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INVITED REVIEW – OPEN ACCESS

Impact of the Novel Coronavirus Disease 2019 (COVID-19) Pandemic on Cardiac Emergencies and Future Perspectives in Turkey

Ali Çoner[1], Afşin Emre Kayıpmaz[2], Elif Çelikel[2]

ABSTRACT

SARS-CoV-2-associated COVID-19 pandemic has affected the daily life of people across the world in 2020. Data about the course of viral involvement continues to be accumulated. COVID-19 is a multi-systemic disease, and the clinical presentations and possible complications may vary widely in different patient groups. The cardiovascular system is a primary target of COVID-19, and direct or indirect effects of viral involvement are observed. In addition to the direct effects of viral involvement on the cardiovascular system, decrement in acute cardiac emergencies has been experienced in many cardiology clinics in Turkey during the pandemic. Moreover, there may be a possible increase in out-of-hospital cardiac arrests in the near future. In this narrative review, we aimed to discuss the cardiac manifestations of COVID-19, the possible drug interactions related to the drugs used for COVID-19 management, and the effect of the pandemic on cardiac emergencies. We believe that understanding the natural mechanism of cardiac involvement of SARS-CoV-2 and emphasizing the data about out-of-hospital arrests will help clinicians effectively deal with the preventable cardiovascular causes of death in the forthcoming waves of COVID-19.

Keywords: Cardiovascular diseases, coronaviruses, COVID-19, pandemics

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[1]Department of Cardiology, Başkent University Alanya Hospital, Antalya, Turkey
[2]Department of Emergency, Ankara City Hospital, Ankara, Turkey

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Correspondence
Ali Çoner,
Başkent University Alanya Hospital, Department of Cardiology, Antalya, Turkey
Phone: +90 242 510 25 25
e-mail: conerali@hotmail.com

INTRODUCTION

SARS-CoV-2 virus-associated coronavirus disease (COVID-19) has caused a worldwide pandemic in 2020 that is ongoing at the time of writing this report (1). The health systems of countries around the world have faced various challenges during this pandemic. An increased need of intensive care beds, insufficient mechanical ventilators, and high rates of the COVID-19 infection among healthcare workers are the main challenges. In addition, government restrictions and policies to prevent infection spread continue to affect daily economic life. Turkey was one of the last countries to have proven COVID-19 cases, and following the diagnosis of the first COVID-19 cases, the central government announced a partial lockdown for citizens aged >65 y. A curfew order for weekends was also announced for the general population (2).

Although COVID-19 patients mostly present with a primary clinical presentation of pneumonia, many other systemic involvement findings have been reported (3, 4). In addition, cardiac involvement is observed in COVID-19. Cardiac problems may be attributable to direct myocardial involvement of the virus or in the form of myocardial infarction due to an increased tendency to thrombosis in the course of disease (Fig. 1). In addition, antiviral agents used for COVID-19 treatment are reported to exert arrhythmic effects (5). Another issue that concerns cardiologists in this process is decreased cardiac emergency admissions to hospitals during the pandemic (6, 7). With the onset of the global pandemic and the first proven case in Turkey, the Turkish Society of Cardiology published a consensus paper on the management of acute cardiac emergencies during the COVID-19 outbreak (8).

In this narrative review, we aimed to emphasize the effects of the COVID-19 pandemic on our daily cardiology practice and discuss future implications of the global outbreak on cardiovascular diseases.

Cardiovascular Manifestations of Novel Coronavirus Infection

The course of COVID-19 consists of the following 3 intertwined phases: early infection phase, pulmonary involvement phase, and hyperinflammation phase (9). The first phase includes the passage and replication of the virus into the lung tissue. Monocytes and macrophages that are innate immunity elements are responsible for fighting against the virus during this period, and the patient may have mild constitutional symptoms. Pulmonary tissue damage develops in the next step, and vasodilatation, increased endothelial permeability, and leukocyte activation occur in the second stage; this pathogenesis results in pulmonary damage, hypoxemia, and increased cardiovascular stress. Ten percent of the patients in the second stage progress to the hyperinflammation stage. The hyperinflammation phase is characterized by the development of acute respiratory distress syndrome

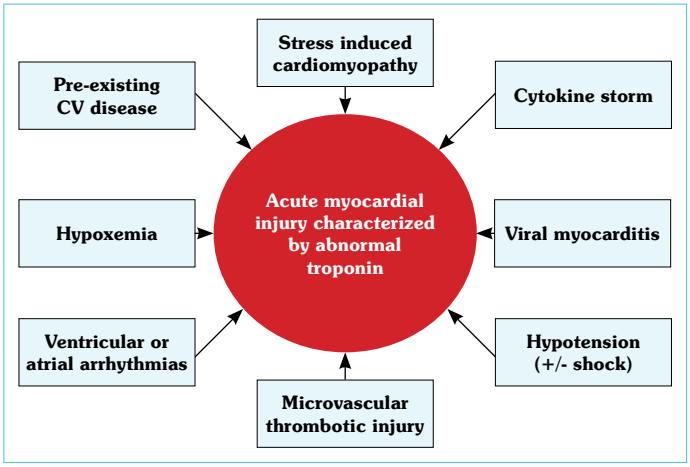

Figure 1. Mechanisms playing a role in the development of cardiac injury in COVID-19 patients
CV: Cardiovascular

(ARDS), acute cardiac damage, multiple organ failure, secondary bacterial infections, sepsis, and increased need for intensive care (10–12). Although the exact mechanism of cardiac injury remains unclear, some possible mechanisms have been suggested. Acute cardiac injury, distinguished by an increase in high-sensitivity cardiac troponins, has been reported in 8%–12% of COVID-19 patients (13). Acute myocardial injury is a strong negative predictor of prognosis in COVID-19 patients. COVID-19 patients with underlying cardiovascular issues have worse prognosis; therefore, we must ensure careful treatment for these patients. The primary concerns in patients who develop cardiovascular complications are the increased need for mechanical ventilation and the possible onset of malign arrhythmias related to either strained myocardial tissue or arrhythmical side effects of antiviral and anti-inflammatory agents.

There are 2 receptors on the host cell surface to which SARS-CoV-2 is attached (angiotensin- converting enzyme-2 and transmembrane protease serine-2). Clinicopathological reports revealed a relationship between severe COVID-19 and viral coagulopathy interaction with ARDS that develops because of pulmonary embolism, venous/arterial/microvascular thrombosis, lung endothelial damage, and associated thrombotic complications (14). An increase in the vasoconstrictor angiotensin-II, a decrease in the vasodilator angiotensin, and sepsis-related cytokine release trigger coagulopathy in COVID-19 patients. Half of those with severe COVID-19 develop coagulopathy. An increase in the D-Dimer level is the most striking finding with respect to coagulation parameters in COVID-19 patients, and the progressive increase has worse clinical consequences. Deep vein thrombosis and pulmonary embolism have been observed in up to 40% of the patients who were administered standard doses of low molecular weight heparin (LMWH). Moreover, pulmonary microvascular thrombosis may play a role in the development of progressive lung failure. It is suggested that higher doses of LMWH may be preferred, considering the patient-based risk and D-Dimer level in terms of preventing thrombosis development. LMWH can also positively affect the complex coagulopathy in COVID-19 patients by suppressing the interleukin-6 (IL-6) levels and exerting anticoagulant effects (15, 16).

Possible Adverse Effects of Drug Therapies Used for Treating COVID-19

Drugs used for COVID-19 treatment have various cardiovascular adverse effects. Considering that one third of the patients have a history of underlying cardiac disease, these adverse effects may cause serious comorbidities, even mortality (17). Hydroxychloroquine that is used for COVID-19 treatment is included in the treatment protocols of many countries of the world. In the initial period of the COVID-19 pandemic, despite the lack of a proven positive clinical effect, hydroxychloroquine was used widely owing to the lack of any other effective treatment (18). High-dose hydroxychloroquine is believed to reduce the viral load, and its efficacy can increase when it is used in combination with azithromycin or various antiviral drugs (19).

Hydroxychloroquine is a hECG potassium channel blocker that can increase the QTc interval and triggering fatal arrhythmias. Significant QTc prolongation of up to 20% has been reported in a patient series that examined the proarrhythmic effects of hydroxychloroquine treatment in COVID-19 patients (20, 21). The potential clinical benefit of hydroxychloroquine in the initial phase of the pandemic has pushed the QTc interval evaluation into the background. In fact, the decision regarding the use of hydroxychloroquine in combination with other hECG blocking drugs, such as azithromycin, lopinavir, and ritonavir should be made carefully.

We do not have any data on the use of hydroxychloroquine in patients with a basal QTc interval ≥500 ms; however, it is known that prospective studies are designed to study this subject. No difference was found between the use of hydroxychloroquine as monotherapy or in combination with azithromycin in a sample of COVID-19 patients with a basal QTc interval of 433 ms (20). Significant prolongation in the QTc interval was observed in 2% of the patients. However, the use of hydroxychloroquine in this study was short-term (median 9 d). The reported time to reach steady-state plasma levels of hydroxychloroquine is 180 d. The effect of the long-term use of hydroxychloroquine on the QTc interval can be explained more clearly with observational studies on patients using hydroxychloroquine for other indications (22). It has been suggested that prolongation of the QTc interval may be more pronounced with more extended use. In conclusion, underlying cardiovascular diseases and the use of drugs that can prolong the QTc interval should be questioned in the COVID-19 patients in whom hydroxychloroquine is started as monotherapy or in combination with other medication. Drugs that prolong the QTc interval, which are not vital, should be discontinued. Basal serum electrolytes should be measured before treatment, and low values ($K^+/Mg^{++}/Ca^{++}$) should be replaced. In patients with a basal QTc interval >470 ms, hydroxychloroquine should be used cautiously under close monitoring. The algorithm for the use of hydroxychloroquine with respect to the basal and follow-up QTc intervals is shown in Figure 2.

Demographics and Management of Acute Cardiac Emergencies in the Pandemic Era

With the onset of the COVID-19 pandemic, many cardiologists have observed a decrease in the emergency admissions because of acute coronary syndrome (ACS). Studies conducted in various European countries on this subject have shown a decrease in the emergency room admissions because of acute cardiac emergencies

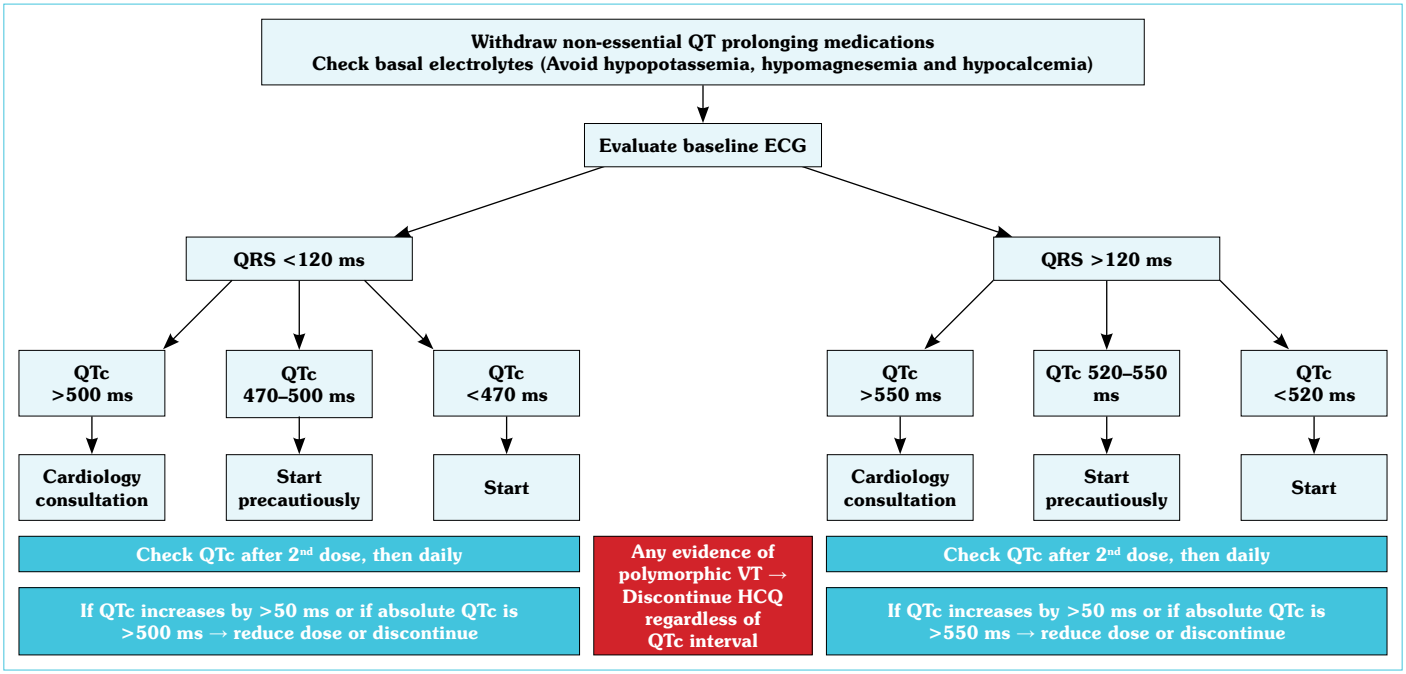

Figure 2. Management of hydroxychloroquine therapy as per the evaluation of basal and follow-up QTc intervals

(23–25). Italy was the most affected country in the first weeks of pandemic onset, and a 48.4% reduction in the acute myocardial infarction admissions compared to that during the same period in 2019 was reported across the country (23). In addition to the reduction in acute cardiac emergency admissions, an increase in myocardial infarction complications, such as acute mitral regurgitation and myocardial rupture, were reported in the patient population. Similarly, in a study conducted in our country on this topic, a sharp decrease in the number of acute myocardial infarction was observed even in cardiology referral centers, with high patient volumes with the onset of the pandemic (7). An increased time interval between symptom onset and emergency admission was observed in a study conducted in Turkey (26).

Following the announcement of the first proven case in Turkey, the national government developed and implemented various policies and arrangements to restrict the effects of the pandemic around the country. Curfew order for the population aged >65 y and curfew order covering the general population for weekends were the main precautions (27, 28). These curfew orders raised some concerns among cardiologists about the medical management of ACS patients aged >65 y (8). The Turkish Society of Cardiology published a consensus paper about the management of ACS patients during the COVID-19 pandemic, and periodic updates of this consensus paper continue to be published, with updates on the knowledge regarding cardiac involvement in COVID-19. However, we do not have any data about the probable cardiac death rates in older patients during the COVID-19 outbreak. We believe that a study that assesses the prevalence of out-of-hospital sudden deaths and their possible detectable causes, especially in subjects aged >65 y, during the ongoing COVID-19 pandemic, will provide helpful results. In Italy, a preliminary study conducted on the residents of the Lombardia region demonstrated a 52% increase in out-of-hospital deaths in 2020 as compared to those in 2019 (29). We need similar statistical data about Turkey to identify the possible increase in out-of-hospital deaths. These concerns also exist with respect to the possible future increase in patients with intractable heart failure symptoms. Further, we believe that statistical analysis of patients with de novo heart failure admissions should be performed carefully in Turkey in the future.

Social isolation and decrease in physical activity may have some effects on the health status of the population. Physical inactivity, even for short periods of 1–4 wk may exert adverse effects on an individual's physical health. Some preliminary studies have investigated the possible negative effects of social isolation and physical inactivity on the increasing burden of cardiovascular diseases (30). The pandemic may have some indirect, adverse effects on the general population even though increasing social isolation.

In the COVID-19 era, cardiologists and cardiovascular surgeons may tend to finish the revascularization treatment of coronary artery disease patients in the catheter laboratory. In a preliminary study, coronary artery bypass grafting (CABG) surgery rates were lower with the onset of the COVID-19 pandemic (31). Thus far, we do not have any data on the rates of PCI and CABG in the ACS population; however, concerns about the possibly higher complication rates with more complex revascularization techniques and the need of longer hospitalizations may withdraw the heart team members from getting a CABG decision.

CONCLUSION

The COVID-19 pandemic has exerted distinct effects on daily social and work life. Cardiovascular issues are among the most common reasons for the use of emergency services during the ongoing pandemic era. Viral infection may exert a direct effect via myocardial involvement or indirect effects through drug interactions. In addition, the risk of viral transmission raises concerns among the general population with respect to hospital admissions, even for emergent situations, such as myocardial infarction. The rates of

out-of-hospital deaths without a definable etiology and the prevalence of de novo heart failure patients should be researched in our country. These data may help clinicians manage the preventable cardiovascular causes of death in the forthcoming waves of the COVID-19 outbreak.

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