Review

Cardiovascular Implications of COVID-19 and the QT Prolongation Associated with Pharmacotherapy

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Submission Details:

Submitted: 29 January 2025; Reviewed: 20 February 2025; Accepted: 28 February 2025.

Abstract:

The coronavirus pandemic has significantly impacted a substantial part of the global population, and the cardiovascular repercussions of COVID-19 infection have been unveiled for the first time. While the arrhythmogenic effects of the severe inflammatory syndrome associated with the infection are well-established, another critical cause of arrhythmias, particularly ventricular arrhythmias such as ventricular tachycardia, torsades de pointes, or ventricular fibrillation, which can result in cardiac arrest, is the pharmacological treatment employed to manage the disease in hospitalized patients. Among all arrhythmogenic mechanisms, the QT interval prolongation is the most alarming. This review aims to provide a more in-depth exploration of these effects and the potential mechanisms underlying their occurrence.

Keywords: COVID-19; pharmacotherapy; QT prolongation; arrhythmias.

Citation:

Haj Ali, L.; Dăniluc, L.; Suhov, L.; Pecingina, R.; Ivan, M.V. Cardiovascular Implications of COVID-19 and the QT Prolongation Associated with Pharmacotherapy. *J. Exp. Pharmacol. Toxicol.* 2025, 1, 1-11.

1. Introduction

In December 2019, a pneumonia of unknown origin surfaced in Wuhan, China, with a rapid progression, especially in individuals with pre-existing comorbidities. The virus responsible, identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was isolated from the respiratory system. The disease disseminated quickly, prompting the World Health Organization (WHO) to classify it as a pandemic on March 12, 2020 [1].

The localization of the virus in the airways is facilitated by angiotensin-converting enzyme 2 (ACE2), which functions as a receptor for the spike protein (S). This interaction is subsequently triggered by a series of immune responses. The cellular injury induced by the virus leads to the release of pathogen-associated molecular patterns (PAMPs), which are identified by receptors on macrophages and endothelial cells, such as Toll-like receptors (TLRs), in the extracellular space. This represents one of the mechanisms that activates the cascade of pro-inflammatory cytokine secretion [2].

A malfunction related to interferon (IFN) has been noted, particularly with type 1 IFN, which plays a key role in the initial stages of infection and in the viral replication phase. Elevated levels of type II-IFN have been associated with severe forms of the disease and a poor outcome. In contrast, type III-IFN has been linked to less severe forms of the disease [3]. This disturbance is followed by an overproduction of Interleukin-1, Interleukin-6 (IL-1, IL-6), Tumor Necrosis Factor-α (TNF-α), and other cytokines, which mediate the onset of what is commonly known as the inflammatory storm. The T lymphocytes play a crucial role in SARS-CoV-2 pathogenesis, with CD4+ T cells and CD8+ T cells mediating cytotoxicity, while B lymphocytes contribute to humoral immunity through the secretion of specific antibodies. In more severe cases, an elevation in the levels of C-X-C motif chemokine 10 (CXCL10)/Interferon gamma-induced protein 10 (IP-10), chemokine (C-C motif) ligand 2 (CCL2)/monocyte chemoattractant protein 1 (MCP-1), and Macrophage Inflammatory Protein (MIP)-1A/CCL3 has been observed, and these elevations are linked to an unfavorable prognosis [4].

All of these sequential reactions have a profound impact, particularly on the respiratory and cardiovascular systems. In light of the data mentioned above, this review aims to emphasize the impact of this virus on the cardiovascular system, with a particular focus on aspects related to arrhythmias, especially those associated with QT interval prolongation linked to side effects of COVID-19 pharmacotherapies. **Figure 1**. Represents the main cardiovascular complications of COVID-19 infection.

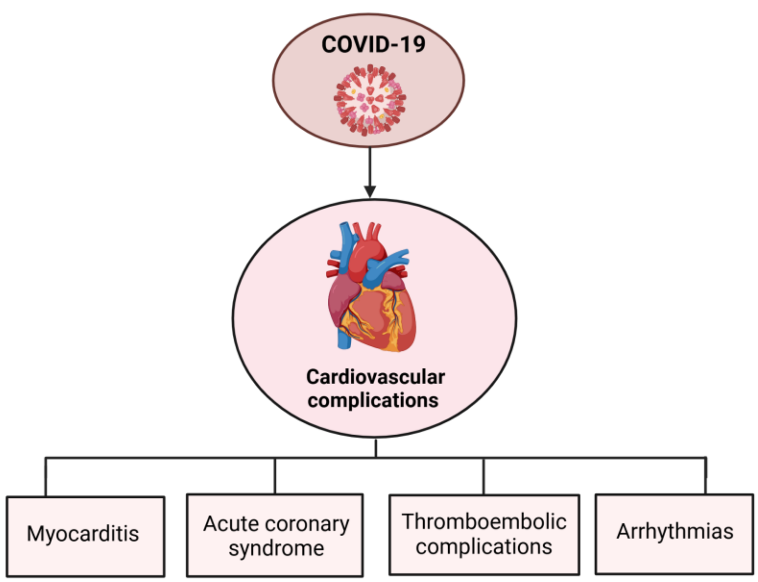


Figure 1. The main cardiovascular complications of COVID-19 infection (created using https://BioRender.com).

2. Cardiovascular complications in Covid-19

2.1. Myocarditis

It refers to the presence of an inflammatory infiltrate within the myocardium. In the context of COVID-19, it presents as part of the inflammatory syndrome affecting multiple organs and systems. This condition is associated with changes in the electrocardiogram and left ventricular (LV) systolic dysfunction, as confirmed by transthoracic echocardiography. Biologically, it is characterized by the elevation of inflammatory markers, N-terminal pro b-type natriuretic peptide (NT-pro BNP), high-sensitivity cardiac troponin I (hs-cTnI), Creatine kinase (CK), and CK-MB (creatine phosphokinase - MB). Clinical manifestations and complications are diverse and may include chest pain, heart failure symptoms, and the onset of arrhythmias [5]. Buckley *et al.* report in a study involving 718,365 patients with COVID-19 that 5.0% developed myocarditis. Among all cases of myocarditis, the mortality rate at 6 months was 3.9% [6].

2.2. Acute coronary syndrome

A potential mechanism contributing to the onset of acute coronary syndrome involves the expression of ACE2 on the vascular endothelium, which leads to endothelial injury, as well as the destabilization and rupture of pre-existing atherosclerotic plaques. The severity of the inflammatory response is also implicated in the occurrence of myocardial infarction. Conditions such as hypoxia, sepsis, fever, and dehydration can exacerbate the risk of an acute coronary event. Moreover, the presence of coagulopathies and the associated thrombotic risk should also be considered [7]. Schiavone *et al.* report in a study including 138 patients with COVID-19, that coronary events occurred in 7.2% of all patients, and in 22.2% of those admitted to the Intensive Care Unit [8].

2.3. Thromboembolic complications

COVID-19 is linked to a hypercoagulable state, with increased fibrinogen and D-dimer levels, and prolonged prothrombin time. Thromboembolic events are more frequent in patients with severe forms of the disease [9]. A study conducted by Lodigiani *et al*. involving 388 patients, with a mean age of 66 years, included 16% who required admission to the intensive care unit (ICU). Thromboprophylaxis was administered to all ICU patients (100%) and to 75% of non-critical patients. Thromboembolic events occurred in 27.6% of ICU patients and 6.6% of non-critical patients. Half of the thromboembolic events were diagnosed within 24 hours of hospital admission. Computed tomography pulmonary angiography (CTPA) was performed on 30 patients, representing 7.7% of the total cohort, with pulmonary embolism confirmed in 10 cases, accounting for 33% of the CTPA procedures [10].

2.4. Arrhythmias

Arrhythmias are among the complications frequently observed during the course of the disease, either resulting from the direct impact of the virus on the heart or as a secondary effect of the inflammatory syndrome. While supraventricular arrhythmias are most prevalent, particular attention should be given to life-threatening ventricular arrhythmias. One key arrhythmogenic mechanism is QT interval prolongation, which may occur either as a result of other cardiac complications or due to the pharmacological treatments administered for disease management [11].

3. QT Prolongation in COVID-19

3.1. The QT interval

Is measured from the onset of the QRS complex to the end of the T wave and represents the duration of both ventricular depolarization and repolarization. Factors influencing depolarization can prolong the QT interval by increasing the duration of the QRS complex. From the J point to the end of the T wave, the interval reflects ventricular repolarization, which can also lead to QT prolongation due to factors that affect ventricular repolarization [12].

3.2. Drugs Associated with QT Prolongation in COVID-19

Prolonged QTc interval and potentially fatal arrhythmias are possible complications induced by drugs, with prior associations to antimalarials, antivirals, and antibiotics [13]. Although these classes of drugs have been utilized for an extended period in medical therapy, and their safety profiles were relatively well-known prior to their application in COVID-19 treatment, the risk of QT interval prolongation is notably elevated in COVID-19 patients. This increased risk can be attributed to several factors, including the interaction of these medications with hypokalemia induced by diarrhea and excessive sweating in COVID-19 patients, as well as the effects of inflammatory cytokines [14]. The mechanisms responsible for QT prolongation induced by pharmacological agents can be varied; however, the most well-established mechanisms involve the blockade of human ether-a-go-go-related-gene (hERG) and inwardly rectifying potassium (Kir2.1) channels [15]. Furthermore, this adverse effect seems to be more prevalent in elderly patients, those already receiving antiarrhythmic treatment, as well as in individuals with severe underlying conditions such as multiple organ failure, metabolic disorders, and sepsis [16]

3.2.1. Antimalarials

Among antimalarials, *in vitro* studies have revealed the antiviral activity of aminoquinolines particularly chloroquine and hydroxychloroquine (Figure 2) [17]. This antiviral activity appears to be mediated by the perturbation of pH at the endosomal level, leading to sub-glycosylation of the ACE2 receptors, which are involved in facilitating the entry of COVID-19 into the respiratory tract [18]. Thus, it is proposed that aminoquinolines may be beneficial in the prevention of COVID-19 due to their action on ACE2, as well as in the treatment of already infected patients, owing to their potential to attenuate the inflammatory response and exert an immunomodulatory effect [19]. Chloroquine and hydroxychloroquine, can cause QT prolongation by binding to and inhibiting the potassium channel protein encoded by the KCNH2 gene, thus blocking the fast component of the delayed rectifier potassium current (IKr). This effect may be exacerbated by other risk factors such as congenital long QT syndrome, hypokalemia, and hypomagnesemia [20]. A study by Mercuro *et al.* shows that a QT interval prolongation >500 ms was more prevalent with the use of certain medications. In particular, 31% of patients who were treated with a loop diuretic experienced this effect, compared to 12% in those not taking a loop diuretic. Moreover, 21% of patients receiving quinolones and azithromycin developed QT prolongation [21]. In a retrospective study conducted by Chorin *et al.* involving 251 patients treated with a combination of hydroxychloroquine (initially 2x 400 mg on day one, followed by 2x200 mg for 4 days) and azithromycin (500 mg single dose for 5 days), with electrocardiogram monitoring before and during treatment, a QTc prolongation >500 ms was observed in 13% of patients. Those with significant QTc interval prolongation had lower body weight, a higher incidence of kidney disease, and greater exposure to amiodarone [22]. In addition, the concomitant administration of quinolones with specific medications, such as clarithromycin, isoniazid, piperacillin-tazobactam, rosuvastatin, and tramadol, has been demonstrated to create conditions that predispose to the exacerbation of this adverse effect [23].

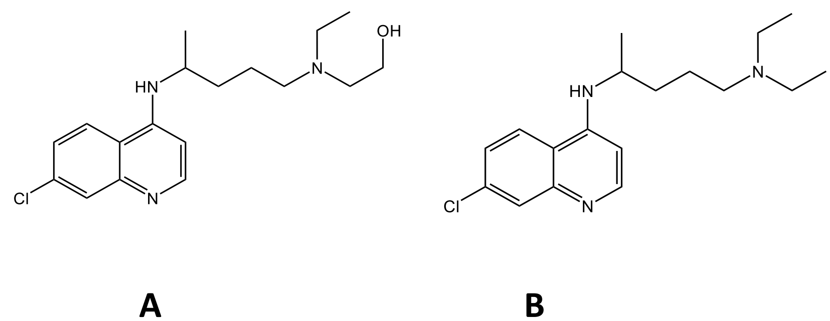


Figure 2. Chemical structures of: A) Hydroxychloroquine, B) Chloroquine. The figures were performed using KingDraw V.3.6.1

3.2.2. Antivirals

Lopinavir/Ritonavir

Lopinavir (Figure 3) and ritonavir are antiretroviral protease inhibitors, with ritonavir increasing the half-life of lopinavir, thereby enhancing its pharmacological effect when used together. This combination exerts a synergistic action. Lopinavir inhibits the viral 3-chymotrypsin-like protease (3CLpro). Clinical studies have demonstrated therapeutic benefits of this combination in individuals with mild forms of the disease. However, concurrent administration of lopinavir/ritonavir with amiodarone or furosemide significantly increases the risk of QT interval prolongation and secondary torsades de pointes. Additionally, hypokalemia is a notable risk factor that may further exacerbate these arrhythmogenic effects [24].

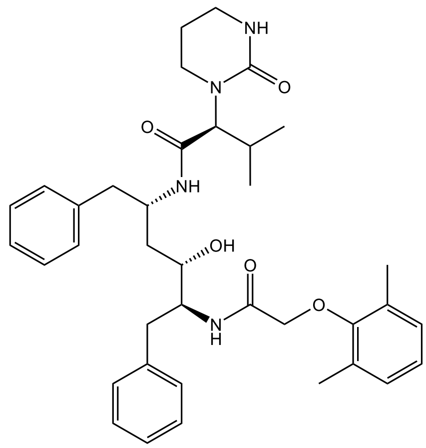


Figure 3. Chemical structure of Lopinavir (figure performed using KingDraw V.3.6.1.).

Remdesivir

Remdesivir (Figure 4) is an adenosine analog that integrates into viral RNA, causing premature chain termination and inhibiting viral replication. Sinus bradycardia is frequently observed at the initiation of treatment, while QT interval prolongation is more likely to occur in the presence of hypokalemia or when used in combination with other medications, such as azithromycin [25]. Intravenous administration of remdesivir can result in rapid peak plasma concentrations, thereby increasing the risk of arrhythmias. Therefore, it is advisable to monitor the electrocardiogram [26].

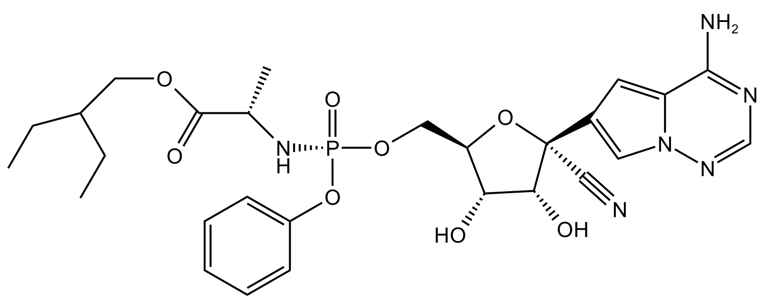


Figure 4. Chemical structure of Remdesivir (figure performed using KingDraw V.3.6.1.).

Favipiravir

Favipiravir (Figure 5) selectively inhibits RNA-dependent RNA polymerase (RdRP). It integrates in place of guanine and adenine, leading to the inhibition of viral replication. Within the cell, favipiravir is converted into its active phosphorylated form, which is recognized by RdRP [27]. A study conducted by Karadavut *et al.* evaluated the effect of Favipiravir compared to hydroxychloroquine on electrocardiogram changes. It found that 19.8% of patients treated with Favipiravir experienced arrhythmic events, while 13.9% of those treated with hydroxychloroquine did. In the Favipiravir group, the most common arrhythmia was sinus bradycardia, which accounted for 65% of cases, followed by grade III heart block in 20%. In contrast, among patients treated with hydroxychloroquine, 69% of those with arrhythmias had a prolonged QT interval. A smaller proportion of Favipiravir-treated patients experienced this effect [28].

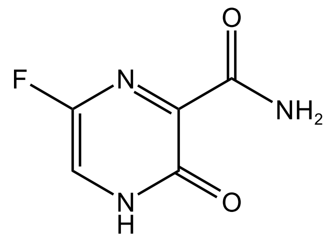


Figure 5. Chemical structure of Favipiravir (figure performed using KingDraw V.3.6.1.).

3.2.3. Antibiotics

Azithromycin

Azithromycin (Figure 6) is a macrolide antibiotic, a mild inhibitor of cytochrome P450, and also exhibits immunomodulatory and anti-inflammatory properties. This positions it as a potential candidate for the treatment of viral diseases, including Zika, Ebola, influenza, and COVID-19 [29, 30]. Connell *et al.* investigated the effects of combining hydroxychloroquine and azithromycin, finding that 21% of patients had a QTc >500 ms. However, 65% of these patients were also receiving other medications with the potential to prolong the QT interval [31]. In a study where all patients received hydroxychloroquine, and 59% were treated with the hydroxychloroquine/azithromycin combination, the majority of patients had at least one comorbidity. Among those on hydroxychloroquine monotherapy, 19% developed a QTc interval greater than 500 ms, while 21% of those receiving the combination of hydroxychloroquine and azithromycin experienced QTc >500 ms [21].

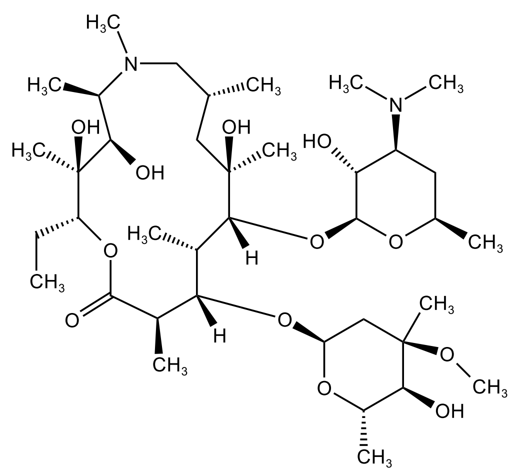
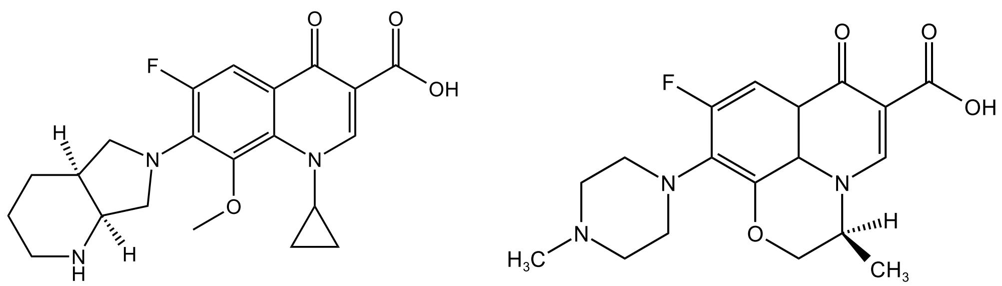


Figure 6. Chemical structure of Azithromycin (figure performed using KingDraw V.3.6.1.).

Fluoroquinolones

In the case of a bacterial infection, the use of fluoroquinolones may be considered; they have the potential to cause bradyarrhythmias or QT interval prolongation [32, 33]. Sertbas *et al.* conducted a retrospective study with 193 patients, divided into four groups based on the medications they received: group 1 received favipiravir, group 2 received favipiravir plus hydroxychloroquine, group 3 received favipiravir plus moxifloxacin, and group 4 received favipiravir, moxifloxacin, and hydroxychloroquine. While mild QT interval changes were noted in groups 1 and 2, significant increases in the QT interval were observed in groups 3 and 4 [33].



A **B**

Figure 7. Chemical structures of**:** A) Moxifloxacin, B) Levofloxacin (the figures were performed using KingDraw V.3.6.1.).

5. The risk management of QT prolongation in COVID-19

The occurrence of QT prolongation is influenced by several factors, including electrolyte imbalances, bradycardia, pre-existing renal and hepatic diseases, as well as demographic factors such as age over 65 and female gender [34]. Therefore, it is advised to identify the risk factors and conduct an electrocardiogram (ECG) prior to initiating treatments associated with the risk of QT prolongation. If the patient presents a QT interval exceeding 500 ms, the initiation of therapy associated with QT prolongation should generally be avoided, except in cases where the administration of these drugs is deemed essential. In these instances, drug administration should be carried out under continuous ECG monitoring and regular assessment of serum potassium levels, which should be maintained above 4 mmol/L [35]. Additionally, it may be prudent to consider the preventive administration of magnesium to reduce the risk associated with QT prolongation [36]. It is also recommended to administer the lowest effective dose of drugs known to cause this adverse effect, with dose adjustments made throughout the treatment based on ECG monitoring, and to avoid combining medications that are known to induce the prolongation of QT interval [37, 38]. A measure that may be taken in cases of QT interval prolongation is the administration of lidocaine and mexiletine; this can be justified by the fact that both antiarrhythmic drugs, which block the late sodium current, have been shown to counteract the blockade of hERG channels [39, 40].

6. Conclusions

COVID-19 is a multisystem disease that affects various organs, with a notable impact on the cardiorespiratory system. Cardiovascular complications, in addition to those directly related to the disease, can also result from pharmacological treatments. The most concerning of these effects is QT interval prolongation, which increases the risk of sudden cardiac death due to ventricular arrhythmias. Therefore, it is crucial to monitor the electrocardiogram in these patients to enable early detection of arrhythmic risk and the timely implementation of preventive interventions.

Author Contributions:
Conceptualization, [L.H.A. and M.V.I.]; Methodology, [L.H.A.]; Validation, [L.D. and M.V.I.]; Writing—Original Draft Preparation, [L.H.A. and L.S.]; Writing—Review & Editing, [M.V.I. and R.P.]; Visualization, [L.H.A and L.S.]; Supervision, [M.V.I.]. All authors have read and agreed to the published version of the manuscript.

Funding:
This research received no external funding.

Conflicts of Interest:
The authors declare no conflict of interest.

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