

POSSIBLE EFFECTS OF CORONAVIRUS INFECTION (COVID-19) ON THE CARDIOVASCULAR SYSTEM

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Acute viral respiratory infections can increase the risk of progression of a pre-existing condition, including a cardiovascular pathology. Life-threatening complications of Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) necessitate research into the cardiovascular effects of COVID-19 crucial for developing adequate treatment strategy for infected patients, especially those of advanced age. This article reviews the literature on the clinical and functional characteristics of patients with COVID-19, including those with poor outcomes. The article looks at the pathophysiological processes occurring in the cardiovascular system in the setting of SARS-CoV-2 infection, risk factors and death predictors. It also discusses continuation of therapy with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with COVID-19.

Keywords: coronavirus, cardiovascular diseases, infection, severe acute respiratory syndrome, coronavirus infection 2019, angiotensin-converting enzyme, SARS-CoV-2, COVID-19

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ВЛИЯНИЕ КОРОНАВИРУСНОЙ ИНФЕКЦИИ (COVID-19) НА СЕРДЕЧНО-СОСУДИСТУЮ СИСТЕМУ

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Острые вирусные инфекции дыхательных путей могут увеличить вероятность прогрессирования имеющейся сопутствующей патологии, в том числе сердечно-сосудистого происхождения. Появление жизнеугрожающих осложнений на фоне коронавируса 2 (severe acute respiratory syndrome coronavirus 2, или SARS-CoV-2), вызывающего коронавирусную болезнь 2019 (Coronavirus disease 2019, или COVID-19), обуславливает необходимость изучения кардиоваскулярных эффектов COVID-19 с целью оказания рациональной медицинской помощи пациентам, особенно старшего возраста. В статье представлен обзор литературных данных, посвященных анализу клинико-функциональных особенностей пациентов с COVID-19, в том числе имевших неблагоприятный прогноз. Уделено внимание патофизиологическим особенностям, происходящим на фоне инфекционного процесса в сердечно-сосудистой системе, факторам риска и предикторам летальности при COVID-19. Обсуждается вопрос о возможности продолжения приема ингибиторов ангиотензин-превращающего фермента или антагонистов рецепторов ангиотензина II большинством пациентов с сердечно-сосудистыми заболеваниями и COVID-19.

Ключевые слова: коронавирус, сердечно-сосудистые заболевания, инфекция, тяжелый острый респираторный синдром, коронавирусная болезнь 2019, ангиотензин-превращающий фермент, SARS-CoV-2, COVID-19

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Coronaviruses (CoVs) are a family of positive-sense single-stranded RNA viruses organized into two subfamilies and, as of January 2020, numbering 40 different species. CoVs infect animals and humans and are capable of rapid mutation and genetic recombination. CoVs owe their name to their appearance: their spike-like projections resemble the sun's corona. The spikes allow the virus to penetrate the cell membrane by mimicking the molecules recognized by the transmembrane receptors. Once the receptor has bound to the "impostor" molecule, the virus pushes it into the cell and the viral RNA gets inside.

Acute respiratory infections, such as influenza, respiratory syncytial virus infection and bacterial pneumonia, are widely acknowledged as triggers for cardiovascular diseases (CVD); in turn, pre-existing CVD are associated with other comorbid

conditions and can increase the risk of inflammation or aggravate its progression.

The outbreak of the novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly escalated into a pandemic; the majority of the infected patients are reported to have CVD [1].

The prospective cohort observational ARIC (atherosclerosis risk in communities) study has demonstrated that there is a higher risk of coronary heart disease (CHD) and ischemic stroke within up to 90 days after a past infection. The study looked at 1,312 CHD and 712 ischemic stroke cases with a past history of infections within one or two years preceding the cardiovascular event. The mean age of the participants was 75 years; 57.4% of the patients with CHD were male, whereas

54.1% of the patients with stroke were female. Of 1,312 individuals with CHD, 119 (9.1%) had a history of an inpatient infection, whereas 366 (27.9%) had a history of an outpatient infection. The most common were urinary tract infections (29%), pneumonia or respiratory infections (27%), skin/subcutaneous infections (11%), and blood infections (8%). Inpatient infections remained a stronger trigger of cardiovascular events throughout the entire follow-up period (day 14 OR = 12.83, day 30 OR = 8.39, day 42 OR = 6.24, day 90 OR = 4.48) than outpatient infections ($p < 0.05$). Therefore, hospitalized patients with an inpatient infection should be closely monitored in order to take timely measures to prevent CHD or stroke [2].

In light of this, pathophysiological processes triggered by coronavirus infections in the cardiovascular system certainly pose a great interest. Since our knowledge of the mechanisms underlying COVID-19 effects is scarce yet, the analysis of data collected during the outbreaks of viral pneumonia and MERS (Middle East respiratory syndrome coronavirus, MERS-CoV), as well as seasonal influenza, will provide a better understanding of how coronaviruses exert their effects on the cardiovascular system. This has important implications for the development of comprehensive strategies for the timely management of infected advanced-age patients with CVD.

Effects of coronavirus on human organism

Coronaviruses get their name from the crown-like spikes on their surface. These viruses are members of the Coronaviridae subfamily clustered into 4 phylogenetic groups: α , β , γ , and δ CoVs. Only α and β CoVs can cause infection in humans. Coronaviruses have 4 main structural proteins: the spike protein (S), which ensures attachment to the host cell receptor and subsequent fusion with the cell membrane, the nucleocapsid protein (N), the membrane protein (M), and the envelope protein (E).

Human coronaviruses (HCoVs) were discovered in 1965 when the first HCoV was isolated from the culture of human embryo tracheal tissue. By 2003, two types of HCoVs had been identified: HCoV-229E and HCoV-OC43.

Today, 7 different CoV strains are known to infect humans, including HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 that normally cause self-resolving symptoms. The virus can also cause severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and fatal acute respiratory syndrome resulting from SARS-CoV-2 infection.

Endemicity of coronavirus

Four types of HCoVs, including HCoV-229E (α -CoV), HCoV-NL63 (α -CoV), HCoV-OC43 (β -CoV), and HCoV-HKU1 (β -CoV), are endemic to humans and normally cause a mild respiratory infection with self-resolving symptoms, accounting for 15 to 30% of acute respiratory infections (ARI). As a rule, mild symptoms develop in young patients; in older patients, especially those with cardiovascular or bronchopulmonary pathology, the infection can provoke hospitalization and require emergency care [3].

Severe acute respiratory syndrome caused by coronavirus

The first SARS-CoV outbreak occurred in Guangdong province, South China, in 2002 [4]. Shortly after SARS-CoV was isolated and identified, similar SARS-like CoVs were detected in Himalayan palm civets and raccoon dogs; their nucleotide sequence was 99.8% homologous to that of SARS-CoV isolated from humans [5].

SARS-CoV is a representative of the β -CoV group; it binds to a zinc peptidase angiotensin-converting enzyme 2 (ACE2), which is a surface molecule exploited by the virus to enter the host cell. ACE is present in various organs and tissues; it is an integral plasma membrane protein found in endothelial, specialized epithelial, neuroepithelial, nerve terminal, and reproductive system cells. The role of ACE is not limited to the regulation of cardiovascular system functions. It also participates in hematopoiesis and the metabolism of some bioactive peptides [6].

ACE2 is found in arterial and venous endothelial cells, smooth muscle cells of the arterial wall, the epithelium of the respiratory tract and the small intestine, and immune system cells. It is hypothesized that the inhibition of ACE2 expression in patients infected with SARS-CoV is implicated in the pathological changes to pulmonary tissue, causing severe pneumonia and acute respiratory failure.

Research studies on wild animals proved that SARS-CoV could have originated in bats: Chinese horseshoe bats were found to harbor a SARS-like CoV with high nucleotide homology (87–92%) to SARS-CoV isolated from humans. Palm civets and raccoon dogs are putative intermediate hosts for SARS-CoV amplification preceding its transmission to other animals through contact at a market. SARS-CoV is transmitted from human to human by respiratory droplets during close contact (airborne spread).

There is a proposition about the possibility of the fecal-oral transmission route for SARS-CoV-2 predicated on the fact that patients stricken by SARS or MERS during the past outbreaks often had gastrointestinal symptoms, such as diarrhea and abdominal pain, and SARS-CoV RNA was detected in the feces of 14.6% patients with SARS or MERS [7]. Some patients presented with fever and diarrhea before developing pronounced respiratory symptoms [8]. In vitro studies have demonstrated that MERS-CoV can infect and replicate in the intestinal epithelium of humans using dipeptidyl peptidase 4 as a receptor. In vivo studies have revealed that inflammation and epithelial degeneration in the small intestine can precede pneumonia in MERS, confirming that pulmonary MERS-CoV-induced infection can be secondary to the enteric infection [9].

According to some authors, the incubation period for SARS-CoV-2 varies between 2 and 11 days, being 5.2 days on average (95% CI 4.1–7.0) [10]; other researchers report that the incubation period lasts up to 14 days [11].

SARS-CoV can be excreted into the environment and transmitted by hand contact between patients and healthcare workers; this means that surfaces must be sanitized and the nose, mouth and eyes must be protected against the virus [12].

The ability of an infected individual to spread the virus to other people is inferred from the R_0 (basic reproduction number) value. For SARS-CoV, R_0 is about 3, i.e. a person infected with SARS-CoV will potentially infect 3 other people in a susceptible population. The average R_0 value for seasonal flu (swine flu, H1N1) is about 1.3 [13] (Table 1).

So far, no effective vaccine or medication against SARS-CoV has been developed. The clinical management of patients with SARS includes supportive symptomatic treatment and prescription of broad-spectrum antimicrobials against secondary bacterial infection. Advanced age (upwards of 60 years), multimorbidity (diabetes mellitus, CVD, cancer, chronic obstructive pulmonary disease), and elevated lactate dehydrogenase are predictors of death in patients with SARS-CoV infection. Some authors point to insignificant morbidity and mortality rates in children and adolescents in the past SARS outbreaks [14].

At the same time, preliminary data on 4,226 confirmed COVID-19 cases in the USA suggest high mortality in patients aged ≥ 85 years (10–27%). In patients aged 65–84 years, the case mortality rate ranged from 3 to 11%; in patients aged 55–64 years, it was 1–3%, whereas in patients aged 20–54 years, less than 1%. No deaths were reported in patients aged ≤ 19 years. There were young patients among the hospitalized individuals. Deaths registered in the group of patients aged 20–64 years amounted to 20% of overall case mortality; in this age group, hospitalized patients aged 20–44 years made 20% [15].

Currently, there is a paucity of published studies investigating risk factors and death predictors in patients with COVID-19. Starting on December 25, 2019 through January 26, 2020, a study was conducted in 201 patients with COVID-19 aged 43 to 60 years (the median age was 51), of whom 63.7% were men, revealing that 32.8% of the participants had a pre-existing condition. The median hospital stay was 13 (10–16) days; 33% of the patients required mechanical ventilation; the median interval between admission to hospital and progression to SARS was 2 (1–4) days. Blood tests revealed that the majority of the patients had elevated lactate dehydrogenase (98%), elevated C-reactive protein (85.6%), elevated interleukin 6 (48.8%), and elevated D-dimer (23.3%). Age upwards of 65 years, neutrophilia, organ dysfunction, and coagulation dysfunction were associated with progression to acute respiratory distress syndrome (ARDS) and death. In the patients who developed ARDS, administration of methylprednisolone was associated with lower mortality (46%), as compared to methylprednisolone-free treatment (61.8%) (OR 0.38) [16].

Clinical presentations of COVID-19

The most prevalent COVID-19 symptoms include fever, cough, labored breathing (shortness of breath or rapid breathing). Myalgia, anorexia, nausea, malaise, sore throat, nasal congestion, and headache are less common. The symptoms can set in as early as 2 days after contact with an infected person or by day 14 following such contact. The viral load does not differ between symptomatic and asymptomatic patients, suggesting a possibility of transmission from an asymptomatic individual or a patient with mild symptoms to another person. The highest number of viral copies is detected in nasal swabs, as compared to throat swabs. The diagnosis of COVID-19 is confirmed by PCR. Mucosal specimens for PCR are collected either from the upper or the lower respiratory tracts. A case of COVID-19 is assumed to be confirmed if the laboratory test for the presence of SARS-CoV-2 RNA returns a positive result even in the absence of clinical symptoms. Point-of-care serological tests are expected to be available in the nearest future.

Potential mechanisms underlying the effects of coronavirus infection on the cardiovascular system

The danger of ARI lies surging mortality from chronic diseases during an epidemic, especially among patients with cardiovascular pathology. According to a systematic review which included 42 publications and 39 clinical studies and was published in 2009 patients were at heightened risk of

myocardial infarction (OR 4.95; 95% CI 4.4–5.5) and stroke (OR 3.2; 95% CI 2.8–3.6) in the first few days following the onset of ARI; over time, this risk was gradually decreasing [17].

The hypothesis that influenza can provoke acute cardiovascular events and death was proposed in the 1930s. It was then that a link was noticed between the seasonal activity of flu viruses and higher mortality from all causes, including bronchopulmonary pathology, pulmonary TB, diabetes mellitus, organic heart disease, and hemorrhagic stroke [18].

In 2004, another study reported a vast array of life-threatening clinical manifestations of coronavirus infection, including death from myocardial infarction (2 of 5 deaths); this unveiled the need for prompt treatment of CVD patients during a potential epidemic of a respiratory infection [19].

The lessons learnt from past epidemics caused by coronaviruses inspired a hypothesis that viral infections can provoke acute coronary syndrome, arrhythmias, heart failure, and thromboembolic complications resulting from the pronounced systemic inflammatory response combined with localized vascular inflammation.

In this respect, COVID-19 should not be an exception. It seems to affect the clinical course of pre-existing CVD and trigger development of life-threatening complications [20].

The severity of clinical manifestations, long- and short-term cardiovascular effects of COVID-19, and the effects of specific treatment are yet to be researched. It should be noted that during flu epidemics the majority of patients die of cardiovascular complications and not of virus-induced pneumonia itself. Considering the extreme inflammatory load caused by COVID-19 and the available clinical data on other coronavirus-related infections, one can expect to see serious cardiovascular complications in patients with COVID-19; their prevalence and severity will probably be lower in outpatients than in hospitalized individuals.

In a recently published study [21], 73% of 41 inpatients with laboratory-confirmed COVID-19 were men and 32% had pre-existing conditions, such as diabetes mellitus (20%), arterial hypertension (AH) (15%), and other CVD (15%). The median age of the patients was 49 (41–58) years. Among the most common symptoms of COVID-19 were fever (98%), cough (76%), sputum production (28%), myalgia or fatigue (44%), headache (8%), hemoptysis (5%), and diarrhea (3%). Lymphopenia was observed in 63% of the patients, shortness of breath, in 55%. The median time from the onset of symptoms to developing shortness of breath was 8 (5–13) days. Some of the complications included ARDS (29%) and acute cardiac injury (12%).

Another study conducted in 1,099 in- and outpatients with laboratory-confirmed COVID-19 (median age of 47 years; 42% women) found that the most common pre-existing conditions were AH (14.9%), diabetes mellitus (7.4%) and CAD (2.5%). ARDS (3.4%) and shock (1.1%) were the most severe complications [22].

In most patients with myocarditis, viral infection and the immune response to it are the root causes of inflammation. The leading mechanisms underlying myocardial injury in the acute phase of myocarditis are invasion of cardiomyocytes by viral particles that have tropism for myocardial tissue, the direct

Table 1. Characteristics of coronaviruses

Coronavirus species	Receptor	Incubation period (days)	R0	Co-existing CVD, %	Mean case fatality rate, %
SARS-CoV	ACE2	2–11	3	10	10
SARS-CoV-2	ACE2	2–14	2–3	от 3.4* до 40**	0.7–8***

Note: * — overall rates; ** — in hospitalized patients; *** — depending on time, geographical area and medical help available.

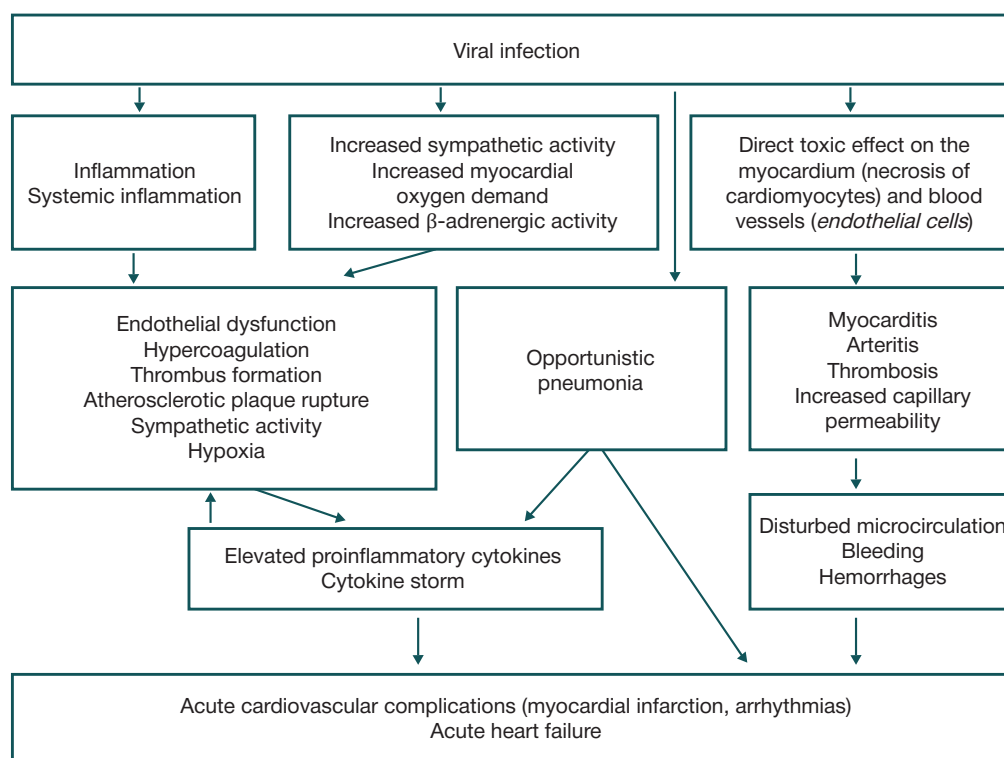


Fig. 1. Effects of viral infection on the cardiovascular system and the myocardium

cytopathic effect of the virus and the activation of nonspecific mechanisms of antiviral defense implemented by macrophages and NK cells. Activated macrophages and other immune cells start to produce chemokines and thus recruit T and B cells to the inflammation site. The recruited cells drive cell-mediated cytotoxicity and launch production of antiviral antibodies, thus triggering the mechanism of cardiomyocyte apoptosis, which eventually results in systolic heart failure.

The findings of sporadic autopsies and reports of severe myocarditis with left ventricular systolic dysfunction after a past COVID-19 infection suggest that the myocardium gets infiltrated by interstitial mononuclear inflammatory cells [23]. A study of cardiac biomarkers points to the high prevalence of myocardial injury in hospitalized patients; this condition is an important prognostic factor for COVID-19 [24].

Myocarditis is a polyetiological disease. It can be caused by viral or bacterial agents, as well as by non-infectious factors. Over 50% of myocarditis cases are associated with a viral infection. Parvovirus B19, Coxsackie A and B enteroviruses, ECHO-viruses, rubella virus, adenoviruses, human herpesvirus 6, Epstein-Barr virus, influenza virus, cytomegalovirus, etc. have high tropism for cardiomyocytes [25].

Clinical presentations of myocarditis are diverse and nonspecific. The diagnosis relies on a triad of medical history findings: the acute onset of the disease, the established link between the onset or exacerbation of symptoms/arrhythmias and the infection, and the time elapsed from the infection (≤ 1 year). Additional criteria include systemic immune manifestations, the combination of arrhythmia and conductivity disorders, and the positive effect of prescribed steroids [26].

In a recently published paper, researchers describe the results of observation of 416 inpatients with COVID-19; 57 (13.7%) of the patients eventually died [27]. Of them, 10.6% had CAD; 5.3%, cerebrovascular disease; 4.1%, heart failure; one in 5 patients had elevated high-sensitivity troponin levels. Patients with elevated troponin were of advanced age, had

more comorbidities, lymphopenia, higher white cell count and higher levels of atrial natriuretic peptide, C-reactive protein and procalcitonin than those with normal troponin levels. Patients with acute inflammatory heart disease developed ARDS more often than those without acute cardiac condition (58.5% vs 14.7 %, respectively; $p < 0.001$); the proportion of deaths in this group was also higher (51.2% vs 4.5%, respectively; $p < 0.001$). Multivariate analysis confirmed that acute heart failure (OR 4.26) and ARDS (OR 7.89) were predictors of poor outcome in patients with COVID-19.

Similar results are reported by other authors [24], who found that 27.8% of 187 included patients with confirmed COVID-19 had developed acute cardiovascular complications resulting in cardiac dysfunction and arrhythmias; a combination of cardiovascular complications with elevated high-sensitivity troponin was associated with high mortality.

Although pathophysiological mechanisms underlying myocardial injury in patients with COVID-19 are heavily understudied, there is evidence that the SARS-CoV genome is found in the myocardium of 35% of patients with SARS. These findings increase the probability of direct damage to cardiomyocytes by the virus. SARS-CoV-2 might utilize the same mechanism of action as SARS-CoV as these two species are genetically close, although not identical. The close correlation between elevated high-sensitivity troponin and C-reactive protein levels implies the inflammatory origin of myocardial injury in the progressive disease phase. As viral particles spread along the respiratory tract and invade host cells, they may trigger a cytokine storm ensuing from the imbalance in Th1 and Th2 production and a cascade of immune reactions that lead to myocardial injury. In the setting of infection, secretion of cytokines can cause a reduction in coronary blood flow and oxygen supply, atherosclerotic plaques destabilization and formation of microclots (Fig. 1).

Myocarditis is often manifested as arrhythmias, progressive heart failure and sudden cardiac arrest that can occur at any stage of the disease.

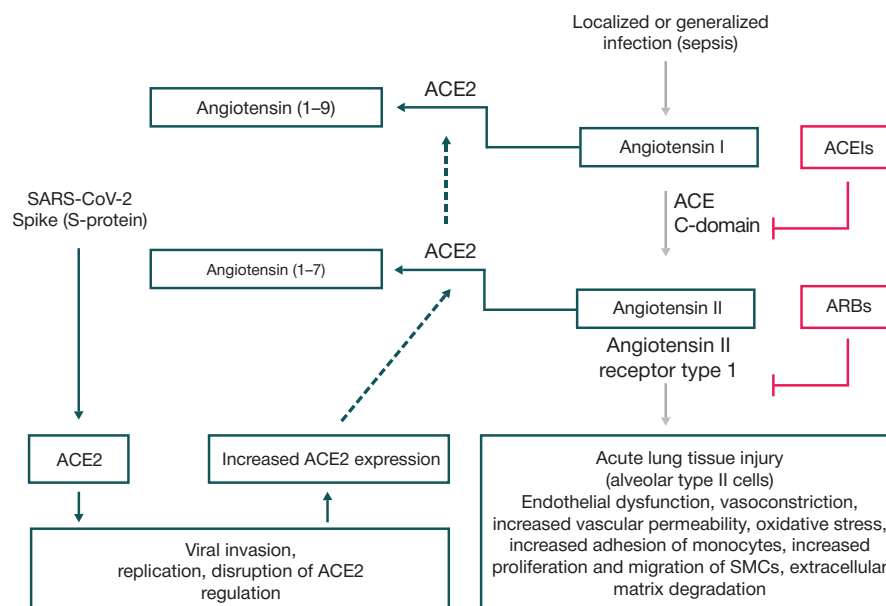


Fig. 2. Interactions between SARS-CoV-2 and the renin-angiotensin-aldosterone system. Interaction between SARS-CoV-2 and the renin-angiotensin-aldosterone system. Invasion of host cells (alveolar type II cells, in particular) by SARS-CoV-2 occurs through the binding of the virus to the functional domain of ACE2. ACE2 expression changes following endocytosis of the viral complex. This results in the accumulation of a potent vasoconstrictor angiotensin II and, possibly, mitigates the vasodilator effect of angiotensin (1–7). Local activation of the renin-angiotensin-aldosterone system can mediate damage to the lungs in response to viral infection, whereas increased ACE2 expression can aggravate pulmonary damage in patients with COVID-19. ACE2 converts angiotensin I to angiotensin (1–9) (its functions are being studied) and angiotensin II to angiotensin (1–7). This process is accompanied by inactivation of angiotensin II and synthesis of angiotensin (1–7); the latter stimulates vasodilation, reduces oxidative stress and fibrosis. ACE — angiotensin-converting enzyme; ACEI — ACE inhibitors; ARB — angiotensin II receptor blockers; SMC — smooth muscle cells. ACE — angiotensin-converting enzyme; ACEIs — ACE inhibitors; ARBs — angiotensin II receptor blockers; SMCs — smooth muscle cells

Among the first symptoms of myocarditis are malaise, fatigue, myalgia, and sometimes low-grade temperature caused by the inflammatory response to the virus but not by myocardial injury itself. Other manifestations of myocarditis include sudden cardiac arrest due to ventricular tachycardia or ventricular fibrillation following damage to the conducting system of the heart, thromboembolism, syncope, cardiogenic shock, and acute heart failure. The first clinical symptoms can set in at the onset of ARI or a few days after its onset.

There are a number of obstacles complicating the diagnosis of viral myocarditis. The primary diagnostic criterion for myocarditis is the established link between cardiac symptoms and a past infection and the signs of inflammation. The diagnosis can be facilitated by a full medical examination of the patient, which includes clinical, laboratory and instrumental tests, and by endomyocardial biopsy performed to rule out the inflammatory nature of myocardial injury [28].

Unfortunately, currently there is no substantiated evidence about the efficacy of existing antivirals and vaccines against COVID-19. Patients with pre-existing CVD are at high risk of complications, a more severe course of the disease and poor outcomes; therefore, CVD patients with COVID-19 should be stratified depending on their primary condition (CVD) and its severity in order to decide on the treatment strategy. Electrocardiography and cardiac biomarker tests (NT-proBNP) can be employed to control the condition of the patient and the course of treatment.

There is a lot of controversy over whether patients infected with a coronavirus should continue angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs). The fears are predicated on the fact that the protease domain of ACE2 is a potential target for SARS-CoV and SARS-CoV-2 and that increased expression of ACE2 can aggravate damage to the lungs in patients with COVID-19 (Fig. 2) (adapted from [29]).

ACE2 exists in 2 forms: as a structural transmembrane protein with an extracellular domain, which serves as a target

for the S protein of SARS-CoV-2, and as a soluble circulating form. Invasion of host cells (alveolar type II cells in the first place) by SARS-CoV-2 occurs through the binding of the virus to the protease domain of ACE2. Upon endocytosis of the viral complex, ACE2 expression changes, causing increased accumulation of a potent vasoconstrictor angiotensin II. The local activation of the renin-angiotensin-aldosterone system (RAAS) can mediate damage to the lungs in response to viral infection [30].

Angiotensin (1–7) is a substrate for the N-domain of ACE; it suppresses the activity of ACE C-domain and limits pressor and vasoconstrictive effects of angiotensin II.

The role of this process in the development of COVID-19-related complications and the effects of the possible modulation of the ACE2 receptor are not fully clear and expected to be investigated in the clinical trials of human recombinant ACE2 (NCT04287686) and other therapeutic agents.

In the group of patients with COVID-19 and high troponin levels, the duration of therapy with ACEIs/ARBs prescribed for pre-existing CVD did not have any effect on mortality [22]. In another study, a positive effect of ACEIs/ARBs was observed in patients with viral pneumonias because the drugs significantly reduced inflammation and secretion of proinflammatory cytokines triggered in response to infection [31]. The beneficial effect of ACEIs/ARBs might be associated with the compensatory increase in ACE2 production. So far, there are no data on the use of ACEIs/ARBs in patients with COVID-19, which raises the need for further large-scale clinical studies.

At present, the experts from the European Society of Cardiology [32], the American Heart Association [33] and the Russian Society of Cardiology [34] recommend that patients with COVID-19 who had indications for ACEIs/ARBs and were taking these drugs before the infection should continue them because there is no evidence of their inefficacy in such patients.

Also, there are no experimental or clinical data demonstrating positive or negative effects of ACEIs/ARBs or other RAAS antagonists in patients with COVID-19, as well as in patients

Table 2. A non-exhaustive list of clinical trials of drugs for the prevention and treatment of COVID-19

Drug	Start date	Estimated completion date	Trial ID at ClinicalTrials.gov
Remdesivir	February 21, 2020	April 1, 2023	NCT04280705
Human recombinant ACE2	February 2020	April 2020	NCT04287686
Remdesivir	March 2020	May 2020	NCT04292899
Injections and infusions of the LV-SMENP-DS and antigen-specific cytotoxic T cell vaccines	February 24, 2020	December 31, 2024	NCT04276896
Fingolimod	February 22, 2020	July 1, 2020	NCT04280588
Human mesenchymal stem cells	February 24, 2020	February 1, 2021	NCT04293692
Carrimycin	February 23, 2020	February 28, 2021	NCT04286503
Methylprednisolone	February 14, 2020	May 30, 2020	NCT04273321
Washed microbiota transplantation	February 2, 2020	April 16, 2020	NCT04251767
Losartan	March 16, 2020	April 1, 2021	NCT04312009
2019-nCoV vaccine (mRNA-1273)	March 3, 2020	June 1, 2021	NCT04283461
Lopinavir / ritonavir tablets combined with xiyangping injection	March 14, 2020	April 14, 2021	NCT04295551

with COVID-19 and a history of CVD. If a patient with CVD is infected with COVID-19, the treatment strategy should account for their overall symptoms and hemodynamics.

RAAS activation plays a crucial role in the pathogenesis of many CVD. Long-term effects of increased renin and angiotensin II production and the activity of the sympathetic nervous system include left ventricular hypertrophy, dyslipidemia, arrhythmias, hypercoagulation, endothelial dysfunction, insulin resistance, and metabolic syndrome. ACEIs and ARBs that have been studied and successfully used in the clinical setting for many years are first-choice drugs for treating chronic heart failure, AH, renal disorders, and diabetes mellitus [35, 36].

The ACE2-dependent entry of SARS-CoV-2 into the host cell can be blocked by camostat mesylate, the inhibitor of serine protease TMPRSS2 used by SARS-CoV-2 for S protein priming. Camostat mesylate is a promising candidate for further trials [37].

Among the antivirals for treating flu, oseltamivir does not have any effect on SARS-CoV-2 although preliminary studies have demonstrated some positive effects of favipiravir. Table 2 features a few drugs which are now in clinical trials or being considered as candidates for clinical trials in patients with COVID-19.

CONCLUSIONS

The data collected so far suggest a high prevalence of comorbidities in middle-aged and old patients with COVID-19. The most common cardiovascular conditions are AH (about 15%), diabetes mellitus (7.4–20%) and CAD (about 2.5%). Patients with COVID-19 and a pre-existing cardiovascular pathology are at high risk of developing ARDS, shock and death. Acute cardiac failure and ARDS are regarded as predictors of poor outcomes in patients with COVID-19.

It is crucial to study different aspects of screening, diagnostics, clinical manifestations, prevention and management of patients with COVID-19. As the infection spreads and more data are accumulated, risk factors for cardiovascular complications should be thoroughly investigated.

Perhaps, creating a registry of patients with COVID-19 and systemic reporting of clinical symptoms and cardiovascular and other complications will help to elucidate the characteristics of the infected patients, develop approaches to the treatment and prevention and design a risk model for predicting complications.

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