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Risk of long *QT* syndrome in novel coronavirus COVID-19

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Abstract

The article is devoted to the risk of cardiovascular disease in coronavirus infection. In March 2020, the World Health Organization announced the COVID-19 pandemic. The virus set many tasks for practicing doctors, including the study of its pathogenesis and the creation of a therapy suitable for all patient groups. This paper presents information about cellular entry of the coronavirus, the development of cardiovascular diseases, in particular, the heart, and the latest data on experimental therapy with hydroxychloroquine. Coronavirus has been shown to affect the synthesis of angiotensin 2, which increase the *QT* interval. At the same time, the combination therapy using chloroquine and azithromycin caused a critical prolongation of the *QT* interval in some cases. On 4 July 2020, WHO accepted the Solidarity Trial's International Steering Committee recommendation has stop the trial of these drugs. Cardiologists should review the latest information on the effects of coronavirus on the cardiovascular system and based on this, make recommendations the management and treatment of severe patients.

Keywords: COVID-19, *QT* interval, hydroxychloroquine, angiotensin.

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Introduction

At present, many articles have been published in leading medical journals and online resources on the efficacy of coronavirus infection COVID-19 treatment in different groups of patients, and many studies are still being performed. Although some of these studies are contradictory, but the results obtained enable to develop certain recommendations on patient management.

The group of patients with cardiovascular diseases, which are the leading cause of death and disability throughout the world, is of particular interest. The June 15, 2020 release of the US Centers for Disease Control Weekly Morbidity and Mortality Report describes demographic characteristics, comorbidities, symptoms, and outcomes for 1,320,488 laboratory-confirmed COVID-19 cases as of May 30, 2020. A total of 184,673 patients (14%) were hospitalized, 29,837 (2%) were admitted to the intensive care unit, and 71,116 (5%) patients died. It was found that cardiovascular diseases (32%) were the most frequent among 287,320 (22%) cases with data on individual comorbidities. The hospitalization rate was 6 times higher, and the death rate was 12 times higher among patients with concomitant diseases [1].

Pathogenesis of COVID-19 and Its Relationship with Angiotensin

Despite the fact that COVID-19 has the form of a respiratory viral infection, the pathogenesis also includes the links of the cardiovascular system. The virus enters the cell by endocytosis, attaching the peplomer protein to the receptor, angiotensin-converting enzyme 2 (ACE2). ACE2 is also expressed in the cardiovascular system, in addition to the respiratory system, namely in the heart, which causes myocardial damage. In particular, damage includes the processes involving disruption of the ACE2 signaling pathways. Animal studies revealed that when infected with the SARS-CoV virus, the cellular content of ACE2 decreased, a cytokine storm began, and myocarditis developed [2]. However, the occurrence and severity of myocardial lesions vary among patients.

As the cell is destroyed with the release of new viral particles, ACE2 cannot perform its function in full due to the lack of receptors. As a result, almost

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the entire volume of angiotensin-1, formed from angiotensinogen, is sent for synthesis of angiotensin-2 under the action of the ACE, which explains its high blood content in COVID-19 patients [3]. A further increase in Na reabsorption and K secretion leads to hypokalemia, impaired repolarization of cardiomyocytes, and prolongation of the *QT* interval with the development of arrhythmias. Lack of proper therapy can lead to sudden cardiac death.

High levels of angiotensin-2 should theoretically be associated with high blood pressure in SARS-CoV patients. However, all studies do not confirm this hypothesis. The mean age of patients hospitalized in Lombardy and New York was 63 years, and the percentage of people with established hypertension did not exceed that in the general population. Since the information was obtained in the course of research based on general monitoring, this issue remains debatable.

The American College of Cardiology, the American Heart Association, and the Heart Failure Society have a cautious stance. They published a joint statement that recommends the intake of inhibitors of the renin–angiotensin–aldosterone system if clinically indicated. Their views are shared by major international scientific communities, including the International Society of Hypertension, the European Society of Hypertension, the European Society of Cardiology, the Canadian Cardiovascular Society, and Canadian Heart Failure Society [4].

Already inside the cell, endosomes mature and function, requiring an acidic environment. It is supported by Na^+–H^+-exchange transport, similar to Na^+–Li^+-exchange transport. Accelerated operation of exchangers with active entry of H^+ ions leads to rapid acidification of the endosome and early decapsidation (uncoating) of enveloped viruses that include the coronavirus. However, this should be proven for it. This mechanism has already been identified in influenza A virus and human immunodeficiency virus [5]. There was an association between the rate of Na^+–Li^+-exchange transport in the erythrocyte membrane (characteristic genetically determined by 80%) and an increase in the *QT* interval in treatment of extrasystole with the antiarrhythmic drug class I propafenone [6].

Therapy for Coronavirus Infection and the QT Interval

The arrhythmogenic effect was studied in a group of 138 patients hospitalized with COVID-19. Arrhythmia was reported in 17% of the total number of patients, and 16 of 36 patients referred to the intensive care unit [7]. The risk associated with COVID-19 has been described for patients with various hereditary arrhythmia syndromes, including long *QT* syndrome with a risk of torsades de pointes–type polymorphic ventricular tachycardia [changes in the electrocardiogram (ECG) resemble the coils of a pointe band].

The determining factor in malignant arrhythmias in patients with long *QT* syndrome is the use of one and/or more *QT*c-prolonging drugs in case of a COVID-19 infection. Many of these drugs used for both cardiac and other indications are capable of blocking cardiac K-channels of cardiomyocytes, disrupting ventricular repolarization, with subsequent elongation of the *QT* interval and the risk of malignant arrhythmia. Many drugs can also affect the pharmacokinetics, for example, by inhibiting cytochrome P450 3A4 (CYP3A4), which can further increase the plasma levels of *QT*-prolonging drugs.

Chloroquine and hydroxychloroquine were considered as potential drugs in the therapy of COVID-19 in the early months of the new coronavirus infection by researchers and medical practitioners.

Chloroquine is one of the most widely used antimalarial drugs in the world. It has also been investigated as a potential broad-spectrum antiviral drug. It affects the final glycosylation of ACE2, eliminating infection [8]. However, chloroquine is similar to quinidine (chinidinum). Although it is used as an antiarrhythmic drug for the Brugada syndrome and idiopathic forms of ventricular fibrillation, the drug is also known for its side effect of *QT* interval elongation. However, the effect of chloroquine to increase the *QT* interval is mild and, in general, it does not lead to clinically significant *QT* elongation in patients without long *QT* interval syndrome [9].

Hydroxychloroquine (sulfate) is a less toxic chloroquine derivative. It is widely used in the treatment of chronic autoimmune diseases without significant influence to ECG parameters. Chloroquine and hydroxychloroquine have recently been shown to inhibit SARS-CoV-2 infection *in vitro* effectively [10].

Both chloroquine and hydroxychloroquine are metabolized by CYP3A4, so COVID-19 treatment with both of these drugs can be combined with additional antiviral drugs such as ritonavir and lopinavir (potent drugs that inhibit CYP3A4; the combination is associated with *QT* interval elongation).

Azithromycin is used as a macrolide antibiotic. It is further investigated for the presence of antiviral properties, as well as low inhibition of CYP3A4 and associated elongation of the *QT* interval. The effectiveness of remdesivir against many other viruses is currently being analyzed. Thus, the combination of hydroxychloroquine with these drugs can

lead to higher plasma levels and significant elongation of the *QT* interval. The α-blocking effect of hydroxychloroquine that leads to arterial hypotension has been noted.

The possibility of prescribing hydroxychloroquine alone or in combination with other antiviral drugs for the treatment of COVID-19 was first studied in the international clinical study Solidarity initiated by the World Health Organization (WHO) and its partners.

In a study conducted at the Cedars-Sinai Medical Center (Los Angeles, CA), 98 patients were chosen, 73 were infected with the SARS-CoV virus, and 25 were followed up to confirm the diagnosis. Azithromycin was prescribed in 28% of patients, hydroxychloroquine in 10%, and the combination thereof was prescribed in 62% of patients. It was found that the elongation of the *QT*c interval reached a critical level, *QT*c was 500 ms or higher (with a *QRS* complex lower than 120 ms), *QT*c was 550 ms or higher (with a *QRS* complex of 120 ms or lower) in 12% of patients. *QT*c values were found to be the highest in the combination of hydroxychloroquine and azithromycin group, and *QT*c elongation by 18 ms was recorded in the combination therapy group, whereas with azithromycin alone, elongation by only 1 ms occurred [11]. Although the risk of torsades de pointes–type polymorphic ventricular tachycardia is very low when hydroxychloroquine is used alone or in combination, it can be much higher in patients hospitalized with COVID-19 infection, as well as in patients with metabolic disorders, organ failure, or in case of administration of other drugs that increase the risk of drug interaction.

Similar concerns are noted in recent studies, and clinical cases have started to be described, where the authors tried to find an approach to such comorbid patients. The need to prescribe a course of intravenous lidocaine or mexiletine after using a combination of hydroxychloroquine with azithromycin is being published. The authors describe a case when the *QTc* was possible to reduce from 620 to 550 ms within half an hour following one injection [12].

A special group is consisted of patients with a slowdown in intraventricular conduction, with blockages of the bundle branch and ventricular pacing with a pacemaker. Their duration of the *QT* interval is increased due to the expansion of the *QRS* complex, but this does not mean that they are automatically included in the group of patients with high arrhythmic risk. When calculating the *QT* interval duration in such a situation, the Bogossian formula is most convenient ($QTc = QTc_{LBBB/ECS} - 50\% \times QRS_{LBBB/ECS}$[1]) or the formula $QTc = QTc -$ (*QRS* – 100 ms). Thus, the *QT* interval of a patient with constant ventricular pacing (with a baseline heart rate of 60 per minute) on an ECG may exceed 500 ms, but its significant part will be presented by a deformed *QRS* complex. When using the Bogossian formula, *QT*c = 540– (200 × 50%) = 440 ms, which is within the normal range of values and does not require specific therapy [13].

Recommendations from International Associations

As experimental drug treatment without proven efficacy is chosen for COVID-19, it is recommended to focus on reliable drug evaluation in clinical trials whenever possible. At the same time, they should reduce the risk for patients with a known and predictably high risk of torsades de pointes–type polymorphic ventricular tachycardia in order to avoid even greater elongation of the *QT* interval. All this led to the formulation of a number of recommendations of the cardiological associations both in Russia [14] and internationally, in particular, the Canadian Heart Rhythm Society [15], including the following provisions for monitoring the *QT* interval.

– Before starting treatment with azithromycin, chloroquine/hydroxychloroquine, lopinavir + ritonavir, the duration of the *QT* interval, corrected by the Bazett formula (*QTc*) should be assessed; it should not exceed 480 ms; further monitoring should be performed once in every 5 days or in case of complaints.

– If *QTc* is 500 ms or higher, reassessment should be performed after correcting electrolyte disorders or discontinuing other drugs that elongate the *QT* interval. It is necessary to seek specialist advice and assess carefully the benefits and risks of the therapy prescribed if the *QTc* remains 500 ms or higher.

– If *QTc* is 470 ms or higher (males) or 480 ms or higher (females) but lower than 500 ms, antimicrobials should be prescribed, and a repeated ECG after 48 h should be considered.

– If patients have a clinical severe illness or are taking several medications that can increase *QT*, it is recommended to recheck the *QT*c 48 h after the start of antimicrobial therapy.

– If *QT*c increases by 60 ms or higher or becomes 500 ms or higher on follow-up, the administration of antimicrobials should be stopped and the patient should seek specialist advice.

– Daily ECG recording should be taken for severe COVID-19 infection.

QTc_{LBBB}—corrected duration of the *QT* interval with left bundle branch block; ECS—electrocardiosignal; QRS_{LBBB}—duration of the *QRS* complex in left bundle branch block.

Conclusion

WHO recently announced the discontinuation of the trial of hydroxychloroquine and lopinavir/ritonavir as per the recommendations of the International Steering Committee for the Solidarity Clinical Trial of July 4, 2020. Preliminary trial results with regard to the use of hydroxychloroquine and lopinavir/ritonavir treatment produce little or no reduction in mortality rates of hospitalized COVID-19 patients when compared to clinical practice standards. In light of this, the question of searching more and more new treatment methods for patients with cardiovascular pathology remains relevant, requiring practitioners, and researchers to select not only effective, but also safe therapy.

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