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Prevalence, Management, and Outcome of Atrial Fibrillation and Other Supraventricular Arrhythmias in COVID-19 Patients

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INTRODUCTION
Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is the causative agent of coronavirus disease 2019 (COVID-19); it was officially detected for the first time in Wuhan and has spread throughout the world becoming a pandemic.1,2

Although COVID-19 causes respiratory symptoms in most patients, several studies showed an extrapulmonary involvement, including the cardiovascular system.3-5 COVID-19 patients may be affected by myocarditis, thromboembolic events, heart failure and cardiogenic shock, acute coronary syndromes,

KEYPOINTS
• Supraventricular arrhythmias are common in COVID-19 patients, especially in critically ill.
• Arrhythmias occur after direct viral damage, but also due to systemic involvement.
• Atrial fibrillation represents the most common supraventricular arrhythmias and it is independently associated with in-hospital mortality.
• Supraventricular arrhythmias will be safely treated, minimizing exposure and paying attention to general clinical conditions.
and atrial and ventricular arrhythmias. Notably, cardiac arrhythmias occur in 6% to 17% of patients, rising to 44% in patients admitted to the intensive care unit, resulting the second most frequent complication after acute respiratory distress syndrome. Several possible mechanisms lead to an increased risk of cardiac arrhythmias during COVID-19 infection, ranging from direct myocardial injury to extracardiac involvement. Arrhythmias are mainly caused by the hypoxia related to direct viral damage in the lungs, myocarditis, or abnormal inflammatory response and secondarily as a result of myocardial ischemia, myocardial strain, or electrolyte imbalances. As a matter of fact, arrhythmias are not simply caused by the direct effect of COVID-19 infection, but instead are probably the result of a multifactorial condition.

Supraventricular arrhythmias are the most frequent arrhythmias observed in COVID-19 patients and among them, atrial fibrillation (AF) is the most common occurring in about 15% to 30% of them. The presence of AF is associated with increased clinical manifestations of severe COVID-19 and is independently associated with in-hospital mortality, posing a significant burden to patients, physicians, and health care systems globally. The complexity of this clinical condition requires a multifaceted and multidisciplinary approach; thus, we provide a comprehensive guidance for monitoring and management of cardiac arrhythmias in COVID-19 patients.

**MECHANISMS OF ARRHYTHMOGENESIS IN COVID-19**

COVID-19 infection can lead to an increased risk of cardiac arrhythmias by several pathophysiological mechanisms, which are summarized in Fig. 1. These include different types of myocardial injury and extracardiac processes that may exacerbate arrhythmias in patients with a pre-existing propensity.

**Hypoxia**

The most recurrent COVID-19 manifestation is respiratory involvement, which may progress to acute respiratory distress syndrome. Hypoxia results in anaerobic glycolysis causing a decrease of intra-cellular pH and electrolyte imbalance, mainly an increase of calcium levels. A higher cytosolic Ca\(^{2+}\) concentration alters cellular action potentials and contribute to the development of early and late afterdepolarizations, which are a known trigger for atrial and ventricular arrhythmias. Anaerobiosis also results in an increased potassium concentration and, as a consequence, increased cellular excitability and electrical conduction velocity. In addition, hypoxia reduces electrical coupling and tissue anisotropy via inactivation of connexin-43 in the gap junctions.

Moreover, respiratory failure causes a hyper-drenergic tone, which contributes to the risk of cardiac arrhythmias. Indeed, hypersympathetic activity leads to an amplified calcium influx into cardiomyocytes, resulting in a calcium overload and frequently delayed afterdepolarizations.

**Myocarditis**

Several findings suggest that SARS-CoV-2 is the causative agent of myocarditis and that myocardium involvement may occur by direct virus infection or through infected alveolar macrophages. The virus penetrates the myocardial cell, binding the receptors of the angiotensin-converting enzyme-2 (ACE-2) that will be internalized, leading to a consequent inhibition of angiotensin II degradation. The downregulation of myocardial ACE-2 expression is associated with excessive accumulation of angiotensin II, which causes myocardial injury, remodeling, and even adverse cardiac outcomes. Thus, downregulation of ACE-2 in COVID-19 might increase AF vulnerability and its perpetuation.

Another potential mechanism is that virus-activated CD8+ T lymphocytes reach the myocardium and can cause myocardial inflammation, as a result of the release of proinflammatory cytokines and activation of T lymphocytes. In the acute phase of myocarditis, arrhythmogenesis is caused by cellular damage, ionic imbalance, and gap junction dysfunction due to impaired cardiac connexin expression. In myocarditis, inflammation leads to impaired cellular calcium and potassium homeostasis, producing early and delayed afterdepolarizations and increasing cellular repolarization and conduction time. Prolonged repolarization time leads to triggered activity, whereas coupling with increased conduction time leads to re-entry circuits.

**Myocardial Ischemia**

Myocardial ischemia in COVID-19 patients could be caused by coronary dysfunction and hyperinflammatory response. The release of cytokines promotes the activation of T lymphocytes and monocytes within a pre-existing atherosclerotic plaque; the resulting histotoxic effect may cause plaque rupture, thereby leading to an acute coronary syndrome. Moreover, the release of the aforementioned cytokines, specifically interleukin (IL)-6, may exert proatherogenic effects, characterized by vascular smooth muscle proliferation, endothelial cell, and platelet activation.
Myocardial ischemia can also be caused by microvascular dysfunction due to endothelial impairment. Endothelial dysfunction in COVID-19 patients is caused primarily by the downregulation of ACE-2 receptors, triggering the kallikrein-bradykinin system and resulting in increased vascular permeability. Neutrophils and T lymphocytes release inflammatory cytokines and vasoactive molecules increasing endothelial cell contractility and vascular permeability. Virus-mediated vasculitis is another possible mechanism of microvascular dysfunction because the virus penetrates vascular endothelial cells via ACE-2 receptors, leading to inflammation and apoptosis.

**Cytokine Storm**

COVID-19 infection causes systemic inflammation and hyperactivation of lymphocytes and monocytes cells, resulting in a cytokine storm (IL-1β, IL-2, IL-6, IL-7, and interferon-γ) and an imbalance between lymphocytes T-helper-1 and T-helper-2 cells. Distinctive cytokines have been shown to induce AF: tumor necrosis factor-α (TNF-α) increases AF vulnerability and exerts direct effects on atrial structural and electrical remodeling; TNF-α and IL-1β may impair cardiac contractility, which is a known risk factor for arrhythmogenesis; IL-6 reduces cardiac connexins and promotes electrical remodeling during acute inflammation. Furthermore, IL-6, TNF-α, and IL-1 can lead to prolongation of the cardiac action potential due to impairment of K+ and Ca2+ channels.

**Electrolyte Imbalance and Fluid Overload**

Electrolyte abnormalities are a well-known trigger of arrhythmogenesis. In a study of 416 hospitalized patients with COVID-19 infection, 7.2% of patients had electrolyte disturbances, such as hypokalemia, hypomagnesemia, and hypophosphatemia. In particular, hypokalemia is very frequent in patients with COVID-19, affecting up to 61% of hospitalized patients. These electrolyte imbalances were primarily caused by COVID-19–associated diarrhea and renal impairment. Indeed, in a retrospective study of hospitalized patients with COVID-19 infection, 27% of patients had acute renal failure. In addition, SARS-CoV-2 causes downregulation of ACE-2 receptors and thereby reduces the feedback effects of ACE-2 on the renin-angiotensin-aldosterone system. This leads to increased reabsorption of sodium and water, resulting in increased blood pressure and excretion of potassium. The resulting hypokalemia causes hyperpolarization of the myocardiocytes, predisposing to atrial arrhythmias.

**SUPRAVENTRICULAR TACHYCARDIA PREVALENCE AND OUTCOME**

Supraventricular arrhythmias are the most frequent arrhythmias among COVID-19 patients. In a recent worldwide survey, about 18% of enrolled patients developed any arrhythmias: most of them were supraventricular arrhythmias (81.3%), AF representing the most common (61.5%). In another retrospective study,
166 patients experienced atrial arrhythmias (15.8%) and newly diagnosed atrial arrhythmias occurred in 101 patients (9.6%), corroborating the central role of virus infection in the pathogenesis of cardiac arrhythmias.\textsuperscript{14} Overall, a recent meta-analysis demonstrated that the occurrence of supraventricular arrhythmias was more frequent in critically ill patients (relative risk: 12.1; 95% confidence interval, 8.5–17.3), in particular those treated with invasive mechanical ventilation.\textsuperscript{47,48} The occurrence of supraventricular arrhythmias is associated with worse outcomes. Indeed, hospital admission in the intensive care unit and thromboembolic risk (pulmonary embolism, stroke, or deep vein thrombosis) was higher in COVID-19 patients with atrial arrhythmia than the general population.\textsuperscript{49} Therefore, giving the critical conditions of these patients, it is not unexpected that AF should be considered as an independent predictor of 30-day mortality (adjusted odds ratio: 1.93; \textit{P} = .007).\textsuperscript{14}

**MANAGEMENT OF SUPRAVENTRICULAR ARRHYTHMIAS**

The correct management of supraventricular arrhythmias has a central role in COVID-19 patients, especially those hospitalized with more severe forms of the disease and whose outcomes strictly depend on hemodynamic stability. Although there are few studies about the treatment of arrhythmia in COVID-19 patients, it is necessary to take particular attention to the paroxysmal features of arrhythmias, drug-drug interactions, and limitation of exposure.\textsuperscript{50,51} Given the overwhelming prevalence of AF and atrial flutter (AFL) in patients with COVID-19, we will focus on the treatment of these arrhythmias.

**Rhythm Control**

Patients with hemodynamic instability due to new-onset AF and AFL should undergo electrical cardioversion (Fig. 2). The choice for electrical cardioversion inevitably involves the need for personnel at bedside, and the possibility of invasive mechanical ventilation, that would increase the development of viral aerosols.\textsuperscript{50} Intravenous infusion of amiodarone is recommended for rhythm control in critically ill patients.\textsuperscript{51,52} Moreover, we should be aware of the combination of amiodarone with hydroxychloroquine and/or azithromycin, as the benefit of the eventual combination has to be weighed against the arrhythmic risk caused by QT prolongation.\textsuperscript{50,53} All interactions between medications for AF and COVID-19 are summarized in **Table 1**.

Class Ic antiarrhythmic agents should be administered with great caution because of their arrhythmogenic and negative inotropic effect, especially in critically ill COVID-19 patients, who are prone to or have already developed myocarditis and heart failure.\textsuperscript{54} Because of possible increases in plasma concentration of flecainide when co-administered with hydroxychloroquine and lopinavir/ritonavir and/or the potential QT-prolonging effects of these drugs, serial ECG monitoring is recommended before and after initiating drug therapy.

However, the only rhythm control strategy is not sufficient to achieve a long-term benefit in patients with acute respiratory failure, if the other existing comorbidities (eg, hypoxemia, inflammation, electrolyte imbalances, metabolic acidosis, volume overload, increased sympathetic tone, bacterial superinfection) are not properly treated.\textsuperscript{50,53} In stable hospitalized patients with AF, antiarrhythmic drugs (such as sotalol, flecainide, amiodarone, and propafenone) should be discontinued and rate control therapy initiated with beta-blockers (or nondihydropyridine calcium channel blockers, unless contraindicated, with or without digoxin) because these drugs represent a safer option when administered in combination with an antiviral therapy.\textsuperscript{50} The combination of verapamil with hydroxychloroquine should be avoided because both drugs exert a negative effect on sinoatrial and atrioventricular nodes causing bradycardia and conduction disturbances.\textsuperscript{56} Therefore, ECG monitoring for bradycardia and conduction disturbance should be considered. All interactions between medications for AF and COVID-19 are summarized in **Table 1**.

**Anticoagulation Therapy**

In COVID-19 patients, anticoagulation is prescribed according to the CHA\textsubscript{2}DS\textsubscript{2}-VASc score.\textsuperscript{57} It is important to highlight that some drugs for the treatment of COVID-19 infection have significant interactions with direct oral anticoagulants (DOACs; **Table 1**).\textsuperscript{58} In particular, lopinavir and ritonavir may have interactions with cytochrome P450 CYP3A4 and antimalarial drugs through P-glycoprotein inhibition.\textsuperscript{59} In these cases, DOACs should be avoided to reduce the risk of bleeding.\textsuperscript{50} In general, DOACs should be favored over vitamin K antagonists (VKAs), given their better safety profile and the standard, international normalized ratio-independent dosing modalities.\textsuperscript{61} Indeed, VKAs treatment requires regular monitoring of the international normalized ratio,\textsuperscript{62} increasing contact with medical staff, so VKAs should be used preferably only in patients with mechanical prosthetic valves or antiphospholipid syndrome.\textsuperscript{62} Heparins have no
pharmacologic interactions with drugs for the treatment of COVID-19, making them a safe alternative to oral anticoagulants. Moreover, heparin could provide an anti-inflammatory role in addition to its anticoagulant effect. In fact, heparan sulfate proteoglycans, binding to SARS-CoV-2 spike proteins, decrease host protein binding capability and reduce cytokine cascade.63

**Echocardiography**

Regarding instrumental examinations in COVID-19 patients, the use of echocardiogram should be limited in order to limit unnecessary contacts among health care providers and patients.50 Echocardiography should be performed only if crucial for immediate therapeutic management of critically ill patients.50 In this case, transthoracic echocardiography must be chosen over transesophageal echocardiography, thereby avoiding the creation of aerosols.50,64 Transesophageal echocardiography should be avoided for early initiation of anticoagulation in new-onset AF, or maintenance of anticoagulant therapy in patients with known AF.65 Cardiac computed tomography may be an alternative to transesophageal echocardiography, as it allows ruling out the presence of a left atrial appendage thrombus before cardioversion is performed.66

**Ablation Procedure**

Catheter ablation for AF patients with an ongoing infection is contraindicated; this same criterion applies to COVID-19 patients. Therefore, both AF or AFL ablation procedures should be postponed to optimize antiarrhythmic therapy and control/correct all COVID-19 and non–COVID-19–related modifiable risk factors.50,67 A different scenario is represented by AF/AFL patients showing evidence of tachycardiomyopathy or syncope; in these patients, an early ablation is pivotal to prevent cardiac remodeling and dysfunction and improve outcomes.68 Also, ablation of drug-refractory AF and AFL with repeated emergency room visits should be performed within less than 3 months.50,69–71 Of note, universal testing is of utmost importance to create a safe workplace for patients and health care workers, as asymptomatic carriers can be highly contagious and could be unexpectedly admitted.72 In case of intubation procedure, this needs to be done out of the electrophysiology laboratory to prevent contamination.

**Follow-up in COVID-19 Patients Suffering from Arrhythmias**

The follow-up of patients suffering from arrhythmias must be safe in order to prevent patients from being reinfected by COVID-19. Indeed, as the pandemic progressed, telemedicine has been extensively adopted,73,74 allowing face-to-face outpatient appointments to be replaced by teleconsultations.75,76 In the TeleCheck-AF project, telemedicine was implemented with remote monitoring of rhythm and frequency of AF, allowing a
complete management of patients, thanks to a mobile phone app using photoplethysmography technology through the built-in camera.\textsuperscript{77} Probably, this model of outpatient management of arrhythmias, thanks to the new wearable technologies, leading to the reduction of the number of hospital visits and health care costs, will remain even after the pandemic and represent an additional weapon in the diagnosis and management of arrhythmias in the near future.\textsuperscript{78}

**SUMMARY**

Cardiac arrhythmias occur in 6\% to 17\% of COVID-19 patients. Their prevalence is significantly higher (up to 44\%) in patients admitted to intensive care unit, becoming the second most frequent complication after acute respiratory distress syndrome. Supraventricular arrhythmias, mainly AF, are more frequent than ventricular ones. Several mechanisms can contribute to an increased risk of cardiac arrhythmias during COVID-19 infection, ranging from direct myocardial damage to electrolyte imbalance. The main aim of COVID-19–related supraventricular arrhythmia management is to establish a safe treatment plan according to each patient’s overall clinical conditions, keep in mind any possible drug-to-drug interactions, and minimize the risk of exposure for the staff and other non–COVID-19 patients.

**CLINICS CARE POINTS**

- Arrhythmogenesis is correlated to several pathophysiological mechanisms: hypoxia, myocardial ischemia, inflammation, electrolyte and fluid imbalance.
- Rate Control should be preferred in critically ill COVID-19 patients.
- Atrial fibrillation is an independent predictor of mortality.
- COVID-19 patients who experienced atrial fibrillation should be monitored to evaluate the burden of arrhythmia.
DISCLOSURE

Dr J.D. Burkhardt is a consultant for Biosense Webster and Stereotaxis. Dr L. Di Biase is a consultant for Biosense Webster, Boston Scientific, Stereotaxis, and St. Jude Medical; and has received speaker honoraria from Medtronic, Atricure, EPiEP, and Biotronik. Dr A. Natale has received speaker honoraria from Boston Scientific, Biosense Webster, St. Jude Medical, Biotronik, and Medtronic; and is a consultant for Biosense Webster, St. Jude Medical, and Janssen. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

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