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Cardiovascular Disorders as a Result of COVID-19

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Abstract

Based on the literature data, we present current literature information about frequency, main spectrum, and prognostic value of cardiovascular complications of the SARS-CoV-2 infection. We have highlighted in detail the variants of cardiovascular disorders in the case of patients with SARS-CoV-2 infection caused by concomitant diseases of hypertension, acute coronary syndrome, myocardial infarction, arrhythmias, virus-associated myocarditis, and heart failure. We have described the adverse cardiovascular effects of medicines of different groups used to treat COVID-19 disease and possible medical interactions. We have summarized some current recommendations on cardiotonic and cardioprotective therapy in the case of patients with cardiovascular complications.

Introduction

At present, clinicians postulated following meaning: The development of cardiovascular disorders exacerbates the severity of conditions of those patients who have COVID-19, and increases the level of mortality [1]. Thus, we could come up with the impression that the risk of cardiovascular complications (CVC) of a new coronavirus infection is higher than in the case of those epidemics that were caused by SARS-CoV (severe acute respiratory syndrome) [2] as well as in case of MERS-CoV (Middle East respiratory syndrome) [3]. Italian colleagues have provided us with the following information. There was a 53 years old patient without cardiac comorbidity whose clinical manifestation of the verified COVID-19 was not pneumonia but severe myopericarditis with fever, laboratory changes (increased white blood cells and erythrocyte sedimentation rate, lymphocytosis or lymphopenia, increased fibrinogen, and C-reactive protein levels) as well as hemodynamic destabilization [4].

The meta-analysis, which has covered 1527 clinical observations from different Chinese clinics, has shown that the incidence of hypertension (HP) in case of COVID-19 patients reaches up to 17.1%, cardiovascular diseases (CVD) – by 16.4%, and diabetes mellitus (DM) – by 9.7%, by corresponding to the average frequency of these diseases in case of the Chinese population [5].

It was postulated that the presence of concomitant CVD, including HP, does not increase the risk of COVID-19 morbidity. The data on the frequency of concomitant HP in case of COVID-19 patients have a direct relation to an actively discussed interconnection between the risk of SARS-CoV-2 infections and using of renin-angiotensin-aldosterone system blockers (RAAS) - angiotensin-converting enzyme inhibitors (ACE inhibitors) and blockers of the receptor angiotensin II (BRA).

It is known that the initial stage of SARS-CoV-2 entrance into the target cells is an interaction of the peplomer (spike protein, S-protein) of the virus with ACE of the II type receptors (ACE II), an essential role of which is obtained by transmembrane serine protease TMPRSS2, which is activating the viral peplomer [6]. We have to remind that the ACE II structures are providing, first of all, a formation of angiotensin II from inactive angiotensin I. Several researchers postulated a suggestion that long-term use of ACE inhibitors and/or BRA for the treatment of HP

could increase the expression of the ACE II receptors in respiratory tracts by increasing the risk of COVID-19 morbidity [7]. As a primary basis for these concerns, we could name experimental research demonstrating that ACE inhibitors and BRA could increase the number of ACE receptors in tissues and change their functional activity [8]. However, there were no confirmations of the results mentioned above in other experiments [9], which is why an active discussion on a possible role of an increased number of ACE II receptors on the background of activity of RAAS blockers, as a factor, which is contributing to the SARS-CoV-2 morbidity took place [6], [7].

There was also a discussion on the advisability of ACE inhibitors and BRA discounting in the case of patients with COVID-19. Such suggestions became a subject for debate at the level of scientific cardiology communities in the USA, Europe, and Russia [10], [11], [12], which have postulated their position quite clearly - they have a totally negative opinion on the possibility of discounting ACE and BRA inhibitors in case of COVID-19. There is strong evidence of the fact that ignoring these medicines will definitely increase the risk of cardiovascular events (heart attack, and stroke). The cardiovascular community of Russia strongly recommends clinicians and patients to proceed with taking ACE inhibitors and BRA, as these are life-saving medicines that protect against severe CVC and prolong life, while people with high blood pressure are at risk of developing the most potent forms of COVID-19. Unreasonable withdrawal of taking these medicines could lead to definitely severe consequences on a national scale, significantly exceeding the potential risks associated with coronavirus infection [12].

Indisputable evidence in favor of this position was gained in a recent study provided by Spanish clinicians that included 1139 COVID-19 patients [13]. The severity of the condition is a combination of COVID-19 and CVD could be particularly explained by a high frequency of myocardial damage in the case of patients from this group. It was shown, that pathological increase of level of cardio specific troponin (cTn) in the blood of COVID-19 and HP patients is being disclosed 2.5 times more often than in case of patients without comorbidity (59.8 и 23.4%; $p < 0.0008$), COVID-19 and coronary heart disease (CHD) - 4.9 times more often (29.3 и 6%; $p < 0.001$), COVID-19 and DM - 2 times more often (24.2 и 12%; $p < 0.008$) [14]. There is no doubt that concomitant CVD increases the mortality risk in the case of COVID-19. In a cohort study from two clinics of Wuhan city it was postulated that the frequency of HP in case of COVID-19 patients who died reached up to 48%, when in case of survivors - 23% ($p < 0.0008$); CHD – 24 and 1%, respectively, ($p < 0.0001$) and DM – 31 and 14% ($p < 0.0051$) [15]. We have to underline that patients who died were older (69 y.o. and 52 y.o. $p < 0.0001$), which explains their more pronounced cardiovascular comorbidity with a high degree of probability [15]. Age (EOR 1.14; 95%- AR 1.09–1.18), CHD (EOR 21.4; 95% - AR 4.64–98.76), HP (EOR 3.05; 5%- AR 1.57–5.92), and DM (EOR 2.85; 95% AR 1.35–6.05) are independent predictors of the COVID-19 mortality; however, in case of multivariate analysis it is only age, which retains a predictor significance (EOR 1.10; 95% AR 1.03–1.17) [15], it is obvious, by combining risks that are characteristic for various concomitant CVD. Thus, by not affecting the risk of the SARS-CoV-2 infection, concomitant CVD determines a more severe clinical course of COVID-19 and is a factor in the mortality risk. Regular use of ACE inhibitors and/or BRA for treating HP does not affect the morbidity risk, course severity, and mortality in the case of COVID-19.

The risk factors of CVC in the case of COVID-19 are diverse: CVD and DM, elderly and senile age, concomitant diseases of lungs and kidneys, systemic inflammation and immune reactions, coagulopathy and metabolic disorders, multiple organ dysfunction, prolonged immobilization, and finally, adverse cardiotropic effects of medicines [16], [17], [18]. Types of CVC are also varying widely: Myocardial injury and myocarditis, acute coronary syndrome (ACS) and myocardial infarction (MI), arrhythmias, heart failure (HF) and cardiomyopathy, cardiogenic shock and cardiac arrest, and venous thromboembolism [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29]. We will take a closer look at some of the types of CVC.

Myocardial Injury and Myocarditis

In the case of COVID-19, it is proposed to apply two definitions of myocardial injury: extended and reduced. In the first case, a myocardial injury is defined as one or a couple of the following signs [15], [30]: cTn content in blood, which exceeds the 99th percentile of the upper limit of the reference values; new electrocardiogram (ECG) changes - supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, ventricular fibrillation, bundle branch block, ST-segment elevation/depression, T-wave flattening/inversion, QT prolongation; new echocardiographic (EchoCG) changes - a decrease in the left ventricular ejection fraction (LVEF < 50%) or a subsequent reduction of LVEF in case of patients with LVEF < 50%, impaired general or segmental contractility, pericardial effusion, and pulmonary hypertension. The reduced definition is limited only to ascertaining a level of cTn in blood, which is exceeding the 99th percentile of the upper limit of the reference values, regardless of changes in ECG and EchoCG [14]. In case of applying detailed definitions, the signs of myocardial injury are disclosed in the case of 12–17% of all hospitalized COVID-19 patients and 31% of patients in the respiratory intermediate care unit RICU [19]. According to other data, myocardial injury, which is diagnosed only by the level of

cTn, is characteristical for 19.7% of COVID-19 patients who receive inpatient treatment [14].

The pathological level of cTn I (>28 ng/l by applying a sensitive method of determination) in the case of patients in RICU is being disclosed 8 times more often than in the case of other clinical observations [30]. In the case of patients who died, the content of cTn I, on average, is 10 times higher than that of discharged patients [31]. The patients with a myocardial injury are older than others; they have more significant comorbidity, more pronounced leukocytosis, D-dimer concentration, hyperenzymia, and other clinical and laboratory changes [14]. Among characteristics typical for them we name: Clearly higher ($p < 0.001$) mortality: 51.2–59.6% against 4.5–8.8% in the case of patients without increase of cTn I or cTn T [4], [31]. It was shown that the frequency of an acute myocardial injury in the case of patients, who died, reaches up to 59%, while in the case of survivors – 1%; $p < 0.0001$. The level of cTn I cTn I > 28 ng/l is a predictor of mortality in case of COVID-19: EOR 4.26; 95% AR 1.95–9.49 ($p < 0.001$) [14]. There are several pathogenetic mechanisms of the myocardial injury in the case of COVID-19, which are being discussed: direct myocardial injury, which is meditating by the interaction of the SARS-CoV-2 with myocardial receptors ACE 2, and viral myocarditis - damage of the heart muscle by cytokines and other pro-inflammatory factors, microcirculation disorders and endothelial dysfunction in the coronary bed, and, finally, hypoxic changes of cardiomyocytes [6], [8], [16], [17], [18], [32]. There are inflammatory changes as well as fibrosis in the myocardium of patients who died due to COVID-19 were described [33]. However, there is still no direct evidence of the presence of viral ribonucleic acid (RNA) in cardiomyocytes. On the other hand, in a similar clinical situation, in the case of patients who died due to severe acute respiratory syndrome, there was gained appropriate evidence of the interaction of the SARS-CoV-2 virus with myocardial ACE 2 receptors. What is more, there was RNA of this virus detected in the myocardium [34]. If the myocardium was “SARS-CoV-positive,” morphological signs of its damage were manifested much more transparent, while the life expectancy of patients in the hospital was shorter than in the case of “SARS-CoV-negative” biopsy specimens [34]. The high probability of development and the severity of myocarditis in the case of COVID-19 are beyond doubt [1]. Moreover, the HF, objective features of severe inflammatory damage to the heart muscle (wall thickening, hypokinesis, etc.), and pericarditis may be the main symptoms of COVID-19 [4]. Myocarditis and HF are reported to account for up to 7% of the general structure of COVID-19 mortality [31].

Acute coronary syndrome and myocardial infarction

There are still no precise results of targeted studies related to acute coronary syndrome (ACS) and myocardial infarction (MI) in the case of COVID-19 patients; however, many experts are pointing out a probability of an increased risk of these complications [8], [18]. There are no doubts that in the case of COVID-19, we can postulate the presence of pathogenetic factors of MI of the types I and II [35]. Systemic inflammation may contribute to destabilization and rupture of unstable atherosclerotic plaques, while the increase of procoagulative blood potential - thrombosis of the coronary artery, as a result of what the MI of the I type could develop. The MI of the II type is facilitated by: On the one hand, increased level of cytokines, hypercatecholaminemia, hyperthermia, and tachycardia, which are increasing myocardial oxygen demand, and, on the other hand, hypoxemia, the diastolic myocardial perfusion period shortening in case of tachycardia as well as decrease of contractility with an increase of end-diastolic pressure in ventricles, which are reducing oxygen delivery to cardiomyocytes [8], [18].

There are no MI statistics in the case of COVID-19 patients; however, in the case of other viral respiratory infections and incidence of MI is likely to be significantly increased. According to Kwong, the risk of MI is definitely increased on the chance of laboratory-confirmed flu of A-type (EOR 10.11; 95% AR 4.37–23.38), flu of B type (EOR 5.17; 95% AR 3.02–8.84), and other viral diseases (EOR 2.77; 95% AR 1.23–6.24) [26]. All observations above have prompted clinicians to develop protocols for intensive MI treatment in the case of COVID-19 patients. All detail algorithms described before are designed to provide revascularization of myocardium in combination with minimal risks likewise for patients, as for medical personnel [36], [37], [38]. Considering all possible complications in the sphere of the patients’ transportation in a critical condition with crucial hypoxemia or lack of anti-epidemically equipped X-ray operating rooms, there is a possibility of more active application of systemic fibrinolysis, which is currently considered [38].

Arrhythmias

As etiopathogenetic factors of the cardiac arrhythmias as well as conduction disorders in the case of COVID-19, we could name hypoxia, hyperthermia, agitation, hypercatecholaminemia, electrolyte, and metabolic disorders, myocardial damage, myocardial ischemia/infarction and, finally, side effects of medicines [8], [16], [17], [18], [19]. Among patients, who were hospitalized, the frequency of arrhythmias reaches up to 17%, while in the case of patients, who stay in the RICU, it grows up to 44% [39]. It is noted that arterial hypoxemia increases the probability of the development of atrial fibrillation, especially in the case of older people [17], [19]. As an essential arrhythmogenic factor, we can name myocardial damage, accompanied by an increased content of cardio-specific troponin in blood. In the case of patients with an average level of

biomarkers, the frequency of life-threatening ventricular arrhythmias (VA) reaches up to 5.2%, while in the case of hypertroponinemia, it reaches up to 11.5% [32].

According to recently published data from extensive international research, the antimalarial medicines and macrolide antibiotics prescribed for the treatment of COVID-19 contribute to the VA development [40]. Comparing to the control group, where the VA frequency reached up to 0.3%, in case of monotherapy by hydroxychloroquine the frequency of VA reached up to 6.1% (EOR 2.369; 95% AR 1.935–2.900), in case of prescribing hydroxychloroquine with macrolides – 8.1% (EOR 5,106; 95% AR 4.106–5.983), chloroquine– 4.3% (EOR 3.561; 95% AR 2.760–4.596) as well as combination of chloroquine and macrolides – 6.5% (EOR 4.011; 95% AR 3.344–4.812). There is a possibility that other medicines, which are being applied for the treatment of COVID-19, could also adversely affect the conduction system of the heart as well as could stimulate ectopic foci of excitation [8], [18].

Heart failure

The data on frequency, severity, and clinical significance of HF in the case of COVID 19 are rather limited. The overall frequency of HF reaches up to 23%, and, what is more, if, in the case of survivors, it reaches up to 12%, then, in the case of patients, who died, it increases up to 57% ($p < 0.0001$) [15]. As a laboratory feature of the HF in a couple of researches, its early marker is considered - namely, the level of the N-terminal segment of the B-type natriuretic peptide precursor (NT-proBNP); it is indicated that the biomarker assessment of the myocardial tension in combination with EchoCG allows diagnosing HF [4], [8]. It was described as a normal level of NT-proBNP in the case of patients without signs of myocardial injury (139–141 pg/ml) and a significantly decreased in case of hypertroponinemia (817–1 689 pg/ml) [14], [32]. The development of severe HF is accompanied by increases in the content of NT-proBNP in blood up to 8000–8500 pg/ml [4]. Moreover, in the case of COVID-19 patients, the direct correlation between the index of NT-proBNP and cTn T was shown [32].

In the case of patients, who died due to COVID-19, the biomarker level before death with the presence of morphological signs of myocardial injury was 12 times higher than in observations, where the symptoms above were not detected [33]. There are reasons to believe that it is not a level of NT-proBNP increase affecting the unfavorable prognosis of COVID-19 but its dynamics during the medical treatment process. An increase in the biomarker's indexes is characteristical of negative outcomes of disease [32]. There is no doubt that the diagnostic and prognostic role of biomarkers of the myocardial tension in the case of COVID-19 needs to be studied for further periods. We cannot also exclude the possibility that its increase could be connected with direct cytokines stimulations of the BNP synthesis, as it is assumed in the case of sepsis [41]. There are also other possible reasons for the increase of NT-proBNP content in the blood. However, under other equal conditions, the excessive BNP secretion indicates more likely a progressive dysfunction of the cardiac muscle.

Adverse cardiovascular effects of the medicines prescribed for COVID-19 treatment

It is known that medicines of different pharmacological groups, which are being prescribed for the COVID-19 treatment, could have adverse effects on the cardiovascular system, both due to direct toxic effects as well as due to changes in the pharmacodynamics of other medicines [8], [18]. Combinations of medicines are also quite often prescribed for coronavirus infection treatment, while the risk of dangerous side effects also increases. For example, in the case of combined prescription of antimalarial medicines with azithromycin, the risk of VA is increased not only in the control group but also concerning patients who received hydroxychloroquine/chloroquine monotherapy [40], [41], [42]. Medical interactions may alter the effects of anticoagulants and antiplatelets, antiarrhythmics, and statins. At the same time, pharmacological effects can both increase and decrease [8]. By prescribing medicines for COVId-19 treatment, it is recommended to consider possible interactions with other medicines by adjusting dosages of the latter if necessary [8]. In the table, there are side effects of the most commonly used medicines, which are being prescribed for COVID-19 treatment, are presented. The most acute attention clinicians pay to possible unfavorable cardiotropic effects of hydroxychloroquine/chloroquine. The antimalarial impact of these medicines is connected with its accumulation in lysosomes, an increase in lysosomal pH, a decrease in phospholipase activity, and the inactivation of some proteins. All these effects are assumed to create a background for side effects on the conduction system and cells of the heart's pacemaker. As a result, the risk of atrial and ventricular arrhythmias and conduction disorders up to atrioventricular blockades of varying degrees increases [17] (Table 1).

Prolongation of the QT interval is a hazardous electrophysiological disorder, which can be accompanied by polymorphic ventricular tachycardia and ventricular fibrillation. The mechanism, which is underlying this adverse effect of antimalarial medicines, is not precise. It is possible that the latter are disrupting ion currents in pacemaker cells, slowing down the processes of depolarization and repolarization [17]. The possibility of the QT interval prolongation requires regular ECG control, especially in case of patients with a concomitant CVD and/or with an impaired renal function, in case of electrolyte disorders, as well as in case of prescribing other medicines at the same time,

Table 1: Cardiovascular side effects of the medicines prescribed for the COVID-19 treatment

Medical preparation	Mechanism of action	Side effects	Reference
Remdesivir	Nucleotide analogue blocking RNA-dependent RNA-polymerase	May cause arterial hypotension, arrhythmias	Zhu *et al*. 2020 Williams and Zhang, 2020 Kochi *et al*. 2020
Ribavirin	An inhibitor of viral RNA and DN replication	Interacts with anticoagulants. May cause severe hemolytic anemia	Wang *et al*. 2020
Lopinavir/ritonavir	Protease inhibitor, cytochrome P450-3A4 inhibitor	Interacts with anticoagulants, antiplatelet agents, statins, antiarrhythmics. May cause prolongation of the QT interval, atrioventricular blockade, and ventricular arrhythmias	Long *et al*. 2020 Ruan *et al*. 2020
Favipiravir	RNA-dependent RNA polymerase inhibitor	Interacts with anticoagulants, statins, and antiarrhythmics. May cause severe hemolytic anemia	Guo *et al*. 2020 Oudit *et al*. 2009 Welt *et al*. 2020
Hydroxychloroquine/ Chloroquine	Change in the pH of endosomes and organelles	Interacts with antiarrhythmics. May cause direct cardiotoxicity, cardiomyopathy, causes ventricular arrhythmias, myocardial conduction disturbances, atrioventricular block, bundle branch block, prolongation of the QT interval, polymorphic ventricular tachycardia	Mehra *et al*. 2020
Azithromycin	Binding to bacterial ribosome 5OS, inhibits mRNA translation	Interacts with anticoagulants, statins, antiarrhythmics, and other QT-prolonging agents. May cause ventricular arrhythmias, QT interval prolongation, etc.	Yang and Jin, 2020 Lomivorotov and Lomivorotov, 2019
Interferone -α and–β	Immunostimulator	May cause direct cardiotoxicity, cardiomyopathy, disrupt myocardial conduction. May cause hypotension and myocardial ischemia	Oudit *et al*. 2009 Welt *et al*. 2020
Methylprednisolone	Complex anti-inflammatory effect	Interacts with anticoagulants. May cause fluid retention, hypertension, electrolyte disturbances	Inciardi *et al*. 2020 Williams and Zhang, 2020 Aghagoli *et al*. 2020
Tocilizumab	Interleukin-6 inhibitor	May increase statin metabolism. May cause hypertension	Yu *et al*. 2006 Aghagoli *et al*. 2020 Guo *et al*. 2020

which cause electrophysiological disturbances, for example, azithromycin [42]. Thus, medicines, applied for the COVID-19 treatment can significantly increase a CVC risk in this clinical situation, especially in the case of concomitant CVD and/or development of myocardial injury and myocarditis.

Cardiotropic therapy for COVID-19

The high level of CVC in the case of COVID-19 determines the interest of clinicians in the correct tactics of prescribing sympathomimetic cardiotonics and vasopressors, as well as the advisability of applying for cardioprotective medicines. The possibility of myocardial injury and HF has determined great attention to a current prescription of dobutamine. In the guidelines "Anesthesiological and resuscitation support for patients with a new coronavirus COVID-19 infection" [41], the following fact was postulated, namely: In case of patients with arterial hypotension, despite norepinephrine application, as well as with signs of myocardial dysfunction, it was necessary to prescribe dobutamine, and not to increase norepinephrine dose. This is an important recommendation, as dobutamine is the only sympathomimetic cardiotonic capable of inducing pulmonary vasodilation [43]. Pulmonary hypertension is highly likely in case of community-acquired pneumonia and ARDS [44], including coronavirus infection [30], [45], as well as could lead to severe right ventricular dysfunction/failure [46]. Dobutamine is the sympathomimetic of choice for a treat this acute viral HF.

It is effective in the case of community-acquired pneumonia [47] and the case of treatment of HF as a result of myocarditis due to COVID-19 [4]. Another Russian recommendation [42] for cardiotropic therapy is prescribing phosphocreatine in case of complex treatment of myocarditis and/or myocardial injury, which is associated with COVID-19. In the case of viral myocarditis, the latter's effectiveness was demonstrated in several works performed by Chinese researchers [46], [48]. The mechanism of the complex cardioprotective effect of exogenous phosphocreatine is described in detail [48]. This effect is realized in the case of patients of all age groups, including children [46], [49]. It is essential that phosphocreatinine has no side effects and medical interactions with medicines applied for COVID-19 treatment - lopinavir/ritonavir, hydroxychloroquine, ribavirin, and tocilizumab [41].

Conclusion

It can be postulated that the SARS-CoV-2 virus has a pronounced cardiotropism, which is caused, on the one hand, by the mechanism of infection mediated by ACE 2 receptors, and, on the other hand, by the ability to injure the myocardium due to systemic inflammation, hypercytokinemia hypercoagulability, and the oxygen delivery/consumption imbalance. These pathological processes are especially significant in the case of patients with concomitant CVD, which increases both the risk of severe COVID-19 and death. Myocarditis and HF are not only typical clinical manifestations of the coronavirus infection but also obtain an important place in the structure of mortality. The problem is aggravated due to possibly cardiotoxicity and arrhythmogenicity of some medications prescribed for COVID-19 infection treatment. There is no doubt that it requires maximum cardiological vigilance in the COVID-19 patients'

treatment, the timely use of EchoCG, and ECG, control of biomarkers of damage in the tension of the myocardium, and pathogenetically justified prescription of cardiotonic and cardioprotective medicines.

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