

## Genesis of arrhythmia in the course of COVID-19

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Coronavirus disease 2019 (COVID-19) is associated with severe acute respiratory syndrome (SARS) this connection and effect has been exacerbated by the new strain of coronavirus (SARS-CoV-2) which has rapidly spread across the globe, posing a significant medical challenge [1, 2]. An analysis of various national health records demonstrates that many COVID-19 patients develop cardiac arrhythmias as the disease progresses. Several studies have found that these aberrant rhythms worsen the medical outcome of patients with COVID-19. However, the current medical science is unclear as to how SARS-CoV-2 infection might generate such arrhythmias [3].

The arrhythmia in COVID-19 may occur due to a large range of causes such as damage to the heart muscle, myocardial ischemia as well as in the case of myocarditis [4]. Arrhythmia can also occur in patients who have hypoxia, septic or cardiogenic shock, indications of broad systemic inflammation, or electrolyte problems such as hypokalemia. In addition, in the case of treatment of remdesivir for COVID-19, some cardiac arrhythmias have been documented [5]. Arrhythmias in the course of COVID-19 are a serious problem that occurs both in hospitalized patients and in convalescents who have already had the disease.

Tachycardia is a common symptom reported in COVID-19 patients, from their electrocardiogram results. However, recent reports have demonstrated that bradycardia is prevalent in up to 56% of hospitalized COVID-19 patients with a fever [6]. There is growing evidence and medical investigations suggesting that SARS-CoV-2 is able to infect the specialized cardiac cells known as pacemaker cells.

In healthy individuals, the primary pacemaker of the heart is the sinus node; as part of the heart's conductive system, the node is one of the main electrical regulators of cardiac rate and rhythm. Disruption to the sinus node's structure can cause bradycardia. Researchers have used animal models combined with human stem cell-derived pacemaker cells to further understand this condition and set of effects.

Researchers using a type of pluripotent stem cell (hPSC) called human embryonic stem cells (hESC), have found that SARS-CoV-2 can readily infect pacemaker cells and induce a process known as ferroptosis [7]. Apoptosis, necrosis, autophagy, and other kinds of cell death are all distinct from ferroptosis, which is an iron-dependent cell death. The buildup of fatal lipid species resulting from lipid peroxidation defines the process of ferroptotic

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cell death, which can be avoided by iron chelators — deferiprone, deferoxamine and tiny lipophilic antioxidants — ferrostatin and liproxstatin [8]. Researchers discovered that during the process of ferroptosis the human pacemaker cells produce angiotensin-converting enzyme 2 receptors and other complimentary components that facilitates and improves SARS-CoV-2 ability and frequency to enter cells, thus increasing infected cell rates by SARS-CoV-2 in human cells. These same SARS-CoV-2 infected cells also showed a significant rise in inflammatory immune gene activity. It is hypothesized that pacemaker cells infected with SARS-CoV-2 commence a self-destructive process of ferroptosis, an iron-dependent cell death and that commences early in COVID-19 patients within the sinus node, which explains the high incidence of bradycardia in patients.

Researchers have also investigated whether the damaging consequences of ferroptosis might be reversed by utilizing chelating agents; chemical molecules that closely attach to metal ions. The researchers examined the impact of chelating agents on the elimination of iron from the circulation and thus prevent the ferroptosis process. The chelating agents deferoxamine and imatinib were shown to prevent SARS-CoV-2-induced ferroptosis in the heart's pacemaker cells [7].

From these research findings, it indicated that patients with COVID-19 could theoretically be treated with ferroptosis inhibitors to protect the sinoatrial (sinus node) cells, antiviral drugs that block the effects of SARS-CoV-2 infection in all cell types would be a preferred course of treatment. Although there is a worldwide medical push to protect all organs in both the severe course and the post-COVID-19 syndrome, other treatments do need to be considered.

The development of arrhythmias in the course of COVID-19 can have many reasons, but there is mounting research evidence demonstrating the involvement of pacemaker cells. This highlights the complexity of COVID-19 in the context of the cardiovascular system. Future research will need to be conducted into whether this phenomenon plays an important role among convalescents and patients

struggling with the long-COVID-19 syndrome [9]. There is a need for further clinical and cellular research to clearly understand the mechanisms and the implementation of appropriate treatment strategies for the cardiac and other organs, both protective and symptomatic [10].

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