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AHA SCIENTIFIC STATEMENT

Cardiac Arrhythmias and Autonomic Dysfunction Associated With COVID-19: A Scientific Statement From the American Heart Association

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ABSTRACT: Cardiac arrhythmias are commonly noted in patients during infections with and recovery from COVID-19. Arrhythmic manifestations span the spectrum of innocuous and benign to life-threatening and deadly. Various pathophysiological mechanisms have been proposed. Debate continues on the impact of incident and exacerbated arrhythmias on the acute and chronic (recovery) phase of the illness. COVID-19 and COVID-19 vaccine–associated myocardial inflammation and autonomic disruption remain concerns. As the pandemic has transformed to an endemic, with discovery of new SARS-CoV-2 variants, updated vaccines, and potent antiviral drugs, vigilance for COVID-19–associated arrhythmic and dysautonomic manifestations remains. The objective of this American Heart Association scientific statement is to review the available evidence on the epidemiology, pathophysiology, clinical presentation, and management of cardiac arrhythmias and autonomic dysfunction in patients infected with and recovering from COVID-19 and to provide evidence-based guidance. The writing committee's consensus on implications for clinical practice, gaps in knowledge, and directions for future research are highlighted.

Key Words: AHA Scientific Statements ■ atrial fibrillation ■ autonomic nervous system diseases ■ COVID-19 ■ heart arrest ■ myocarditis

Coronavirus disease 2019 (COVID-19) infections can have serious short- and long-term cardiovascular consequences, including a wide range of arrhythmias. Growing evidence indicates that COVID-19 infections result in autonomic dysfunction (AD), leading to postural orthostatic tachycardia syndrome (POTS) or inappropriate sinus tachycardia.[1,2] Although the pandemic has ended, an endemic continues with several viral strains. Associated arrhythmia and autonomic complications persist. Clinicians need guidance to care for patients in the acute and convalescent phases of the illness.

In this American Heart Association scientific statement, we discuss common arrhythmic and autonomic manifestations of COVID-19, consider pathophysiological mechanisms and the clinical significance and persistence of arrhythmias, and address comparative data with other viral illnesses. Risk for recurrent arrhythmias after recovery and implications for long-term follow-up, monitoring, and treatment strategies are considered.

The writing group performed a comprehensive literature search (MEDLINE, PubMed, EMBASE, Cochrane Library) and identified relevant original articles, any applicable guidelines and scientific statements, review articles, and meta-analyses. This scientific statement does not provide formal clinical recommendations or list levels of evidence but provides suggestions/implications for practice for health care professionals, specifically those involved in caring for patients with COVID-19 who have arrhythmic and AD. The writing group was diverse and included individuals with expertise in cardiac electrophysiology, autonomic disorders, and infectious disease. Available evidence includes randomized trials, prospective registries, observational studies, and meta-analyses. Knowledge gaps for which future research

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should be directed are considered. Consensus summary statements required 80% agreement among the writing group.

PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING ARRHYTHMIC MANIFESTATIONS

Table 1 and Figure 1 summarize postulated pathophysiological mechanisms contributing to cardiac arrhythmias seen with COVID-19 infections. Mechanisms include but are not limited to direct autonomic effects, hemodynamic disruption, and immune-related causes (eg, inflammation and direct viral injury).[3] More than 1 mechanism may be operative in any given case. Autopsy studies have demonstrated cardiac infiltration by SARS-CoV-2 virions, but this phenomenon appears to occur primarily in the interstitium rather than cardiomyocytes, with evidence that tissue disruption (and therefore electrophysiological changes) may be driven more by the inflammatory response than the virus in isolation.[4,5] The mechanism of cell entry of the angiotensin-converting enzyme 2 receptor SARS-CoV-2 virus, expressed at high levels in the heart, may explain cardiac effects, including arrhythmias.

Alteration in autonomic tone, particularly enhanced sympathetic activation, and adverse consequences of hemodynamic instability, most relevant among the critically ill, persist into recovery.[6–8] In the initial phase of the pandemic, COVID-19 infections associated with hypoxic lung disease and cytokine release syndrome with elevated inflammatory markers were associated with life-threatening arrhythmias and a high prevalence of arrhythmias, including atrial fibrillation (AF).[9–13]

Inflammation, a risk factor for arrhythmias, including AF and ventricular arrhythmias,[14–16] can lead to fibrosis, itself a nidus for enhanced automaticity and reentry.[17,18] Direct viral infiltration into the myocardium, causing myocarditis,[4] and deleterious effects of severe systemic illness such as hypoxemia, electrolyte disturbances, volume shifts, or fever could contribute to increased risk of ventricular tachycardia (VT). This is amplified by concomitant comorbidities (obesity, diabetes, and occult and manifest cardiovascular disease). Antiviral drugs, in lieu of preexisting cardiac disease, may compound the risk for ventricular arrhythmias, including torsades de pointes and ventricular fibrillation (VF). QT interval prolongation may result from elevated interleukin-6 levels, specific proven and unproven therapies, and electrolyte disturbances.[19]

The pathogenesis of myocarditis is multifactorial. Direct cell injury may occur from T cell–mediated cytotoxicity augmented by cytokine storm.[20] Cardiotropism may be due to hepatocyte growth factor produced by myocardial cells and c-Met and a hepatocyte growth factor receptor on the T lymphocytes.[21] The altered surface major histocompatibility complex class 1 antigen triggers T-lymphocyte and cytokine response (Figure 2).[22] Comparing SARS-CoV-2–infected human induced pluripotent stem cell–derived cardiomyocytes with mock human induced pluripotent stem cell shows that 6 differently expressed critical genes (*CDK1*, *KIF20A*, *PBK*, *KIF2C*, *CDC20*, *UBE2C*) were likely related to COVID-19 myocarditis.[23] Whereas some infections have a predilection for myocarditis (eg, Coxsackie B or parvovirus 1948) or anatomic locations pertinent to arrhythmias (Lyme disease),[24] evidence for a specific proarrhythmic effect of COVID-19 has not yet been established.

The pathogenesis of bradyarrhythmias and conduction system damage in patients infected with COVID-19 is poorly understood but hypothesized to be associated with direct myocardial injury and inflammatory damage to pacemaker cells, ferroptosis of sinoatrial pacemaker cells, angiotensin-converting enzyme 2 receptor downregulation, hypoxia, vagal overstimulation due to neuroinvasion, or an exaggerated medication response[25–29] (Supplemental Figure 1). Inflammatory cytokines acting directly on cardiac pacemaker cells may alter heart rate and neurotransmitter responsiveness.[26]

Table 1. Pathophysiological Mechanisms and Treatment of Arrhythmias Associated With COVID-19

Arrhythmia	Mechanisms
Atrial	Sympathetic hyperactivation
	Changes in electrophysiological properties (eg, conduction velocity heterogeneity related to inflammation)
	Neurohormonal perturbations, especially the renin-angiotensin-aldosterone system
	Atrial myocyte injury and subsequent fibrosis attributable to viral invasion or inflammatory cytokines
	Electrolyte abnormalities
Atrioventricular conduction abnormalities	Atrial myocyte injury and subsequent fibrosis attributable to viral invasion or inflammatory cytokines
	Increased vagal activity
	Adverse effects of drug therapy
	Myocarditis
Sinus node dysfunction/asystole	Atrial myocyte injury and subsequent fibrosis attributable to viral invasion or inflammatory cytokines
	Acute complication from SARS-CoV-2 infection (acute pulmonary embolism, severe hypoxemia)
	Electrolyte abnormalities
Ventricular	Ventricular myocyte injury and subsequent myocarditis attributable to viral invasion or inflammatory cytokines
	Changes in ionic currents
	Adverse effects of drug therapy, particularly QT prolongation

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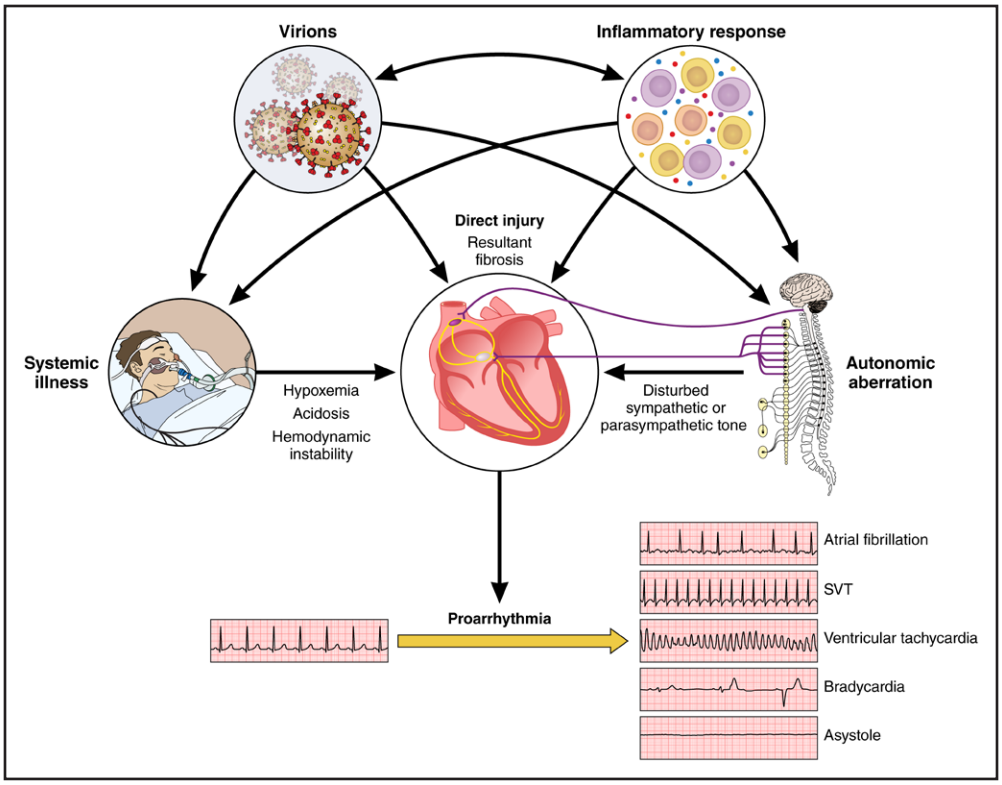

Figure 1. Overview of the pathophysiological mechanisms associated with arrhythmogenesis in the setting of COVID-19 infection.
SVT indicates supraventricular tachycardia.

SPECIFIC ARRHYTHMIAS ASSOCIATED WITH COVID-19

Rates of arrhythmias observed in the ill do not extend to clinically stable patients with COVID-19 or those recently positive for COVID-19.[30,31]

Bradyarrhythmias

Various bradyarrhythmias have been reported during COVID-19 infection, including sinus bradycardia, sinus pauses, and atrioventricular block. Of 4526 patients from 12 countries identified by a positive polymerase chain reaction test (from January to June 2020) in a worldwide retrospective survey of COVID-19–associated arrhythmias, 22.6% had bradyarrhythmias, including sinus bradycardia (12.8%), atrioventricular block (8.6%), and pauses >3 seconds (1.2%).[32] In 1 study, almost one-third of patients with severe COVID-19 pneumonia developed sinus bradycardia (49–58 bpm) without apparent myocarditis or myocardial infarction.[33] In another report, 36% of patients hospitalized with COVID-19 and 56% of those with fever (>38.3°C) had bradycardia.[34] Relative bradycardia (a rise in heart rate <10 bpm/1°C rise in temperature from the basal rate) occurred in 61% of patients hospitalized with COVID-19, but this was not associated with adverse outcomes.[35]

A recent systematic review of 43 articles that included 11 observational studies and 59 cases from case reports and series suggested that severe bradycardia occurred most often in patients with severe or critical COVID-19. This included some cases of complete heart block that required temporary or even permanent pacing in critically ill patients despite preserved ventricular function.[36] However, the observational nature of the reports, small sample sizes, and paucity of comparator groups limit interpretation of causality or the impact of bradycardia on outcomes.

Bradyarrhythmia incidence varies by continent; atrioventricular block is commonly reported in Asia.[32] The TriNetX COVID-19 global research network that includes 44 health care organizations and 81 844 patients with COVID-19 reported sinus bradycardia in 1.9% and complete heart block in 0.01%.[37] The striking difference in bradyarrhythmia prevalence in various reports is likely due to the observational nature of studies, data sources, arrhythmia definition, method of detection, patient selection, and illness severity. In addition, many of the patients with COVID-19 who presented to an intensive care unit (ICU) setting may have had preexisting comorbidities and could have been admitted for other conditions but were found to have COVID-19 infection as a result of a positive polymerase chain reaction. This is a limitation of the retrospective nature of the COVID-19 studies and may result in an overestimation of events.

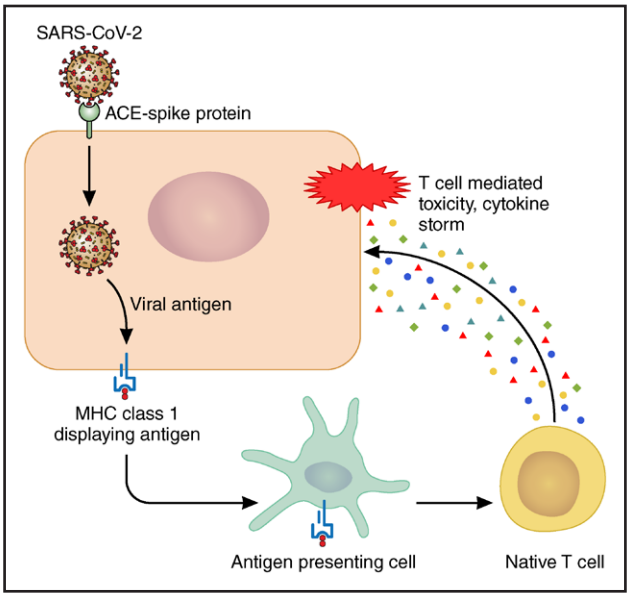

Figure 2. Proposed pathophysiology of myocarditis associated with COVID-19 infection.
ACE indicates angiotensin-converting enzyme; and MHC, major histocompatibility complex. Adapted with permission from Siripanthong et al.[22] Copyright © 2020 Elsevier.

Asystole attributable to transient sinus node dysfunction may occur in patients with severe COVID-10 infection and has been reported in the context of vagal hypersensitivity.[25] For these patients, long-term pacing is rarely needed.

Remdesivir has been associated with bradycardia in 17% to 47% of cases.[38–42] Bradycardia can be managed by drug discontinuation or atropine or dopamine if necessary. A meta-analysis of mostly observational data demonstrated that the incidence of bradycardia was 22.3% in those taking remdesivir compared with 9.8% in those not taking remdesivir (odds ratio [OR], 2.11 [95% CI, 1.65–2.71]; $P<0.001$).[43] Lopinavir-ritonavir treatment has been associated with bradycardia, particularly in older patients admitted to the ICU.[44] Many studies report improvement in bradycardias with resolution of infection, but occasionally pacing is required.[45,46] In the American Heart Association Get With The Guidelines COVID-19 Registry, only 44 of 32636 patients (0.13%) hospitalized with COVID-19 developed bradyarrhythmias requiring pacing. For patients admitted to the ICU, 31 of 9792 patients (0.31%) developed bradyarrhythmias requiring pacing.[47]

A meta-analysis of 1320 inpatients with COVID-19 that compared outcomes of patients with bradycardias during admission with outcomes of those without bradycardias suggested that bradycardia was not independently associated with mortality (OR, 1.25 [95% CI, 0.41–3.84]; $P=0.7$).[48] In summary, severe bradyarrhythmias during COVID-19 infection tend to occur in patients who have more severe infection.[47,49] Bradyarrhythmias typically improve with resolution of infection, and most patients do not require permanent pacemakers. Larger prospective studies or registries with follow-up of patients presenting with bradyarrhythmias during COVID-19 infection are needed to determine longer-term outcomes. Until then, patients with bradycardia should receive standard-of-care, guideline-directed therapy.[50]

AF/Flutter

A single-center observational study aiming to investigate the incidence of AF in patients hospitalized with COVID-19 and to understand its impact on in-hospital mortality rate reported that 17.6% experienced AF (12.5% new onset). AF was an independent predictor of in-hospital mortality (relative risk, 1.56).[51] Similar results have been reported in other centers/countries.[52] Whether this high incidence of AF and the associated excess mortality are specific to COVID-19 or instead manifestations of illness severity and systemic inflammation is uncertain. A multicenter retrospective cohort study of 3970 patients hospitalized with COVID-19 found an ≈13% incidence of AF, similar to a comparative cohort admitted with severe influenza. Patients with COVID-19 with AF tended to be older and to have higher levels of interleukin-6 and cardiac troponin. Presence of AF was associated with higher mortality among patients with COVID-19 and influenza (relative risk, 1.77 and 1.78, respectively).[53]

These data were confirmed by the American Heart Association COVID-19 registry that included 30999 patients from 120 US centers. New-onset AF was common (5.4%) among patients hospitalized with COVID-19. Almost half with new-onset AF died during their index hospitalization. After multivariable adjustment for comorbidities and disease severity, new-onset AF was not statistically significantly associated with death, supporting the concept that AF in patients with COVID-19 may be a marker of disease severity and underlying comorbidities rather than an independent driver of mortality.[54] The association between AF and outcomes does not appear to be affected by concomitant anticoagulant or antiplatelet therapy.[52,55]

Management goals for AF in patients with COVID-19 should include reducing short- and long-term stroke risk, optimizing hemodynamic status, and improving symptoms. Hemodynamically unstable patients should undergo prompt electrical cardioversion. Whether patients with COVID-19 with AF are at higher risk of thromboembolism beyond what would be expected by the CHA_2DS_2Vasc score based on the heightened thrombotic risk associated with inflammation is uncertain.

Anticoagulation and rate and rhythm control strategies remain similar to strategies in patients without COVID-19. However, acute triggers (hypoxia, oxidative stress, inflammation, electrolyte imbalance, organ dysfunction) should be addressed. Rate control strategies

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should consider the adverse consequence of tachycardia; patients who cannot be rate controlled or experience consequences from loss of atrioventricular synchrony should undergo rhythm control. Recovered patients with COVID-19 should be counseled about the risks of recurrent AF and need for long-term monitoring strategies and anticoagulation because recent evidence not specific to the COVID-19 population suggests that AF observed after an acute precipitant has a high risk of recurrence.[56,57]

Ventricular Arrhythmias

Premature ventricular contractions, nonsustained VT, and sustained VT/VF have been observed with acute COVID-19 infection. Myocardial injury was associated with mortality, whereas those with underlying heart disease without myocardial injury had more favorable prognosis. In patients with COVID-19 infection, the overall prevalence of ventricular arrhythmias is 0.1% to 8%[49,58–60] according to mainly retrospective data. In a retrospective study of 187 hospitalized patients with confirmed COVID-19 early during the pandemic in China, patients with elevated troponin T levels were more likely to have VT/VF compared with those with normal troponin levels (11.5% versus 5.2%).[9] In a prospective observational study, of 143 patients hospitalized in the United States with COVID-19 and monitored on telemetry, 1.4% were reported to have sustained VT and 0.7% had VF.[60]

Pooled data from 21 studies of 132 790 patients with COVID-19 infection revealed a 5% (95% CI, 4%–6%) prevalence of ventricular arrhythmias.[61] Ventricular arrhythmias were independently associated with an increased risk of death in patients with COVID-19 (OR, 2.83 [95% CI, 1.78–4.51]).[61] Another meta-analysis of 12 499 participants from 28 studies found ventricular arrhythmias in 2.5% (95% CI, 1.8%–3.1%). The incidence of ventricular arrhythmias was higher among critically ill patients and nonsurvivors.[62] A study of 107 patients with COVID-19–induced acute respiratory distress syndrome in the ICU demonstrated sustained monomorphic VT in 6 (5.6%).[63] Because cardiac arrests and incident nonsustained VT were associated with ICU admission after multivariate analysis, arrhythmias may be a consequence of systemic illness rather than the direct effect of COVID-19.[49]

Arrhythmic risks associated with COVID-19 vary between studies and may be related to severity of illness and underlying comorbidities, with outcomes evolving through various phases of the pandemic. It is possible that more severe infection in hospitalized patients during the early phase of the pandemic may have been associated with greater arrhythmic risk and worse outcomes associated with more virulent viral strains and limited antiviral therapies, with lower arrhythmic risks during the current endemic phase.

Older age and ventricular tachyarrhythmias were independently associated with mortality in critically ill hospitalized patients.[64] COVID-19 infection can precipitate VT storm in patients with cardiac sarcoidosis and those with ischemic heart disease.[65] Fever in the setting of Brugada syndrome may increase risk for ventricular arrhythmias.[66] Polymorphic VT or torsade de pointes may occur in the setting of QT prolongation provoked by COVID-19 drug prescription, including lopinavir, ritonavir, chloroquine/hydroxychloroquine, and azithromycin.[67,68] Proarrhythmia may occur in patients with or without preexisting heart disease; women with preexisting heart disease may be particularly susceptible.[67]

There are limited outpatient data on ventricular arrhythmia occurrence with COVID-19. In a prospective arrhythmia surveillance study of 51 individuals who underwent 14-day ambulatory electrocardiographic monitoring after a positive COVID-19 diagnosis, there was no evidence for sustained ventricular arrhythmias. Nearly all (96%) had an ectopic burden of <1%; only 1 had a 15.4% ventricular ectopic burden. Although palpitations were common, symptoms correlated with sinus rhythm, sinus tachycardia, isolated ectopy, or nonsustained VT.[31] One study evaluating arrhythmias 3 months after hospitalization for COVID-19 using 24-hour ambulatory monitoring found premature ventricular contractions in 18% and nonsustained VT in 5% without sustained ventricular arrhythmias.[69]

In those patients with COVID-19 with VT/VF arrest, implantable cardioverter defibrillator therapy should be considered according to ventricular arrhythmia guidelines for the management of cardiac arrest in the absence of clear transient or reversible causes.[70] The role of cardiac magnetic resonance imaging in identifying patients at increased risk for VT after COVID-19 infection is uncertain.

Similarly, acute management of ventricular arrhythmias should be based on the guidelines, with attention to acuity of illness that may also require concomitant antimicrobial or anti-inflammatory drugs to treat SARS-CoV-2 infection.[70] Because electrical storm may also be seen in the absence of acute myocarditis with normal troponins, potentially precipitated by a hyperinflammatory state, anti-inflammatory drugs might have a therapeutic role.[71] Close monitoring of QT-prolonging drugs in high-risk patients, avoidance of multiple drugs that prolong the QT interval, treatment of electrolyte abnormalities, or use of antipyretics to treat fever in patients with Brugada syndrome is recommended.[66] Patients with congenital long QT syndrome should be monitored closely given the increased risk for drug-induced proarrhythmia if antiviral QT-prolonging drugs are prescribed.[66] Substrate-based VT ablation and left stellate ganglion blockade may effectively treat electrical storm, resulting in multiple implantable cardioverter defibrillator therapies during COVID-19 infection.[72,73]

The current COVID-19 literature, composed primarily of retrospective studies, typically during hospitalization, does not provide guidance to differentiate transient ventricular arrhythmias in critically ill patients with hypoxemia, electrolyte abnormalities, acute myocarditis, or preexisting structural heart disease from those at continued risk. The impact of myocarditis on outcomes after hospital discharge is uncertain. Continued investigations to better understand the impact of viral mutations, preexisting heart disease, comorbidities, vaccination status, and contemporary treatment of COVID-19 infection on risk for acute and chronic ventricular arrhythmias are needed.

SUDDEN CARDIAC ARREST

Out-of-Hospital Cardiac Arrest

Early in the pandemic, a high rate of out-of-hospital cardiac arrest (OHCA) was reported, particularly in high–COVID-19–burden areas such as, Italy, France,[74] and New York City.[75,76] Higher risk for cardiovascular and total mortality persisted past the acute phase.[77,78] Proposed mechanisms for cardiac arrest in acute COVID-19 infection include direct cardiac injury, as indicated by elevation in cardiac troponin levels, myocarditis, endothelial/vascular dysfunction, and thrombotic events.

A population-based study in Paris reported that the rate of OHCA increased from 13.4/1 000 000 to 26.6/1 000 000 during the pandemic compared with a matched prepandemic period.[74] A meta-analysis reported an annual OHCA incidence of 86/100 000 before the pandemic compared with 121.7/100 000 after the pandemic.[79] Higher rates of OHCA during the COVID-19 pandemic compared with before the pandemic have been reported in several systematic reviews and meta-analyses, with a 38% to 120% increase in OHCA incidence.[77,79,80] Mortality was higher (OR, 1.95) during the pandemic, with a pooled case fatality rate of 93.1% before COVID-19 and 96.4% during COVID-19.[79] These studies report 38% higher rates of OHCA at home (60.5%–85.5% before the pandemic versus 64.2%–92.9% during the pandemic), lower rates of bystander cardiopulmonary resuscitation (61% before the pandemic versus 51% during the pandemic; nonsignificant 6% reduction in another study, range 25%–73% versus 18.2%–78.7%) and bystander defibrillation (5.2% to 1.4%; 35% lower in another study), a 27% reduction in presenting shockable rhythm (28% to 23%), and longer delays to intervention. Emergency medical service response times were ≥6 minutes in 57% to 71%. Accordingly, there was a 35% lower return of spontaneous circulation (from 23%–31% to 11%–23% in 1 review), 35% reduced survival to hospital admission, and 48% reduced survival to discharge (14.7% to 7.9%).[77,79,80] In 1 prospective study in a US community, differences were most marked among Hispanic individuals, who had a 77% increase in sudden cardiac arrest (SCA) incidence and were less likely than non-Hispanic individuals to receive bystander cardiopulmonary resuscitation (45% versus 55%) or to present with shockable rhythm (15% versus 24%).[78] The authors noted the complexity of potential explanations for these ethnic differences, including potential differences in delayed contact with health care systems or differences in baseline clinical profiles such as diabetes, renal disease, or obesity.

In-Hospital Cardiac Arrest

In-hospital cardiac arrest has a poor prognosis in patients infected with COVID-19. A World Heart Federation COVID-19 study of 5313 patients with COVID-19 from 40 hospitals in 23 low- to middle-income countries reported that the most frequently reported cardiovascular discharge diagnosis was cardiac arrest (5.5%).[81] Among the most common causes of death were respiratory failure (39.3%) and sudden cardiac death (20.0%). Of 8518 American Heart Association COVID-19 registry patients hospitalized with COVID-19 (6080 not in an ICU),[82] in-hospital cardiac arrest occurred in 5.9%, of which 73.7% occurred in the ICU and 76.5% were without a shockable rhythm. Only 6.9% survived to discharge (9.1% in the ICU and 0.7% not in the ICU). In-hospital cardiac arrest was associated with older age, Hispanic ethnicity, non-Hispanic Black race, oxygen use on admission, hypertension, and a high organ failure assessment score. A systematic review and meta-analysis of prevalence and death resulting from ventricular arrhythmias and SCA in hospitalized patients with COVID-19 that included 13 790 patients reported that SCA occurred in 1.8% of hospitalized patients with COVID-19 and 10% of those who died.[61]

A mainstay to avoid SCA in acute, severe COVID-19 infection may be prompt treatment with antiviral therapies for high-risk patients. A large Australian registry reported no association between COVID-19 vaccination and OHCA.[83] One nonrandomized retrospective study reported a lower risk of SCA in patients discharged on rivaroxaban after hospitalization for COVID-19,[84] although the effectiveness of this approach requires additional study.

EXCESS CARDIOVASCULAR DEATHS DUE TO COVID-19

In 7584 patients with COVID-19 infection followed up for up to 18 months from the UK Biobank, compared with contemporary and historical control subjects, there was a ≈50% increase in risk of major cardiovascular death and up to 5 times the risk for all-cause mortality.[77] In the United States from March 2020 to March 2022, 4.9% (90 160) excess cardiovascular deaths were reported,

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occurring in 2 major peaks correlating with major peaks of COVID-19 mortality.[85] There was variability by region, age, sex, and race and ethnicity, with higher excess cardiovascular deaths reported in men (5.7% versus 4.0% in women), Black people (8.8%), Asian people (7.5%), and Hispanic people (7.7%).

A mainstay to avoid SCA in acute, severe COVID-19 infection may be prompt treatment with antiviral therapies for high-risk patients, but a large Australian registry reported no association between COVID-19 vaccination and OHCA.[83] One nonrandomized retrospective study reported a lower risk of SCA in patients discharged on rivaroxaban after hospitalization for COVID-19,[84] although the effectiveness of this approach requires additional study.

LONG-TERM ARRHYTHMIC RISK AND OUTCOMES IN PATIENTS RECOVERED FROM COVID-19

Cardiac arrhythmias and AD have been associated with acute, subacute, and post–COVID-19 infection.[1–3,86,87] Patients who develop COVID-19 myocarditis may also have increased risk of VT/VF[22] and may require longer arrhythmia monitoring. With the advent of consumer-available smartwatches, wristbands, and other digital health tools, options now exist for self-monitoring for QTc[88] and for symptomatic or routine sporadic monitoring.[89,90] Long-term arrhythmic outcomes after COVID-19 infection were evaluated in ≈4.1 million patients in the US Collaborative Network (TriNetXln). At the 1-year follow-up (starting 30 days after the initial positive test), the incidences of AF/atrial flutter (hazard ratio [HR], 2.41 [95% CI, 2.30–2.52]), sinus tachycardia (HR, 1.68 [95% CI, 1.63–1.74]), bradycardia (HR, 1.60 [95% CI, 1.52–1.68]), and ventricular arrhythmias (HR, 1.60 [95% CI, 1.54–1.67]) were significantly higher in COVID-19 survivors.[91]

In another study from the US Department of Veterans Affairs, 153 760 individuals with COVID-19 were compared with 2 sets of control cohorts of 5 637 647 (contemporary controls) and 5 859 411 (historical controls) individuals to assess the risks and burden of several cardiovascular conditions at the 1-year mark in the overall cohort and by care setting at the time of acute infection. Beyond 30 days after infection, COVID-19 survivors had increased overall arrhythmic risk (HR, 1.69 [95% CI, 1.64–1.75]) and risk of AF (HR, 1.71 [95% CI, 1.64–1.79]), sinus tachycardia (HR, 1.84 [95% CI, 1.74–1.95]), sinus bradycardia (HR, 1.53 [95% CI, 1.45–1.62]), and ventricular arrhythmias (HR, 1.84 [95% CI, 1.72–1.98]). These increased risks were evident even among those who were not hospitalized during the acute infection but increased in a graded fashion with higher level of hospital care during acute infection.[92] These findings support the need for continued arrhythmia surveillance and care after COVID-19.

AD ASSOCIATED WITH COVID-19

AD, defined as "altered autonomic function that adversely affects health," after SARS-CoV-2 infection is well described and can result in severe symptoms.[1,2,93] It is unclear when AD develops during the course of SARS-CoV-2 infection, but manifestations most salient in the postacute convalescent phase, usually weeks to months after initial infection, are called postacute sequelae of SARS-CoV-2 (PASC) by the National Institutes of Health RECOVER (Researching COVID to Enhance Recovery) initiative.[94,95] In PASC, a constellation of symptoms persist months after initial infection without other explanation.[42,96,97] Symptoms consisting of fatigue, dyspnea, palpitations, and cognitive dysfunction occur in a large but variable proportions of patients, depending on the strain and severity of infection.[95,96,98] Development and persistence of symptoms in PASC approach 68% for infections attributable to the initial SARS-CoV-2 strain from Wuhan, China. PASC occurs in 10% to 11% of those who recover from more recent SARS-CoV-2 variants.[95,99]

Various forms of AD after COVID-19 infection (PASC-AD) have been identified and characterized (Table 2).[100–102] POTS, a heterogeneous syndrome consisting of orthostatic intolerance and other symptoms accompanied by the cardinal finding of a persistent and reproducible increase in heart rate by 30 bpm with standing, in the absence of orthostatic hypotension, is one of the more commonly diagnosed conditions.[100–102] North American studies have shown that ≈30% of patients with PASC undergoing autonomic testing met the criteria for POTS, but an Australian report indicated that this figure may be higher, with 79% of patients with PASC meeting criteria for POTS.[100–102] It is unclear whether differences in disease severity or infection by certain variants account for the variability in POTS prevalence, but multiple studies have shown that POTS occurs in 25% to 35% of patients with PASC.[100–103]

Orthostatic hypotension, a drop in systolic blood pressure with standing by 20 mm Hg or diastolic blood pressure by 10 mm Hg or >30 mm Hg in patients with supine hypertension regardless of symptoms, occurs in 3% to 5% of patients with PASC.[100,103–105] Inappropriate sinus tachycardia, defined as average sinus rate >100 bpm with a resting heart rate >90 bpm, appears to occur in a smaller proportion of patients with PASC (<2%), although further studies are required to determine the true incidence of inappropriate sinus tachycardia in PASC.[100,102]

The remaining proportion of patients with PASC (50% to 60%) do not appear to have significant autonomic function abnormalities except for perhaps immediate orthostatic hypotension or provoked orthostatic intolerance with nitroglycerin.[100,105] They may be better characterized as patients with normotension with orthostatic intolerance without tachycardia.[93,100,102,105] These patients with PASC have less severe disease compared

Table 2. Incidence of Specific Autonomic Disorders From Recent PASC-AD Studies

Study	Total patients, n	POTS, %	Normotensive, OI, no tachycardia, % (n)	IST, % (n)	OH, % (n)	Notes
Hira et al[100]	70	30 (21)	61 (43)	1.4 (1)	2.9 (2)	Active stand test
Seeley et al[101]	33	78 (26)	15 (5)	0	6 (2)	Tilt table testing; compared 33 patients with PASC and 33 patients with POTS
Shouman et al[102]	27	22 (6)	41 (11)	3.7 (1)	0 (0)	Tilt table testing
Eldokla and Ali[103]	14	21 (3)	57 (8)	0	0 (0)	Tilt table testing, 3 remaining patients had small fiber neuropathy (2) or vasovagal syncope (1)
Blitshteyn and Whitelaw[104]	20	75 (5)	15 (3)	0	10 (2)	Tilt table testing and active stand test
Jamal et al[105]	24	16 (4)	62 (15)	0	4 (1)	Tilt table testing
Composite	188	40 (60)	45 (82)	1 (2)	4 (7)	

Most of these studies involved patients referred to major autonomic disorder centers, and these distributions will likely vary depending on the population tested.
AD indicates autonomic dysfunction; IST, inappropriate sinus tachycardia; OI, orthostatic intolerance; PASC, postacute sequelae of SARS-CoV-2; and POTS, postural orthostatic tachycardia syndrome.

with those with POTS; larger studies with formal autonomic assessment are needed to better characterize these patients.[101,102,106]

PATHOPHYSIOLOGY OF PASC-AD

Although the mechanisms of AD after SARS-CoV-2 infection are not well understood, multiple theories have been proposed (Figure 3).[94,97,107] Immune-mediated causes, including development of autoantibodies against autonomic receptors or peripheral nerves, are a purported mechanism, but this is controversial because autoantibodies are ubiquitous and found in those without AD.[97,107] Another possible immune-mediated cause is upregulation of proinflammatory cytokines that directly or indirectly through activation of monocytes or neutrophils disrupt normal endothelial barriers to cause vascular dysfunction and microthrombi.[94,107]

Experts disagree on whether deconditioning is a contributing mechanism or simply a manifestation/complication for the impaired exercise response and AD seen in PASC.[108–111] An important cause of dyspnea and other respiratory symptoms is destruction and fibrosis of lung tissue.[1] It is unclear how this can cause AD, but if the damage is great enough to cause chronically impaired gas exchange and hypoxemia, then pulmonary hypertension, which has been linked to AD, may develop.[97,112] In addition, the SARS-CoV-2 virus can invade components of the central nervous system involved in autonomic reflexes after gaining entry through the olfactory bulb, which can cause AD in PASC.[94,97,107,113]

DIAGNOSIS OF PASC-AD

Ascertainment and quantification of symptoms are important during the initial encounter with the patients with PASC. Many patients with PASC have severe and incapacitating symptoms that prevent return to work months after infection.[1,99] The Composite Autonomic Symptom 31 and the Vanderbilt Orthostatic Symptoms Score are validated symptom assessment tools to quantify AD symptoms in patients with PASC.[1,97,100] These are useful to assess symptomatology initially and during follow-up.[97] As part of a complete history and physical, orthostatic vital signs in the form of a 10-minute stand test should be completed and are sufficient to delineate AD in many

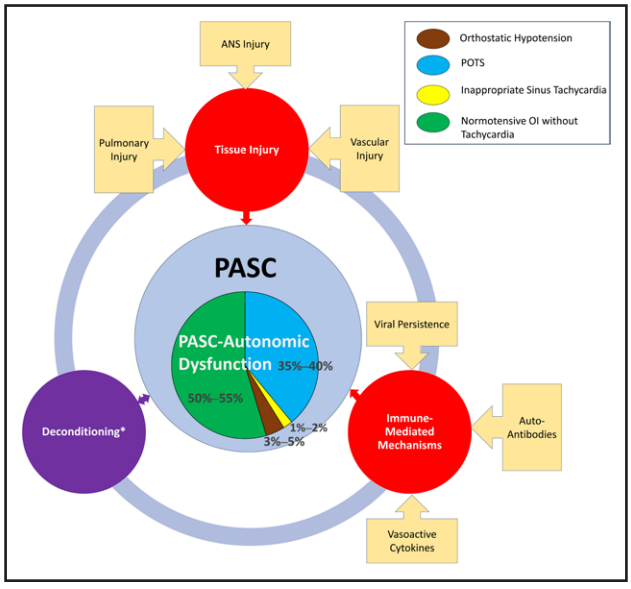

Figure 3. Putative pathophysiological mechanisms for PASC-AD.
Red circles represent major domains of pathology that could lead to development of postacute sequelae of COVID-19 (PASC) and autonomic dysfunction (AD). *There are conflicting data on whether deconditioning (purple circle) may represent a pathophysiological mechanism or a manifestation of PASC-AD. Within the population of patients with PASC, a variable proportion will have PASC-AD. Among those with PASC-AD, estimated incidences of distinct autonomic disorders are shown in the pie graph according to recent studies from AD referral centers. The proportions are highly variable and likely depend on the severity of the index SARS-CoV-2 infection, the strain involved, and the severity of AD.

patients with PASC.[114] If conservative treatment is ineffective, patients can be referred for more extensive autonomic function testing that could involve head-up tilt table testing with beat-to-beat hemodynamic monitoring, deep breath testing, Valsalva maneuver, thermoregulatory sweat testing, ambulatory electrocardiographic monitoring, ambulatory blood pressure monitoring, cardiopulmonary exercise testing, stress testing, and transthoracic echocardiography.[97,107,114,115]

TREATMENT OF PASC-AD

Because these PASC-associated autonomic disorders may represent a new clinical entity, conventional treatment for AD may be ineffective; however, given the lack of treatment data for PASC-AD, the most prudent strategy is to manage this condition according to existing autonomic disorder guidelines.[114,116]

PROGNOSIS OF PASC-AD

There are no long-term data on hard outcomes or time to symptom improvement for PASC-associated AD, and data 1 year out for PASC after initial SARS-CoV-2 infection are conflicting.[98,117] However, POTS and other autonomic disorders with symptoms of orthostatic intolerance that predate the SARS-CoV-2 pandemic are not known to increase mortality and eventually resolve, although the course can vary substantially among individual patients.[114]

DRUG INTERACTIONS BETWEEN COVID-19 DRUGS AND CARDIOVASCULAR MEDICATIONS

Patients with symptomatic COVID-19 may be treated with nirmatrelvir-ritonavir (Paxlovid) to prevent progression to severe disease; however, Paxlovid may interact with antiarrhythmics, anticoagulants, antibiotics, and immunosuppressives.[118]

Interactions With Antiarrythmic Drugs

Plasma levels of class III antiarrhythmic drugs such as amiodarone and dofetilide and Class IA drugs (quinidine, procainamide and disopyramide) may be elevated when coadministered with Paxlovid (Table 3).[119] Sotalol is cleared renally and does not interact with Paxlovid. Antiarrhythmic agents such as dofetilide, propafenone, and quinidine have a short half-life and can be withheld for 2.0 to 2.5 days (4–5 half-lives) before the initiation of Paxlovid. Discontinuation of flecainide, dronedarone, or amiodarone may not be practical because the time to elimination of these drugs is >5 days, which is greater than the efficacy of Paxlovid.[118,119] Plasma levels of ranolazine, which has been reported to be used off-label as an antiarrhythmic, may increase substantially when taken with Paxlovid, thereby increasing the risk of clinically significant QT prolongation and torsade de pointes.[121,122] Discontinuation of ranolazine is advisable. Rebound of COVID-19 infections and symptoms has been reported with Paxlovid, but the overall incidence is low (1%).[123]

Interactions With Anticoagulant Drugs

Patients with AF may be on anticoagulation for prophylaxis of systemic thromboembolism (Table 3). If warfarin is prescribed with Paxlovid, close international normalized ratio monitoring is suggested because warfarin is metabolized by CYP450 enzymes and the ritonavir component of Paxlovid first causes CYP inhibition and then induction of CYP.[120] Unfractionated heparin and low-molecular-weight heparin are not metabolized by CYP450 enzymes and therefore can be given in conjunction with Paxlovid. The risk of bleeding with apixaban is increased when given with Paxlovid; hence, in patients

Table 3. Antiarrhythmic and Anticoagulation Drug Interactions With Paxlovid (Nirmatrelvir and Ritonavir)

	Substrate drug	Mechanism of interaction[119]	Recommendation
Antiarrhythmic	Amiodarone	CYP3A4 and P-gp inhibition	Hold amiodarone while on Paxlovid
	Dronedarone	CYP3A4 and P-gp inhibition	Hold dronedarone while on Paxlovid
	Flecainide	CYP2D6 inhibition	Hold flecainide while on Paxlovid
	Propafenone	CYP2D6 inhibition	Hold propafenone while on Paxlovid
	Quinidine	CYP3A4 Inhibition	Hold quinidine while on Paxlovid
Anticoagulant	Warfarin	CYP3A4 inhibition	More frequent INR monitoring while on Paxlovid[120]
	Apixaban	CYP3A4 and P-gp inhibition	Reduce dose of apixaban by 1/2 while on Paxlovid[120]
	Dabigatran	P-gp inhibition	If CrCl >50 mL/min, administer Paxlovid 2 h after dabigatran[120]
			If CrCl is 30–50 mL/min, reduce dose of dabigatran by 1/2[120]
			If CrCl <30 mL/min, hold while on Paxlovid[120]
	Rivaroxaban	CYP3A4 and P-gp inhibition	Hold rivaroxaban[120]

CrCl indicates creatinine clearance; INR, international normalized ratio; and P-gp, P-glycoprotein.

receiving 10 mg or 5 mg twice-daily dosing, the dose should be reduced by 50%.[120]

Rivaroxaban taken together with Paxlovid may increase the risk of bleeding, especially in elderly patients with moderate renal dysfunction. Therefore, on a case-by-case basis, withholding rivaroxaban may be considered if a patient at high risk for bleeding is prescribed Paxlovid. For patients with AF on 60 mg edoxaban daily, their anticoagulation dose can be reduced by 50% for a total of 8 days from the start of Paxlovid. For those on 30 mg daily, switching to another anticoagulant such as enoxaparin while taking Paxlovid is an alternative possibility.[118,120]

For dabigatran in the absence of renal dysfunction, no dose adjustment is required when dabigatran is prescribed with Paxlovid. However, if the creatinine clearance is <30 mL/min, Paxlovid should not be given with dabigatran. For patients with AF and creatinine clearance of 30 to 50 mL/min, the dose may be decreased to 75 mg twice daily and continued for a total of 8 days. In those with creatinine clearance >50 mL/min, the dose can be reduced to 110 mg twice daily when coadministered with Paxlovid. However, this dose is not approved in the United States.[118]

Interactions With Macrolide Drugs

Azithromycin may prolong the QTc interval and increase the risk for torsade de pointes in those with COVID-19 infections.[68] However, patients hospitalized with acute COVID-19 infection may have a prolonged QTc for other reasons.[118,124] Multivariable analyses indicate that age ≥80 years, severe renal disease, and elevated high-sensitivity troponin and lactate dehydrogenase levels are associated with QTc prolongation.[118]

VACCINE AND ARRHYTHMIAS

Studies have failed to convincingly demonstrate that COVID-19 vaccines cause arrhythmias except those associated with myocarditis. There have been numerous reports of suspected myocarditis and pericarditis after COVID-19 vaccination, but the association between vaccines and arrhythmias, independently of myocarditis, is less clear.[125] In a case series from England involving >38 million patients, myocarditis was documented in 1 to 10/1 000 000 the month after vaccination. An increased risk of arrhythmias after vaccination was not identified except 1 to 28 days after a second dose of the mRNA-1273 vaccine, which was most likely related to patients who developed vaccine-mediated myocarditis and with a risk still lower than for COVID-19 infection.[126]

An analysis of the Vaccine Adverse Event Reporting System, a postlicensure vaccine safety monitoring in the United States, reported 2611 cases of AF after COVID-19 vaccination, of which 315 were new onset. This translates to ≈5/1 000 000 AF cases after COVID-19 vaccine, an incidence less than would be expected for the general population.[127] In an analysis of a post-marketing pharmacovigilance European database, AF represented only 0.3% of all adverse events related to COVID-19 vaccines.[128]

A meta-analysis of arrhythmias after COVID-19 reported a low incidence rate of cardiac arrhythmia after COVID-19 vaccination, ranging between 1 and 76 per 10 000. Of note, the incidence of these arrhythmias generally fell within the range of what is reported in the general population and most reported arrhythmias in general; thus, AF events were just a fraction of the overall numbers.[129] A systematic review of vaccine-associated myocarditis indicates that recovery from myocarditis is excellent and the prognosis is good.[130,131]

Thus, we can conclude that there is no evidence that arrhythmias occur after vaccines with higher frequency than in the general population and that perhaps some arrhythmias observed are just a manifestation of myocarditis, of which the incidence is higher with COVID-19 infection.

COVID-19 INFECTION AND VACCINE-ASSOCIATED MYOCARDITIS/ CARDIOMYOPATHY

In early reports from Wuhan, China, of 150 patients, 7% of fatal cases were attributed to myocarditis.[132] In a retrospective study of 718 365 patients with COVID-19 from the United Kingdom, 35 820 (5.0%) developed new-onset myocarditis, and 10 706 (1.5%) developed new-onset pericarditis.[133] That risk may be even lower in patients getting vaccinated after prior COVID-19 infections.[134]

Although biomarkers such as C-reactive protein, erythrocyte sedimentation rate, procalcitonin, cardiac troponin I, cardiac troponin T, and NT-BNP (N-terminal B natriuretic peptide) point to inflammation and its effects, cardiac magnetic resonance imaging remains the cornerstone to diagnose acute myocarditis and its sequelae such as arrhythmias.[135] T2-weighted images can identify tissue edema resulting from capillary leak, interstitial myocardial edema, and hyperemia (Supplemental Figure 2). Abnormal T2 and T1, supported by delayed enhancement in mid or epicardial regions in noncoronary distribution, could potentially indicate risk for ventricular arrhythmias.[136]

Prognosis and Arrhythmic Impact

In a large retrospective cohort study from the United Kingdom, patients with a diagnosis of COVID-19 and new-onset myocarditis (3.9% versus 2.9%; $P<0.0001$) and pericarditis (15.5% versus 6.7%; $P<0.0001$) had higher 6-month mortality compared with a propensity-matched (age, sex, and comorbidities) control group of

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patients with COVID-19 without myocarditis/pericarditis. Those with pericarditis had a higher risk of cardiac arrest (OR, 2.9), heart failure (OR, 2.9) and AF (OR, 2.5).[133] Ventricular arrhythmias occurred more with evidence of cardiac injury (17.3% versus 1.5%; $P \leq 0.001$).[137] QT prolongation, described in patients with myocarditis,[19] could be a potential cause for cardiac arrest. Atrial arrhythmias were more common in those requiring ventilatory support than in those who did not (17.7% versus 1.9%). Thus, the occurrence of AF may not be directly related to myocarditis.[138] In a report of 4 cases 5 to 21 days after COVID-19 diagnosis, new-onset atrioventricular block was suspected to be a late manifestation of subtle myocarditis.[139]

No specific targeted treatment for COVID-19–associated myocarditis exists. Patients with fulminant myocarditis may require circulatory and ventilatory support.[140] Corticosteroids, intravenous immunoglobulin, and plasma exchange have been used. Clinical trials are evaluating the efficacy of an interleukin-6 receptor antagonist in COVID-19 myocarditis.[141]

Thus, myocarditis attributable to COVID-19 infection is infrequent but associated with an adverse prognosis. Although rare, COVID-19 vaccine can be associated with a mild myocarditis that generally has a good prognosis. Myocarditis can be associated with ventricular arrhythmias and atrioventricular block; however, atrial arrhythmias may be a manifestation of illness severity. Supportive management and corticosteroids are mainstays of COVID-19–related myocarditis management.

LIMITATIONS/PITFALLS OF RESEARCH RELATED TO ARRHYTHMIAS IN PATIENTS WITH COVID-19

Outcome ascertainment concerning arrhythmias is critical and generally not present. Although data support a relationship between COVID-19 infection and heart failure, myocardial infarction, and cardiovascular death,[9,12,140] establishment of a relationship between COVID-19 and arrhythmias ideally requires some form of arrhythmia surveillance. Selection bias can occur when findings are limited only to those who are critically ill or seeking care.[142] This bias may not threaten internal validity but rather limits application of the data to all patients after COVID-19. General population studies help mitigate this bias. A causal association and medical outcome can be too easily attributed to what came before it.[143,144] Recognizing and accounting for ambient levels of other risk factors or a particular outcome and considering other putative causes are important. As opposed to a confounding variable, a mediator may miss the direct causal relationship between COVID-19 and the arrhythmia.[145,146] The mechanism such as inflammation may be the mediator, not COVID-19 per se.[53] Similarly, COVID-19 may lead to sinus tachycardia purely by deconditioning. Mechanisms are not well understood. Evolving viral strains and clinical manifestations of COVID-19 challenge the generalizability of available studies, especially in terms of the understanding of the pathogenetic mechanisms and outcomes.

The vast majority of studies evaluating COVID-19 and arrhythmias were done during the pandemic phase (initial phase and the delta wave phase) and mostly in hospitalized patients with more severe illness. There is limited information on disease spectrum and severity during the transition between different phases. Hence, the data on arrhythmias provided in this document may not be applicable to some of the clinical cases of COVID-19 that we are seeing now.

IMPLICATIONS FOR CLINICAL PRACTICE AND KNOWLEDGE GAPS

The writing committee's consensus view on the suggestions/considerations/implications for clinical practice based on the evidence presented in this scientific statement is summarized in Table 4. In addition, the writing committee has identified important knowledge gaps and outlined our suggestions for future research in Table 5.

Table 4. Summary of the Writing Group's Consensus View on the Suggestions/Considerations/Implications for Clinical Practice Based on the Evidence Presented in This Scientific Statement

The development of arrhythmias and AD during and after COVID-19 infection is likely multifactorial in most cases.
Bradyarrhythmias during COVID-19 infection tend to occur in severe infections and improve with resolution of the infection, with most patients not requiring permanent pacemakers.
Patients with newly diagnosed AF during COVID-19 infection should be monitored long term for recurrence and receive anticoagulation per current guidelines.
Ventricular arrhythmias and sudden cardiac death occur at a higher frequency among patients with COVID-19, and the best treatment currently is prompt treatment of COVID-19.
AD occurs primarily in the setting of PASC, and the precise cause of PASC remains elusive.
Many cases of PASC-AD represent POTS, orthostatic hypotension, or inappropriate sinus tachycardia.
Ritonavir, a component of Paxlovid, is a strong inhibitor of CYP-3A4 and can cause significant drug-drug interactions.
Continued long-term arrhythmia surveillance is prudent in any patient who develops a COVID infection.
Myocarditis is a well-documented adverse effect of COVID-19 infection but seldom results in serious arrhythmias. There is currently no consistent evidence to demonstrate a heightened risk of arrhythmia or sudden death attributable to COVID-19 vaccination in the general population.
Clinically stable and ambulatory COVID-19–positive individuals are at substantially less risk for arrhythmias compared with those with severe infections.
Management of arrhythmias/AD during and after COVID-19 infection should be based on current guidelines for the respective arrhythmia/AD.

AD indicates autonomic dysfunction; AF, atrial fibrillation; PASC, postacute sequalae of Sars-CoV-2; and POTS, postural orthostatic tachycardia syndrome.

Table 5. Knowledge Gaps and Areas for Future Research

Long-term arrhythmic risk	The recurrence of arrhythmias after COVID-19 infection requires further study. Firm suggestions in the form of long-term surveillance and treatment, beyond current guideline recommendations for these arrhythmias, depend on further research in this area.
Long-term arrhythmic risk	Wearable ambulatory monitors represent a potential solution for long-term arrhythmia surveillance after COVID-19 infection given their ubiquity; however, their utility in this setting is unclear and remains an area ripe for research.
Autonomic dysfunction	There is currently no good universal treatment for PASC-AD; prospective, randomized controlled studies in this population are needed.
	The cause and long-term prognosis of PASC-AD are unknown. More studies are needed to better characterize this condition and its long-term effects.
Vaccine and arrhythmias	Long-term data on the effects of myocarditis and development of arrhythmias after COVID-19 vaccination are lacking. Further study in this area will assuage safety concerns pertaining to myocarditis.
Arrhythmia recurrence	The COVID-19 pandemic has evolved into an endemic with cardiovascular manifestations that are different from the initial pandemic. The virus will continue to evolve, and research will need to be ongoing to stay up to date on cardiovascular consequences of future infection.

AD indicates autonomic dysfunction; and PASC, postacute sequalae of Sars-CoV-2.

CONCLUSIONS

Various arrhythmic manifestations have been associated with COVID-19, ranging from relatively benign sinus bradycardia to life-threatening ventricular tachyarrhythmias and sudden cardiac death. AF is the most common arrhythmia seen in acutely ill patients with COVID-19. Although specific pathophysiological mechanisms underlying these arrhythmias are not well understood, direct viral invasion, changes in autonomic tone, hypoxemia, inflammation, and immune-mediated phenomena have been implicated. Clinically stable and ambulatory COVID-19–positive individuals are at substantially less risk than those with severe infections.

Arrhythmia management should be based on published evidence-based guidelines, with special consideration for the severity of COVID-19 infection, the concomitant use of antimicrobial and anti-inflammatory drugs, and the transient nature of some arrhythmias. Ventricular arrhythmias in hospitalized patients with COVID-19 have been associated with in-hospital death. COVID-19 can precipitate PASC-AD with consequent long-term symptoms. There is a need to better characterize the presence and severity of AD in patients with PASC through more consistent and standardized autonomic testing. The pathophysiology, short- and long-term consequences, and effective treatment for PASC-AD require more investigation because studies performed thus far have been inconclusive and do not provide guidance. There is currently no consistent evidence to demonstrate a heightened risk of arrhythmia or sudden death attributable to COVID-19 vaccination in the general population. Last, as we have transitioned to an endemic phase of the illness, with discovery of new, less virulent SARS-CoV-2 variants, newer drugs to treat acute COVID-19 infection, and widespread administration of vaccines, health care professionals must remain vigilant for changes in the presentation in arrhythmic and dysautonomic manifestations that may occur with this novel disease.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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*Modest.

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