central hypothalamus-mediated (inflammatory reflex) and peripheral (left stellate ganglion activation) pathways, thus acting as a trigger for life-threatening arrhythmic events in LQTS patients. Also, IL-6 inhibits cytochrome p450 (CYP), particularly CYP3A4, thereby increasing the bioavailability of several medications, including QT-prolonging drugs. Inflammation, regardless of the presence of infection, also may play a role in the development of AF. The profound hypoxia associated with COVID-19 infection also can lead to pathologic increase in late sodium current via the p.Ser1103Tyr-SCN5A Nav1.5 sodium channels, thus prolonging ventricular action potential duration and predisposing to ventricular arrhythmias and sudden cardiac death. The exclusivity of the p.Ser1103Tyr-SCN5A Nav1.5 sodium channels in African Americans partly could explain the higher mortality observed in this patient population with COVID-19.

There is increasing evidence that the coagulation system is impaired in critically ill patients with COVID-19 with a high incidence of hypercoagulable disorders. Although patients with pre-existing coronary artery disease have worse outcomes and increased risk of death, a direct relationship between coagulation impairment from COVID-19 and propagation of arrhythmias due to exacerbation of pre-existing coronary artery disease has not been described. Although anticoagulation and improved survival have been described in small observational studies, the direct impact of anticoagulation on incidence of arrhythmias needs further careful evaluation.

Drug Therapy

An important risk factor for the development of arrhythmias in COVID-19 patients is polypharmacy and associated drug interactions. Indeed, multiple commonly used medications contribute to a pro-arrhythmic state in a patient population already at risk. Furthermore, impaired drug clearance due to critical illness and associated organ dysfunction promotes drug accumulation, thereby accentuating these interactions. There is increasing recognition of the potential role of pharmacologic treatments in increasing the susceptibility to QT-related life-threatening VAs, particularly TdP. In fact, the off-label use of some drugs used to counteract viral invasion and replication may promote QTc prolongation. Importantly, the additional risk of QT prolongation, with some potential combinations of these medications, may be synergistic rather than simply additive. Chloroquine/hydroxychloroquine, the antimarial...
agents that potentially block infection by increasing the endosomal pH required for virus/cell fusion, and lopinavir/ritonavir, protease inhibitors that interfere with the virus RNA replication, are 2 common culprits. Notably, in both cases, the impact on ventricular repolarization is direct, via inhibition of the hERG-K+ channel, and also indirect by increasing circulating levels of other concomitant QT-prolonging drugs. In fact, chloroquine and hydroxychloroquine inhibit CYP2D6, which metabolizes several antipsychotics, antidepressants, and antihistamines, while ritonavir inhibits CYP3A4, actively involved in the metabolism of some macrolides, azole antifungals, antidepressants, and antihistamines. In addition to these drugs, macrolides (particularly azithromycin, which also are reported to inhibit SARS-CoV-2 in vitro), as well as fluoroquinolones, are well-recognized QT-prolonging antibiotics. These classes of medications are considered frequently when treating patients with COVID-19 for potential bacterial superinfections. Compounding the situation is that patients receiving these drugs in the ICU frequently possess other concomitant risk factors for QTc prolongation/TdP, such as pre-existing cardiac diseases, electrolyte imbalances, and concomitant use of other drugs with QT-prolonging properties (antiemetics, proton pump inhibitors, antibiotics, sedative agents, etc.). As newer therapies are being investigated, further investigation of their arrhythmogenic potential is warranted, especially because some of these also are prescribed on an outpatient basis.40,41 A simplified strategy for QTc surveillance in the clinical practice is available at www.crediblemeds.com.

Management

Management of arrhythmias in these patients follows the same considerations as in other critically ill patients, with heightened attention to drug interactions and the pathophysiology changes specific to COVID-19. Management decisions should involve multidisciplinary discussions among the critical care providers, pharmacists, and cardiologists, with input from electrophysiologists on a case-by-case basis. Specific considerations are briefly discussed here.

Ventricular Arrhythmias

As previously stated, the presence of systemic inflammation seen in patients infected with COVID-19 and concurrent use of QT-prolonging medications are important risk factors for development of LQTS and TdP in this patient population. Most concerning, sustained TdP commonly leads to hemodynamic instability or pulseless electrical activity. At this time, it is recommended to continue to treat patients with TdP per standard resuscitation guidelines,82 and to discontinue any offending agents whenever feasible. In hemodynamically stable patients with recurrent TdP triggered by long-QT–related ventricular ectopic beats, intravenous magnesium is recommended as the first line for treatment, as it decreases the influx of calcium, thereby lowering the amplitude of early after depolarization. However, caution needs to be exercised with the use of magnesium in patients with COVID-19. As many of these patients require neuromuscular blockade, judicious use of magnesium is important, with frequent neuromuscular monitoring, because high levels of magnesium may potentiate the effect of nondepolarizing neuromuscular blocking agents and can lead to worsening muscle weakness.43 Nonetheless, correction of hypomagnesemia is equally important, because that may predispose to arrhythmias,44 and hence regular monitoring of magnesium levels should be considered, especially in patients with altered renal clearance. In addition to careful consideration of drug interactions and altered metabolic milieu, which may be contributory, the onset of malignant tachyarrhythmias in the setting of elevated troponins may herald the development of myocarditis, which should trigger urgent echocardiographic assessment.45,46

In light of the hyperinflammatory state associated with COVID-19, dampening the systemic inflammatory response might be crucial not only to control lung involvement but also to reduce QT-related arrhythmic events. In particular, it may be important to block the IL-6 pathway, and there may be a potential beneficial effect of the anti–IL-6 receptor monoclonal antibody tocilizumab on COVID-19 survival.3 Tocilizumab has been shown to cause rapid and significant QTc shortening, which correlated with both the decrease in C-reactive protein and cytokine levels in patients with rheumatoid arthritis.32 The role of tocilizumab and similar drugs targeting the inflammatory pathway in preventing and treating ventricular arrhythmias associated with COVID-19 needs further evaluation, but small studies have shown promising results.27 The routine use of IL-6 blockers to mitigate the risk of QTc-related arrhythmias currently is not recommended. Figure 2 describes the treatment options for TdP in patients with COVID-19.

Atrial Arrhythmias

AF is one of the most common arrhythmias observed in the ICU, and is incited by systemic inflammation, rapid fluid shifts, and critical illness.48 While determining appropriate treatment, consideration must be given to identifying potential underlying causes, such as myocarditis or cytokine storm, as potential inciting factors in this specific patient population. In addition, volume status, medication history, and adjunctive therapies should be reviewed in detail prior to treatment selection. Figure 3 provides a treatment algorithm for AF in patients with COVID-19, highlighting the importance of discontinuing offending agents and correcting precipitating factors. In patients with preserved hemodynamics, a range of medical therapies is available for rate or rhythm control. Although neither strategy is more advantageous than the other, rate control often is chosen over rhythm control unless adverse effects of AF are considered to be due to loss of atrial systole or a rate control strategy is ineffective or has unacceptable side effects. Medications most commonly used for rate control in AF are beta-blockers, non-dihydropyridine calcium channel blockers (CCBs), amiodarone, and digoxin. Careful consideration for the most appropriate agent should be employed via a multidisciplinary approach in which varying presentations and risk factors for decompensation are evaluated. Since intravenous
esmolol and metoprolol both have little-to-no effect on beta-2 adrenergic receptors, risk of both hypotension and respiratory compromise are low, making them the preferred agents in the setting of COVID-19 infection. Additionally, in the event hydroxychloroquine is used against COVID-19 or continued as a chronic regimen, careful monitoring for severe bradycardia is crucial, as there is cited evidence of additive effects with concomitant use of beta-blockers or CCBs with hydroxychloroquine. Regarding non-dihydropyridine CCBs, a prominent drug interaction exists with protease inhibitors (ie, lopinavir/ritonavir), leading to decreased metabolism of both verapamil and diltiazem, thereby increasing the need for close hemodynamic monitoring. In patients unable to tolerate beta-blockers or CCBs due to their blood pressure–lowering effects, digoxin may be considered. If used in patients receiving lopinavir/ritonavir, serum levels should be monitored, because digoxin toxicity can result from the inhibition of p-glycoprotein.

Patients presenting with COVID-19 are at an increased risk for pulmonary damage and acute respiratory distress syndrome, and it may be desirable to avoid medications such as amiodarone, which can cause pulmonary toxicity even when used short-term. At this time, there are no data regarding the effects of amiodarone on pulmonary function in the acute setting of COVID-19 infection. Interestingly, there are data from in vitro studies suggesting that amiodarone inhibits spreading of SARS coronavirus, and in vivo studies are underway to confirm these findings. While the risk is relatively low, amiodarone also can increase QT interval and periodic electrocardiogram monitoring should be instituted, especially if used concomitantly with other QT-prolonging therapies including azithromycin and hydroxychloroquine. In addition, amiodarone undergoes metabolism via CYP-3A4, and it should be used with caution in patients receiving lopinavir/ritonavir therapy.

One of the clinical dilemmas related to management of atrial arrhythmias in critically ill patients is the decision to start arterial thromboembolism prophylaxis. Patients with critical illness and AF have an increased risk of in-hospital as well as post–hospital discharge ischemic stroke compared to those without AF. However, this risk has to be balanced against the higher bleeding risk and frequent requirements for invasive procedures that may necessitate interruption of anticoagulation. Considering that SARS-CoV-2 infection is associated with a hypercoagulable state and predisposes patients to venous thromboembolism (VTE), critically ill patients with COVID-19 who develop atrial arrhythmias might be at a higher risk of developing an ischemic stroke and may benefit from early initiation of anticoagulation. Although there are no

Fig 2. Management of Torsades de Pointes in patients with COVID-19. COVID-19, coronavirus disease 2019; IV, intravenous; PEA, pulseless electrical activity; TdP, Torsades de Pointes.
data specific for this patient population, the incidence of ischemic stroke is high in patients with COVID-19, especially those who are young. The decision to initiate anticoagulation for stroke prophylaxis usually is based on the CHA2DS2-VASc score (congestive heart failure, hypertension, age older than 75 years, diabetes, stroke, vascular disease, female sex); however, in patients with COVID-19, using d-dimer levels in addition to the score might be reasonable, because d-dimer levels have been shown to correlate well with venous thromboembolic disease. Also, every effort should be made to prescribe anticoagulants on hospital discharge in these patients unless contraindicated.

The decision regarding the choice and dosing of anticoagulant should involve a multidisciplinary discussion to evaluate the risks/benefit profile of each agent. Since critically ill adult COVID-19 patients may develop VTE with standard pharmacologic prophylaxis, and higher doses of unfractionated heparin and low-molecular-weight heparin have short half-lives and a low degree of drug-drug interactions, thus making them attractive first-choice agents for critically ill patients. Regarding oral anticoagulation, warfarin may not be preferred in these patients due to the many pharmacokinetic/dynamic alterations that can occur. Interruptions in tube feeding and varying vitamin K content, as well as initiation/discontinuation of antibiotics, steroids, and antiviral medications, can lead to fluctuations in the international normalized ratio. However, due to the ease of monitoring, warfarin remains a viable option once a patient has recovered and is no longer receiving drugs affecting warfarin metabolism. Direct oral anticoagulants, such as anti-Xa inhibitors or dabigatran, may be considered for long-term anticoagulation but should be used with caution in the acutely ill COVID-19 population due to potential drug-drug interactions, administration limitations, and impaired absorption. Antiviral therapies, including lopinavir/ritonavir, which...
may be used in certain COVID-19 patients, are potent enzyme inhibitors and can slow down metabolism and prolong the duration of action of many medications including anti-Xa inhibitors.66 On the other hand, anti-Xa inhibitors may have decreased efficacy if tocilizumab is used in COVID treatment through an increase in CYP450 activity. These interactions have not been reported with dabigatran. Direct oral anticoagu- lants may prove a reasonable option in appropriate patients able to take oral medications and/or are unable or unwilling to receive routine international normalized ratio monitoring following discharge. Ultimately, decisions on inpatient and dis- charge therapies should be based on hospital protocols, patient-specific factors, and a thorough review of concomitant medications.

In conclusion, critically ill patients with COVID-19 are highly predisposed to the development of both supraventricu- lar and ventricular arrhythmias due to the presence of pre- existing comorbidities, physiologic alterations imposed by critical illness, unique pathology associated with SARS-CoV-2 infection, and multiple drug interactions. It is crucial for critical care providers to be aware of these risk factors and to apply interventions based on pathophysiologic and pharmaco- logical considerations. Multidisciplinary discussions among the ICU team members, pharmacy, and cardiology teams are essential for optimal care of these highly complex patients. Clinicians should maintain a heightened degree of suspicion for arrhythmias being a harbinger of worsening cardiac function. The role of specific therapies that potentially could mitigate the risk of arrhythmias by targeting inflammatory pathways needs further systematic evaluation.

Financial Disclosure

None.

Conflicts of Interest

None.

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