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New-onset atrial fibrillation among COVID-19 patients: A narrative review

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Abstract

Over the last three years, research has focused on examining cardiac issues arising from coronavirus disease 2019 (COVID-19) infection, including the emergence of new-onset atrial fibrillation (NOAF). Still, no clinical study was conducted on the persistence of this arrhythmia after COVID-19 recovery. Our objective was to compose a narrative review that investigates COVID-19-associated NOAF, emphasi-

zing the evolving pathophysiological mechanisms akin to those suggested for sustaining AF. Given the distinct strategies involved in the persistence of atrial AF and the crucial burden of persistent AF, we aim to underscore the importance of extended follow-up for COVID-19-associated NOAF. A comprehensive search was conducted for articles published between December 2019 and February 11, 2023, focusing on similarities in the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management of NOAF in COVID-19 were investigated. Considerable overlaps between the mechanisms of emerging NOAF after COVID-19 infection and persistent AF were observed, mostly involving reactive oxygen pathways. With potential atrial remodeling associated with NOAF in COVID-19 patients, this group of patients might benefit from long-term follow-up and different management. Future cohort studies could help determine long-term outcomes of NOAF after COVID-19.

Key Words: COVID-19; SARS-CoV-2; New-onset atrial fibrillation; Atrial fibrillation

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Core Tip: In this literature review, we have observed resemblances between the fundamental pathophysiology of coronavirus disease 2019 (COVID-19)-related new-onset atrial fibrillation (NOAF) and the mechanisms proposed for the persistence of AF, particularly those involving oxidative stress and reactive oxygen species. The mechanisms responsible for the development of AF following a COVID-19 infection could potentially contribute to atrial remodeling, further perpetuating AF. However, while short-term outcomes of COVID-19-related NOAF have been well-studied, as we transition into an endemic era of COVID-19, there is a need for more research to investigate the long-term outcomes of patients who develop NOAF after COVID-19 infection.

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INTRODUCTION

Background

As atrial fibrillation (AF) incidence was approaching an epidemic proportion[1], in January 2020, the world health organization announced the preliminary determination of a novel coronavirus in Wuhan, China. By March 2020, the novel virus was recognized as a global pandemic[2,3]. AF was reported as the most common arrhythmia in a multicenter review of coronavirus disease 2019 (COVID-19) cases in 76 countries, with a prevalence of 19% to 21% of all hospitalized cases[4]. The new onset of AF (NOAF) among COVID-19 patients (referred to as COVID-19-related NOAF) raises concerns for unfavorable outcomes, especially in critically ill patients, regarding in-hospital mortality, length of stay in the intensive care unit, and survival[5,6].

In individuals whose AF has progressed, it has previously been observed that various factors, such as oxidative stress, atrial dilatation, calcium overload, inflammation, and myofibroblast activation, interact in a way that significantly contributes to the remodeling of the atrial extracellular matrix (ECM) and electrical properties. This ultimately results in the continuous presence of AF. Nevertheless, the possibility of AF persisting following a COVID-19 infection has not undergone comprehensive investigation, and there is currently a dearth of prolonged studies that evaluate the consequences of COVID-19-related NOAF[7,8]. Furthermore, maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks [9]. However, there is a paucity of the data regarding persistence of AF after COVID-19 infection. The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer and a significant increase in peripheral thromboembolic events observed in NOAF patients, calls for further investigation of the management of COVID-19-related NOAF[10,11].

Similar to past pandemics in history, the COVID-19 pandemic presents a chance to broaden our knowledge despite the challenges it poses[3]. Our objective was to explore the underlying mechanisms of NOAF in COVID-19 patients, with a particular emphasis on factors that could sustain the occurrence of this arrhythmia. To peruse this, a comprehensive, structured literature search was conducted through EMBASE and MEDLINE for articles published between December 2019 and May 20, 2023, that reported the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management of NOAF in COVID-19 were investigated. The search terms include each of the following terms individually and in combination: "new-onset atrial fibrillation", "NOAF", "AF persistence", "persistent atrial fibrillation", "SARS-CoV-2", "COVID-19", "SARS", coronavirus as described in the [Supplementary Table 1](#)[12]. Two investigators (Talaei F and Banga A) independently screened studies for eligibility. We focused primarily on published research articles, systematic reviews, and observational cohorts. The title, abstract, and keywords were checked for relevance initially. Studies were excluded if not written in English.

NOAF

NOAF is defined as AF detected after diagnosis of COVID-19 without a prior history[13]. In the course of the disease, AF might indefinitely appear as short (< 7 d) self-limiting episodes (*i.e.*, paroxysmal). However, it is more likely to transform into long-lasting forms of AF[14]. AF is considered persistent when perpetually lasting more than seven days[15,16].

Epidemiology

An October 2021 meta-analysis involving over 21000 hospitalized COVID-19 patients revealed that NOAF had a prevalence of 11%. Elderly COVID-19 patients (aged ≥ 60) had a higher NOAF prevalence (13%) compared to younger patients (5%). Among different ethnic subgroups, Europeans (15%) and Americans (11%) had the highest NOAF prevalence, while Africans had the lowest (2%). Additionally, NOAF was significantly linked to a higher risk of all-cause mortality among COVID-19 patients (odds ratio = 2.32)[17].

A report from the American Heart Association COVID-19 Cardiovascular Disease Registry revealed that 5.4% of patients hospitalized for COVID-19 infection developed NOAF during their hospital stay. Moreover, NOAF was associated with higher rates of death (45.2% *vs* 11.9%) and major adverse cardiovascular events of cardiovascular death, myocardial infarction, cardiogenic shock, and heart failure (23.8% *vs* 6.5%) compared to those who did not develop NOAF. The unadjusted hazard ratio for mortality was 1.99 [95% confidence interval (CI): 1.81-2.18], and for major adverse cardiovascular events was 2.23 (95%CI: 1.98-2.53) for patients with *vs* without new-onset AF[18].

COVID-19-related NOAF was demonstrated to be an independent prognostic factor for in-hospital embolic events, irrespective of anticoagulant use and prolonged hospital stay. Potential co-factors contributing to the development of NOAF could include older age, arterial hypertension, a history of myocardial infarction, renal dysfunction, and elevated D-dimers[19], which align with previously reported risk factors associated with the emergence of NOAF in critically ill patients[20].

Etiology and pathophysiology

There are ongoing debates regarding underlying mechanisms involved in provoking arrhythmias in COVID-19 infection. While some attribute arrhythmias and hence AF directly to the virus itself[21]; others highlight the connection between inflammatory markers and arrhythmias, considering it as a consequence of a systemic illness not exclusive to COVID-19 [11,22]. A third group points towards the long-term changes required to make atrial structural abnormalities and the relatively short incubation period of COVID-19 and concludes that it might be a symptom of prior undetected structural heart diseases[23,24].

There are limited studies concerning the pathophysiology of NOAF in COVID-19; nonetheless, several of them are built upon earlier research conducted on severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or Middle East respiratory syndrome coronavirus (MERS-CoV). Considering the resemblances in structure and potential pathogenicity among MERS-CoV, SARS-CoV-1, and SARS-CoV-2[25], various mechanisms have been suggested to elucidate the processes that might trigger arrhythmia in the context of COVID-19[26,27].

Angiotensin-converting enzyme-2 (ACE2)-related signaling pathways, endothelial dysfunction, spike protein interaction, cytokine storm, hypoxia, alteration in the autonomous nervous system, and metabolic disarray in the setting of viral infection are some proposed mechanisms[21,23].

Modulation of myocardial ACE2 expression: ACE2 is found in abundance in the lungs. It is thought to play an essential role in the pathogenesis of SARS-CoV-2-associated severe acute respiratory syndrome by acting as a receptor for this family of viruses. However, this enzyme is not exclusive to the lungs, as it is also highly expressed in the heart and kidneys[19,28].

The catalytic action of this enzyme in the heart leads to the degradation of angiotensin-II (Ang II) to cardioprotective Ang1-7. In doing so, ACE2 plays a cardioprotective counterbalance role in the renin-angiotensin-aldosterone system (RAAS)[19].

Binding the viral spike protein to the ACE2 receptor activates catalytic processes that lead to ACE2 shedding, decreasing antifibrotic Ang1-7. Consequently, the Ang II/Ang1-7 ratio will move toward Ang II production, which is a growth factor for fibroblasts, and promote inflammation, fibrosis, oxidative stress, and vasoconstriction[19,29,30]. Decreasing Ang1-7 also leads to an increase in disintegrin and metalloproteinase 17, which will prompt further cardiac injury and subsequent potential AF[23,27].

Endothelial dysfunction: The cardioprotective role of ACE2 has been discussed, yet it extends beyond that by serving as a regulator of the kallikrein-bradykinin pathway, imparting a significant vasodilator effect. This effect acts as a counterbalance to the vasopressor effect of RAAS[19,31]. Declined vascular levels of ACE2 in COVID-19 patients lead to over-activation of the kallikrein-bradykinin system and increased permeability[31]. The heightened permeability leads to the recruitment of diverse immune cells, inflammatory cytokines, and vasoactive molecules to the site. Consequently, the production of reactive oxygen species (ROS) and other cytotoxic mediators by activated neutrophils synergizes with the release of vasoactive molecules, including thrombin, histamine, bradykinin, thromboxane A2, and vascular endothelial growth factor. This, in turn, enhances the contractility of endothelial cells and the loosening of inter-endothelial junctions, ultimately leading to vascular leakage[32]. Also, interleukin (IL)-1 β and tumor necrosis factor (TNF)- α are recognized for their ability to promote fluid retention by increasing glycocalyx degradation and upregulating hyaluronic acid synthesis, the ultimate result of which is an increased deposition of hyaluronic acid in the compromised ECM, promoting fluid retention[32]. Both mechanisms ultimately converge on vascular impairment as an endpoint.

While the impact of AF on the vasculature has been better studied, recent discoveries indicate a bidirectional relationship between the two[33,34]. Endothelial dysfunction would further increase oxidative stress, proinflammatory cytokines, and impaired nitric oxide-dependent vasorelaxation[29]. Excessive production of endothelial ROS has been linked to atrial oxidative injury, resulting in structural and electrical remodeling, contributing to AF. Interestingly, there is evidence that patients with coronary endothelial dysfunction are at increased risk for developing persistent AF[33,34]. Up to date, no similar human studies are available, and the current pandemic could present an opportunity to investigate this link.

Spike protein binding to cardiomyocyte: Spike protein of COVID-19 plays an essential role in host cell invasion, including cardiomyocytes[35]. Viral spike protein interacts with CD147 as an ECM metalloproteinase inducer. CD147 is a potent stimulator of several cytokines, including IL-18, *in vitro*, and IL-18 is an essential element of the inflammatory cascade, acts as a cardiotropic metalloproteinase, and correlates with cardiac remodeling and AF[36,37].

Spike protein also binds to N-acetylneuraminic acid (Neu5Ac), the predominant sialic acid in human cells, including cardiomyocytes. Higher levels of Neu5Ac are associated with left atrial enlargement, and it plays a crucial role in severe coronary artery diseases (CAD) and cardiac fibrosis[38], but how this cardiac fibrosis could lead to AF is under study[23].

Cytokine storm: The sustained infiltration of neutrophils, macrophages, and CD4+ T-lymphocytes associated with the COVID-19 cytokine storm can promote the transformation of fibroblasts to myofibroblasts, which in the long run could lead to pathological cardiac remodeling and fibrosis[39].

On the other hand, atherosclerotic plaques in the coronary artery are more prone to rupture in the state of inflammation anticipated by cardiac injury and arrhythmias. Production of several cytokines, either by inducing direct myocardial necrotic effect or releasing pro-atherogenic cytokines like IL-6, will develop proliferation in vascular smooth muscle accompanied by endothelial cell and platelet activation[40,41].

Hypoxemia: COVID-19 causes hypoxia by several different mechanisms that can transform into acute respiratory syndrome[42]. Pneumonia in COVID-19 deteriorates gas exchange and complicates cell metabolism. This enhances anaerobic fermentation, resulting in intracellular acidosis and oxygen free radicals destroying the phospholipid layer of the cell membrane. Meanwhile, the hypoxia-induced influx of calcium ions also leads to injury and subsequent apoptosis of injured cardiomyocytes[43]. Also, COVID-19 systemic infection, being a situation of increased cardiometabolic demand, collaterals with hypoxia caused by an acute respiratory illness. This coincidence leads to an unmatched myocardial demand-supply ratio and subsequent acute myocardial injury[44].

The above should also add hypoxemia-induced dynamic changes in transmural pressure gradients, promoting increased pulmonary pressure, which leads to tricuspid regurgitation and further impairment in the right atrium, followed by possible changes in atrial conduction properties and refractoriness[45].

Gramley *et al*[46] previously observed a close association between prolonged hypoxic and increased angiogenic markers in the atrium with AF. With the persistence of hypoxia, an endoglin called CD105 would up-regulate, which is a homolog to the type III receptor of transforming growth factor- β , leading to ECM formation. It was hypothesized that cardiac hypoxia could provoke AF through the hypoxia-inducible factor pathway and over-expression of connective tissue growth factor and angiogenic genes like vascular endothelial growth factor[46].

Autonomic nervous system alteration: Severe infections generally activate the sympathetic nervous system (SNS), which also relates to AF[23]. Among cytokines released in COVID-19 infection, IL-6 can hyperactivate SNS, either centrally by a hypothalamus-mediated mechanism or peripherally *via* the left stellate ganglia[47].

SNS activation likely increases calcium influx into the cardiomyocytes and calcium overload in the sarcoplasmic reticulum, further increasing the frequency of spontaneous diastolic calcium releases, resulting in delayed afterdepolarizations and triggered action potentials, increasing the likelihood of AF induction[48].

On the other hand, hypoxemia might activate the parasympathetic system. Combined sympathetic and vagal activation creates a more pronounced AF substrate than sympathetic or parasympathetic stimulation alone. In an experimental animal model, changes in intrathoracic pressure, dynamic hyperinflation, and obstructive respiratory events that were followed by hypoxia-activated the parasympathetic nervous system, reducing the right atrial effective refractory period and increasing the susceptibility to AF. Autonomic nervous system (ANS) activity and AF have a reciprocal interaction that could help the arrhythmia continue to evolve[49].

Fluid and electrolyte abnormality: Renal dysfunction in COVID-19 can lead to a decrease in serum potassium levels due to increased excretion[50]. Increased ACE/ACE2 ratio imbalance would also affect the RAS and potassium metabolism [51]. Increased ACE2 degradation augments RAS activity, increasing sodium and water reabsorption and collateral increase potassium excretion[52]. Hypokalemia frequently happens in hospitalized patients with COVID-19, with reported rates ranging from 41% to 55% of cases[53]. The occurrence of hypokalemia, which increases resting potential, leads to cell membrane hyperpolarization, thus accelerating atrial conduction and potentially creating a susceptibility to AF. Hypokalemia, by increasing resting potential, leads to cell membrane hyperpolarization, thus accelerating atrial conduction, which could possibly predispose to AF[54]. Hypokalemia frequently happens in hospitalized patients with COVID-19, reported in 41% to 55% of cases[55].

Association with CAD

Growing evidence highlights a strong link between CAD and AF, and several observational studies have indicated that CAD and AF aggravate each other. Shared risk factors encompassing hypertension, diabetes mellitus, and obesity substantiate this linkage. Notably, AF incidence has been found to be higher in people with CAD compared to age-matched

adults without CAD[56].

Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. CAD adversely affects AF by promoting progression *via* re-entry and increasing the excitability of atrial tissue as a result of ischemia and electrical inhomogeneity. AF, in turn, accelerates atherosclerosis and, together with enhanced thrombogenicity and hypercoagulability contribute to micro and macrothrombi throughout the cardiovascular system. Inflammation and endothelial dysfunction remain central to both disease processes[57].

Patients with CAD associated with NOAF or persistent AF have significantly higher morbidity and mortality, predisposing to heart failure, life-threatening ventricular arrhythmias, and major adverse cardiovascular events[57]. A recent comprehensive analysis supports heightened AF risk in CAD patients, yet a causal AF-to-CAD link remains unestablished[56]. Management of concurrent CAD and AF centers on anti-thrombotic strategies, balancing stroke prevention and stent thrombosis avoidance while cautiously mitigating bleeding risk. Current guidelines recommend up to one year of combined oral anticoagulant (OAC) and antiplatelet therapy, preferably P2Y12 inhibitors or OAC monotherapy. However, the limited quality of evidence in these guidelines and persistently high bleeding risk constrain their clinical applicability[50,52].

Management of NOAF

Recognition: NOAF recognition in patients with COVID-19 can be done with electrocardiography, telemetry, or implantable device interrogation. Close observation of vital signs and regular electrocardiograms help monitor for dysrhythmias such as AF in patients with COVID-19[51].

Evaluation: The initial evaluation of COVID-19-related NOAF parallels the standard management for AF. This involves conducting a routine two-dimensional transthoracic echocardiogram to assess for structural irregularities. However, if indications of heart failure, hemodynamic instability, unexplained clinical deterioration, or planned cardioversion are present, expedited evaluation is warranted[15].

Transesophageal echocardiography should be obviated by the early start of anticoagulation in NOAF to detect left atrium thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures[53].

Treatment goals: Treatment goals are regardless of the type, treatment goals encompass three primary objectives: Managing heart rate during episodes of AF; and achieving the restoration, sustained maintenance of normal sinus rhythm (rhythm control), and mitigating the risk of systemic or cerebral embolism linked to the heightened embolic risk associated with AF all while minimizing the impact of drug interactions[15,58].

Rate and rhythm control: The contemporary therapy of AF with rate control *vs* rhythm control strategies is still disputed, there is a scarcity of data regarding the effectiveness of rhythm and rate control approaches for COVID-19-related AF. Current recommendations are based on acute management of AF in COVID-19 disease and long-term data is not available[53,58]. Enhancing the treatment of underlying factors such as hypoxemia, inflammation, and potentially reversible triggers (like hypokalemia, hypomagnesemia, and acidosis) seems to form the empirical foundation for managing these cases. As with other setting, if NOAF is suspected to be a contributing factor to hemodynamic instability immediate cardioversion should be considered. Although, for the remaining patients who do not urgently require cardioversion, the decision to proceed should be weighed against the availability of necessary equipment and medical personnel, as well as the potential risk of virus transmission with intubation. In critically ill patients with compromised hemodynamics due to NOAF, intravenous amiodarone is the preferred antiarrhythmic medication for rhythm control[59].

Hospitalized patients who have developed COVID-19-related NOAF and are undergoing antiviral treatment while maintaining hemodynamic stability should give precedence to discontinuing their anti-arrhythmic medications. Instead, the preferred approach involves initiating rate control therapy using beta-blockers or non-dihydropyridine calcium channel blockers, along with or without digoxin, unless contraindicated[58]. This approach ensures the safe administration of antiviral medication without the potential risk of QT prolongation[53,58].

Amidst a COVID-19 infection, the potential for QT interval-related risks could be heightened due to the simultaneous utilization of anti-arrhythmic medications with other QT-prolonging medications (such as hydroxychloroquine, azithromycin, lopinavir/ritonavir), along with factors like myocardial inflammation and electrolyte imbalances (like hypokalemia, hypomagnesemia, and/or hypocalcemia)[60]. It's crucial to assess potential drug interactions, including those between antiviral and antiarrhythmic drugs, prior to initiating therapy[53].

Unless dealing with highly symptomatic AF cases, such as individuals with AF-related heart failure or those experiencing medically refractory AF resulting in frequent emergency room visits, all AF ablation procedures ought to be delayed for a minimum of three months after recovering from a COVID-19 infection[53].

Prevention of thromboembolic events: As a general guideline, for patients with a history of prior stroke, transient ischemic attack, or a CHA2DS2-VASc score > 2 who subsequently develop AF, oral anticoagulation is recommended[15]. Given that hospitalized COVID-19 patients are generally over the age of 65 and often have multiple underlying health conditions, a significant proportion of individuals with AF necessitate prolonged anticoagulation therapy[11]. Hemodynamically stable COVID-19 patients presenting with atrial AF during their hospitalization have treatment including unfractionated heparin, low molecular weight heparin, or direct OACs (DOACs). The specific choice among these options is influenced by factors like the suitability of oral administration, renal function, and additional clinical aspects. It's important to highlight that certain medications for COVID-19 treatment could potentially interact with DOACs. Lopinavir/ritonavir may create a potential interaction with DOACs through cytochrome P450 CYP3A4 interaction, and antimalarial drugs could influence DOACs *via* P-glycoprotein inhibition. If such interactions are pertinent, there may be

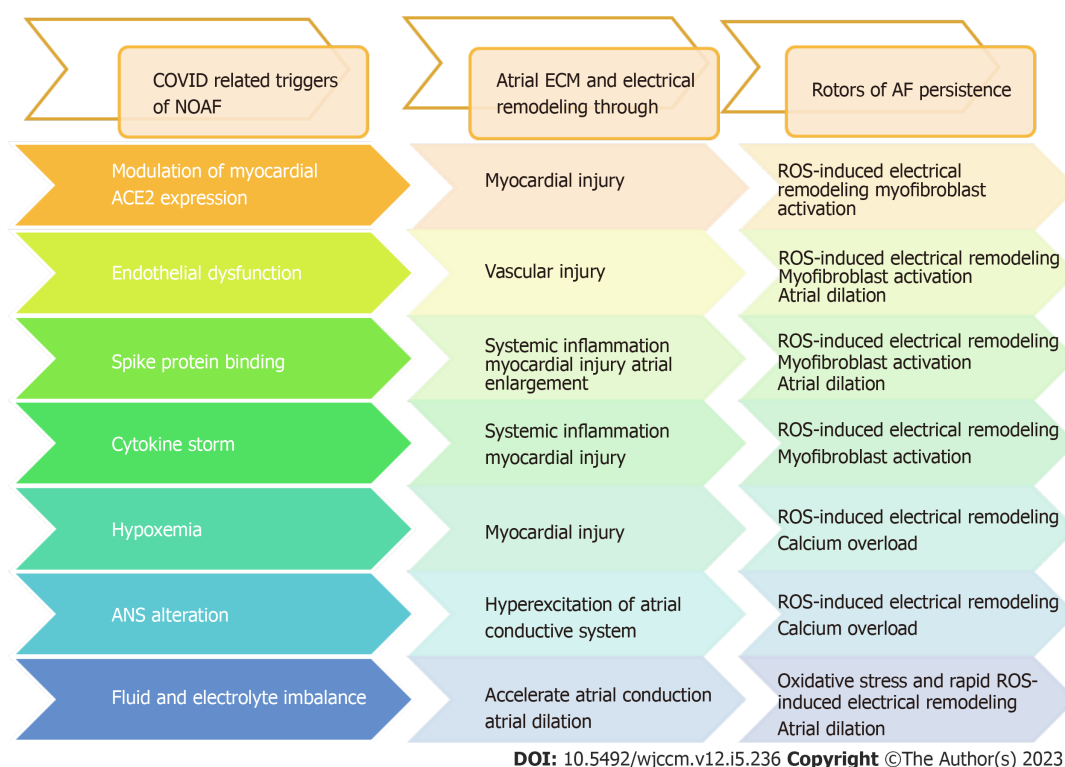


Figure 1 Comparing available studies on new-onset atrial fibrillation pathophysiology in coronavirus disease 2019 patients and rotors of atrial fibrillation persistence (including oxidative stress, calcium overload, atrial dilation, micro-RNA, inflammation, and myofibroblast activation). COVID: Coronavirus disease; ECM: Extracellular matrix; NOAF: New-onset atrial fibrillation; AF: Atrial fibrillation; ROS: Reactive oxygen species; ACE2: Angiotensin-converting enzyme-2; ANS: Autonomic nervous system.

an increased risk of bleeding, underscoring the need to avoid DOACs. Given this scenario, DOACs are favored over vitamin K antagonists (VKAs) due to their more favorable safety profile and standardized dosing schedule[58].

VKAs are also considered for specific subsets of patients, including individuals with mechanical prosthetic valves or antiphospholipid syndrome. While VKAs typically induce a temporary deficiency of vitamin K, the observed lower levels of vitamin K in patients with COVID-19 compared to healthy individuals suggest a need for additional investigation regarding the utilization of VKAs in COVID-19 patients[61]. The precise mechanisms driving this connection are yet to be fully understood.

The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer and a significant increase in peripheral thromboembolic events observed in NOAF patients, calls for further investigation of the management of COVID-19-related NOAF[10,11]. Since heparins are unlikely to interact with drugs used in COVID-19 treatment, they represent a safe and attractive option for stroke prevention in AF patients who are hospitalized due to COVID-19. Remarkably, beyond their antithrombotic effects, heparins also possess anti-inflammatory properties that could be pertinent in this context[53]. Following recovery from COVID-19, the continuation of long-term anticoagulation should be based on the CHA2DS2-VASc score.

Discussion

COVID-19-related NOAF is still not well studied. Mechanisms involved in the development of NOAF after COVID-19 infection could potentially lead to atrial remodeling and fibrosis, which can further perpetuate AF, as shown in Figure 1. Clinical studies suggested that the majority of the patients with AF remain paroxysmal, though the electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal [62]. However, in this study, a sizable overlap was noted in mechanism inducing COVID-19 associated NOAF and those persisting AF.

The mechanism involved in the progression of AF is a constellation of oxidative stress, inflammation, atrial dilatation, calcium overload, and myofibroblast activation, all of which are likely to be involved in one way or another in AF-induced ECM and electrical remodeling[7,8]. Interestingly, many of these mechanisms seem to be mutual with suggestive models of COVID-19-related NOAF (Figure 2), and looking back to the mutual mechanisms of persistent AF and COVID-19-related NOAF could explain the possible risk of developing persistent AF after NOAF in COVID-19 patients (Table 1 and Figure 2).

In the working model of AF perpetuation by Jalife and Kaur[8], oxidative stress and ROS are the cornerstones of maintaining AF. In that model, a putative mechanism of AF perpetuation involves Ang II stimulation, which triggers the release of ROS from activates nicotinamide adenine dinucleotide phosphate oxidases 2/4. This process leads to a rapid reduction in L-type Ca^{2+} current and an increase in inward rectifier K^{+} current within a short timeframe (*i.e.*, hours or

Table 1 Comparing coronavirus disease 2019-related new-onset atrial fibrillation and persistent atrial fibrillation in terms of etiology, pathophysiology, contributing risk factors, outcome, and management

	COVID-19-related NOAF	Persistent AF
Etiology and pathophysiology	(1) Diminished availability of ACE-2 receptors contributes to myocardial hypertrophy, vasoconstriction, ROS production, oxidative stress, tissue inflammation, and fibrosis, all of which play a role in the development of AF; (2) Endothelial dysfunction leads to increased vascular permeability and leakage culminating in an overproduction of ROS leading to structural and electrical remodeling predisposing to AF; (3) CD147- and myocyte's sialic acid-spike protein interaction upregulate the expression of several cytokines and ROS that induce extracellular matrix degradation, cardiac remodeling, and fibrosis; (4) Excessive release of proinflammatory cytokines in cytokine storm leads to ROS production, progressive myocardial cell apoptosis or necrosis, which may lead to conduction disturbances leading to AF; (5) Impaired gas exchanges and intrathoracic pressure swings lead to cardiomyocyte injury and increased frequency of premature atrial beats and induce AF; (6) ANS alteration: SNS-mediated calcium influx increases the frequency of delayed afterdepolarization and triggers AP; PNS activation mediated by intrathoracic pressure swing leads to shortening of right atrial ERP, and APD both induce AF; and (7) Sodium and water resorption increases blood pressure and excretion of potassium increase the resting membrane and enhances depolarization predisposing to AF	Steady generation of ROS triggered by sustained high-electrical activity, followed by intracellular Ca^{2+} overload together with atrial dilatation, mitochondrial ROS and activation of inflammatory and pro-fibrotic pathways progressively alters gene expression clinically relevant sheep model of persistent AF, leading to myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling, all of which would occur relatively slowly but reach critical levels when AF becomes persistent at a median time of about 2 mo: (1) Oxidative stress by ROS released either by NOX2/4 or mitochondria is the first consequence, the persistence of which leads to shortened APD and RF through reducing rapid L-type Ca^{2+} current and increasing inward rectifier K^{+} current promoting the formation and stabilization of rotor that would in a vicious cycle to preserve sustained high electrical activity; and (2) Inflammation leads to profibrotic signaling in response to cardiac injury by promoting fibroblast-to-myofibroblast trans-differentiation leading to either through increased expression of TRP channels or miR-21 resulting in structural remodeling by atrial dilation and fibrosis that maintains AF
Risk factors	(1) Older age; (2) A history of myocardial infarction; (3) Renal dysfunction; (4) Raised D-dimer levels; and (5) Hypertension	Risk factors for progression to more persistent forms of AF among patients with paroxysmal AF and varying degrees of CVD per HATCH score is [62]: (1) Heart failure; (2) Older age; (3) Previous transient ischemic attack or stroke; (4) Chronic obstructive pulmonary disease; and (5) Hypertension
Outcomes	Among patients hospitalized with COVID-19 infection, 5.4% could develop NOAF. All-cause mortality rates are 45.2% <i>vs</i> 11.9% and MACE is 23.8% <i>vs</i> 6.5% for patients with <i>vs</i> without NOAF [67]	Among patients with persistent AF all-cause mortality rate is 4.41% and MACE is 5.09% [67]
Treatment	<p>The initial approach is to enhance the treatment of underlying factors. Hemodynamic instability warrants immediate cardioversion, provided that the risk of embolism is low</p> <p>Rate control therapy is preferred over rhythm control unless hemodynamic instability warrants the addition of rhythm control <i>e.g.</i>, with amiodarone</p> <p>Anticoagulation: Unfractionated heparin, LMWH is safe to use. Use DOACs with caution as interact with some antiviral medications. VKAs induce a state of vitamin K deficiency that could potentially influence susceptibility to contracting COVID-19</p>	<p>Hemodynamic instability warrants immediate cardioversion provided that the risk of embolism is low [15]</p> <p>A similar efficacy of rate <i>vs</i> rhythm control in all-cause mortality and MACE had been noted. Thus, current guidelines recommend an individualized decision taking into consideration that a rhythm control is most likely to fail in patients with long-term persistent AF (> 1 yr), in whom atrial substrate alteration is greatest</p> <p>The choice of anticoagulation should be individualized based on the patient's comorbidities, like other indications for anticoagulation and renal function</p>

COVID-19: Coronavirus disease 2019; ECM: Extracellular matrix; NOAF: New-onset atrial fibrillation; AF: Atrial fibrillation; ROS: Reactive oxygen species; ACE2: Angiotensin-converting enzyme-2; SNS: Sympathetic nervous system; AP: Action potential; PNS: Peripheral nervous system; ERP: Effective refractory period; APD: Action potential duration; TRP: Transient receptor potential; CVD: Cardiovascular disease; MACE: Major adverse cardiovascular events; LMWH: Low molecular weight heparin; DOAC: Direct oral anticoagulant; VKA: Vitamin K antagonist; ANS: Autonomic nervous system.

days). These alterations result in the shortening of the atrial action potential duration and refractory period, promoting the formation and stabilization of rotors of persistent AF. Subsequently, intracellular Ca^{2+} overload ensues, promoting triggered activity and apoptosis [63,64].

Nevertheless, Ca^{2+} overload, together with atrial dilatation, mitochondrial ROS, and activation of inflammatory and pro-fibrotic pathways, progressively alters gene expression. The eventual outcomes of these persistent alterations entail myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling. When these processes collectively escalate to a critical threshold, it could lead to the persistence of AF. In an animal study, after two months of tachypacing, the arrhythmia progressed to persistent AF [65]. However, no study is available on the same time frame in COVID-19 patients.

In addition to Ang II, sustained AF is fostered by the release of proinflammatory cytokines and tissue injury mediators such as $\text{TNF-}\alpha$, IL-6, and IL-8. While the initial purpose of this cascade is to facilitate a beneficial "self-destroy and rebuild" process [66], its continuous activation is a widely recognized initiator of fibroblast-to-myofibroblast transformation leading to atrial remodeling [8]. Therefore, the prolonged presence of inflammatory cascades and myocyte apoptosis, whether through spike protein binding to cardiomyocyte, cytokine storm, prolonged hypoxemia, or altered ANS, could also potentially lead to ion channel dysfunction and excessive matrix production, likely generating electrical and structural remodeling and predisposing persistent AF.

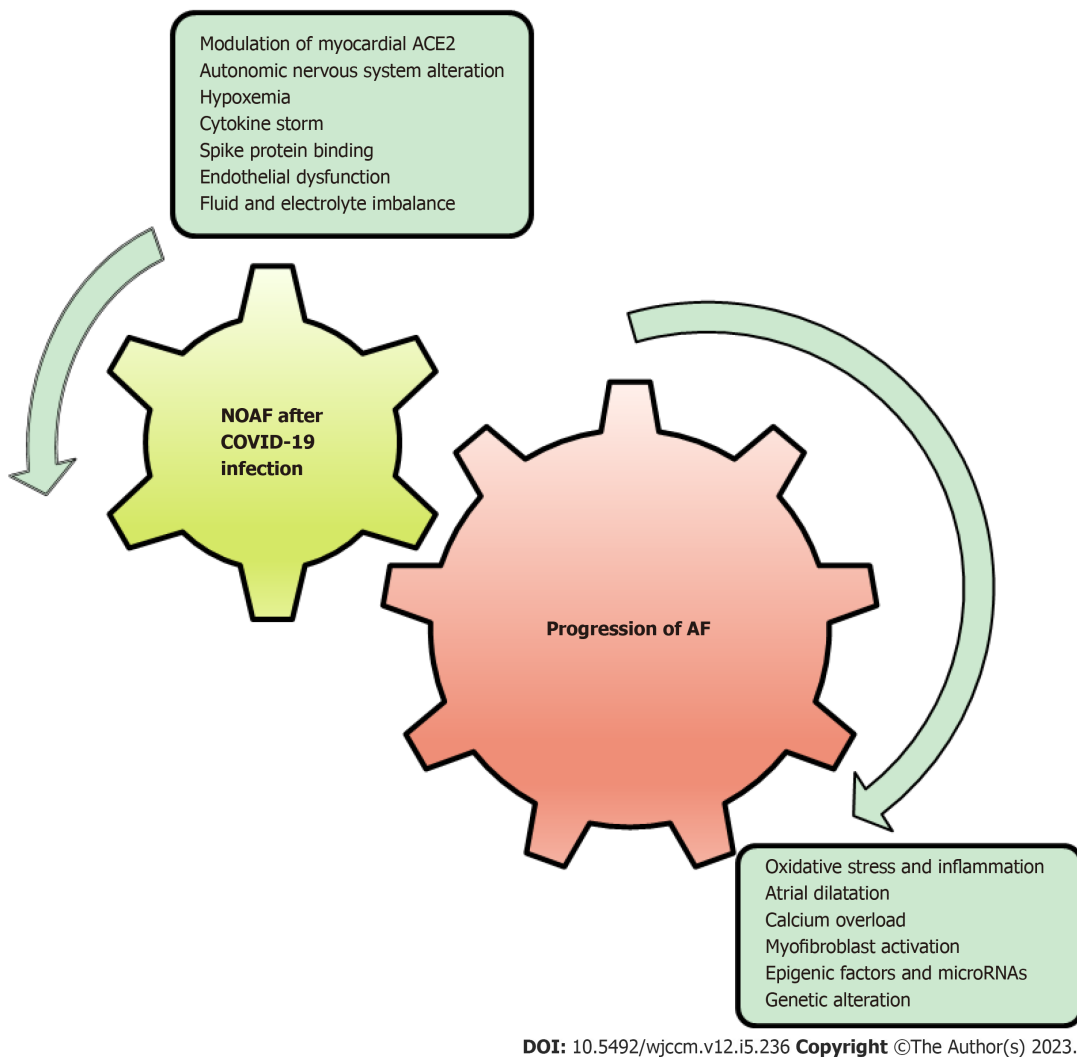


Figure 2 Long-term studies needed to assess progression from coronavirus disease 2019-related new-onset atrial fibrillation to more sustained forms of atrial fibrillation. COVID-19: Coronavirus disease 2019; NOAF: New-onset atrial fibrillation; ACE2: Angiotensin-converting enzyme-2; AF: Atrial fibrillation.

Conversely, potential risk factors associated with COVID-19-related NOAF, such as advanced age, hypertension, and a previous myocardial infarction, exhibit resemblances to independent factors that are linked with the progression toward persistent AF[62].

Progression from paroxysmal to more sustained forms of AF is associated with increased adverse events, including thromboembolic events, although the long-term outcomes of COVID-19-related NOAF infection are unknown (Figure 1) [67]. Early recognition of COVID-19-related NOAF is essential due to the high mortality risk associated with it. It is unknown if the management of COVID-19-related NOAF should follow the same pattern as routine management of paroxysmal or persistent AF. The disturbed coagulation system resulting from COVID-19 infection appears to elevate the potential for thromboembolic events in individuals with NOAF, although this necessitates additional research and confirmation.

While the conclusions drawn from this review are limited due to its non-experimental nature, it is evident that among various factors contributing to the development of COVID-19-related NOAF, some have the potential to perpetuate AF. These factors include modulation of myocardial ACE2 expression, spike protein binding, cytokine storm, endothelial dysfunction, increased permeability, and hypoxemia, which have the potential to induce atrial, ECM, or electrical remodeling, thereby perpetuating AF. To gain a more comprehensive understanding, further fundamental studies are required to explore the interplay between these factors. Additionally, prospective long-term studies are necessary to investigate the outcomes of patients who develop NOAF after experiencing COVID-19 infection in the long run (Figure 1).

CONCLUSION

Among several mechanisms that contribute to COVID-19-related NOAF, those exerting oxidative stress, such as modu-

lating myocardial ACE2 expression, endothelial dysfunction, spike protein binding, and cytokine storms, have the potential to contribute to changes in atrial structure, ECM, and electrical characteristics, which are common factors perpetuating AF. The electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal as maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks. The long-term outcomes of NOAF, including the persistence of AF after COVID-19 infection, remain unknown. Long-term prospective studies are needed to follow up on patients with COVID-19-related NOAF to address this knowledge gap.

FOOTNOTES

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