



COVID-19 and Cardiac Arrhythmias: a Contemporary Review

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Abstract

Purpose of Review A significant proportion of patients infected by the severe acute respiratory syndrome-coronavirus (SARS-CoV2) (COVID-19) also have disorders affecting the cardiac rhythm. In this review, we provide an in-depth review of the pathophysiological mechanisms underlying the associated arrhythmic complications of COVID-19 infection and provide pragmatic, evidence-based recommendations for the clinical management of these conditions.

Recent Findings Arrhythmic manifestations of COVID-19 include atrial arrhythmias such as atrial fibrillation or atrial flutter, sinus node dysfunction, atrioventricular conduction abnormalities, ventricular tachyarrhythmias, sudden cardiac arrest, and cardiovascular dysautonomias including the so-called long COVID syndrome. Various pathophysiological mechanisms have been implicated, such as direct viral invasion, hypoxemia, local and systemic inflammation, changes in ion channel physiology, immune activation, and auto-

nostic dysregulation. The development of atrial or ventricular arrhythmias in hospitalized COVID-19 patients has been shown to portend a higher risk of in-hospital death.

Summary Arrhythmic complications from acute COVID-19 infection are commonly encountered in clinical practice, and COVID-19 patients with cardiac complications tend to have worse clinical outcomes than those without. Management of these arrhythmias should be based on published evidence-based guidelines, with special consideration of the acuity of COVID-19 infection, concomitant use of antimicrobial and anti-inflammatory drugs, and the transient nature of some rhythm disorders. Some manifestations, such as the long COVID syndrome, may lead to residual symptoms several months after acute infection. As the pandemic evolves with the discovery of new SARS-CoV2 variants, development and use of newer anti-viral and immuno-modulator drugs, and the increasing adoption of vaccination, clinicians must remain vigilant for other arrhythmic manifestations that may occur in association with this novel but potentially deadly disease.

Introduction

In December 2019, an outbreak of 27 cases of pneumonia due to the severe acute respiratory syndrome—coronavirus (SARS-CoV2) was reported from Wuhan, China, to the China National Health Commission, prompting the World Health Organization (WHO) to issue a Public Health Emergency of International Concern (PHEIC) in March 2020 [1••]. Since then, the disease labeled coronavirus 2019 (COVID-19) caused by SARS-CoV2 has reached pandemic proportions—infected a total of more than 276 million people as of December 23, 2021, including 5.4 million deaths worldwide (<https://covid19.who.int>) [2•]. The majority of cases tend to be asymptomatic or associated with mild systemic and respiratory symptoms (fever, cough, fatigue), but a significant minority of patients develop severe symptoms that may lead to ARDS and hypoxemic respiratory failure, shock, multi-organ failure, and death.

There are major disparities in care related to racial, ethnic, demographic, geographic, socio-economic, and political factors, resulting in variability in incidence of new infections and access to appropriate healthcare resources for the management of severe cases. Data from the American Heart Association's COVID-19 Cardiovascular Disease Registry showed that Hispanic and Black patients comprised more than half of the patients hospitalized with COVID-19; these patients were younger; had higher prevalence of underlying conditions such as hypertension, diabetes mellitus, and obesity; were more often uninsured; had lower socio-economic status; and had longer delays from

symptom onset to COVID-19 diagnosis. Although Asian patients had the highest risk-adjusted cardiorespiratory disease severity at presentation compared to the other racial subgroups, no significant differences in in-hospital mortality or occurrence of major adverse cardiovascular events were seen between the racial subgroups after adjustment for sociodemographic characteristics, clinical comorbidities, and clinical presentation [3•]. However, multiple “waves” of COVID-19 in various countries around the world continue to occur, in spite of significant advancements in our understanding of the disease and its management as well as development of an effective vaccine. Due to the sheer magnitude of the pandemic, the ferocity with which the SARS-CoV2 virus mutates leading to several new variants which respond variably to various treatment regimens, and the slow implementation of effective and widespread vaccination strategies worldwide, the disease continues to ravage humanity and take an enormous toll on our collective physical, social, and psychological well-being.

The most common extra-pulmonary manifestations of COVID-19 involve the cardiovascular system, and case series early in the evolution of the disease reported that cardiac injury (manifested as elevated cardiac biomarker levels) occurs in 20–30% of hospitalized COVID-19 patients, and that cardiac injury is independently associated with adverse outcomes including mortality [4••]. Risk factors associated with increased mortality from COVID-19 include age [5•], African-American ancestry [6, 7], history of

pre-existing cardiovascular disease [8], and co-morbid conditions such as hypertension, diabetes mellitus, obesity, heart failure, renal dysfunction, and chronic lung disease [9]. Cardiac manifestations of acute COVID-19 infection include acute myocardial infarction, myocarditis leading to cardiomyopathy and potentially cardiogenic shock, bradyarrhythmias including atrioventricular block, and a plethora of supraventricular (SVT) and ventricular arrhythmias (VA) [10]. There is also growing evidence suggesting the association of COVID-19 infection with development of autonomic dysfunction leading to postural orthostatic tachycardia syndrome (POTS) and inappropriate sinus tachycardia (IST). Clinicians caring for patients with severe COVID-19 infection need to be vigilant for the development of cardiac

manifestations, with prompt diagnosis and treatment of these complications in conjunction with pulmonary manifestations of the disease in the acute setting, followed by institution of measures to monitor patients following recovery.

In this review, we discuss the most common arrhythmic manifestations of COVID-19, which include atrial fibrillation, other supraventricular arrhythmias, bradycardia and atrioventricular (AV) block, VA, and conditions associated with autonomic dysfunction as well as the clinical features of “long COVID-19.” We will summarize published guidelines for the management of arrhythmias associated with COVID-19 and provide practical guidance for clinicians caring for COVID-19 patients with these arrhythmic complications in both inpatient and outpatient settings.

Pathophysiological mechanisms underlying arrhythmic manifestations in COVID-19 patients

Table 1 summarizes the various pathophysiological mechanisms that are associated with the myriad arrhythmias seen in COVID-19 patients. Both atrial and ventricular arrhythmias can be caused by direct cardiomyocyte invasion [11] and downstream effects such as reduced expression and activity of ACE2 leading to activation of the renin–angiotensin–aldosterone axis and increased angiotensin II levels, as well as activation of cellular immune responses leading to a hyperinflammatory state and increased production of pro-inflammatory cytokines. Critically ill COVID-19 patients may develop a state called cytokine release syndrome (CRS), characterized clinically by rapid deterioration of respiratory status and ARDS, accompanied by signs of multi-organ dysfunction or failure, arterial and venous thromboses, and hemodynamic compromise that can progress to shock. CRS in COVID-19 patients is characterized biochemically by elevated levels of interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 12 (IL-12), monocyte chemoattractant protein 1 (MCP-1), and other biomarkers such as ferritin, fibrinogen, C-reactive protein (CRP), D-dimer, procalcitonin, lactate dehydrogenase (LDH), and von Willebrand factor antigen and activity [12], which makes them vulnerable to both atrial and ventricular arrhythmias.

In addition, activation of the immune system leads to reduced Treg lymphocyte number and activity, increased recruitment and activation of CD4+ CD28-null T cells and differentiation into Th1 subtype of helper T cells, and increased sympathetic activation (both at the central and peripheral levels) leading to increased catecholamine levels, further increasing the potential for atrial and ventricular tachyarrhythmias. Atrial fibrillation can also occur as a result of hypoxemia, acute changes in pulmonary artery and

Table 1 Summary of the pathophysiology and management of arrhythmias in COVID-19 patients

Arrhythmia type	Pathophysiological mechanisms	Management
Atrial fibrillation/flutter [68–70]	<ul style="list-style-type: none"> • Atrial pericyte and endothelial cell invasion with resultant microvascular leakage and local tissue inflammation • Activation of RAAS (increased angiotensin II, reduced angiotensin 1–7 levels), downregulation of ACE-2 receptor expression and activation • Direct atrial cardiomyocyte invasion and immune response (cytokine release syndrome with increased secretion of IFN-gamma, TNF-alpha, IL-6, IL-8, IL-12, MCP-1, etc.)* • Immune system activation (reduced Treg lymphocyte number and activity, increased recruitment and activation of CD4+ CD28-null T cells, differentiation into Th1 subtype)* • Changes in ionic currents (decreased conductance for ICaL, upregulation of Ito and IKur, shortened atrial action potential duration)* • Sympathetic hyperactivation (central/hypothalamus or peripheral/stellate ganglion stimulation), increased psychological stress leading to increased catecholamine levels* • Atrial stretch (pulmonary vascular dysfunction, acute cor pulmonale, acute pulmonary embolism, reduced ventricular wall compliance) • Atrial wall stiffness (atrial wall edema) due to microvascular leakage, ischemia, and fibrosis • Atrial fibrosis (elevated interferon-gamma from Th1 lymphocytes, increased programmed cell death-1 [PD-1] levels from pericytes) 	<p>Rate control:</p> <ul style="list-style-type: none"> • Beta-blockers (esmolol, metoprolol, propranolol, carvedilol) • Calcium channel blockers (if systolic function is preserved), avoid in patients on lopinavir/ritonavir • Digoxin (avoid in patients on lopinavir/ritonavir) <p>Rhythm control:</p> <p>Unstable patients:</p> <ul style="list-style-type: none"> • DC Cardioversion ± initiation of anti-arrhythmic agent <p>Stable patients:</p> <ul style="list-style-type: none"> • Amiodarone (oral/intravenous) • Atrial fibrillation ablation • AV node ablation and pacing <p>Anticoagulation:</p> <p>Use the CHA2DS2-VASc score to determine need</p> <ul style="list-style-type: none"> • Antithrombin inhibitors (dabigatran) • Factor Xa inhibitors (apixaban, rivaroxaban)—avoid in patients on lopinavir/ritonavir or tocilizumab • Warfarin

Table 1 (continued)

Arrhythmia type	Pathophysiological mechanisms	Management
Atrioventricular conduction abnormalities [32, 33, 35]	<ul style="list-style-type: none"> ● Direct cardiomyocyte invasion and cytopathic effect and activation of immune response (cytokine release syndrome) affecting AV conduction tissue function and/or integrity ● Focal myocarditis and edema causing extrinsic compression of AV conducting cells ● Increased vagal activity (endotracheal suctioning, prone positioning) ● Drug induced adverse effects on AV conduction (chloroquine, hydroxychloroquine, lopinavir/ritonavir, azithromycin) 	<ul style="list-style-type: none"> ● Close cardiac monitoring ● Avoid AV nodal blockers, antimalarial drugs (chloroquine, hydroxychloroquine) ● Temporary pacemaker placement as needed ● If persistent symptomatic bradycardia or high degree AV block, consider permanent pacemaker implantation
Sinus node dysfunction (including asystole) [33, 35]	<ul style="list-style-type: none"> ● Direct cardiomyocyte invasion and cytopathic effect and activation of immune response (cytokine release syndrome) within sino-atrial cells ● Acute complications from COVID-19 infection (acute pulmonary embolism, severe hypoxemia, etc.) ● Electrolyte abnormalities (severe acidosis, hyperkalemia) 	<ul style="list-style-type: none"> ● Close cardiac monitoring ● Temporary pacemaker placement as needed ● If persistent symptomatic bradycardia, consider permanent pacemaker implantation

Table 1 (continued)

Arrhythmia type	Pathophysiological mechanisms	Management
Ventricular arrhythmias [69–72]	<ul style="list-style-type: none"> ● Myocarditis leading to a hyperinflammatory state with prolongation of ventricular action potential duration (IL-1, IL-6, TNF-α affecting KCNH2/hERG channel function) ● Hypoxia causing pathological increases in late sodium currents via the SCN5A Nav 1.5 channels and increased ventricular action potential duration, increased extracellular K⁺ levels reducing depolarization threshold, reduced electrical coupling and more tissue anisotropy due to altered connexin 43 function ● Prolonged repolarization and reduced conduction velocity leading to triggered ectopy due to after-depolarizations and re-entry ● Cytochrome system inhibition (e.g., IL-6 inhibiting CYP3A4, or drugs such as lopinavir/ritonavir) causing altered drug metabolism of QT-prolonging medications such as azithromycin, hydroxychloroquine (and statins) and increased risk of torsade de pointes (and rhabdomyolysis) ● Myocardial cell death and fibrosis/scar formation, promoting scar-mediated re-entrant arrhythmias (direct cytopathic effects, microvascular dysfunction and micro-thrombi, large-vessel thrombosis causing acute myocardial infarction) 	<p>Unstable patients:</p> <ul style="list-style-type: none"> ● Electrical cardioversion/defibrillation \pm initiation of anti-arrhythmic agent <p>Stable patients:</p> <p>Monomorphic VT:</p> <ul style="list-style-type: none"> ● IV amiodarone ● IV lidocaine ● IV procainamide <p>Polymorphic VT (no QT prolongation):</p> <ul style="list-style-type: none"> ● IV lidocaine ● IV sedation, anxiolytics <p><i>Torsade de pointes:</i></p> <ul style="list-style-type: none"> ● IV isoproterenol ● IV magnesium ● Temporary pacing ● Stop QT-prolonging meds <p>Refractory VT/VT storm:</p> <ul style="list-style-type: none"> ● IV amiodarone ● IV lidocaine ● Deep sedation ● VT ablation

Table 1 (continued)

Arrhythmia type	Pathophysiological mechanisms	Management
Autonomic dysfunction (POTS, IST, long COVID syndrome) [16, 57, 58, 59]	<ul style="list-style-type: none"> ● Hypovolemia (reduced fluid intake, fever, excessive perspiration) ● Physical deconditioning due to prolonged illness ● Direct viral invasion and destruction of extracardiac sympathetic neurons and increased cardiac sympathetic outflow (similar to neurogenic POTS) ● Increased central sympathetic outflow due to viral invasion of cells in the brainstem and/or medullary centers ● Increased catecholamine levels due to psychological stress or depression associated with illness ● Immune activation (autoantibodies to alpha/beta adrenergic receptors or muscarinic acetylcholine receptors) leading to dysregulation of autonomic responses ● Post-infectious small fiber neuropathy, acute inflammatory demyelinating polyneuropathy 	<p>General treatment:</p> <ul style="list-style-type: none"> ● Reassurance ● Adequate hydration ● Specialist referral as appropriate ● Structured exercise/rehabilitation program <p>Orthostatic intolerance:</p> <ul style="list-style-type: none"> ● Counterpressure maneuvers ● Adequate salt and fluid intake ● Regular structured exercise ● Compression garments ● Avoid known triggers (sudden position changes, caffeine, warm environments, prolonged standing) <p>POTS, long COVID syndrome:</p> <ul style="list-style-type: none"> ● Education, reassurance ● Hydration ● Exercise (swimming, recumbent bike) ● Avoid known triggers, small frequent meals ● Counterpressure maneuvers (orthostatic intolerance) ● Fludrocortisone, midodrine (hypovolemic states) ● Clonidine, methyl dopa, propranolol (adrenergic POTS)

*These mechanisms may also contribute to other tachyarrhythmic manifestations such as ventricular arrhythmias

right ventricular hemodynamics from acute pulmonary embolism or cor pulmonale, changes in atrial wall compliance and stiffness due to microvascular dysfunction and changes in atrial perfusion and contractility, and in later stages, development of atrial fibrosis. Patients with COVID-19-induced CRS may develop *Atrial fibrillation* (AF) (de novo or recurrence of pre-existing PAF) due to the impact of cardiorespiratory compromise on intra-cardiac hemodynamics and/or electrophysiologic properties of atrial cardiomyocytes, as well due to the development of a viral-mediated inflammatory atrial cardiomyopathy. This inflammatory cardiomyopathy is characterized by lymphocytic infiltration within the atrial cardiomyocytes, myocardial necrosis, and microangiopathic changes within the atrial vasculature. In addition, direct viral invasion and lymphocytic infiltration of the ganglionated right atrial plexi have been reported, which may predispose to the development of AF as well as sinus node dysfunction (discussed later in this paper). Finally, endothelial cell activation, as well as the activation of various elements of the clotting cascade, can lead to widespread thromboses within the pulmonary vessels (both arterial and venous), as well as in atypical locations such as the right atrial appendage [13].

Other pathophysiological mechanisms can contribute to the development of VA and sudden cardiac arrest (SCA) in COVID-19 patients. These include ischemia due to thrombosis of small vessels within the myocardium and consequent changes in ion channel function and metabolic changes in ischemic myocytes, and QT interval prolongation both due to increased IL-6 levels and the use of QT-prolonging medications [14]. Other important considerations that affect the risk of VAs in COVID-19 include the following: hepatic and renal insufficiency that can cause electrolyte derangements such as hyperkalemia as well as affect metabolism and excretion of QT-prolonging medications; hyperadrenergic state related to critical illness, anxiety, or agitation due to respiratory difficulties; disruption of the sleep-wake cycle and aggravation of pre-existing sleep disorders; nutritional deficiencies due to reduced appetite, prolonged ICU hospitalization, and intubated status; and the use of antimicrobials that can cause QT prolongation either individually or in combination with other antimicrobials or medications used to treat other co-morbid conditions. Of note, most fatal cardiac events in COVID-19 patients are due to non-shockable rhythm disorders such as asystole or pulseless electrical activity, rather than VAs [15].

Various pathophysiologic mechanisms have been proposed to explain the autonomic abnormalities seen in acutely ill COVID-19 patients as well as long COVID syndromes. There is renewed understanding of the interplay between the sympathetic and parasympathetic nervous systems and other neuroendocrine systems including the hypothalamus-pituitary-adrenocortical axis, the renin-angiotensin-aldosterone system, and the arginine-vasopressin system. During the acute phase of COVID-19, hypovolemia due to fever, reduced oral intake due to anorexia or nausea, and diaphoresis, along with deconditioning from prolonged bed rest and immobility, can lead to enhanced sympathetic outflow through the adrenergic and noradrenergic axes, with subsequent development of tachycardia, exertional dyspnea and intolerance, and generalized fatigue. Direct viral invasion of the medullary centers controlling central sympathetic outflow, as well as invasion of extracardiac postganglionic

sympathetic neurons, may also lead to chronic increases in sympathetic outflow. There is increasing evidence that patients with COVID-19 have increased levels of autoantibodies directed against beta 1-adrenergic receptors as well as muscarinic cholinergic receptors, which could cause receptor dysregulation and increased sympathetic outflow as well as reduction in parasympathetic outflow [16].

Specific arrhythmic manifestations of COVID-19

Atrial fibrillation/flutter (AFL)

AF is a commonly encountered arrhythmia in critically ill patients, in patients post cardiac surgery, and in hospitalized patients with risk factors for AF including advanced age, history of hypertension, diabetes mellitus, coronary artery disease, or congestive heart failure, among others. There is considerable evidence linking AF with states of systemic inflammation as evidenced by raised levels of inflammatory markers (CRP, IL-6, and tumor necrosis factor- α [TNF- α]) [17]. COVID-19 infection has been shown to cause increased levels of both CRP and IL-6, and therefore, it is not surprising that the incidence of AF is significantly higher in critically ill COVID-19 patients. In a recent retrospective study of 3970 hospitalized patients with reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed COVID-19 infection, the incidence of AF/AFL was 10% (13% in a manually analyzed subset), and 4% in patients without a prior history of atrial arrhythmias. Another study of 301 critically ill patients showed that the incidence of new-onset AF was as high as 14.9% [18]. Patients with new-onset AF/AFL were older and had increased serum IL-6 levels and greater myocardial injury (troponin-I levels) [19]. The occurrence of AF and AFL was associated with increased mortality in this [19] and other studies [20]. A recently published retrospective analysis of hospitalized PCR-confirmed SARS-CoV2 infection in a single healthcare system in New York showed that AF occurred in 17.6% of these patients, of which a majority (65.7%) had new-onset AF. In propensity-matched analysis, AF was independently associated with a higher risk of in-hospital mortality, and new-onset AF was associated with a 56% higher risk of in-hospital mortality compared to patients with a prior history of AF [21•].

The management of AF in COVID-19 patients, as in non-COVID AF patients, involves 2 domains: rate and/or rhythm control, and thromboprophylaxis. In hemodynamically unstable patients, acute management includes the use of electrical cardioversion with or without the concomitant initiation of an anti-arrhythmic agent to prevent AF recurrence. In patients with hemodynamically stable AF, a decision between rate control and rhythm control is dictated by the need to restore sinus rhythm using anti-arrhythmic agents versus the risk of pro-arrhythmia in patients who are critically ill or need to stay on other drugs which may alter atrial cellular electrophysiology or cause drug-drug interactions. In general, rate control with medications such as metoprolol or esmolol is preferred due to relatively shorter half-lives, less risk of hemodynamic consequence compared to other agents, less chances

of bronchospasm due to beta-1 selectivity, and less risk of drug-drug interactions. Diltiazem or verapamil may be used, but these agents are less desirable as rate control agents in patients with cardiomyopathy, as well as patients on protease inhibitors such as lopinavir/ritonavir which can reduce the metabolism of the non-dihydropyridine calcium channel blockers. Digoxin may also be used for rate control, but serum levels need to be closely monitored in the elderly, those with renal insufficiency, and those on lopinavir/ritonavir which can inhibit p-glycoprotein and cause higher serum digoxin levels. If rhythm control is desirable, then the use of amiodarone (oral or intravenous) can be considered, but close monitoring of QTc interval on ECG, hepatic and renal function, and pulmonary function (as some cases of acute pulmonary toxicity with short-term use of amiodarone have been reported) is needed. Caution should also be exercised in patients on lopinavir/ritonavir which can affect CYP3A4 function and inhibit amiodarone metabolism. The role of tocilizumab, an IL-6 inhibitor, on the occurrence of AF in critically ill COVID-19 patients with CRS, deserves further study.

COVID-19 has been shown to induce a hypercoagulable state [22] and can predispose patients to venous thromboembolism in the setting of acute COVID-19 infection [23, 24]. Patients with COVID-19 and AF are thought to have a higher risk of thromboembolic complications, and young critically ill COVID-19 patients were found to have a higher incidence of ischemic stroke [25]. The optimal use of anticoagulation in hospitalized patients (non-ICU setting and ICU setting) with COVID-19 has recently been summarized [22] and incorporated into the recent NICE guidelines (<https://www.nice.org.uk/guidance/ng191/chapter/Recommendations>). A recently published open-label, randomized clinical trial with combined data from 3 separate clinical trials assessed the impact of therapeutic-dose anticoagulation on hospitalized COVID-19 patients across 393 sites in 10 countries. Among 2219 non-critically ill hospitalized COVID-19 patients, the use of therapeutic-dose anticoagulation (mostly enoxaparin) was associated with a higher probability of survival to hospital discharge with reduced need for ICU-level organ support compared to prophylactic-dose anticoagulation, and this prompted early termination of this study due to superiority of the therapeutic-dose anticoagulation strategy. The authors opined that for every 1000 hospitalized non-critically ill COVID-19 patients, therapeutic-dose anticoagulation would be associated with survival of 40 additional patients until hospital discharge without ICU-level organ support at the expense of 7 additional major bleeding events, as compared with usual-care thromboprophylaxis [26]. However, in a cohort of 1098 patients hospitalized with severe COVID-19 disease (defined as needing ICU-level care for organ support), the use of therapeutic-dose anticoagulation did not affect the probability of survival to hospital discharge or the number of days free of cardiovascular or respiratory organ support, compared to usual-care pharmacologic thromboprophylaxis [27].

Whether factor Xa inhibitors such as apixaban or rivaroxaban have differential effects on thrombotic complications of COVID-19 compared to heparin or warfarin is currently uncertain and needs further study. The recently completed MICHELLE trial studied the effect of extended thromboprophylaxis using rivaroxaban 10 mg daily versus control post-hospitalization in 320 COVID-19 patients. After a follow-up period of 35 days, the incidence of the

composite primary outcome (symptomatic venous thromboembolism [VTE], VTE-related death, bilateral VTE, symptomatic arterial thromboembolism, myocardial infarction, nonhemorrhagic stroke, major adverse limb event, or cardiovascular death) was significantly lower in the rivaroxaban group compared to control (3.14% versus 9.43%, $p=0.03$), with no major bleeding events reported in either of the two groups [28]. The role of vorapaxar, an inhibitor of protease-activated receptor 1, shown to reduce activated factor Xa levels and consequently reduce cytokine expression in alveolar epithelial cells in inflammatory lung diseases [29], also deserves more study for its effect on activation of the clotting cascade in COVID-19 patients with CRS and ARDS. More studies are needed to determine the subgroups of COVID-19 patients who would benefit the most from use of thromboprophylaxis, as well the optimal drugs, doses, and treatment durations for the use of thromboprophylactic agents in COVID-19 patients.

The decision to initiate anticoagulation in COVID-19 patients who develop AF should be determined based on their long-term thromboembolic risk assessed by the CHA₂DS₂-VASc score (OAC recommended for a score of ≥ 2 for men and ≥ 3 for women). Although some have advocated higher doses of therapeutic anticoagulation for COVID-19 patients with AF citing the hypercoagulable milieu and instances of VTE despite standard-dose anticoagulation in these patients, recent studies have questioned this approach, and more research is needed. Currently, no data exist to support a change in the dose of the anticoagulant used, and standard dosage guidelines should be used. Oral anticoagulation using factor Xa inhibitors (apixaban, rivaroxaban) can be used, but caution should be exercised in patients on lopinavir/ritonavir (higher serum drug levels due to reduced drug metabolism) and tocilizumab (lower serum drug levels due to enhanced CYP activity). Dabigatran, an oral antithrombin inhibitor, can be used with the above antimicrobials, but being in capsule form cannot be crushed and given to patients who are intubated and/or receiving enteral or parenteral nutrition. Warfarin should be used with close monitoring of the INR levels due to the risk of multiple pharmacokinetic and/or pharmacodynamic interactions with other medications, as well as altered dietary intake of vitamin K in ill patients.

There is currently no evidence to support the prophylactic use of anti-arrhythmic agents in hospitalized patients with COVID-19. Pre-hospitalization medications for the treatment of AF including rate control agents, anti-arrhythmics, and anticoagulation should be continued without interruption if feasible, with pharmaco-vigilance to adjust the dose or modify the agent used based on clinical, biochemical, and electrocardiographic parameters, and pharmacokinetic/pharmacodynamic interactions with other drugs used during the hospitalization. Unless clinically indicated, the medications used for long-term AF management should not be changed due to COVID-19 infection, and close post-discharge monitoring and follow-up are needed to determine the impact of COVID-19 on the natural history of AF in each patient. Decisions related to long-term changes in AF management—changes in medications, consideration of catheter ablation of AF, or use of implantable cardiac devices with or without AV nodal ablation—should be deferred to the outpatient setting as much as possible in stable patients, to allow time for recovery from the acute infection and assessment of lingering symptoms of “long COVID syndrome.” Based on the

published literature, ablation of atrial fibrillation is rarely needed in the acute setting, and established guidelines should guide the choice of ablation in the long-term management of atrial arrhythmias [30].

Atrioventricular block and sinus node dysfunction

The incidence of AV block in COVID-19 patients varies from 1–12% and is usually transient in nature [31]. These can manifest as high-grade second-degree AV block, such as Mobitz II second-degree AV block or 2:1 AV block, which may progress to intermittent complete heart block [32, 33]. Many of these patients do not have pre-existing cardiovascular disease or abnormalities on prior echocardiograms, and clinicians need to be aware of the association between acute COVID-19 infection and transient AV block. Potential mechanisms for the development of AV block in COVID-19 patients include the following: focal myocarditis or myocardial edema in the region of the AV node or proximal conduction system, electrolyte disturbances, increased vagal activity during periods of endotracheal suctioning and prone positioning, and the effects of drugs including chloroquine (increases Purkinje fiber refractory period and action potential duration, resulting in AV nodal and infra-Hisian conduction disturbance) [34], hydroxychloroquine, lopinavir/ritonavir, and azithromycin.

As these conduction abnormalities can be transient, management is directed at treatment of the infection, use of intravenous atropine (for transient bradyarrhythmias) or isoproterenol, or insertion of a temporary transvenous pacemaker (in more sustained cases) as needed to allow time for recovery. Development of heart block in COVID-19 patients is thought to be a poor prognostic sign especially in patients with comorbidities such as hypertension and diabetes mellitus [35, 36]. However, in milder cases of COVID-19 with new-onset AV block early in the course of the illness, close cardiovascular monitoring, discontinuation of AV nodal blocking agents, and treatment of COVID-19 may be enough to allow recovery of AV conduction. Echocardiography to look for new right or left ventricular dysfunction and assessment of pulmonary arterial pressures is reasonable. Ambulatory heart rhythm monitors should be considered after recovery from acute illness to determine the need for further electrophysiologic evaluation and/or permanent pacemaker implantation based on current guidelines [37].

Sinus node dysfunction leading to severe sinus bradycardia has been reported in up to 15% of cases with the SARS-CoV1 infection [38] and has also been reported in a few patients with COVID-19 caused by SARS-CoV2 [35]. The SARS-CoV2 virus interacts with the ACE2 receptor to enter the host cell, and the sino-atrial nodal cells are known to have a high degree of ACE2 expression [39]. The development of sinus pauses/arrest may be a reflection of the severity of the acute illness and is also a poor prognostic sign. Management of sinus node dysfunction in COVID-19 patients is similar to that for AV block as described above.

Ventricular arrhythmias

The incidence of ventricular arrhythmias in COVID-19 patients, in large, published case series, has ranged from 1.6 to 5.9% [40, 41]. VAs reported in COVID-19 patients include polymorphic ventricular tachycardias including torsade de pointes (TdP), ventricular tachycardia (VT) storm, and ventricular fibrillation. Although the presence of underlying structural heart disease significantly increases the risk of VAs during acute illness, other factors that impact patients with COVID-19 may contribute to the risk of developing VA even in the absence of underlying structural heart disease. Acute myocardial injury in patients with COVID-19, as evidenced by increased cardiac troponin levels, was noted to significantly increase the risk of VA [41].

Management of VAs in patients with COVID-19 needs to employ a multi-pronged approach. For hemodynamically stable and unstable VA in patients with COVID-19, standard ACLS protocols should be followed. Contributing factors such as hypoxia, hypovolemia, electrolyte abnormalities such as hypokalemia and hypomagnesemia, and metabolic acidosis should be corrected aggressively. Vasopressor medications, sedation, and neuromuscular blockade should be employed judiciously. Other factors such as volume overload, increased sympathetic tone, and use of pro-arrhythmic drugs should be closely monitored and managed appropriately. Echocardiography to assess biventricular and valvular function should be obtained in all patients with new-onset VAs during COVID-19 infection, especially those with elevated cardiac biomarkers.

Beta-blockers and/or anti-arrhythmic drug therapy should be considered for symptomatic nonsustained VA. In patients with polymorphic VT without QT prolongation, underlying myocardial ischemia should be considered as a potential cause. IV beta-blockers or IV lidocaine may be used, in conjunction with intravenous sedation and use of anxiolytics in patients with respiratory distress, agitation, and anxiety. In patients who have QT prolongation and TdP, the use of QT-prolonging drugs should be stopped or modified, and IV magnesium, IV isoproterenol, or temporary transvenous pacing should be used. For patients with VT storm or recurrent or refractory VT, consider use of IV amiodarone and/or lidocaine, along with deep sedation and endotracheal intubation with ventilatory support. There is limited data supporting the use of substrate-based VT ablation in critically ill COVID-19 patients with VT storm and multiple ICD shocks [42]. Tocilizumab, a monoclonal antibody that blocks the IL-6 receptor and is being used in critically ill COVID-19 patients, can cause QT interval shortening in association with reduction in CRP and cytokine levels and may be beneficial for use in COVID-19 patients with QT prolongation and VAs [43, 44]. Currently, there is no data supporting the use of prophylactic anti-arrhythmic therapy for the prevention of VAs in hospitalized COVID-19 patients.

Sudden cardiac arrest

A worldwide survey of cardiovascular professionals early in the COVID-19 pandemic reported that cardiac arrest due to VT/VF was seen in 4.8% and pulseless electrical activity (PEA)/asystole was seen in 5.6% of hospitalized

COVID-19 patients [10]. In addition, data from Italy [45] and France [46] show that the incidence of out-of-hospital cardiac arrest (OHCA) has also increased significantly during the COVID-19 pandemic. The incidence of OHCA increased by up to 200% in the first few weeks of the COVID-19 pandemic in New York City compared to the same period in 2019, with higher rates of PEA (OR 1.99) and asystole (OR 3.5) accounting for the increase in OHCA even though the prevalence of pre-existing illnesses and the percentage of bystander CPR were similar between the two time periods [47]. Even in areas with low rates of COVID-19 infection, the incidence of OHCA was up to 25% higher during the early months of the pandemic. A larger proportion of OHCA occurred at home, and the rate of bystander CPR was lower than that in the same period in 2019 [48]. Patients with in-hospital VT/VF arrest would need evaluation for underlying structural heart disease (ischemia, myocardial inflammation, cardiomyopathy) and those with no clear transient or reversible causes should be considered for implantable defibrillator implantation for secondary prevention of SCA per current guidelines [49].

Both bradyarrhythmias and tachyarrhythmias may be the cause of SCA in patients with COVID-19. As noted previously, critically ill COVID-19 patients with elevated cardiac troponin are at higher risk for malignant VAs and mortality. In addition, ECG abnormalities such as QRS and QTc prolongation have been observed in patients with COVID-19 pneumonia [50], and a small study of 63 patients with COVID-19 pneumonia showed that an index of cardiac electrophysiologic balance (iCEB), computed by the QTc/QRS ratio, was significantly higher in the critically ill COVID-19 pneumonia patients, leading to a potentially higher risk of TdP, compared to less severe cases [51].

Interestingly, in a cohort of 100 COVID-19 patients (1/3rd needing hospitalization) who underwent cardiac MRI at a median interval of 71 days after the diagnosis of COVID-19, 78% had evidence of cardiac involvement, and 60% had evidence of myocardial inflammation [52] independent of the severity and course of illness, presence of pre-existing conditions, or time since diagnosis. However, this was a small sample of patients and performed at a single center and included a large proportion of patients with new or persistent symptoms. In a prospective study of 44 recovered COVID-19 patients, late gadolinium enhancement was observed in 30% of patients, with a scattered lesion distribution localized in the mid-myocardium and/or sub-epicardium [53]. A study of 26 elite athletes who had recovered from COVID-19 and underwent cardiac MRI at a median of 32 days since the diagnosis revealed that cardiac abnormalities were seen in 19% of subjects, manifested as myocardial edema and focal mid-myocardial LGE [54]. These studies suggest that a significant proportion of patients who have recovered from COVID-19 may still have residual cardiac abnormalities weeks after the initial diagnosis and clinical recovery, and this may in part explain residual symptoms of exertional dyspnea, fatigue, and palpitations seen in the so-called long-haul COVID-19 syndrome.

Other factors associated with the observed increase in SCA during the COVID-19 pandemic, especially the alarmingly higher incidence of OHCA,

are the shelter-in-place and lockdown restrictions that were imposed during different periods during the pandemic, patients' reluctance to seek medical care due to fear of contracting COVID-19 at their doctor's office or hospital, strained EMS infrastructure due to the increased volume of activations and consequently longer EMS response times, the additional need to have access to and use personal protective equipment for first responders and front-line healthcare personnel, and the diversion of clinical personnel, administrative focus, and other resources from ongoing chronic disease management to controlling the spread of COVID-19. Although the impact of some of these factors has waned in recent months, the emergence of new SARS-CoV2 variants and waves of new COVID-19 cases in different parts of the world, slow and disparate rates of adoption of COVID-19 vaccination, premature loosening of restrictions related to social distancing, use of face masks, and travel pose a looming threat of creating a similar clinical and social environment if the number of cases continues to increase in the weeks and months ahead.

Cardiac dysautonomias associated with COVID-19

A significant minority of COVID-19 patients have symptoms related to autonomic dysfunction, either concomitantly during the acute phase of the illness or, more commonly, up to several weeks after the acute respiratory and constitutional symptoms have resolved. Although the true prevalence of residual symptoms in COVID-19 patients is still unknown, smaller studies have shown that fatigue was reported by more than 50% of patients, dyspnea was reported by about 30%, and chest pain by about 20% of patients up to 4–8 weeks after hospital discharge [55, 56]. Some COVID-19 patients have symptoms of lightheadedness, orthostatic intolerance, palpitations, and headaches that linger for several weeks beyond the acute phase, and many of these patients receive multiple referrals to subspecialties such as cardiology, neurology, psychiatry, and physiatry. It has also led to the coinage of terms such as “chronic COVID” or “long-haul COVID” within the general public and parts of the medical community, leading to confusion and ambiguity related to diagnosis and management of these syndromes. It is important for clinicians managing COVID-19 patients to be aware of these clinical entities and correlate these symptoms with current or prior SARS-CoV2 infection, and to initiate treatment directed at these symptoms as well as make the appropriate referrals for additional objective testing and management.

Retrospective case series show that lightheadedness, orthostatic intolerance, postural tachycardia, and fatigue are the most common symptoms reported by post-COVID syndrome patients [57, 58, 59]. These case series show the patients are generally young, predominantly female, and report residual symptoms for up to 6 months or longer after the acute phase of the illness. In a retrospective study of 20 patients referred for autonomic testing due to persistent cardiac and/or neurologic symptoms after suspected or confirmed acute COVID-19 infection, the use of a 10-min stand test or a

tilt table test led to a diagnosis of postural orthostatic tachycardia syndrome (POTS) in 75% of patients, with a minority diagnosed with neurocardiogenic syncope and orthostatic hypotension [57•]. In another study, 27 patients with laboratory-confirmed prior SARS-CoV2 infection referred for autonomic testing were subjected to a rigorous battery of tests to assess postganglionic sympathetic sudomotor function, cardiovagal function, cardiovascular adrenergic function, and thermoregulatory function. Eighty-one percent of patients reported symptoms during the head-up tilt table test, of which 63% reported lightheadedness, 26% reported dyspnea, 19% reported chest pain, and 7% reported palpitations. The most commonly diagnosed clinical syndrome was orthostatic intolerance without significant orthostatic tachycardia or orthostatic hypotension which was observed in 41% of patients, while POTS was diagnosed in 22% and mild orthostatic hypotension was seen in 11% [58]. In another case series of 11 post-COVID patients (mean age 46 ± 18 years, 9 females), predominant symptoms included palpitations (82%), chest pain (64%), dyspnea (73%), fatigue (82%), or dizziness (27%). Mean time to symptoms from COVID diagnosis was 40 ± 57 days. Two patients (18%) were diagnosed with inappropriate sinus tachycardia (IST), 2 (18.2%) were diagnosed with POTS, and the remaining patients (63.6%) either were still undergoing evaluation or did not meet formal criteria for IST or POTS. Nine patients received medications (beta-blockers in 5, ibuprofen in 2, midodrine and colchicine in 1 each). Six out of 9 patients reported improvement or resolution of symptoms with medical therapy [59].

The American Autonomic Society has published a guidance statement to help clinicians sift through the confusing terminologies and define the scope of long COVID POTS [60•]. They endorsed the terminologies used for the different phases of COVID-19 by the NICE guidelines from the UK. According to these guidelines, “long COVID” includes both ongoing symptomatic COVID-19 (presence of symptoms between 4 and 12 weeks after onset) and chronic COVID (symptoms for > 12 weeks without an alternative explanation; <https://www.nice.org.uk/guidance/ng188>). In addition to dyspnea, palpitations, and chest pain, other symptoms of long COVID include joint or muscle pain, headache, cognitive impairment (“brain fog”), sleep disturbances, tingling and/or numbness in the hands and feet, dizziness, earache, tinnitus, loss of taste and/or smell, abdominal discomfort or irregularities in bowel function, skin rashes, anxiety, and depression.

Patients with chronic medical conditions such as hypertension, congestive heart failure, diabetes mellitus, and chronic kidney disease have increased sympathetic activity, which can contribute to progression of the disease process and related complications. It is therefore plausible that in these patients, further increases in sympathetic outflow caused by hypoxemia and activation of inflammatory pathways from acute COVID-19 can lead to rapid worsening of clinical status and sudden decompensation. Critically ill COVID-19 patients may develop afferent baroreceptor failure in the carotid body, which in combination with changes in central sympathetic outflow from brainstem structures such as the nucleus tractus solitarius (which has high ACE2 expression and therefore vulnerable to direct SARS-CoV2 invasion) can cause lability of blood pressure and sudden hemodynamic compromise [61]. In addition, withdrawal of the

vagal parasympathetic outflow, due to viral invasion of the vagal nerve fibers and/or auto-antibody-mediated dysfunction, can blunt the protective anti-inflammatory effects of the vagal pathways, thus accentuating the hemodynamic and neuro-humoral impact of the heightened sympathetic activity in the setting of acute COVID-19 [62].

A recently published review also identifies other putative mechanisms related to the development of long COVID, including T cell dysregulation, tonically increased secretion of autoantibodies by B cells, viral invasion of intestinal cells and persistence of virus within the gastrointestinal tract, and alterations in gut microbiome content. Risk factors for the development of long COVID include female gender, history of anxiety or depression, age > 70 years, and the presence of > 5 clinical symptoms by the end of the first week of onset. Interestingly, most studies show that the severity of acute illness did not correlate with subsequent development of long COVID [63–65].

Management of patients with long COVID requires a multi-disciplinary approach centered around empowering the patient through reassurance, education and institution of self-management strategies, symptom-directed non-pharmacologic and pharmacologic therapies, appropriate subspecialty referrals for diagnosis and management of clinical entities (POTS, vasovagal syncope, orthostatic hypotension, other neurologic conditions (such as small fiber neuropathy), arrhythmias and other cardiovascular conditions (such as IST or supraventricular tachycardia), and psychiatric illnesses (such as anxiety disorder, depression, or post-traumatic stress disorder)), and a structured physical rehabilitation program designed to overcome the deconditioning associated with protracted illness. The ACC/AHA/HRS guidelines for the management of syncope are a useful guide for clinicians in managing specific symptoms of long COVID-19 [66]. In patients with orthostatic intolerance, it is helpful to establish correlations between symptoms and objective abnormalities on a tilt table test and then provide targeted recommendations to patients to identify the prodromal symptoms and respond with hydration and counterpressure maneuvers (switch to a seated or supine position, tensing of thigh or buttock muscles, sitting with arms and legs crossed, folding arms and leaning forward with the head down, etc.). A useful educational resource for patients is the STARS initiative from the Heart Rhythm Alliance (www.stopfainting.org). Regular, structured exercise using a recumbent bike or swimming is useful for reconditioning. Adequate fluid (2–3 L/day) and salt intake (5–10 g sodium chloride), avoidance of caffeine or alcohol intake, having smaller meals more frequently rather than large meals, avoidance of known triggers such as prolonged standing or warm environments, and use of compression garments are all measures that can help prevent or alleviate orthostatic symptoms. If medications are used, they should be directed at specific symptoms and/or specific co-morbid conditions. In POTS patients, medications such as fludrocortisone can be used judiciously for patients with hypovolemia, while midodrine may be helpful if orthostatic hypotension is a predominant manifestation. In patients with hyperadrenergic states, clonidine, methyl dopa, or propranolol may be used, with close monitoring for adverse effects and rebound hypertension due to sudden discontinuation [67].

Conclusions

A variety of arrhythmic manifestations have been described in patients with COVID-19, which range from relatively benign conditions such as transient sinus bradycardia to potentially life-threatening conditions such as ventricular tachyarrhythmias and sudden cardiac death. Atrial fibrillation is the most common arrhythmia seen in acutely ill COVID-19 patients. While the pathophysiological mechanisms underlying these arrhythmias in COVID-19 patients are incompletely understood, direct viral invasion, hypoxemia, activation of systemic inflammatory systems with downstream release of cytokines and inflammatory and pro-fibrotic mediators, changes in ion channel physiology, activation of the immune system, and dysregulation of autonomic function have been implicated. Management of these arrhythmias should be based on published evidence-based guidelines, with special consideration of the acuity of COVID-19 infection, concomitant use of antimicrobial and anti-inflammatory drugs, and the transient nature of some arrhythmias. The development of atrial or ventricular arrhythmias in hospitalized COVID-19 patients has been shown to portend a higher risk of in-hospital death. Some manifestations, such as the “long COVID syndrome,” may lead to residual symptoms several months after acute infection and need more clinical study and specific management strategies. Finally, as the pandemic evolves with the discovery of new SARS-CoV2 variants, newer drugs for treatment of acute COVID-19 infection, and the widespread administration of vaccines, clinicians must remain vigilant for other arrhythmic manifestations that may occur in association with this novel but deadly disease.

Compliance with Ethical Standards

Conflict of Interest

Sandeep A. Saha, MD, MS, FHRS: None. Andrea M. Russo, MD, FHRS: Dr. Russo reports research grants from Boston Scientific and Kestra; consulting from Abbott, Boston Scientific, Medtronic and PaceMate; and honoraria from Biotronik. Mina K. Chung, MD, FHRS: None. Thomas F. Deering, MD, FHRS: Dr. Deering reports that Piedmont Healthcare receives on his behalf research grants from Abbott, Biotronik, Biosense Webster, Medtronic and Milestone. He also reports that he has consulted for CVRx, Pacemate, Preventice, and Sanofi while serving as a member of an Adjudication Committee for Abbott. Dhanunjaya Lakkireddy, MD, FHRS: Consultant/honoraria: Abiomed, Biosense Webster, Boston Scientific, Biotronik, Janssen, Abbott medical Rakesh Gopinathannair, MD, MA, FHRS: Consultant/honoraria: Abbott Medical, Boston Scientific, Pfizer, Zoll Medical; Advisory board: Pacemate (no compensation).

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