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## **The Effect of COVID-19 on Cardiovascular Diseases and the Need for Beta-Blocker Dose Modification**

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## **ABSTRACT**

**Introduction and purpose:** The Coronavirus Disease 2019 (COVID-19) and its effects on patients remain the main focus of many researchers across the world. One of the challenges faced by medical professionals is the impact of the infection on the course of chronic diseases. Manifestations of the infection are observed mainly in the respiratory system, but other organs, particularly the cardiovascular system, are also frequently affected. Recent data indicates that arterial hypertension and cardiovascular diseases (CVD) are the most prevalent comorbidities in patients suffering from SARS-CoV-2 infection.

**Material and methods:** This study aimed to investigate the impact of SARS-CoV-2 infection on the cardiovascular system. Apart from the literature review we conducted a retrospective study to check the necessity for modification of chronic treatment in patients with CVD after recovery from COVID-19, particularly regarding the use of beta blockers.

**Results:** Using the Mann-Whitney U test a positive correlation ( $p = 0.04$ ) was found between the presence of coronary artery disease before COVID-19 and a need for an increase in the beta-blockers dose.

**Conclusions:** Patients with preexisting CVD should be closely monitored during and after recovery from SARS-CoV-2 infection due to the higher risk of complications and the potential need for modifications in the treatment of chronic diseases. Patients with coronary artery diseases may need an increase in beta-blocker doses after recovery. This is an important issue for future research, especially in the context of long COVID-19.

**Keywords:** beta-blockers; SARS-CoV-2; cardiovascular diseases; COVID-19 infection

## **INTRODUCTION**

The Coronavirus Disease 2019 (COVID-19) and its effects on patients remain the main focus of many researchers across the world. The mechanism of the infection is nowadays better understood, in comparison to the beginning of the pandemic. However, the influence of the virus on a patient's health, even after the recovery needs to be further examined. One of the many challenges faced by medical professionals is the impact of the infection on the course of

chronic diseases. In many cases, the treatment of chronic conditions has to be adapted, specifically in the context of cardiovascular diseases (CVD).

The COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily affects the respiratory system, but extensive research demonstrates its potential effects on other organs. (1) The virus infects the cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. Besides the respiratory system, the cardiomyocytes and endothelial cells have been identified to have higher expression levels of ACE2. (1) Therefore, due to viral infection, an inflammation in blood vessels can be observed, which leads to dysfunction of the endothelium. Furthermore, ACE2 is a component of the renin-angiotensin-aldosterone system, which heavily influences the homeostasis of the cardiovascular system and plays an important role in its regulation. (6) Consequently, patients with underlying heart diseases are at a higher risk of serious complications after acquiring COVID-19. (2) Recent data has shown that almost one-third of patients, that were hospitalized due to COVID-19, have a history of cardiovascular disease (CVD). (3–5) SARS-Cov-2 infection also leads to various cardiovascular complications, such as myocardial injury, arrhythmias, and coagulation abnormalities. (6)

Recently long COVID-19 has emerged as one of the most frequently stated health problems. WHO defined post-COVID-19 conditions as symptoms, including fatigue, shortness of breath, and cognitive dysfunction, which occur during 3 months after the onset of COVID-19 and last for at least 2 months. (7) Medical care and follow-up examinations are needed, especially in patients, with potential risk factors. (8) In many cases the treatment of chronic diseases has to be adjusted. Lots of patients develop chronic complications that also have to be managed. In this study, we focus on the requirement for the increase of beta-blocker dose or treatment initiation following a recovery from SARS-CoV-2 infection.

Beta-blockers are widely used in the treatment of CVD, such as high blood pressure, angina pectoris, heart failure, or arrhythmias. Drugs from this group block the effects of the hormone adrenaline, by binding to beta receptors. (9) There are two types of these receptors, beta-1, and beta-2, which are found in different tissues. Selective beta-blockers, such as metoprolol, bisoprolol, and nebivolol, preferentially block beta-1 receptors, which are located mainly in the heart and kidneys. These characteristics are used in the treatment of CVD. (10) There are lots of potential benefits of beta-blocker administration in the treatment of COVID-19. (10–13) They reduce renin concentration by inhibiting the sympathetic system activity and decreasing angiotensin II concentration, which may slow down or reverse remodeling processes in the

heart tissue. (13) Other research proved that beta-blockers may reduce cytokine storm, which may be important during acute COVID-19(13) and be potentially effective in sepsis and septic shock. (14) From a cardiological point of view this group of drugs is well-established in arrhythmia prevention and control. (15) It is significant to observe, that lots of drugs used in COVID-19 protocol therapy have the potential for QT prolongation, and beta-blockers may be used as prevention therapy. (15)

Based on a literature review we conducted a retrospective study to investigate the need for additional treatment with beta-blockers or changes in previous dosage after recovery from a SARS-CoV-2 infection.

## **MATERIAL AND METHODES**

The database was prepared using the records from Wroclaw University Hospital. We screened our registry, which contained 1952 subjects hospitalized due to COVID-19 from October 2020 to February 2022, for patients with previously diagnosed CVD or with risk factors for the development of CVD (defined as arterial hypertension, history of smoking, hypercholesterolemia, diabetes, and obesity). In our study, the term CVD, based on ESC Guidelines, was defined as the presence of coronary heart disease, stroke, TIA, and arrhythmias. (16) Inclusion criteria were age above 18 and the need for beta-blocker treatment before or after recovery from COVID-19. Collected data included patient gender, age, medical history, medication taken before and after COVID-19, course of COVID-19, ECG, and vital signs (respiration rate, pulse rate, and blood pressure measurements). For retrospective analysis, a complete chart review was also performed. This approach was chosen to allow a deeper insight into additional chronic diseases and risk factors of CVD.

A total of 70 cases that matched the inclusion criteria, were selected. The patients were then divided into two groups based on the changes in beta-blockers dosing regimen after recovery from COVID-19. The first group consisted of 50 patients who were treated with beta-blockers before the infection without the need for a dose increase after SARS-CoV-2 infection. The second group included 20 patients in which an increase in the dose was necessary. The baseline characteristics of the patients are presented in Table 1.

	Group 1	Group 2
Men	24 (48%)	13 (65%)
Women	26 (52%)	7 (35%)
Mean age	70	66
Chronic diseases and risk factors		
Hypertension	39	13
Lipid disorders	4	2
Heart failure	8	2
Coronary artery disease	8	1
Atrial fibrillation	12	1
Valvular heart diseases	6	0
Type 2 diabetes	16	5
Smoking	16	5
Obesity	5	5
Stroke	8	2

Table 1: Baseline characteristics

After verification with the chi-square test, a non-parametric Mann-Whitney U test was performed to compare both groups investigated in our study. To perform analyses, the StatSoft Statistica 13 software was used. A p-value < 0.05 was considered significant.

## RESULTS

The results of the performed analyses are summarized in Table 2. We found a positive correlation ( $p = 0.04$ ) between coronary artery disease history before COVID-19 and an increase in beta-blocker doses after recovery. This correlation was statistically significant only in patients with pre-existing CVD. There was no evidence that other comorbidities influenced the beta-blocker treatment.

<b>Variable</b>	<b>p value</b>
Hypertension	0.27
Atherosclerosis	0.27
Lipid disorders	0.80
Type 2 diabetes	0.57
Heart failure	0.52
<b>Coronary artery disease</b>	<b>0.04</b>
Atrial fibrillation	0.07
Valvular heart disease	0.11
Venous thromboembolism	0.51
Chronic venous insufficiency	0.57
Chronic lower limbs ischemia	0.55
Stroke	0.53
Smoking	0.82
Obesity	0.11
Sum of diseases group 1	0.07
Sum of diseases group 2	0.11

Table 2:

Mann-Whitney U Test with continuity correction

Relative to variable: Dose modification

The marked results are significant from  $p < 0.05000$

Aside from statistical results, we analyzed other patients' records, as described in Material and Methods. We noted an increased amount of tachycardia episodes during the infection among patients in both groups. Significantly, in the second group, which identified patients who needed additional beta-blocker treatment after recovery, 60% suffered from tachycardia. In contrast, in the first group, these episodes occurred in a minority of cases (12%). These results suggest that

patients, who experienced episodes of tachycardia, needed either to start beta-blocker treatment or to intensify current therapy after recovery from infection.

## **DISCUSSION**

Recent studies show that COVID-19 could cause various cardiovascular complications and lead to worsening of heart function. (5,17,18) Evidence from research, in which patients were undergoing cardiac magnetic resonance (CMR) about 2 months after recovery from COVID-19, has shown a relatively high prevalence of subclinical left ventricle dysfunction among those patients. (19) Comparable study of 134 patients investigated with speckle tracking echocardiography (STE), also about 2 months after recovery from infection, described subclinical dysfunction in the left ventricle in one-third of individuals. (20) The worsening of heart function could be associated with continuing myocardial inflammation, which, according to a paper by Valentina O Puntmann et al (21), may be seen in 60% of patients diagnosed using CMR about 2,5 months after COVID-19. Above mentioned studies support our thesis, that patients with a history of CVD are at increased risk for worse clinical outcomes as a consequence of increased oxygen demand and cardiovascular stress during the infection. In many cases, COVID-19 may contribute to cardiac damage and decompensation of CVD. (22) As a result of this increased beta-blockers treatment could be needed, even after the recovery.

Our observations suggest that the general tendency to tachycardia during and after COVID-19 causes an increased demand for beta blockers. There are several possible explanations for arrhythmias. Firstly, any systemic infection or fever can temporarily increase the heart rate. Other explanations for this are hypoxia, worsening of coronary perfusion, and direct damage to the heart muscle. Both ventricular and atrial arrhythmias might occur due to necrosis caused by viral myocarditis. (23) Hypokalemia can be observed due to the interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system. Consequently, this also increases vulnerability to various kinds of arrhythmia. (24) The influence of the medications used while treating COVID-19 can also contribute to increased heart rate. In a study of 138 patients with COVID-19 in Wuhan, it has been reported that an arrhythmia occurred in a fast 17% of cases. (25)

What also emerges from the results reported in our study is that patients with coronary artery diseases, who suffered from COVID-19, need to start or intensify treatment with beta-blockers and are more likely to develop long-term complications after recovery. This result supports

evidence from previous research. In a study, A Meta-Analysis: Coronary Artery Calcium (CAC) Score and COVID-Prognosis (22), that examined the outcomes of COVID-19 while comparing the CAC scores, the compiled data showed that CAC was associated with mortality increase. Clinical presentation of coronary artery disease may be characterized as chronic or acute, but most of the time the process is described as progressive with clinically silent periods. (26) The World Health Organization recognized cardiovascular diseases as the leading cause of death globally. It is also important to diagnose the patients and correctly adjust the treatment, especially after any infection. The mechanism of coronary artery disease is caused by restriction of the blood flow, which leads to myocardial ischemia(26). The infection increases oxygen demand and cardiac stress, which could be the reason for the decompensation of CVD and the need for beta-blockers. Furthermore, the prolonged impact of SARS-CoV-2 infection on the cardiovascular system was well-established in the literature and already mentioned in this paper. The long-lasting consequences of COVID-19 may explain the need for higher beta-blocker doses in patients with coronary artery disease even after they already recovered. Organ damage is one of the many mechanisms taken into consideration when it comes to symptoms of long COVID-19. Specific long-lasting inflammatory mechanisms have been recognized as the cause of tissue destruction, but the exact explanation is still unclear. (27) The most common symptom of long COVID is fatigue (27), which can be easily associated with many other diseases, including CVD. This has to be included in the treatment of patients after the infection.

Hypertension is one of the most common comorbidities in patients with both acute SARS-CoV-2 infection, as well as in those with long COVID. Moreover, it has been shown that hypertension stands as an independent risk factor contributing to significantly worse COVID-19 outcomes in hospitalized patients. (28–30) Contrary to expectations our analysis did not find a statistically significant correlation in patients with hypertension, but previous observations suggest better outcomes from COVID-19 infection in patients, who were treated with beta-blockers. Laurent Chouchana et al (31) evaluated antihypertensive therapy in 3686 patients with SARS-CoV-2 infection with monthly follow-up and observed reduced mortality among beta-blocker therapy users. Another study conducted across multiple centers, led by Feifei Yan et al (32), concerning individuals with COVID-19, found similarly that the treatment with beta-blockers was linked to a reduction in both mortality rates and instances of dyspnea. These reports are supported by Sara Joan Pinto-Sietsma et al (33) study, which showed that beta-blocker therapy was associated with considerably better outcomes in COVID-19 patients with hypertension.



The small size of the study group makes it necessary to conduct studies on a larger group of patients to determine the exact impact of COVID-19 on patients with cardiovascular diseases. Another issue, that we recognized when analyzing the retrospective data, was the incomplete record regarding cardiac ultrasound, troponin levels, and NT-pro BNP concentration before and after SARS-CoV-2 infection.

## **CONCLUSIONS**

Patients with pre-existing cardiovascular disease should be closely monitored when suffering from Sars-CoV-2 infection because they are more likely to develop complications and need additional treatment. The dosage of beta-blockers should be individualized based on the patient's specific condition, response to treatment, and the presence of any side effects. Patients with coronary artery diseases could potentially need increased beta-blocker doses after recovery. This is an important issue for future research, especially in the context of long COVID-19.

## **DISCLOSURES:**

### **Author's contribution:**

Conceptualization: Jakub Gawryś, Aleksandra Jędrasek, Tomasz Jędrasek

Methodology: Jakub Gawryś

Formal analysis: Jakub Gawryś

Investigation: Tomasz Jędrasek

Writing - rough preparation: Aleksandra Jędrasek, Tomasz Jędrasek

Writing - review and editing: Tomasz Jędrasek, Aleksandra Jędrasek

Supervision: Jakub Gawryś

All authors have read and agreed with the published version of the manuscript.

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**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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