

World Journal of *Critical Care Medicine*

World J Crit Care Med 2023 December 9; 12(5): 236-285



MINIREVIEWS

- 236 New-onset atrial fibrillation among COVID-19 patients: A narrative review
Talaei F, Banga A, Pursell A, Gage A, Pallipamu N, Seri AR, Adhikari R, Kashyap R, Surani S
- 248 Narrative review of traumatic pneumorrhachis
Pothiawala S, Civil I
- 254 Advances in post intensive care unit care: A narrative review
Kumar N

META-ANALYSIS

- 264 Systematic review and meta-analysis of seroprevalence of human immunodeficiency virus serological markers among pregnant women in Africa, 1984-2020
Ebogo-Belobo JT, Kenmoe S, Mbongue Mikangue CA, Tchatchouang S, Robertine LF, Takuissu GR, Ndzie Ondigui JL, Bowo-Ngandji A, Kenfack-Momo R, Kengne-Ndé C, Mbaga DS, Menkem EZ, Kame-Ngasse GI, Magoudjou-Pekam JN, Kenfack-Zanguim J, Esemu SN, Tagnouokam-Ngoupo PA, Ndip L, Njouom R

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Nathan J Smischney, MD, MSc, Assistant Professor, Anesthesiology, Mayo Clinic, Rochester, MN 55905, United States. smischney.nathan@mayo.edu

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine (WJCCM, World J Crit Care Med)* is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, etc.

INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai; **Production Department Director:** Xu Guo; **Editorial Office Director:** Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Hua-Dong Wang

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3141/editorialboard.htm>

PUBLICATION DATE

December 9, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



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

Fahimeh Talaei, Akshat Banga, Amanda Pursell, Ann Gage, Namratha Pallipamu, Amith Reddy Seri, Ramesh Adhikari, Rahul Kashyap, Salim Surani

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Batta A, India; Mahmoud MZ, Saudi Arabia; Yu L, Singapore

Received: May 30, 2023

Peer-review started: May 30, 2023

First decision: August 2, 2023

Revised: August 20, 2023

Accepted: September 11, 2023

Article in press: September 11, 2023

Published online: December 9, 2023



Fahimeh Talaei, Department of Critical Care Medicine, Mayo Clinic, Phoenix, AZ 85054, United States

Akshat Banga, Department of Internal Medicine, Sawai Man Singh Medical College, Jaipur 302004, India

Amanda Pursell, Internal Medicine, Tristar Centennial Medical Center, TriStar Division, HCA Healthcare, Nashville, TN 37203, United States

Ann Gage, Cardiology, TriStar Centennial Medical Center, TriStar Division, HCA Healthcare, Nashville, TN 37203, United States

Namratha Pallipamu, Department of Medicine, Siddharta Medical College, Vijayawada 520008, Andhra Pradesh, India

Amith Reddy Seri, Department of Internal Medicine, McLaren Regional Medical Center, Flint, MI 48532, United States

Ramesh Adhikari, Department of Internal Medicine, Franciscan Health, Lafayette, IN 46237, United States

Rahul Kashyap, Salim Surani, Department of Anaesthesiology & Critical Care Medicine, Mayo Clinic, Rochester, MN 55902, United States

Rahul Kashyap, Department of Research, WellSpan Health, York, PA 17401, United States

Salim Surani, Department of Medicine & Pharmacology, Texas A&M University, College Station, TX 77843, United States

Corresponding author: Salim Surani, FCCP, MD, MHSc, Academic Editor, Professor, Department of Medicine & Pharmacology, Texas A&M University, 400 Bizzell Street, College Station, TX 77843, United States. srsurani@hotmail.com

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

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Talaei F, Banga A, Pursell A, Gage A, Pallipamu N, Seri AR, Adhikari R, Kashyap R, Surani S. New-onset atrial fibrillation among COVID-19 patients: A narrative review. *World J Crit Care Med* 2023; 12(5): 236-247

URL: <https://www.wjgnet.com/2220-3141/full/v12/i5/236.htm>

DOI: <https://dx.doi.org/10.5492/wjccm.v12.i5.236>

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

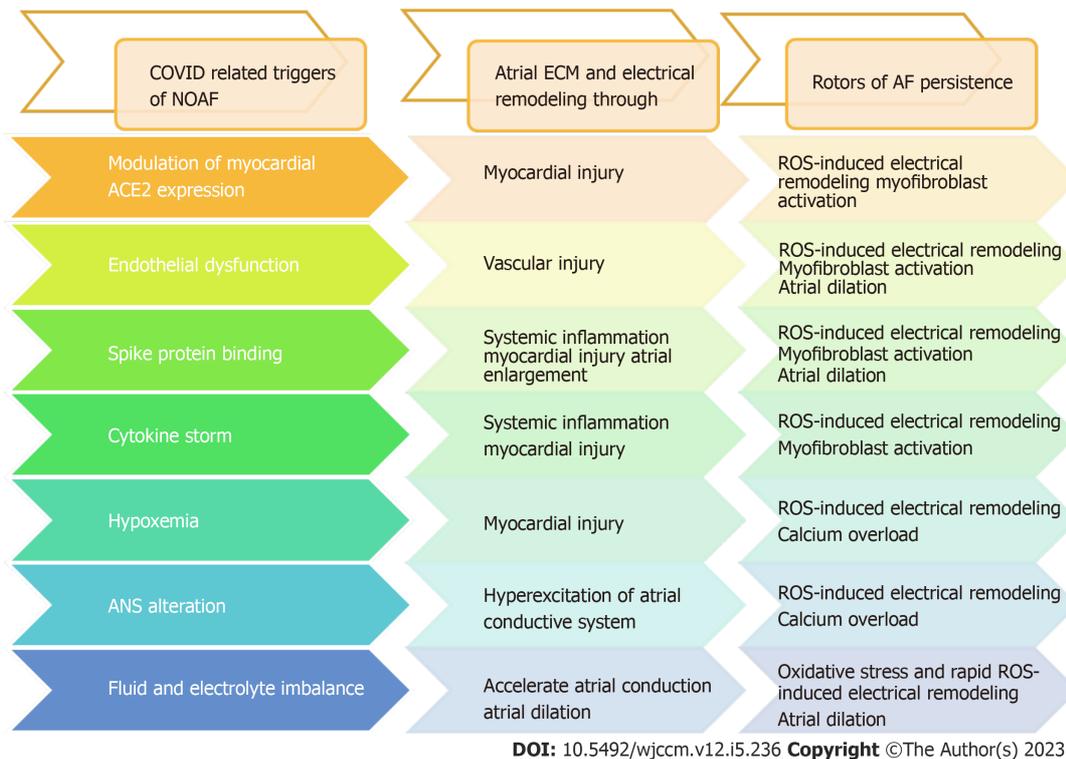


Figure 1 Comparing available studies on new-onset atrial fibrillation pathophysiology in coronavirus disease 2019 patients and rotors of atrial fibrillation persistence (including oxidative stress, calcium overload, atrial dilation, micro-RNA, inflammation, and myofibroblast activation). COVID: Coronavirus 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 Ca²⁺ 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 world 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% vs 11.9% and MACE is 23.8% vs 6.5% for patients with vs without NOAF[67] | Among patients with persistent AF all-cause mortality rate is 4.41% and MACE is 5.09%[67] |
| Treatment | The initial approach is to enhance the treatment of underlying factors. Hemodynamic instability warrants immediate cardioversion, provided that the risk of embolism is low Rate control therapy is preferred over rhythm control unless hemodynamic instability warrants the addition of rhythm control e.g., with amiodarone 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 | Hemodynamic instability warrants immediate cardioversion provided that the risk of embolism is low[15] A similar efficacy of rate vs 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 The choice of anticoagulation should be individualized based on the patient's comorbidities, like other indications for anticoagulation and renal function |

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 Ca²⁺ overload ensues, promoting triggered activity and apoptosis[63,64].

Nevertheless, Ca²⁺ 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 TNF- α , 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.

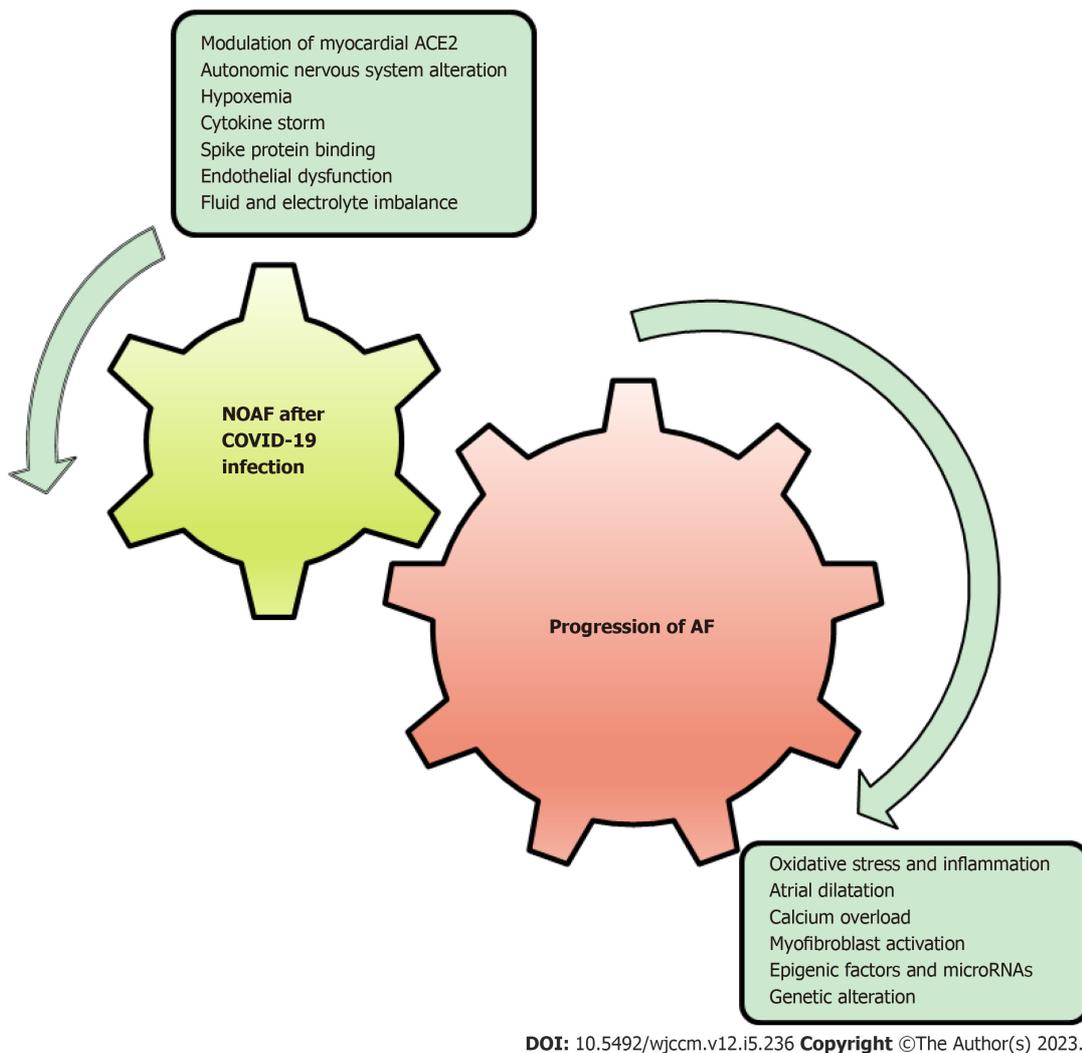


Figure 2 Long-term studies needed to assess progression from coronavirus disease 2019-related new-onset atrial fibrillation to more sustained forms of atrial fibrillation. COVID-19: Coronavirus disease 2019; NOAF: New-onset atrial fibrillation; ACE2: Angiotensin-converting enzyme-2; AF: Atrial fibrillation.

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

Author contributions: Talaie F and Kashyap R contributed to the conceptualization and methodology of this manuscript; Banga A, Adhikari R, and Kashyap R involved in the validation of this study; Talaei F, Banga A, Pursell A, Adhikari R, and Kashyap R participated in the formal analysis; Talaei F, Banga A, Pallipamu N, and Kashyap R investigated the article; Talaei F, Banga A, Pursell A, Gage A, Pallipamu N, Seri AR, Adhikari R, and Surani S contributed to the writing-original draft preparation of this study; Talaei F, Banga A, Pursell A, Seri AR, Adhikari R, Kashyap R, and Surani S involved in the writing-review and editing of this manuscript; Adhikari R, Kashyap R and Surani S participated in project administration.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United States

ORCID number: Fahimeh Talaei 0000-0001-9236-4837; Akshat Banga 0000-0003-2626-8219; Amanda Pursell 0000-0002-6071-5599; Ann Gage 0000-0001-5735-5011; Namratha Pallipamu 0009-0000-9922-6410; Amith Reddy Seri 0000-0002-1770-363X; Ramesh Adhikari 0000-0003-3091-165X; Rahul Kashyap 0000-0002-4383-3411; Salim Surani 0000-0001-7105-4266.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

REFERENCES

- Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TS. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol* 2007; **49**: 986-992 [PMID: 17336723 DOI: 10.1016/j.jacc.2006.10.062]
- World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. [cited 20 March 2023]. Available from: <https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020>
- Sampath S, Khedr A, Qamar S, Tekin A, Singh R, Green R, Kashyap R. Pandemics Throughout the History. *Cureus* 2021; **13**: e18136 [PMID: 34692344 DOI: 10.7759/cureus.18136]
- Gopinathannair R, Merchant FM, Lakkireddy DR, Etheridge SP, Feigofsky S, Han JK, Kabra R, Natale A, Poe S, Saha SA, Russo AM. COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies. *J Interv Card Electrophysiol* 2020; **59**: 329-336 [PMID: 32494896 DOI: 10.1007/s10840-020-00789-9]
- World Health Organization. WHO Coronavirus (COVID-19) Dashboard. [cited 20 March 2023]. Available from: <https://covid19.who.int/?adgroupsurvey={adgroupsurvey}>
- Qian J, Kuang L, Chen F, Liu X, Che L. Prognosis and management of new-onset atrial fibrillation in critically ill patients. *BMC Cardiovasc Disord* 2021; **21**: 231 [PMID: 33952213 DOI: 10.1186/s12872-021-02039-w]
- Corradi D. Atrial fibrillation from the pathologist's perspective. *Cardiovasc Pathol* 2014; **23**: 71-84 [PMID: 24462196 DOI: 10.1016/j.carpath.2013.12.001]
- Jalife J, Kaur K. Atrial remodeling, fibrosis, and atrial fibrillation. *Trends Cardiovasc Med* 2015; **25**: 475-484 [PMID: 25661032 DOI: 10.1016/j.tcm.2014.12.015]
- Sandhu RK, Conen D, Tedrow UB, Fitzgerald KC, Pradhan AD, Ridker PM, Glynn RJ, Albert CM. Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. *J Am Heart Assoc* 2014; **3**: e000916 [PMID: 24786144 DOI: 10.1161/JAHA.114.000916]
- Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020; **18**: 1743-1746 [PMID: 32320517 DOI: 10.1111/jth.14869]
- Pardo Sanz A, Salido Tahoces L, Ortega Pérez R, González Ferrer E, Sánchez Recalde Á, Zamorano Gómez JL. New-onset atrial fibrillation during COVID-19 infection predicts poor prognosis. *Cardiol J* 2021; **28**: 34-40 [PMID: 33140386 DOI: 10.5603/CJ.a2020.0145]
- Chaudhari PB, Banga A. Writing strategies for improving the access of medical literature. *World J Exp Med* 2023; **13**: 50-58 [PMID: 37396881 DOI: 10.5493/wjem.v13.i3.50]
- Ergün B, Ergun B, Sözmen MK, Küçük M, Yakar MN, Cömert B, Gökmen AN, Yaka E. New-onset atrial fibrillation in critically ill patients

- with coronavirus disease 2019 (COVID-19). *J Arrhythm* 2021; **37**: 1196-1204 [PMID: 34518774 DOI: 10.1002/joa3.12619]
- 14 **Kerr CR**, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, Boone J, Sheldon R, Dorian P, Newman D. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. *Am Heart J* 2005; **149**: 489-496 [PMID: 15864238 DOI: 10.1016/j.ahj.2004.09.053]
 - 15 **January CT**, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014; **130**: 2071-2104 [PMID: 24682348 DOI: 10.1161/CIR.0000000000000040]
 - 16 **Saksena S**, Hettrick DA, Koehler JL, Grammatico A, Padeletti L. Progression of paroxysmal atrial fibrillation to persistent atrial fibrillation in patients with bradyarrhythmias. *Am Heart J* 2007; **154**: 884-892 [PMID: 17967594 DOI: 10.1016/j.ahj.2007.06.045]
 - 17 **Li Z**, Shao W, Zhang J, Ma J, Huang S, Yu P, Zhu W, Liu X. Prevalence of Atrial Fibrillation and Associated Mortality Among Hospitalized Patients With COVID-19: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2021; **8**: 720129 [PMID: 34722658 DOI: 10.3389/fevm.2021.720129]
 - 18 **Rosenblatt AG**, Ayers CR, Rao A, Howell SJ, Hendren NS, Zadikany RH, Ebinger JE, Daniels JD, Link MS, de Lemos JA, Das SR. New-Onset Atrial Fibrillation in Patients Hospitalized With COVID-19: Results From the American Heart Association COVID-19 Cardiovascular Registry. *Circ Arrhythm Electrophysiol* 2022; **15**: e010666 [PMID: 35475654 DOI: 10.1161/CIRCEP.121.010666]
 - 19 **Sciolo F**, Daniele A, Amato F, Pastore L, Matera MG, Cazzola M, Castaldo G, Bianco A. ACE2: The Major Cell Entry Receptor for SARS-CoV-2. *Lung* 2020; **198**: 867-877 [PMID: 33170317 DOI: 10.1007/s00408-020-00408-4]
 - 20 **Seguin P**, Signouret T, Laviolle B, Branger B, Mallédant Y. Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. *Crit Care Med* 2004; **32**: 722-726 [PMID: 15090953 DOI: 10.1097/01.ccm.0000114579.56430.e0]
 - 21 **Singh R**, Kashyap R, Hutton A, Sharma M, Surani S. A Review of Cardiac Complications in Coronavirus Disease 2019. *Cureus* 2020; **12**: e8034 [PMID: 32528770 DOI: 10.7759/cureus.8034]
 - 22 **Musikantow DR**, Turagam MK, Sartori S, Chu E, Kawamura I, Shivamurthy P, Bokhari M, Oates C, Zhang C, Pumill C, Malick W, Hashemi H, Ruiz-Maya T, Hadley MB, Gandhi J, Sperling D, Whang W, Koruth JS, Langan MN, Sofi A, Gomes A, Harcum S, Cammack S, Ellsworth B, Dukkupati SR, Bassily-Marcus A, Kohli-Seth R, Goldman ME, Halperin JL, Fuster V, Reddy VY. Atrial Fibrillation in Patients Hospitalized With COVID-19: Incidence, Predictors, Outcomes, and Comparison to Influenza. *JACC Clin Electrophysiol* 2021; **7**: 1120-1130 [PMID: 33895107 DOI: 10.1016/j.jacep.2021.02.009]
 - 23 **Gawalko M**, Kapłon-Cieślicka A, Hohl M, Dobrev D, Linz D. COVID-19 associated atrial fibrillation: Incidence, putative mechanisms and potential clinical implications. *Int J Cardiol Heart Vasc* 2020; **30**: 100631 [PMID: 32904969 DOI: 10.1016/j.ijcha.2020.100631]
 - 24 **Shah A**, Kashyap R, Tosh P, Sampathkumar P, O'Horo JC. Guide to Understanding the 2019 Novel Coronavirus. *Mayo Clin Proc* 2020; **95**: 646-652 [PMID: 32122636 DOI: 10.1016/j.mayocp.2020.02.003]
 - 25 **Lombardi AF**, Afsahi AM, Gupta A, Gholamrezanezhad A. Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), influenza, and COVID-19, beyond the lungs: a review article. *Radiol Med* 2021; **126**: 561-569 [PMID: 33242204 DOI: 10.1007/s11547-020-01311-x]
 - 26 **Madjid M**, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol* 2020; **5**: 831-840 [PMID: 32219363 DOI: 10.1001/jamacardio.2020.1286]
 - 27 **Zheng YY**, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020; **17**: 259-260 [PMID: 32139904 DOI: 10.1038/s41569-020-0360-5]
 - 28 **Chen L**, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 2020; **116**: 1097-1100 [PMID: 32227090 DOI: 10.1093/cvr/cvaa078]
 - 29 **McEwan PE**, Gray GA, Sherry L, Webb DJ, Kenyon CJ. Differential effects of angiotensin II on cardiac cell proliferation and intramyocardial perivascular fibrosis in vivo. *Circulation* 1998; **98**: 2765-2773 [PMID: 9851965 DOI: 10.1161/01.cir.98.24.2765]
 - 30 **South AM**, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol* 2020; **318**: H1084-H1090 [PMID: 32228252 DOI: 10.1152/ajpheart.00217.2020]
 - 31 **van de Veerdonk FL**, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ, van der Hoeven H. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. *Elife* 2020; **9** [PMID: 32338605 DOI: 10.7554/eLife.57555]
 - 32 **Teuwen LA**, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol* 2020; **20**: 389-391 [PMID: 32439870 DOI: 10.1038/s41577-020-0343-0]
 - 33 **Corban MT**, Toya T, Ahmad A, Lerman LO, Lee HC, Lerman A. Atrial Fibrillation and Endothelial Dysfunction: A Potential Link? *Mayo Clin Proc* 2021; **96**: 1609-1621 [PMID: 33775421 DOI: 10.1016/j.mayocp.2020.11.005]
 - 34 **Guazzi M**, Arena R. Endothelial dysfunction and pathophysiological correlates in atrial fibrillation. *Heart* 2009; **95**: 102-106 [PMID: 19109515 DOI: 10.1136/hrt.2007.135277]
 - 35 **Qing E**, Hantak M, Perlman S, Gallagher T. Distinct Roles for Sialoside and Protein Receptors in Coronavirus Infection. *mBio* 2020; **11** [PMID: 32047128 DOI: 10.1128/mBio.02764-19]
 - 36 **Colston JT**, Boylston WH, Feldman MD, Jenkinson CP, de la Rosa SD, Barton A, Trevino RJ, Freeman GL, Chandrasekar B. Interleukin-18 knockout mice display maladaptive cardiac hypertrophy in response to pressure overload. *Biochem Biophys Res Commun* 2007; **354**: 552-558 [PMID: 17250807 DOI: 10.1016/j.bbrc.2007.01.030]
 - 37 **Venkatesan B**, Valente AJ, Prabhu SD, Shanmugam P, Delafontaine P, Chandrasekar B. EMMPRIN activates multiple transcription factors in cardiomyocytes, and induces interleukin-18 expression via Rac1-dependent PI3K/Akt/IKK/NF-kappaB and MKK7/JNK/AP-1 signaling. *J Mol Cell Cardiol* 2010; **49**: 655-663 [PMID: 20538003 DOI: 10.1016/j.yjmcc.2010.05.007]
 - 38 **Hu W**, Xie J, Zhu T, Meng G, Wang M, Zhou Z, Guo F, Chen H, Wang Z, Wang S, Liu H, Jiang H. Serum N-Acetylneuraminic Acid Is Associated with Atrial Fibrillation and Left Atrial Enlargement. *Cardiol Res Pract* 2020; **2020**: 1358098 [PMID: 32351730 DOI: 10.1155/2020/1358098]
 - 39 **Unudurthi SD**, Luthra P, Bose RJC, McCarthy JR, Kontaridis MI. Cardiac inflammation in COVID-19: Lessons from heart failure. *Life Sci* 2020; **260**: 118482 [PMID: 32971105 DOI: 10.1016/j.lfs.2020.118482]
 - 40 **Francis Stuart SD**, De Jesus NM, Lindsey ML, Ripplinger CM. The crossroads of inflammation, fibrosis, and arrhythmia following myocardial infarction. *J Mol Cell Cardiol* 2016; **91**: 114-122 [PMID: 26739214 DOI: 10.1016/j.yjmcc.2015.12.024]
 - 41 **Madjid M**, Vela D, Khalili-Tabrizi H, Casscells SW, Litovsky S. Systemic infections cause exaggerated local inflammation in atherosclerotic

- coronary arteries: clues to the triggering effect of acute infections on acute coronary syndromes. *Tex Heart Inst J* 2007; **34**: 11-18 [PMID: 17420787]
- 42 **Nitsure M**, Sarangi B, Shankar GH, Reddy VS, Walimbe A, Sharma V, Prayag S. Mechanisms of Hypoxia in COVID-19 Patients: A Pathophysiologic Reflection. *Indian J Crit Care Med* 2020; **24**: 967-970 [PMID: 33281323 DOI: 10.5005/jp-journals-10071-23547]
- 43 **Li B**, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; **109**: 531-538 [PMID: 32161990 DOI: 10.1007/s00392-020-01626-9]
- 44 **Bansal M**. Cardiovascular disease and COVID-19. *Diabetes Metab Syndr* 2020; **14**: 247-250 [PMID: 32247212 DOI: 10.1016/j.dsx.2020.03.013]
- 45 **Linz D**, Hohl M, Nickel A, Mahfoud F, Wagner M, Ewen S, Schotten U, Maack C, Wirth K, Böhm M. Effect of renal denervation on neurohumoral activation triggering atrial fibrillation in obstructive sleep apnea. *Hypertension* 2013; **62**: 767-774 [PMID: 23959548 DOI: 10.1161/HYPERTENSIONAHA.113.01728]
- 46 **Gramley F**, Lorenzen J, Jedamzik B, Gatter K, Koellensperger E, Munzel T, Pezzella F. Atrial fibrillation is associated with cardiac hypoxia. *Cardiovasc Pathol* 2010; **19**: 102-111 [PMID: 19211267 DOI: 10.1016/j.carpath.2008.11.001]
- 47 **Lazzerini PE**, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic Risk, and Inflammation: Mind the Gap! *Circulation* 2020; **142**: 7-9 [PMID: 32286863 DOI: 10.1161/CIRCULATIONAHA.120.047293]
- 48 **Denham NC**, Pearman CM, Caldwell JL, Madders GWP, Eisner DA, Trafford AW, Dibb KM. Calcium in the Pathophysiology of Atrial Fibrillation and Heart Failure. *Front Physiol* 2018; **9**: 1380 [PMID: 30337881 DOI: 10.3389/fphys.2018.01380]
- 49 **Linz D**, Elliott AD, Hohl M, Malik V, Schotten U, Dobrev D, Nattel S, Böhm M, Floras J, Lau DH, Sanders P. Role of autonomic nervous system in atrial fibrillation. *Int J Cardiol* 2019; **287**: 181-188 [PMID: 30497894 DOI: 10.1016/j.ijcard.2018.11.091]
- 50 **Malladi S**, Hamid K, Pendyala NC, Veerapaneni V, Deliwala S, Dubre D, Elian SA, Singh A. Management of stable coronary artery disease and atrial fibrillation with anti-thrombotic therapy: A systematic review and meta-analysis. *Medicine (Baltimore)* 2021; **100**: e27498 [PMID: 35049165 DOI: 10.1097/MD.00000000000027498]
- 51 **Chen Q**, Xu L, Dai Y, Ling Y, Mao J, Qian J, Zhu W, Di W, Ge J. Cardiovascular manifestations in severe and critical patients with COVID-19. *Clin Cardiol* 2020; **43**: 796-802 [PMID: 32562427 DOI: 10.1002/clc.23384]
- 52 **Fanaroff AC**, Li S, Marquis-Gravel G, Giri J, Lopes RD, Piccini JP, Wang TY. Atrial Fibrillation and Coronary Artery Disease: A Long-Term Perspective on the Need for Combined Antithrombotic Therapy. *Circ Cardiovasc Interv* 2021; **14**: e011232 [PMID: 34932388 DOI: 10.1161/CIRCINTERVENTIONS.121.011232]
- 53 **Nguyen TN**, Qureshi MM, Klein P, Yamagami H, Mikulik R, Czlonkowska A, Abdalkader M, Sedova P, Sathya A, Lo HC, Mansour OY, Vanguru HR, Lesaine E, Tsvigoulis G, Loochtan AI, Demeestere J, Uchino K, Inoa V, Goyal N, Charidimou A, Siegler JE, Yaghi S, Aguiar de Sousa D, Mohammeden MH, Haussen DC, Kristoffersen ES, Lereis VP, Scollo SD, Campbell BCV, Ma A, Thomas JO, Parsons MW, Singhal S, Slater LA, Tomazini Martins R, Enzinger C, Gattringer T, Rahman A, Bonnet T, Ligot N, De Raedt S, Lemmens R, Vanacker P, Vandervorst F, Conforto AB, Hidalgo RCT, de Oliveira Neves L, Martins RT, Mora Cuervo DL, Rebello LC, Santiago IB, Lameirinhas da Silva I, Sakelarova T, Kalpachki R, Alexiev F, Catanese L, Cora EA, Goyal M, Hill MD, Kelly ME, Khosravani H, Lavoie P, Peeling L, Pikula A, Rivera R, Chen HS, Chen Y, Huo X, Miao Z, Yang S, Bedekovic MR, Bralic M, Budincevic H, Corredor-Quintero AB, Lara-Sarabia OE, Cabal M, Tenora D, Fibrich P, Herzig R, Hlaváčová H, Hrabanovska E, Hlinovsky D, Jurak L, Kadlcikova J, Karpowicz I, Klecka L, Kovar M, Lauer D, Neumann J, Palouskova H, Reiser M, Rekova P, Rohan V, Skoda O, Škorňa M, Sobotková L, Sramek M, Zakova L, Christensen H, Drenck N, Iversen HK, Truelsen TC, Wienecke T, Sobh K, Ylikotila P, Alpay K, Strbian D, Bernady P, Casenave P, Dan M, Fauchez JM, Gentic JC, Magro E, Sabben C, Reiner P, Bohmann FO, Boskamp S, Mbroh J, Nagel S, Nolte CH, Ringleb PA, Rosenkranz M, Poli S, Thomalla G, Karapanayiotides T, Koutroulou I, Kargiotis O, Palaodimou L, Barrientos Guerra JD, Huded V, Menon B, Nagendra S, Prajapati C, Sylaja PN, Krishna Pramana NA, Sani AF, Ghoreishi A, Farhoudi M, Hokmabadi ES, Raya TA, Kalmanovich SA, Ronen L, Sabetay SI, Acampa M, Adami A, Castellán L, Longoni M, Ornello R, Renieri L, Bigliani CR, Romoli M, Sacco S, Salmaggi A, Sangalli D, Zini A, Doijiri R, Fukuda H, Fujinaka T, Fujita K, Imamura H, Sakai N, Kanamaru T, Kimura N, Kono R, Miyake K, Sakaguchi M, Sakai K, Sonoda K, Todo K, Miyashita F, Tokuda N, Matsumaru Y, Matsumoto S, Ohara N, Shindo S, Takenobu Y, Yoshimoto T, Toyoda K, Uwatoko T, Yagita Y, Yamada T, Yamamoto N, Yamamoto R, Yazawa Y, Sugiura Y, Waweru PK, Baek JH, Lee SB, Seo KD, Sohn SI, Arsovska AA, Chan YC, Wan Zaidi WA, Jaafar AS, Gongora-Rivera F, Martinez-Marino M, Infante-Valenzuela A, Groppa S, Leahu P, Coutinho JM, Rinkel LA, Dippel DWJ, van Dam-Nolen DHK, Ranta A, Wu TY, Adebayo TT, Bello AH, Nwazor EO, Sunmonu TA, Wahab KW, Ronning OM, Sandset EC, Al Hashmi AM, Ahmad S, Rashid U, Rodriguez-Kadota L, Vences MÁ, Yalung PM, Hao DY JS, Pineda-Franks MC, Co CO, Brola W, Debiec A, Dorobek M, Karlinski MA, Labuz-Roszak BM, Lasek-Bal A, Sienkiewicz-Jarosz H, Staszewski J, Sobolewski P, Wiacek M, Zielinska-Turek J, Araujo AP, Rocha M, Castro P, Cruz VT, Ferreira PV, Ferreira P, Nunes AP, Fonseca L, Marto JP, Pinho E Melo T, Rodrigues M, Silva ML, Dimitriade A, Falup-Pecurariu C, Hamid MA, Venketasubramanian N, Krastev G, Mako M, Ayo-Martin O, Hernández-Fernández F, Blasco J, Rodríguez-Vázquez A, Cruz-Culebras A, Moniche F, Montaner J, Perez-Sanchez S, García Sánchez MJ, Guillán Rodríguez M, Jood K, Nordanstig A, Mazya MV, Moreira TTP, Bernava G, Beyeler M, Bolognese M, Carrera E, Dobrocky T, Karwacki GM, Keller E, Hsieh CY, Boonyakarnkul S, Churojana A, Aykac O, Ozdemir A, Bajrami A, Senadim S, Hussain SI, John S, Banerjee S, Kwan J, Krishnan K, Lenthall R, Matthews A, Wong K, Zhang L, Altschul D, Asif KS, Bahiru Z, Below K, Biller J, Ruland S, Chaudry SA, Chen M, Chebl A, Cibulka J, Cistrunk L, Clark J, Colasurdo M, Czapa A, de Havenon A, D'Amato S, Dharmadhikari S, Grimmett KB, Dmytriw AA, Etherton MR, Ezepue C, Farooqui M, Feske SK, Fink L, Gasimova U, Guzik AK, Hakemi M, Hovingh M, Khan M, Jillela D, Kan PT, Khatri R, Khawaja AM, Khoury NN, Kiley NL, Kim BS, Kolikonda MK, Kuhn AL, Lara S, Linares G, Linfante I, Lukovits TG, Lycan S, Male SS, Maali L, Mancin J, Masoud H, Mohamed GA, Monteiro A, Nahab F, Nalleballe K, Ortega-Gutierrez S, Puri AS, Radaideh Y, Rahangdale RH, Rai A, Ramakrishnan P, Reddy AB, Rojas-Soto DM, Romero JR, Rost NS, Rothstein A, Omran SS, Sheth SA, Siddiqui AH, Starosciak AK, Tarlov NE, Taylor RA, Wang MJ, Wolfe J, Wong KH, Le HV, Nguyen QV, Pham TN, Nguyen TT, Phan HT, Ton MD, Fischer U, Michel P, Strambo D, Martins SO, Zaidat OO, Nogueira RG; and the SVIN COVID-19 Global Stroke Registry. Global Impact of the COVID-19 Pandemic on Stroke Volumes and Cerebrovascular Events: A 1-Year Follow-up. *Neurology* 2023; **100**: e408-e421 [PMID: 36257718 DOI: 10.1212/WNL.000000000000201426]
- 54 **Kardalas E**, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect* 2018; **7**: R135-R146 [PMID: 29540487 DOI: 10.1530/EC-18-0109]
- 55 **Alfano G**, Ferrari A, Fontana F, Perrone R, Mori G, Ascione E, Magistrone R, Venturi G, Pederzoli S, Margiotta G, Romeo M, Piccinini F, Franceschi G, Volpi S, Faltoni M, Ciusa G, Bacca E, Tutone M, Raimondi A, Menozzi M, Franceschini E, Cuomo G, Orlando G, Santoro A, Di Gaetano M, Puzzolante C, Carli F, Bedini A, Milic J, Meschiari M, Mussini C, Cappelli G, Guaraldi G; Modena Covid-19 Working Group (MoCo19). Hypokalemia in Patients with COVID-19. *Clin Exp Nephrol* 2021; **25**: 401-409 [PMID: 33398605 DOI: 10.1007/s00467-021-0401-0]

- 10.1007/s10157-020-01996-4]
- 56 **Yan T**, Zhu S, Xie C, Zhu M, Weng F, Wang C, Guo C. Coronary Artery Disease and Atrial Fibrillation: A Bidirectional Mendelian Randomization Study. *J Cardiovasc Dev Dis* 2022; **9** [PMID: 35323617 DOI: 10.3390/jcdd9030069]
- 57 **Batta A**, Hatwal J, Batta A, Verma S, Sharma YP. Atrial fibrillation and coronary artery disease: An integrative review focusing on therapeutic implications of this relationship. *World J Cardiol* 2023; **15**: 229-243 [PMID: 37274376 DOI: 10.4330/wjc.v15.i5.229]
- 58 **Rattanawong P**, Shen W, El Masry H, Sorajja D, Srivathsan K, Valverde A, Scott LR. Guidance on Short-Term Management of Atrial Fibrillation in Coronavirus Disease 2019. *J Am Heart Assoc* 2020; **9**: e017529 [PMID: 32515253 DOI: 10.1161/JAHA.120.017529]
- 59 **Mujović N**, Dobrev D, Marinković M, Russo V, Potpara TS. The role of amiodarone in contemporary management of complex cardiac arrhythmias. *Pharmacol Res* 2020; **151**: 104521 [PMID: 31756386 DOI: 10.1016/j.phrs.2019.104521]
- 60 **Kang Y**, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, Chen Y, Han Y. Cardiovascular manifestations and treatment considerations in COVID-19. *Heart* 2020; **106**: 1132-1141 [PMID: 32354800 DOI: 10.1136/heartjnl-2020-317056]
- 61 **Dofferhoff ASM**, Piscaer I, Schurgers LJ, Visser MPJ, van den Ouweland JMW, de Jong PA, Gosens R, Hackeng TM, van Daal H, Lux P, Maassen C, Karssemeijer EGA, Vermeer C, Wouters EFM, Kistemaker LEM, Walk J, Janssen R. Reduced Vitamin K Status as a Potentially Modifiable Risk Factor of Severe Coronavirus Disease 2019. *Clin Infect Dis* 2021; **73**: e4039-e4046 [PMID: 32852539 DOI: 10.1093/cid/ciaa1258]
- 62 **de Vos CB**, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010; **55**: 725-731 [PMID: 20170808 DOI: 10.1016/j.jacc.2009.11.040]
- 63 **Dobrev D**, Nattel S. New insights into the molecular basis of atrial fibrillation: mechanistic and therapeutic implications. *Cardiovasc Res* 2011; **89**: 689-691 [PMID: 21296897 DOI: 10.1093/cvr/cvr021]
- 64 **Mattson MP**, Chan SL. Calcium orchestrates apoptosis. *Nat Cell Biol* 2003; **5**: 1041-1043 [PMID: 14647298 DOI: 10.1038/ncb1203-1041]
- 65 **Martins RP**, Kaur K, Hwang E, Ramirez RJ, Willis BC, Filgueiras-Rama D, Ennis SR, Takemoto Y, Ponce-Balbuena D, Zarzoso M, O'Connell RP, Musa H, Guerrero-Serna G, Avula UM, Swartz MF, Bhushal S, Deo M, Pandit SV, Berenfeld O, Jalife J. Dominant frequency increase rate predicts transition from paroxysmal to long-term persistent atrial fibrillation. *Circulation* 2014; **129**: 1472-1482 [PMID: 24463369 DOI: 10.1161/CIRCULATIONAHA.113.004742]
- 66 **Xu X**, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Biosci Rep* 2019; **39** [PMID: 30530866 DOI: 10.1042/BSR20180992]
- 67 **Link MS**, Giugliano RP, Ruff CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri MF, Antman EM, Braunwald E; ENGAGE AF-TIMI 48 Investigators. Stroke and Mortality Risk in Patients With Various Patterns of Atrial Fibrillation: Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). *Circ Arrhythm Electrophysiol* 2017; **10** [PMID: 28077507 DOI: 10.1161/CIRCEP.116.004267]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

