REVIEW

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Rhythm and Conduction Disturbances in patients with COVID-19 and Their Significance in Family Medicine Practice

ABSTRACT

SARS-Cov-2 (Severe acute respiratory syndrome coronavirus 2) belongs to the group of viruses containing ribonucleic acid (RNA). The most common clinical manifestations include fever, upper and or lower respiratory tract involvement of varying severity. As the incidence of the disease increases and information about its course accumulates, it is known that there is an increased mortality from cardiovascular complications, including as a result of arrhythmias. It is assumed that the main mechanisms by which they occur are the entry of the virus into the heart cell through the expression of angiotensin-converting enzyme receptor 2, which leads to increased levels of angiotensin 2 and its many-sided negative effects, the development of a systemic inflammatory over-response (cytokine storm), directly cardiac damage, hypoxia, electrolyte disturbances, water imbalance. The disorders that are registered are tachyarrhythmias and bradyarrhythmias. In the conditions of the emerging COVID-19 (coronavirus disease of 2019) pandemic, general practitioners in Bulgaria played a significant role in diagnosing and treating this disease. Of particular importance is their competence regarding the establishment of possible complications from the cardiovascular system. Knowledge of the most common rhythm and conduction disorders, as well as the mechanisms of their occurrence, are decisive for the correct management and their potential outcome.

Keywords: SARS-Cov-2, COVID-19, Rhythm and Conduction Disturbances

COVİD-19 Hastalarında Ritim ve İleti Anormallikleri ve Bunların Aile Hekimliği Pratiğindeki Önemi

ÖZET

SARS-Cov-2 (Şiddetli akut solunum sendromu koronavirüsü 2) ribonükleik asit (RNA) içeren virüsler grubuna aittir. En yaygın klinik belirtiler arasında, farklı derecede ateş, üst ve/veya alt solunum yolu etkisi vardır. Hastalığın görülme oranı arttıkça ve bu hastalığın ilerlemesi hakkında bilgi biriktirdiğinde, kardiyovasküler komplikasyonlar, aritmi sonuçları da dahil olmak üzere ölüm oranının arttığı biliniyor. Bunların meydana geldiği ana mekanizmalar, angiotensin dönüştüren enzim reseptör 2'nin ifadesi yoluyla kalp hücresine virüsün girmesidir, bu da angiotensin 2 seviyelerinin artmasına ve çok yönlü olumsuz etkileri, sistemik iltihaplı aşırı tepki (sitokin fırtınası), doğrudan kalp hasarı, hipoksiya, elektrolit bozuklukları, su dengesizliği gelişmesine yol açar. Kayıtlı hastalıklar taşiaritmi ve bradiaritmi'dir. Gelişen COVID-19 (Koronavirüs hastalığı 2019) salgını koşullarında, Bulgaristan'daki genel tıp uzmanları bu hastalığın teşhisinde ve tedavisinde önemli bir rol oynadı. Özellikle kardiyovasküler sistemle ilgili olası komplikasyonların tespiti konusunda yetkinlikleri önemlidir. En yaygın ritm ve iletkenlik bozukluklarının yanı sıra bunların ortaya çıkış mekanizmalarının bilinmesi doğru yönetimi ve potansiyel sonuçları için çok önemlidir.

Anahtar Kelimeler: SARS-Cov-2, COVID-19, ritm ve iletkenlik bozuklukları.

INTRODUCTION

SARS-Cov-2 (Severe acute respiratory syndrome coronavirus 2) belongs to the group of viruses containing ribonucleic acid (RNA). It is assumed to have a zoonotic origin, and its transfer to humans occurred via the intermediate natural reservoir, pangolins (placental mammals) (1). The airborne route of spread makes it possible to infect a huge number very quickly and as a result, on March 11, 2020, the World Health Organization declared a pandemic. The first officially recorded case of the disease caused by the "new" coronavirus (COVID-19) was in Wuhan, China. Most often, the disease manifests with fever, and involvement of the upper and or lower respiratory tract varying from bilateral inflammatory changes in the lung parenchyma to severe respiratory distress syndrome with respiratory failure necessitating intensive treatment with oxygen supply or intubation with mechanical ventilation. As the incidence of the disease increases and information about its course accumulates, it is known that there is an increased mortality from cardiovascular complications, including as a result of arrhythmias (2, 3, 4).

The purpose of this article is to present the pathway of cardiac damage, the causes and mechanism of occurrence of rhythm and conduction disorders associated with COVID-19, and their type, as well as their importance for general medical practice.

Penetration of SARS-Cov-2 into the Human Cell: Entry of SARS-Cov-2 into the cell occurs through its binding via spike (S1 and S2) protein to angiotensin-converting enzyme receptor 2 (ACE 2) (5). It is expressed mainly by type 1 and type 2 pneumocytes in the lung, but also in other tissues such as the heart, kidney, and intestine, thereby reaching their damage (6). According to data from an autopsy study, in 24 of 39 patients who died of COVID-19, the virus was identified in heart tissue, suggesting a possible direct mechanism of damage (7). Another study demonstrated increased values of high-sensitivity troponin I in 27.8% of patients hospitalized for COVID-19 (8). Abnormalities have been associated with a higher risk of complications such as acute respiratory distress syndrome, coagulopathy, and malignant arrhythmias, as well as increased mortality, especially in patients with underlying cardiac pathology and advanced age, compared to these normal levels (9).

Causes and Mechanism of Occurrence of Rhythm and Conduction Disturbances in COVID-19

I. Myocarditis: Myocarditis represents the inflammatory damage of the myocardium with or without the occurrence of necrosis. It is assumed that, on the one hand, it occurs as a result of the penetration of the virus into the cell through the ACE receptor with an increase in the levels of angiotensin II, and on the other hand, a negative effect is exerted by the cytokine storm (10). The subsequent results of this are related to:

1) fibrosis and remodeling, which are the substrate for rhythm-conduction disorders

2) increasing the concentration of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). IL-6 leads to damage to the cell membrane by displacing plakoglobin (desmosomal protein), subsequent inflammatory edema resulting in electrical conduction disturbances with imbalance and arrhythmias (10).

3) endothelial dysfunction leading to ischemia

4) channelopathies

5) change in calcium levels

II. Pericarditis: The exact pathophysiological mechanism by which inflammatory involvement of the pericardium occurs in COVID-19 is not fully understood. It is assumed that the basis is the systemic inflammatory response due to the viral infection. Another possible pathway is associated with inflammatory-induced endothelial damage. The hyperinflammatory response in SARS-Cov-2 infection is characterized by an increase in the levels of interleukins (IL-1, IL-2, IL-6, IL-7), granulocyte-macrophage colony-stimulating factor, interferon-γ, inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor (TNF)-α. The resulting cytokine storm and the additional involvement of an imbalance between T1 and T2 helpers is the cause of multi-organ damage in COVID-19, including the heart (11). According to a study of patients with COVID-19, 26% of them had acute electrocardiographic (ECG) changes, including atrial fibrillation, tachy-brady syndrome, ST-T deviations, and deviations typical of pericarditis (12).

III. Hypoxia and Myocardial Ischemia: In patients with severe COVID-19 and low oxygen levels, shifts toward low cellular pH occur as a result of anaerobic respiration, leading to increases in cytosolic calcium and extracellular potassium. This may account for early and late depolarizations and changes in action potential duration. Increasing extracellular potassium levels can lower the action potential threshold resulting in faster conduction between cardiac cells. Under hypoxic conditions, the junctional protein connexin-43 can be dephosphorylated, thereby reducing electrical coupling. Underlying cicatricial changes secondary to myocardial ischemia can also impair conduction and lead to arrhythmias (13).

IV. Systemic Inflammation, Cytokines, and Sympathetic Activity: The systemic inflammatory response to COVID-19 is associated with an increase in TNF-α and IL-6 levels and the occurrence of a "cytokine storm" that might be part of the mechanism of occurrence of induced coagulopathy (14). As a result, other vascular complications

develop, such as pulmonary embolism with an acute right-sided burden with accompanying rhythm-conduction disorders (15). Acute myocardial ischemia, including myocardial infarction, represents other life-threatening conditions arising as a result of a viral-induced prothrombogenic state and hypercoagulation, inflammatory-induced endothelial dysfunction, rupture of an underlying atherosclerotic plaque, and overactivation of the sympathetic nervous system, which are the substrate for rhythm and conduction disturbances. Continued sympathetic activation after myocardial infarction can lead to lysis of surrounding adipose tissue, inducing ventricular tachyarrhythmias (16). Other mechanisms by which increased neurogenic activity leads to the occurrence of atrial tachyarrhythmias include enhanced automaticity, prolonged action potential duration, and delayed repolarization. On the other hand, IL-6, TNF-α, and IL-1 can affect the function of potassium and calcium ion channels in ventricular cardiomyocytes and prolong the duration of the action potential. This may increase the risk of Torsade de Pointes ventricular tachycardia and subsequent ventricular fibrillation.

V. Electrolyte Disorders and Water Imbalance: Patients with COVID-19 may experience diarrhea, dehydration, and kidney failure, leading to electrolyte disturbances and water imbalance. Altered levels of potassium, calcium, and magnesium significantly increase the risk of life-threatening arrhythmias, especially ventricular. Hypocalcemia, hypomagnesemia, and hypokalemia can lead to QT prolongation and subsequent ventricular extrasystole, ventricular tachycardia including Torsades de Pointes type, and ventricular fibrillation (17).

VI. Medicines Used in the Treatment of COVID-19: Medications used in the treatment of COVID-19 may have a proarrhythmic effect. Countries have adopted different treatment protocols worldwide, but the most frequently used therapeutic regimens include hydroxychloroquine, azithromycin, lopinavir, and ritonavir. Since SARS-Cov-2 is an RNA virus similar to HIV, lopinavir, and ritonavir have been proposed to manage COVID-19. Arrhythmias are reported to be associated with QT prolongation and include ventricular ectopies, ventricular tachycardia including Torsades de Pointes type, and ventricular fibrillation (18). Baseline electrocardiogram (ECG) and further monitoring during the drug administration might be considered to detect QT interval deviations.

VII. Underlying Cardiac Pathology: Patients with **congenital long QT interval syndrome** are at increased risk of malignant tachyarrhythmias, especially in septic conditions or administration of medications that further prolong the QT interval, such as hydroxychloroquine or others with a similar effect (19). **Brugada syndrome** increases the risk of ventricular arrhythmias and sudden cardiac death. Elevated body temperature probably further affects the risk of cardiac arrest in these patients, which is why timely administration of antipyretics is necessary for SARS-Cov-2 infection (19). **Congenital heart abnormalities** such as tetralogy of Fallot, Epstein, valvular defects, and septal defects, are also causes of arrhythmias. They arise based on abnormalities in the conduction system, cicatrixes after corrective surgery, hypoxia, remodeling, changes in cardiac volumes and pressures (20). Patients with **severe heart failure** may develop malignant arrhythmias and die of sudden cardiac death in 40% of cases. Underlying changes in cardiac tissue such as cicatrixes, remodeling, as well as increased levels of catecholamines, and electrolyte disturbances, are the main causes of rhythm and conduction disturbances (21).

VIII.Severe Course of COVID-19 Requiring Intensive Care: Arrhythmias occurring in critically ill patients in intensive care units' account for the majority of cases with these disorders. According to data from a study in China, these were observed in 44% of people (22). Another study reported a 10-fold greater likelihood of developing atrial fibrillation, non-sustained ventricular tachycardia, and bradyarrhythmia. The main factor associated with significance was intensive care unit admission, compared with other variables such as age, sex, race, body mass index, presence of cardiovascular disease, and chronic kidney disease (23). In addition, a strong correlation has been found between mechanical ventilation, high troponin levels, and C-reactive protein in the occurrence of ventricular arrhythmias (24). Atrial arrhythmias were recorded in 17.7% of mechanically ventilated patients treated in an intensive care unit in New York (25). In 23 of 54 critically ill patients, the most common rhythm disturbance was sinus tachycardia (26). The incidence of cardiac arrest in this category of patients is 11% is almost always due to asystole and is significantly associated with in-hospital mortality (23).

Rhythm Disturbances in COVID-19: Data from a survey of 1,197 electrophysiologists worldwide indicated **atrial fibrillation** as the most common tachyarrhythmia (n = 179). Next were ventricular extrasystoles and non-sustained ventricular tachycardia (n = 103), paroxysmal supraventricular tachycardias (n = 39), cardiac arrest due to pulseless electrical activity (n = 38), cardiac arrest due to ventricular tachycardia or ventricular fibrillation (n = 33), sustained monomorphic ventricular tachycardia (n = 26), polymorphic ventricular tachycardia and Torsade de Pointes (n = 24), sustained atrial tachycardia (n = 24). The overall proportion of tachyarrhythmias in this study was 34.26% (27).

Conduction Disturbances and Bradyarrhythmias in COVID-19: Data from the same study indicated sinus bradycardia (n = 51) and complete atrioventricular block (n = 51) as the most

common, followed by hip block and delayed intraventricular conduction (n = 26), second-degree atrioventricular block (n = 21) and first-degree atrioventricular block (n = 18). (27).

In a statistical analysis of 38 published cases of hospitalized patients with COVID-19 in whom bradyarrhythmia was recorded, the second and third-degree atrioventricular block was most commonly registered [in 26 (68%) patients], followed by a bundle branch block (46% left bundle branch block, 54% right bundle branch block) [in 11/26 (42 %)]. Sinus arrest or sick sinus syndrome was described in 12/38 (32%) of them, rarely associated with bundle branch block (8%) (28).

CONCLUSION

Infection with SARS-Cov-2 can lead to severe rhythm and conduction disturbances that increase mortality from COVID-19. A wide spectrum of this pathology has been registered, but the exact mechanisms for its occurrence remain not yet fully understood. It is assumed that the basis is the hyperinflammatory response of the human body combined with a direct toxic effect and penetration of the virus into the heart cell. General practitioners are the most numerous group of medical specialists in Bulgaria and work at the entrance of the healthcare system. They serve a diverse group of patients of different ages and with a variety of co-morbidities, while at the same time, they have established lasting relationships and know their medical and family history well, which helps them and significantly improves their work. In the outbreak of the COVID-19 pandemic, family doctors played an essential role in the diagnosis and treatment of the viral infection, with a number of them themselves losing their lives fighting on the front lines. Given the possible complications from the cardiovascular system during COVID-19, some of which are life-threatening, the competence of general practitioners in this aspect is extremely important. Knowing the rhythm and conduction disturbances accompanying the infection with SARS-Cov-2 determines the timely diagnosis, starting the correct treatment at home, or building a correct judgment about the indications for hospitalization. The high level of clinical training of family doctors and their team is of decisive importance for the prognosis and outcome of the disease and can reduce mortality from cardiovascular complications.

REFERENCES

1. Coronavirus: From bats to pangolins, how do viruses reach us?. // Deutsche Welle, 7 February 2020.
2. Hessami A, Shamshiriand A, Heydari KD, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource center is hosted on Elsevier Connect, the company's public news and information. 2020;(January).
3. Shoar S, Hosseini DM F, D M. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource center is hosted on Elsevier Connect, the company's public news and information. 2020;(January).
4. Zeng L, Wang S, Cai J, Sun S, Wang S, Li J et al. Clinical characteristics of COVID-19 with cardiac injury: a systematic review and meta-analysis. Epidemiol Infect. 2020;148. Published online.
5. Teng S, Tang Q. ACE2 enhance viral infection or viral infection aggravate the underlying diseases. Comput Struct Biotechnol J. 2020;18:2100–6.
6. Alwaqfi NR, Ibrahim KS. COVID-19: an update and cardiac involvement. J Cardiothorac Surg. 2020;15:239.
7. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiol. 2020;5(11):1281-5
8. 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(7):811–8.
9. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang , et al. Association of cardiac injury with mortality in hospitalized patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802–10.
10. Nabeh OA, Helaly MM, Menshawey R, Menshawey E, Nasser MMM, Diaa El-Deen AM. Contemporary approach to understand and manage COVID-19-related arrhythmia. Egypt Heart J. 2021;73:76.
11. Furqan MM, Verma BR, Cremer PC, Imazio M, Klein AL. Pericardial Diseases in COVID19: a Contemporary Review. Curr Cardiol Rep. 2021;23(7):90.
12. Angeli F, Spanevello A, De Ponti R, Visca D, Marazzato J, Palmiotto G, et al. Electrocardiographic features of patients with COVID-19 pneumonia. Eur J Intern Med. 2020;78:101–6.
13. Yang LC, Zhang RT, Guo LJ, Xiao H, Zu LY, Zhang YY, et al. Hypoxia and inflammation are risk factors for acute myocardial injury in patients with coronavirus disease 2019. Beijing Da Xue Xue Bao Yi Xue Ban. 2020;53(1):159-66. Chinese.
14. Dherange P, Lang J. Qian P, Oberfeld B. Sauer WH, Koplan B, et al. Arrhythmias and COVID-19: a review. J Am Coll Cardiol EP. 2020;6:1193–204.
15. Wanamaker B, Cascino T, McLaughlin V, Oral H, Latchamsetty R, Siontis KC. Atrial arrhythmias in pulmonary hypertension: pathogenesis, prognosis and management. Arrhythm Electrophysiol Rev. 2018;7:43–8.
16. Oliver MF. Control of free fatty acids during acute myocardial ischaemia. Heart. 2010;96:1883–84.

17. Gettes L.S. Electrolyte abnormalities underlying lethal and ventricular arrhythmias. Circulation. 1992;85(1 Suppl):I70–6.
18. Darpo B. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. Eur Heart J Supplements. 2001;3(suppl K):S70–S80.
19. 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;17:1456–62.
20. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation. 2007;115:534–45.
21. Parmley W.W. Factors causing arrhythmias in chronic congestive heart failure. Am Heart J. 1987;114:1267–1272. doi: 10.1016/0002-8703(87)90215-8. PMID: 3314442
22. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
23. Bhatla A, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, et al. COVID-19 and cardiac arrhythmias. Heart Rhythm. 2020;17:1439–44.
24. Lakkireddy DR, Chung MK, Gopinathannair R, Patton KK, Gluckman TJ, Turagam M, et al. Guidance for cardiac electrophysiology during the COVID-19 pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. Circulation. 2020;141:e823–e831.
25. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York city. N Engl J Med. 2020;382:2372–4.
26. Chen Q, Xu L, Dai Y, Ling Y, Mao J, Qian J, et al. Cardiovascular manifestations in severe and critical patients with COVID-19. Clin Cardiol. 2020;43:796–802.
27. Gopinathannair R, Merchant FM, Lakkireddy DR, Etheridge SP, Feigofsky S, Han JK, et al. COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies. J Interv Card Electrophysiol. 2020;59:329–36.
28. Gatto MC, Persi A, Tung M, Masi R, Canitano S, Kol A. Bradyarrhythmias in patients with SARS-CoV-2 infection: A narrative review and a clinical report. Pacing Clin Electrophysiol. 2021;44(9):1607-15.