

## VIEWPOINT

## COVID-19 and the Beat-To-Beat Heart

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### Introduction

Since December 2019, the coronavirus disease (COVID-19) has caused an exponential increase in acute respiratory syndrome cases and has rapidly spread to more than 210 regions, countries and territories, resulting in considerable morbidity and mortality in more than 100 countries worldwide.<sup>1</sup>

Over this period, several studies describing the clinical and epidemiological characteristics of COVID-19 have been published, allowing rapid dissemination of knowledge and helping health care professionals and policy makers to help patients with the disease.

Among patients with COVID-19, there is a great number of individuals with cardiovascular disease, such as hypertension, coronary artery disease, and heart failure. These collectively represent the main non-communicable diseases in the world, with mortality rates of approximately 0.9% in individuals without comorbidities 10.5% among COVID-19 cases.<sup>2</sup>

Viral infections can lead to cardiac arrhythmias. A previous study showed that 71.9% of the patients with the severe acute respiratory syndrome virus (SARS-CoV) infection developed tachycardia,<sup>3</sup> and COVID-19 patients may develop life-threatening cardiac arrhythmia.

During the infection, COVID-19 patients may have different degrees of hypoxemia or hypoxia. It is known that a prolonged exposure to hypoxia increases the risk for atrial fibrillation (AF), especially in elderly individuals (9% of prevalence), and hence for cardiovascular events. In addition, hypoxic state can increase sympathetic activation, which, in turn,

leads to a pro-arrhythmogenic state, characterized by changes in ventricular action potential duration, leading to ventricular arrhythmias, such as sustained ventricular tachycardia and/or ventricular fibrillation. Additionally, the systemic inflammatory response in COVID-19 can trigger the rupture or erosion of coronary plaques in patients with coronary artery disease, even in patients on anticoagulation therapy.<sup>1</sup>

Recent evidence has shown that nearly 50% of COVID-19 patients in the intensive care unit who developed cardiac arrhythmias had some degree of cardiac injury (without increased troponin I levels), suggesting that other factors than myocardial damage, such as sinus tachycardia, atrial fibrillation, atrial flutter, and monomorphic or polymorphic ventricular tachycardia can be involved in development of arrhythmias in these patients.<sup>4,5</sup>

Evidence has shown that in the first 5-9 days, patients with COVID-19 have a uniform disease progression, without major changes in inflammatory or cardiac biomarkers; however, after 10-24 days, there is an increase in pro-inflammatory cytokines, mainly interleukin-6 and 1, and TNF alpha, along with increases in myoglobin, D-dimer, and C-reactive protein.<sup>5,6</sup> Data from basic and clinical studies have shown that inflammation plays an important role as a risk factor for long QT syndrome and Torsades de Pointes, mainly through the increase of cytokines. This directly affects myocardial electrophysiology and can lead to unfavorable outcomes of cardiac arrhythmia by increasing oxidative stress in cardiomyocytes and resident macrophages, destabilizing electrical activity, leading to prolongation of the cardiomyocyte action potential and causing lethal ventricular arrhythmias.<sup>6</sup> Furthermore, Zhou et. al.<sup>2</sup> demonstrated an increase in D-dimer (a marker of thrombotic events) in patients with an unfavorable outcome (Figure 1).

### Keywords

COVID-19; Arrhythmias, Cardiac; Heart Failure.

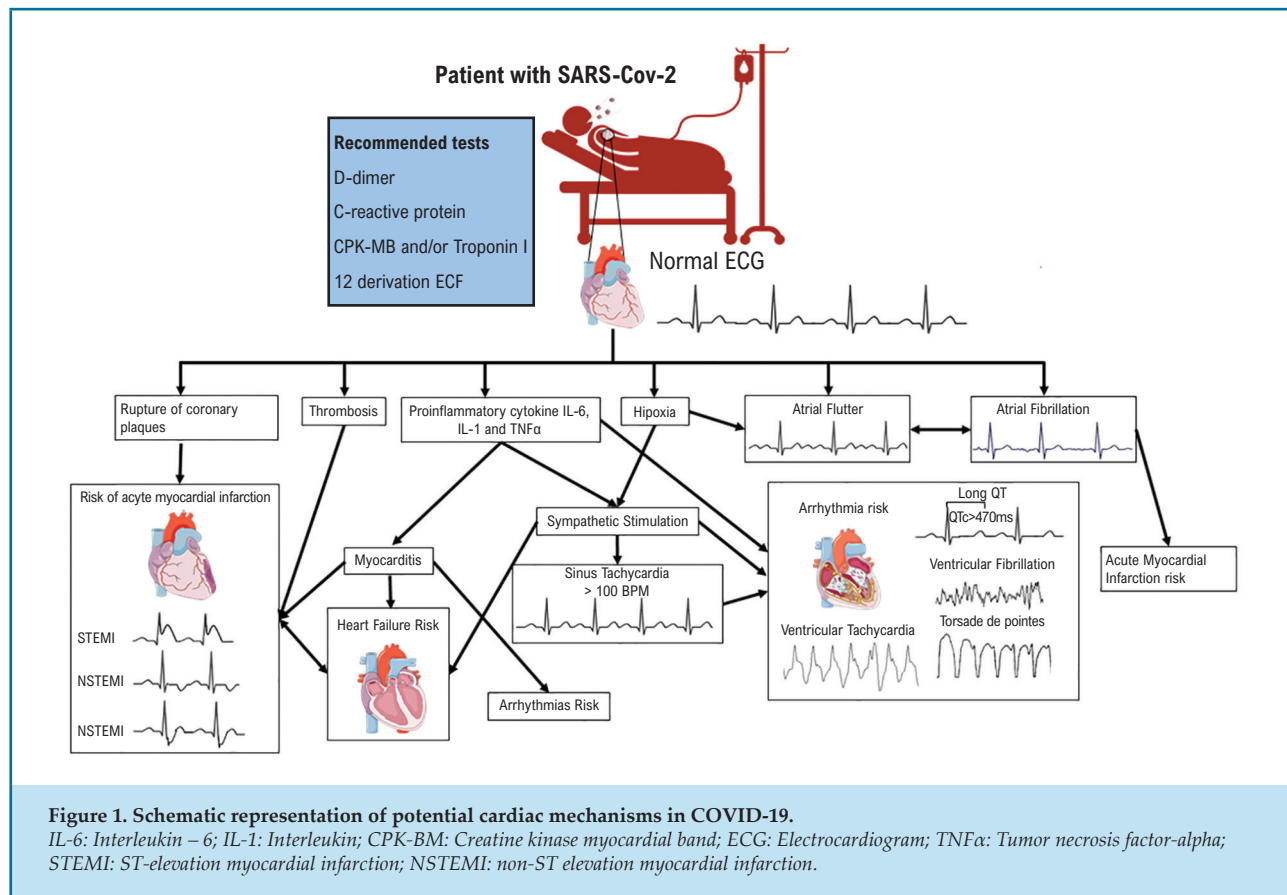
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Electrophysiological studies have demonstrated that during viral infections, there may be a reduction in ATP-dependent potassium channel expression (an outward  $K^+$  current in heart muscle cells that responds to hypoxia and a decrease in ATP).<sup>7</sup> Another experimental study with DENV-3 (dengue virus) showed that at 6 days post-infection, the resting membrane potential was more hyperpolarized, and the current density of L-type  $Ca^{2+}$  was significantly reduced, with a right shift in voltage dependence for channel activation in left ventricular cardiac cells. This means that the membrane potential needs to become more depolarized to activate L-type  $Ca^{2+}$  channels.<sup>8</sup> These inflammatory, oxidative, and ionic responses may in part explain the decrease in cardiac output and stroke volume seen in clinical studies that have shown that cardiac complications are not uncommon in patients with SARS-CoV-2.

It is important to be aware of possible adverse effects of repurposed therapies in COVID-19. For instance, ribavirin and lopinavir/ritonavir specifically interact with other drugs (anticoagulants, antiplatelet

agents, and statins), and are able to increase the risk of prolonged QTc interval and ventricular fibrillation.<sup>9</sup>

Another important indicator of the relationship between cardiac arrhythmia and COVID-19 is the fact that SARS-CoV-2 acts through the angiotensin-converting enzyme receptor 2 (ACE2) and the group of drugs that target this enzyme (angiotensin-converting enzyme inhibitors - ACEI) plays a cardioprotective role in many heart diseases, such as arrhythmia, hypertension, myocardial fibrosis, and cardiac hypertrophy atherosclerosis.<sup>10</sup>

Given the role of hypoxic conditions in the development of cardiac arrhythmias, attention should be given to COVID-19 patients in hospital wards and ICU settings with altered heart rhythm. To avoid life-threatening ventricular arrhythmias, a simple, safe, and low-cost cardiac evaluation can be performed through the measurement of cardiac enzymes (CK-MB and/or troponin I) and electrocardiography.<sup>11</sup> Therefore, the successful management of patients with COVID-19 infection and with known cardiovascular comorbidities depends on a clear understanding of cardiac function, beat-to-beat (Figure 1).

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any thesis or dissertation work.

### Author contributions

Conception and design of the research: Souza DS, Durço AO, Rocha CSG, Conceição LSR. Writing of the manuscript: Souza DS, Durço AO, Rocha CSG, Conceição LSR. Critical revision of the manuscript for intellectual content: Souza DS, Durço AO, Rocha CSG, Conceição LSR.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

## References

1. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac Troponin I in Patients with Coronavirus Disease 2019 (COVID-19): Evidence from a Meta-analysis. *Prog Cardiovasc Dis.* 2020;63(3):390-1. doi: 10.1016/j.pcad.2020.03.001.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet.* 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3.
3. Yu CM, Wong RS, Wu EB, Kong SL, Wong J, Yip GW, et al. Cardiovascular Complications of Severe Acute Respiratory Syndrome. *Postgrad Med J.* 2006;82(964):140-4. doi: 10.1136/pgmj.2005.037515.
4. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol.* 2020;75(18):2352-71. doi: 10.1016/j.jacc.2020.03.031.
5. Dherange P, Lang J, Qian P, Oberfeld B, Sauer WH, Koplán B, et al. Arrhythmias and COVID-19: A Review. *JACC Clin Electrophysiol.* 2020;6(9):1193-204. doi: 10.1016/j.jacep.2020.08.002.
6. Monnerat G, Alarcón ML, Vasconcellos LR, Hochman-Mendez C, Brasil G, Bassani RA, et al. Macrophage-dependent IL-1 $\beta$  Production Induces Cardiac Arrhythmias in Diabetic Mice. *Nat Commun.* 2016;7:13344. doi: 10.1038/ncomms13344.
7. Eleftherianos I, Won S, Chtarbanova S, Squiban B, Ocorr K, Bodmer R, et al. ATP-sensitive Potassium Channel (K(ATP))-dependent Regulation of Cardiotropic Viral Infections. *Proc Natl Acad Sci U S A.* 2011;108(29):12024-9. doi: 10.1073/pnas.1108926108.
8. Kangussu LM, Costa VV, Olivon VC, Queiroz-Junior CM, Gondim ANS, Melo MB, et al. Dengue Virus Infection Induces Inflammation and Oxidative Stress on the Heart. *Heart.* 2022;108(5):388-96. doi: 10.1136/heartjnl-2020-318912.
9. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020;323(18):1824-36. doi: 10.1001/jama.2020.6019.
10. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? *JAMA.* 2020;323(18):1769-70. doi: 10.1001/jama.2020.4812.
11. Doyen D, Mocerí P, Ducreux D, Dellamonica J. Myocarditis in a Patient with COVID-19: A Cause of Raised Troponin and ECG Changes. *Lancet.* 2020;395(10235):1516. doi: 10.1016/S0140-6736(20)30912-0.

