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Review
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Management of Arrhythmias in COVID-19

Yusuf Ziya Şener, Uğur Canpolat, Hikmet Yorgun, Kudret Aytemir

Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Abstract

Coronavirus disease-2019 (COVID-19) disease is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus infection and firstly appeared in China and then became a pandemic. The leading cause of mortality is respiratory failure in COVID-19; however, cardiovascular manifestations are frequent and also important causes of death in COVID-19. The incidence of arrhythmia is increased in patients with COVID-19 due to increased systemic inflammatory response, hypoxia, and administered drugs. All kinds of arrhythmias, including bradyarrhythmias, supraventricular and ventricular arrhythmias, may develop during COVID-19 course. QT prolongation plays a central role in COVID-19 related arrhythmias. Therefore, QT duration should be strictly followed. All the clinicians should know the management of arrhythmias that they might face with frequently during the pandemic.

Keywords: COVID-19, cardiac arrhythmia, QT prolongation

Introduction

Coronavirus disease-2019 (COVID-19), firstly appeared in China and led to the pandemic. There is a significantly increased risk of the development of arrhythmias in COVID-19 due to increased inflammatory response, direct myocardial viral infection, and administered drugs (1). Cardiac arrhythmias are one of the leading causes of mortality in COVID-19. The incidence of cardiac arrhythmias is reported as 19.6 % in hospitalized patients, while it rises to 44.4 % in patients who needed intensive care unit (ICU) admission. Palpitation was the first symptom of COVID-19 in 7.3% of the patients (2). Cardiac arrhythmias were reported in 25.9% of the patients, and most of them were supraventricular arrhythmias in a single-center retrospective study from China (3). Another study from the USA said that; cardiac arrhythmias developed in 7.5% of the cases, and the most common arrhythmia was atrial fibrillation (3.5%). Bradyarrhythmias occurred in 1.2% of the patients and ventricular arrhythmias developed in 1.4% of the patients with COVID-19 (4).

Several mechanisms are responsible for arrhythmia development in COVID-19. Direct viral infection and inflammatory response cause myocardial damage, which may present with chest pain and myocarditis or detected by increased cardiac biomarkers in asymptomatic cases. COVID-19 related lung involvement leads to hypoxemia. Additionally, COVID-19 may cause gastroenteritis and diarrhea, which may result in electrolyte imbalance such as hypokalemia. Drugs used to treat COVID-19 may induce arrhythmogenesis via both causing prolongation of QT duration and affecting microsomal liver enzymes, which play the primary role in the metabolism of certain medications that may affect QT interval (2). Increased inflammatory response changes the configuration and distribution of ion channels located on the myocardial cell membranes and lead to increased action potential duration (5). To summarize, the incidence of cardiac arrhythmias is increased in COVID-19 due to several mechanisms.

Management of Atrial Arrhythmias in COVID-19

In a study with 115 COVID-19 patients in the United Kingdom (6), atrial arrhythmias developed in 19 (16.5%) patients. Twelve patients had atrial fibrillation (AF), six patients had atrial flutter, and one patient had focal atrial tachycardia. It is expressed that all of the patients with atrial arrhythmias were ICU admission requiring patients. Increased age, higher C-reactive protein (CRP), and D-dimer values were defined as risk factors for the development of atrial arrhythmias. BNP and troponin levels were similar between patients with and without atrial arrhythmias.

Corresponding Author: Yusuf Ziya Şener, M.D., Hacettepe University Faculty of Medicine, Department of Cardiology, Ankara, Turkey
E-mail: yzsener@yahoo.com.tr ORCID ID: orcid.org/0000-0001-5151-5133

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The need for mechanical ventilation was established as a strong predictor of atrial arrhythmia development possibly due to hypoxia driven arrhythmogenesis. It has been reported that the use of hydroxychloroquine, azithromycin, and remdesivir were similar between cases with and without atrial arrhythmias. Intravenous amiodarone was administered in nine patients, and conversion to sinus rhythm was achieved in seven patients. Electrical cardioversion was applied to one patient. Five cases with atrial arrhythmias have died during treatment (6).

Thromboembolic events are frightening manifestations of atrial fibrillation. Therefore, the need for anticoagulation should be evaluated in patients with AF. The SARS-CoV-2 virus infects endothelial cells and induces thrombogenesis, so thromboembolic event risk is increased in patients with COVID-19. CHADS-VASc score is developed to estimate thromboembolic risk in AF, and CHADS-VASc score ≥2 in males and ≥3 in females is an indication for anticoagulation. However, due to an increased tendency to thrombosis in COVID-19, the administration of anticoagulant treatment should be considered in males with CHADS-VASc score ≥1 and in females with CHADS-VASc score ≥2 (7). Possible drug interactions should be assessed before the choice of anticoagulant drugs. Direct-acting oral anticoagulants can be used, and the dose of drugs should be accommodated by age, weight, and glomerular filtration rate. Parenteral anticoagulation should be administered in intubated patients. It should be kept in mind that unfractionated heparin should not be used with azithromycin due to drug interaction (7). Administration in a crushed form (e.g., via a nasogastric tube) does not alter the bioavailability of apixaban, edoxaban, and rivaroxaban while dabigatran capsules must not be opened, as it would result in a 75% increase in the drug bioavailability (8,9).

Rate control should be the preferred strategy instead of rhythm control in patients with COVID-19 due to increased arrhythmia recurrence rates unless the patient's hemodynamic parameters are unstable. Antiarrhythmic drugs should be discontinued because of the potential adverse effects, including QT prolongation. If the patient is hypotensive or in cardiogenic shock, electrical cardioversion should be performed urgently. Beta blocking agents should be preferred rather than digoxin or calcium channel blockers in rate control due to having less potential for drug interactions. After the completion of COVID-19 treatment; patients should be re-assessed for rhythm control (7).

Management of Ventricular Arrhythmias in COVID-19

The incidence of ventricular arrhythmias is reported as 5.9% in patients with COVID-19. Ventricular arrhythmias mainly occur in patients with higher troponin levels, and inflammatory biomarkers (10). The prolongation of QT interval plays a significant role in the development of ventricular arrhythmias (11). All of the reversible conditions that facilitate arrhythmogenesis should be corrected. Hypoxemia, acid-base, and electrolyte disorders should be treated. Potassium levels should be kept over 4.5 mEq/L (7). The dose of parenteral vasopressors should be minimized. Fever should be treated with paracetamol.

Defibrillation should be performed emergently in ventricular fibrillation, and direct current cardioversion (DCCV) should be done in unstable sustained ventricular tachycardia (VT).

Treatment algorithm in patients with sustained monomorphic VT;

- If the patient is intubated and under sedation, DCCV should be considered.
- If the patient is hemodynamically unstable, DCCV should be considered.
- In hemodynamically stable patients;
- Intravenous (IV) procainamide or lidocaine should be preferred if the patient is under treatment with drugs which may cause QT prolongation.
- IV amiodarone should be considered if any of the following conditions present; ongoing VT despite IV procainamide or lidocaine, underlying structural heart disease, or decreased left ventricular systolic functions. It should not be forgotten that amiodarone has a QT-prolonging effect itself.
- Amiodarone should be the preferred agent in critically ill patients and cases with recurrent VT/ventricular fibrillation (VF). QT interval must be strictly controlled during the treatment to prevent from QT prolongation. Lidocaine can be an alternative in suspicion of underlying myocardial ischemia.
- IV beta-blocker (esmolol), general anesthesia or overdrive pacing with a temporary transvenous pacemaker should be considered in patients unresponsive to antiarrhythmic drugs (7).

Torsades de Pointes (TdP) is defined as polymorphic VT that develops on the underlying prolonged QT. Drugs used in the treatment of COVID-19 may cause QT prolongation. Therefore, other conditions that lead to QT prolongation, such as bradycardia, deteriorated kidney functions, and electrolyte disorders, should be evaluated and treated. QT interval should be followed strictly (7).

D2 or V5-6 derivations should be preferred for measuring the QT interval. Consequent QT intervals should be measured, and the longest measurement should be recorded. QT interval should

be corrected according to the heart rate. The Bazzett formula is the most commonly used correction formula, and it estimates corrected QT via dividing QT duration (millisecond) to the root mean square of the RR interval duration (second). Normal values of corrected QT (QTc) is <440 msec for men and <460 msec for women. Values of >500 msec are associated with an increased risk of TdP development. Bigger U waves (>1 mV) or U waves adjacent to T waves should be added to the QTc measurement while small U waves or u waves separate from the T wave should not be added in the analysis (12). QTc interval is prolonged in patients with a cardiac pacemaker and pace rhythm or patients with bundle blocks; therefore, 50 msec should be subtracted from the measured QTc value in these cases. One previous study recommended that, in the presence of a left bundle branch block, 70-ms subtraction rule may be employed for QTc estimation, respectively, though 40-ms subtraction may be used in the presence of a right bundle branch block (13). The measurement of QTc is summarized in Figure 1.

Baseline electrocardiography (ECG) should be performed before starting treatment. If baseline QTc interval <480 msec, control ECG should be performed three days later. If the QTc interval is approximately 480-499 msec, ECG should be performed daily, and telemetric follow-up might be considered in conditions that either the patient is bradycardic or ventricular premature beats develop. A combination of azithromycin and hydroxychloroquine should be avoided if baseline QTc >500 msec. If QTc duration prolongs for more than 60 msec during follow-up, dose and combination of the drugs used for COVID-19 should be checked and rearranged. QTc measurement and follow-up are demonstrated in Figure 2.

Before the starting treatment, all of the medications that prolong QTc should be reassessed and discontinued if they are not indispensable. Drugs causing QTc prolongation and useful website addresses were listed in Figure 3. The potassium level should be kept above 4.5 mEq/L, and the magnesium level should be kept between 3-4 mg/L. Drugs that cause bradycardia should be stopped, and the heart rate should be kept between 90 and 110 bpm. Catecholamines such as dopamine and isoproterenol or transvenous pacing can be used to increase heart rate in patients with lower heart rates (7).

Hemodynamic stability determines the treatment algorithm in TdP. If the patient is hemodynamically unstable or TdP is sustained, defibrillation should be performed urgently. Magnesium should be replaced, and electrolyte abnormalities should be corrected. Magnesium and potassium levels should be kept in targeted ranges (3-4 mg/dL for magnesium and >4.5 mEq/L for potassium). Magnesium may reduce the amplitude of early after depolarizations (EADs) by inhibiting the late calcium influx via L-type calcium channels which related to delayed ventricular repolarization. Therefore, EADs are less likely to reach threshold potential and provoke TdP. Magnesium therapy is simple and relatively safe to administer. The recommended dose of intravenous magnesium is 2 gr in adults and it should be given in 10-15 minutes (14). If refractory or recurrent TdP develops, magnesium replacement should be repeated. Heart rate should be increased by catecholamine infusion or overdrive pacing with a transvenous pacemaker. If polymorphic VT is under normal QTc interval, ischemia may play a role in arrhythmogenesis, and lidocaine may be tried terminating VT (7). Approach to polymorphic VT is summarized in Figure 4.

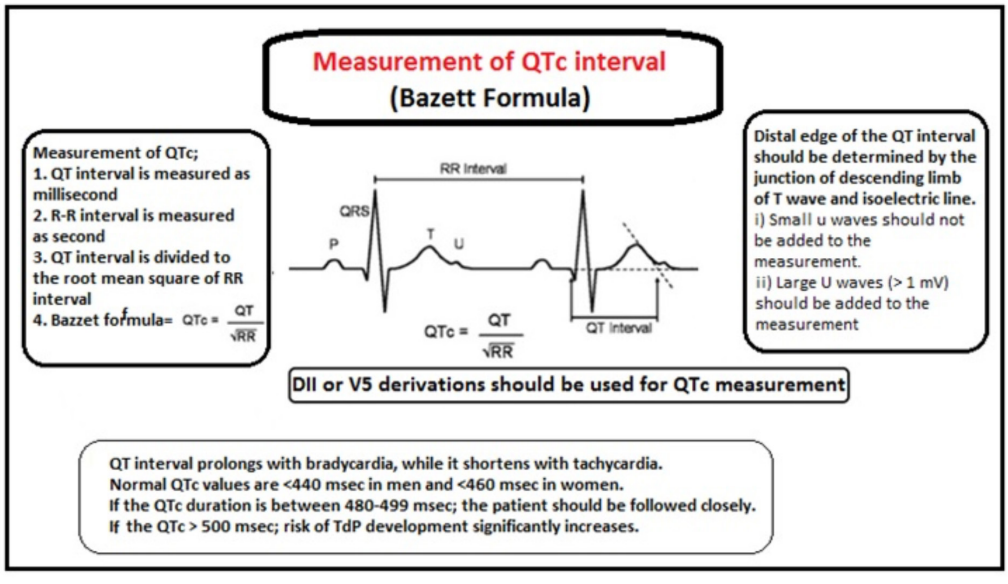

Figure 1. Measurement of corrected QT (QTc) interval

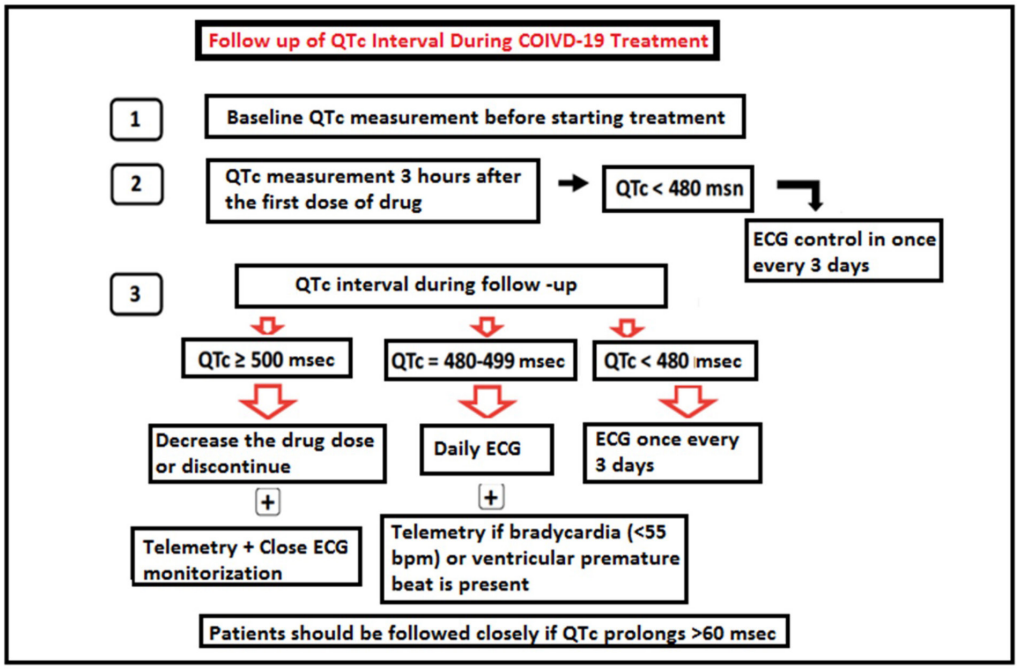

Figure 2. Follow-up of QTc during COVID-19

COVID-19: Coronavirus disease-2019

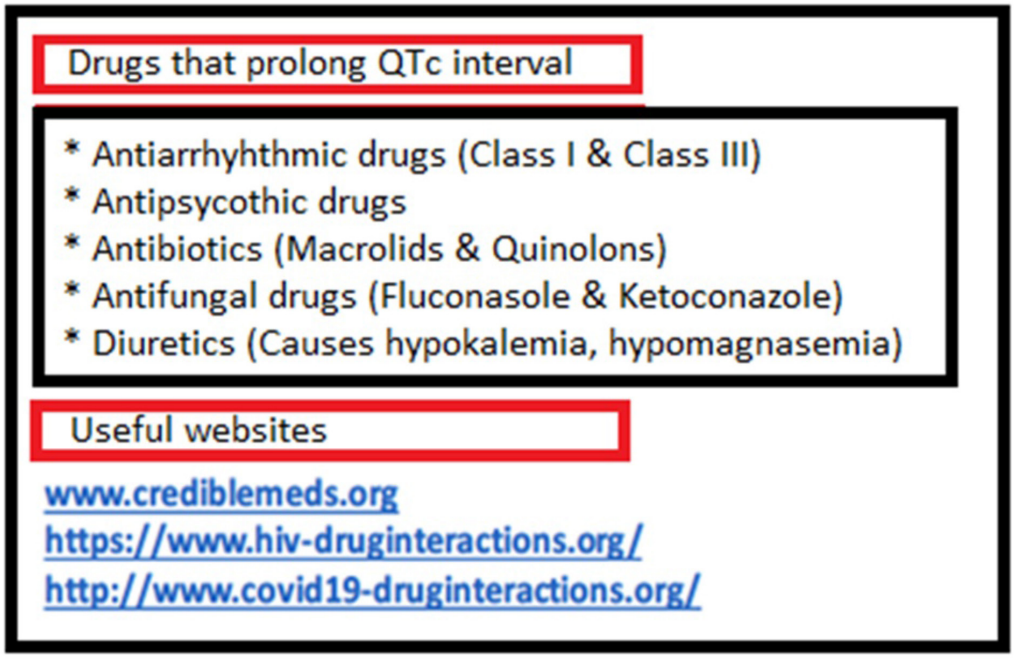

Figure 3. Drugs which prolong QTc interval and useful websites for drug interactions

Management of Bradayarrhythmias During COVID-19

Conduction defects, sinus node dysfunction, and atrioventricular (AV) block might develop during COVID-19. Bradyarrhythmias generally occur in patients with myocardial damage. Hypoxia and neural invasion caused by the SARS-CoV-2 virus lead to increased vagal tone and facilitates bradyarrhythmias. It is demonstrated in animal studies that the AV block develops in coronavirus infection due to myocarditis (15). Intubation, tracheal aspiration, and prone positioning of the patient causes increased vagal activity and bradyarrhythmias (16). Another interesting finding is detected lower heart rates in COVID-19 patients than expected heart rates according to their body temperature values, as seen in typhoid fever (17).

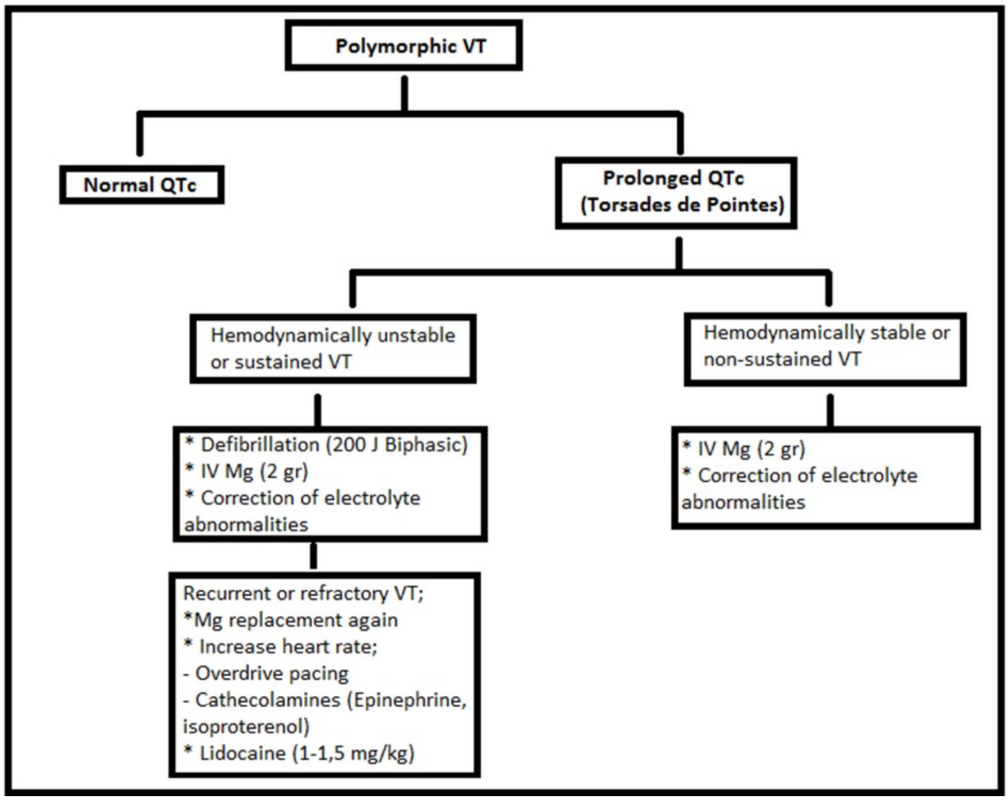

Figure 4. Approach to polymorphic VT during COVID-19

VT: Ventricular tachycardia, COVID-19: Coronavirus disease-2019, IV: Intravenous

Treatment of bradyarrhythmias depends on the hemodynamic parameters of the patients. All of the drugs that may cause bradycardia should be stopped. Atropin may be tried to increase heart rate. A temporary transvenous pacemaker should be implanted if the patient is symptomatic. Permanent pacemaker implantation should be avoided during active disease, and the need for a pacemaker should be re-evaluated after completion of COVID-19 treatment. It should be kept in mind that fingolimod and hydroxychloroquine may cause bradyarrhythmias weeks after the drug cessation (7).

Approach to Patients with Hereditary Arrhythmia Syndromes and COVID-19

Long QT syndromes (LQTs) develop due to ion channel mutations, and KCNQ1, KCNH2, and SCN5A are the most common detected mutations. It is believed that ion channel mutations play a significant role in patients prone to acquired QT prolongation (18). QTc interval should be strictly followed in patients with LQTs, and drug change or cessation should be considered in patients with QTc interval >500 msec or QTc prolongation more than 60 msec. Potassium level should be kept at the level of 5 mEq/L (19). Fever is the trigger of VT, especially in type 2 LQTs. Therefore, fever should be reduced strictly (20).

Brugada syndrome (Brs) develops due to sodium channel mutation (SCN5A) and is associated with sudden cardiac death (SCD). The precise diagnosis of BrS is confirmed by demonstrating type 1 Brugada ECG pattern either spontaneously or induced with conditions such as fever and drugs (21). Fever is the main trigger of VT/VF in patients with BrS. It is reported that fever-induced BrS cases have higher sudden cardiac death risk than cases induced with drugs (22). Patients with established sodium channel mutation or spontaneous type 1 Brugada ECG pattern, patients under 26 years old or older than 70 years old, patients with syncope and patients with fever-induced BrS have a high risk for sudden cardiac death. Therefore, patients with high SCD risk should be hospitalized during COVID-19. Patients with lower SCD risk might be followed without hospitalization. Fever should be treated aggressively in BrS patients, and paracetamol should be the preferred agent (23).

Catecholaminergic polymorphic VT (CPVT) develops due to ryanodine receptor mutation, and it is associated with malign ventricular arrhythmias, especially after sympathetic nervous system activation by exercise or emotional stress. Beta-blockers are gold standard treatment in CPVT, and flecainide is the second-line treatment in refractory cases (24). Fever alone is not the trigger of VT/VF in CPVT. The main possible trigger of VT/VF

in patients with CPVT and COVID-19 is catecholamines used for hemodynamic support. Therefore, catecholamine use should be avoided as much as possible. A combination of beta-blockers and milrinone can be a safe option in patients with CPVT who needs hemodynamic support. Beta-blockers should not be stopped in CPVT patients (25).

Conclusion

Both COVID-19 itself and drugs used for the treatment of the disease are responsible for increased incidence of arrhythmia in patients with COVID-19. QTc prolongation plays a central role in COVID-19 related ventricular arrhythmias. Therefore, the QTc interval should be followed strictly according to the recommendations. Drugs reducing heart rate should be discontinued in patients with bradyarrhythmias, and patients should be reassessed for the need for a permanent pacemaker after completion of the COVID-19 treatment. Fever should be reduced in patients with BrS, and catecholamines should be avoided in patients with CPVT. Clinicians should be aware of the increased risk of arrhythmia during COVID-19.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.Z.Ş., H.Y., K.A., Design: U.C., H.Y., K.A., Data Collection and/or Processing: Y.Z.Ş., Analysis and/or Interpretation: U.C., Literature Search: H.Y., K.A., Writing: Y.Z.Ş., U.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Lazzerini PE, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic risk, and inflammation: mind The gap! Circulation. 2020;142:7-9.
2. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Cardiol. 2020;75:2352-71.
3. Si D, Du B, Ni L, Yang B, Sun H, Jiang N, et al. Death, discharge, and arrhythmias among patients with COVID-19 and cardiac injury. CMAJ. 2020;cmaj.200879.
4. Bhatla A, Mayer MM, Adusumalli S, Lin D, Marchlinski F, Deo R, et al. COVID-19 and Cardiac Arrhythmias. Heart Rhythm. 2020;S1547-5271:30594-4.
5. Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi PL. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. Nat Rev Immunol. 2019;19:63-4.
6. Colon CM, Barrios JG, Chiles JW, McElwee SK, Russell DW, Maddox WR, et al. Atrial arrhythmias in COVID-19 patients. JACC Clin Electrophysiol. 2020;6:1189-90.
7. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. Available from: https://www.escardio.org/The-ESC/Press-Office/Press-releases/ESC-Guidance-for-the-Diagnosis-and-Management-of-Heart-Disease-during-COVID-19
8. Duchin K, Duggal A, Atiee GJ, Kidokoro M, Takatani T, Shipitofsky NL, et al. An open-label crossover study of the pharmacokinetics of the 60-mg edoxaban tablet crushed and administered either by a nasogastric tube or in apple puree in healthy adults. Clin Pharmacokinet. 2018;57:221-8.
9. Song Y, Wang X, Perlstein I, Wang J, Badawy S, Frost C, et al. Relative Bioavailability of Apixaban Solution or Crushed Tablet Formulations Administered by Mouth or Nasogastric Tube in Healthy Subjects. Clin Ther. 2015;37:1703-12.
10. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:811-8.
11. Song MK, Bae EJ, Baek JS, Kwon BS, Kim GB, Noh CI, et al. QT prolongation and life threatening ventricular tachycardia in a patient injected with intravenous meperidine (Demerol®). Korean Circ J. 2011;41:342-5.
12. Viskin S. The QT interval: too long, too short or just right. Heart Rhythm. 2009;6:711-5.
13. Chakravarty S, Kluger J, Chhabra L, Ramu B, Coleman C. Corrected QT in ventricular paced rhythms: what is the validation for commonly practiced assumptions? Cardiology. 2015;130:207-10.
14. Thomas SH, Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. Br J Clin Pharmacol. 2016;81:420-7.
15. Alexander LK, Keene BW, Yount BL, Geratz JD, Small JD, Baric RS. ECG changes after rabbit coronavirus infection. J Electrocardiol. 1999;32:21-32.
16. Boriani G, Fauchier L, Aguinaga L, Beattie JM, Lundqvist CB, Cohen A, et al. Group ESCSD. European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in critically ill and post-surgery patients, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society. Europace. 2019;21:7-8.
17. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
18. Paulussen AD, Gilissen RA, Armstrong M, Doevendans PA, Verhasselt P, Smeets HJM, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. J Mol Med (Berl). 2004;82:182-8.
19. Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr: implications for torsade de pointes and reverse use-dependence. Circulation. 1996; 93:407-11.
20. Amin AS, Herfst LJ, Delisle BP, Klemens CA, Rook MB, Bezzina CR, et al. Fever-induced QTc prolongation and ventricular arrhythmias in individuals with type 2 congenital long QT syndrome. J Clin Invest. 2008;118:2552-61.
21. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, et al. J-wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. Heart Rhythm. 2016;13:e295-324.
22. Mizusawa Y, Morita H, Adler A, Havakuk O, Thollet A, Maury P, et al. Prognostic significance of fever-induced Brugada syndrome. Heart Rhythm. 2016;13:1515-20.
23. Wu CI, Postema PG, Arbelo E, Behr ER, Bezzina CR, Napolitano C, et al. SARS-CoV-2, COVID-19, and inherited arrhythmia syndromes. Heart Rhythm. 2020;S1547-5271:30285-X.
24. van der Werf C, Wilde AAM. Catecholaminergic polymorphic ventricular tachycardia:from bench to bedside. Heart. 2013;99:497.

25. Kobayashi S, Susa T, Ishiguchi H, Myoren T, Murakami W, Kato T, et al. A low-dose b1-blocker in combination with milrinone improves intracellular Ca21 handling in failing cardiomyocytes by inhibition of milrinone-induced diastolic Ca21 leakage from the sarcoplasmic reticulum. PLoS One. 2015;10:e0114314.