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Review article

COVID -19 cardiovascular view and brief therapy overview

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Abstract SARS-CoV-2 virus binds to transmembrane angiotensin-converting enzyme 2 (ACE2), homologue of ACE to enter different cell types, through following mechanism: direct cytotoxic effect, dysregulation of the RAAS, endothelial cell damage with thromboinflammation and dysregulated immune response. Consistent RAAS activation results in imbalance of Ang II hyper-production and inhibition of Ang-(1-7) formation, which increases inflammation, vascular hiperpermeability, prothrombogenesis and decreases anti-inflammatory and antithrombogenic properties. This endotheliopathy begins with impaired endothelium starting coagulation, platelet and fibrinolytic cascade. COVID-19 affect cardiovascular system by ischemic components (myocardial damage, endothelial dysfunction, microvascular dysfunction, plaque instability, ACS), non-ischemic components (cytokines storm, stress cardiomyopathy, metabolic dysfunction, sympathetic neuronal activation, electricity imbalance) and comorbidites (age, hypertension, diabetes, obesity, CAD, COPD, cancer). Consequently CV complications are arrhythmias, cardiac injury (20–40% of hospitalized cases, including MINOCA), myocarditis, heart failure, cardiogenic shock (multiorgan failure), pericardial effusion, pulmonary embolism, disseminated intravascular coagulation. STEMI in COVID-19 had higher rates of stent and multi-vessel thrombosis, higher thrombus burden, use of glycoprotein IIb/IIIa inhibitors.
Standard cardiovascular therapies should be used as appropriate (including ACE inhibitors/ARBs). No convincing evidence was found for the use of reconvalescent plasma, colchicine, hydroxychloroquine, hloroquine, azithromycin and strong evidence in reduced mortality for using corticosteroids, tocilizumab (anti-IL-6R Ab) in severe COVID-19 forms and bamlanivimab (SARS-CoV-2 neutralizing Ab) for the treatment of mild to moderate forms who are at risk for severe progression.

Key words COVID-19, cardiovascular complications, RAAS, endothelial dysfunction, ischemic cardyomiopathy, inflammation

Coronaviruses are RNA viruses within the family Coronaviridae (namely the alpha-, beta-, gamma-, and deltacoronaviruses). Alpha- and betacoronaviruses infect mammals, gamma- and deltacoronaviruses infect birds. There are seven coronaviruses that infect humans: the alphacoronaviruses that cause a mild illness in adults; the betacoronaviruses Middle east respiratory syndrome (MERS) virus and severe acute respiratory syndrome (SARS) virus, which cause a severe respiratory illness. COVID-19 is caused by a novel betacoronavirus, probably originating from bats following gain-of-function mutations within the receptor-binding domain (RBD). WHO named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1]

SARS-CoV-2 after proteolytic cleavage of its S protein by a serine protease, binds to the transmembrane angiotensin-converting enzyme 2 (ACE2), homologue of ACE to enter type 2 pneumocytes, macrophages, perivascular pericytes, cardiomyocytes and endothelial cells. Mechanism of viral entry are comprehensive: direct cytotoxic effect, dysregulation of the RAAS, endothelial cell damage with thromboinflammation and dysregulated immune response.

This may lead to myocardial dysfunction and damage, endothelial dysfunction, microvascular dysfunction, plaque instability and myocardial infarction. While ACE2 is essential for viral invasion, there is no evidence that ACE inhibitors or angiotensin receptor blockers (ARBs) worsen prognosis. There are two trials BRACE CORONA and REPLACE COVID, of patients with COVID-19 taking renin-angiotensin-aldosterone system inhibitors that reported no differences in outcomes between patients with COVID-19 who discontinued their medication and those who did not.[7]

Infection by coronaviruses affect ACE2 receptor function, by SARS CoV-2 virus binding to ACE2 that contributes to the disease burden. There is a consistent activation of the RAAS resulting in elevated Ang II that has been linked to vascular hyperpermeability, severe acute lung injury, hypokalemia as a possible sign of hyperaldosteronism. On the other hand decreased degradation of Ang II to Ang-$^{1–7}$ have pro-inflammatory and prothrombogenic effects. Reduced vascular protection is due to depletion of Ang-$^{1–7}$ and the lack of its anti-inflammatory, antioxidant and vasodilating properties , which arises increased cardiovascular risk in COVID-19. (Figure 1)

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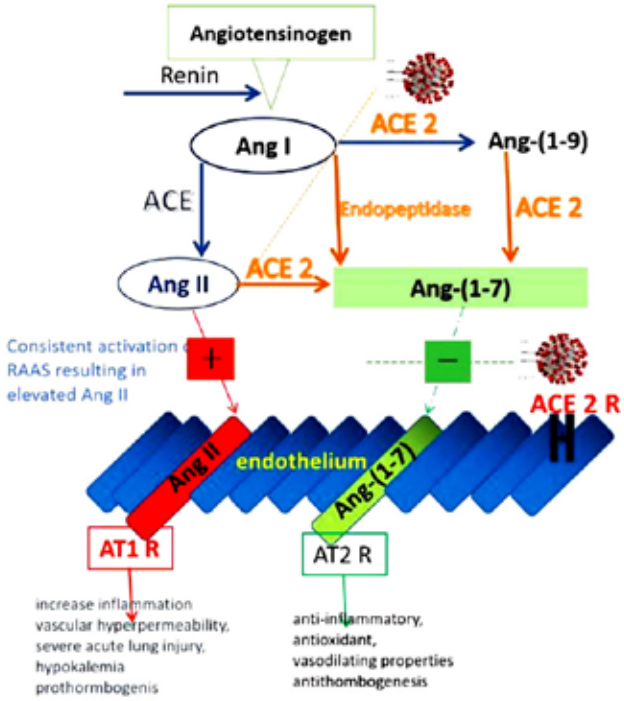

Figure 1. Mechanism of SARS CoV-2 virus influence (binding to ACE2) on disbalance of Ang II hyperproduction and inhibition of Ang -(1-7) formation, which results in increased inflammation, vascular hiperpermeability, prothrombogenesis and decreased anti-inflammatory response, antioxidants and antithrombogenic properties

Renin–angiotensin–aldosterone system (RAAS) inhibitors might be beneficial in COVID-19 not only by its antihypertensive effect but also by their effect on potassium metabolism. Hypokalaemia is a common manifestation of COVID-19, possibly through increased kaliuresis driven by activation of the RAAS, but also there is an impact of gastrointestinal loss. Hypokalaemia in COVID-19 patients is difficult to manage, correlates with the severity of the disease and has been suggested that ACEIs or ARBs might be benefitial.[2] Hypocalcaemia is also common metabolic abnormality in patients infected by COVID-19, could be due to reduced albumin levels, which are commonly seen, and/or calcium consumption through excessive activation of the coagulation cascade.[9] Hypoglicemia may induce an increase in hormonal adrenergic activity resulting in further inflammatory stress, besides representing a risk factor for cardiovascular and total mortality in diabetic patients, could represent a trigger mechanism for the "cytokine storm" during COVID-19 disease. It is recommended achievement of optimal glycemic control, avoiding both hyper and hypoglycemia, to prevent or mitigate cytokine storms and improve prognosis.[8]

Risk of severe infection and mortality increase with advanced age and male sex (sexual dymorfism). Mortality is increased by comorbidities: cardiovascular disease, hypertension (the worst morbidity rate 10.4%), diabetes, chronic pulmonary disease, obesity (in current Italian and Dutch cohorts) and cancer.[3] Similarly, in the recent analysis of 5700 Patients Hospitalized With COVID-19 in the New York City Area the most common comorbidities were hypertension (57%), obesity (42%), and diabetes (34%). Curiously, the prevalence of smoking in hospitalized COVID-19 patients appears far lower than might be expected from assumed population.[1]

Early infection stage is virus spreading and proliferation and initial innate immunity. Initial immune and inflammatory responses induce a severe cytokine storm (IL-6, IL-7 etc) during the rapid progression phase of COVID-19[4]. IL-6 is a biomarker and startes cardiovascular disregulation, connected with progressive aterothrombosis, hypotension, left ventricular disfunction. The main actor is the damaged endothelial barrier- endothelial cells, influenced by increased vascular permeability because of existing endothelial inflammatory response, consequently reduced NO and impaired angiogenesis. Other pathway is associated coagulopathy, begining with this impaired endothelium and releasing of tissue factor, starting coagulation cascade, platelet activation and concurrently the fibrinolitic process. This endotheliopathy in Covid -19 is a result of direct binding of spike (S) protein from SARS CoV2 virus to the cell surface and endocitosis, but on the other hand comorbidity cardiovascular factors (hypertension, obesity, diabetes, etc.) also make a large influence on associated vascular inflammation. Poor control of blood pressure contribute not only to endothelial impairment but to further dysregulation of the immune system. It has been shown that hypertension is associated with circulating lymphocyte counts and T cell dysfunction. Significantly important for the intensity of cytokine storm and the presenting clinical scenarios of Covid -19 manifestations are the amount of SARS CoV-2 virus, time of exposure, as well as number of all existing CV risk factors. There is a possible link between the preexisting endothelial dysfunction and SARS-CoV-2 induced endothelial injury in COVID-19 associated multisystem organ failure and mortality.[9,16]

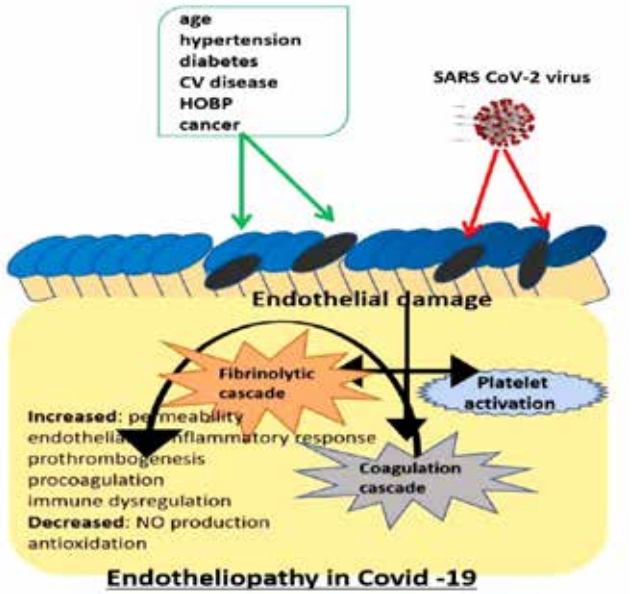

Figure 2. Directly virus SARS CoV-2 and comorbidity factors impact vascular injury on endothelial cell. Endotheliopathy is influenced both directly by virus binding and indirectly by stimulating immuno-inflammatory-coagulation cascade (cytokine storm)

Pulmonary stage is when there is lung tissue injury (starting mostly as interstitial pneumonitis), pulmonary vasodilation, increased endothelial permeability and leukocitye recruitment and consecutive hypoxemia and cardiovascular stress. Common radiological findings include multiple patchy shadows and interstitial changes in moderate disease, with consolidation, a ground glass appearance, in 56.4% of cases and very occasional pleural effusions in severe cases.[1,4]

Hyperinflammation stage is exacerbation of immune response resulting as ARDS, acute cardiac injury, cardiogenic shock, multiorgan failure, secondary bacterial infection, increased intravascular coagulopathy.[4]

The myocardial necrosis originates from an inflammation of the connecting tissues within the heart and the perivascular apparatus, but not the myocytes per se. There are three observed mechanisms: first is that virus is a physiologic stressor that could predispose the heart to damage when the stress outweighs the possibility to bear it, a supply-demand mismatch related infarct can occur (type 2 myocardial infarction). The second mechanism is inflammation mediated by the virus that causes COVID-19 and its initial hyper-inflamatory events and cytokine sindrome resulting in hypercoagulability and microvascular thrombosis that can cause coronary plaque rupture leading to myocardial ischemia/infarction (ACS). The third mechanism is direct viral injury- viral myocarditis.[6] It is challenging to differentiate those causes of cardiac injury in COVID-19 patients since underlying causes can be diverse, as mantioned above - acute coronary syndrome (ACS) caused by plaque rupture or thrombosis (type I MI), supply - demand mismatch (type II MI), stress-induced cardiomyopathy and cytokine release syndrome. Furthermore, other proposed mechanisms of damage attribute to ACE2-related signaling pathways including downregulation of ACE2 expression, dysfunction of the respiratory system causing hypoxemia/low blood oxygenation increases susceptibility of the myocardium to damage.[6,8,12] Myocardial injury is seen in 20–40% of hospitalized cases manifesting as cardiac chest pain, heart failure, cardiac arrhythmias and cardiac death. Patients with cardiac injury have increased signs of severe systemic inflammation including higher leukocyte counts, C-reactive protein, procalcitonin and increased levels of myocardial injury biomarkers such as creatine kinase, NT-proBNP, hsTroponin and myoglobin.[6,12] Symptoms of cardiac chest pain and palpitations are the presenting features in some patients.[10] Early evaluation and continued monitoring of cardiac damage (cTnI and NT-proBNP) and coagulation (D-dimer) after hospitalization may identify patients with cardiac injury and predict COVID-19 complications. Although, cardiac MRI and EMBs as diagnostic tools were inappropriate during the current COVID-19 pandemic and associated healthcare crisis, but should be considered in the future. Consequence of Covid-19 in patients discharged form the hospitals mostly is persistent fatigue, conected with age, female sex and disease severity. Periodic evaluation, except history taking and physical examination, should include a 12-lead ECG and 2D/Doppler echocardiography or cardiac MRI with late gadolinium enhancement.

Complex interaction in COVID -19 infection with cardiovascular system arise from ischemic component (ACS), non-ischaemic components (citokyne storm, stress cardiomiopathy, haemophagocitosis, electrolitic imbalance, adverse drug effects) and comorbidities (age, hypertension, diabetes, CAD, heart failure, atrial fibrillation, cerebrovascular disease). The effect of these interreactions could be cardiovascular complications : arrhythmias (atrial fibrillation, ventricular tachyarrhythmia, ventricular fibrillation), cardiac injury [elevated highly sensitive troponin I (hs-cTnI), myocarditis, heart failure, cardiogenic shock, pericardial effusion, pulmonary embolism, disseminated intravascular coagulation (DIC).[8] Arrhythmiae in COVID 19 could be connected to diverse mechanisms except electrolitic imbalance : metabolic dysfunction, myocardial inflammation and simpathetic neuronal activation.[13]

Coronary disease manifestation in Covid -19 include also MINOCA - myocardial infarction with non occlusive coronary artery disease, stress cardyomiopathy, non-ischaemic cardiomiopathy, coronary spasm. Even 30-39% suspected STEMI have non occlusive coronary disease on coronary angiography. Contributing factors of MINOCA are inflammation of pericites. Pericytes are cells that express particularly high levels of ACE2 in the heart, multipotent myocardial mesenchymal precursors, vascular supportive cells that manifest antigenic response to hypoxia. Furthermore local microvascular inflamation during SARS-CoV-2 infection of the pericytes, leading to severe microvascular dysfunction, contributing to myocardial infarction with non-obstructive coronary arteries (MINOCA) and the cytokine storm have the impact for development of endothelial dysfunction.[15] This could explain recent reports of the clinical course of cases of myocardial infarction during COVID-19, making fibrinolytic therapy for COVID-19 patients who present with suspected STEMI, unnecessary and potentially dangerous. The outcomes in fibrinolysis treatment group, especially with a failed reperfusion of 15% and high incidence of hemorrhagic CVI 9%, questioned its efficacy and safety.[14]

It is proposed that whenever possible, COVID-19 patients with findings suggestive of STEMI should be transferred to a PCI-capable facility.[12,13] During this pandemic, primary percutaneous coronary intervention (PCI) remains the standard of care for STEMI patients at PCI-capable hospitals when it can be provided in a timely manner. Society for Cardiovascular Angiography and Interventions (SCAI), AmerIcan College of Cardiology (ACC), American College of Emergency Physicians (ACEP) recommend primary PCI as a standard of care in COVID-19 patients with STEMI.

A fibrinolysis-based strategy may be entertained at non-PCI-capable referral hospitals or in specific situations where primary PCI cannot be executed or is not deemed the best option. STEMI presenting with concurrent COVID-19 infection had higher levels of troponin T and lower lymphocyte count, but elevated D-dimer and C-reactive protein. There were significantly higher rates of stent thrombosis, multivessel thrombosis, higher modified thrombus grade post first device with consequent-

ly higher use of glycoprotein IIb/IIIa inhibitors and thrombus aspiration. Myocardial blush grade and left ventricular function were significantly lower in patients with COVID-19 with STEMI.[14]

Following the lockdown in England, decline in primary PCI procedures for STEMI (33% and 43% including primary, rescue and facilitated PCI)) was observed and increases in overall symptom-to-hospital and door-to-balloon time for patients with STEMI. The explanation is partly in the fear of people going out, especially to hospitals. Elective revascularizations in stable angina were significantly reduced (66%) as well as invasive approach in NSTEMI (45%). Restructuring health services during COVID-19 has not adversely influenced in-hospital outcomes.[14]

There is a curiosity in COVID-19, the influence of preventive measures (social distancing, isolation, physical distance, loneliness) could also increase cardiovascular risk. Mechanisms of negative effects of social isolation are multiple and are related to the activation of the hypothalamic–pituitary–adrenocortical (HPA) axis, changes in the sympathetic vascular tone, elevated levels of cortisol and a reduced responsivity of the glucocorticoid receptor. Meta analisis on 181 006 patients revealed increased risks for CVD (29%) and CVI (32%) in lonely and socialy isolated people.[13] The social distancing strategies used in COVID-19 was mitigate using available technological internet advances.[11]

COVID-19 infection needs multidisciplinary assessment and treatment, including cardiovascular evaluation and therapy, during the course of the acute disease to reduce and afterwards as well.

Cardiovascular therapies currently used should be initiated or continued as standard for managing : hypertension, heart failure, renal failure, different cardiac disrhythmias, diabetes and antithrombotic therapies should be initiated where appropriate and should be continued during COVID-19 infection. As its mantioned above, ACE inhibitors and AT blockers should be continued. Anticoagulation therapy (due to the growing evidence of DIC as a cause of organ injury) includes LMWH intrahospitaly and vastly used lately post discharge NOAC for the period of time individually estimated. It is going on the phase 2, of interesting clinical trial of Inhaled Unfractionated Heparin (UFH) for the tretatment of Hospitalised Patients with COVID-19, INHALE - HEP (jun 2021). Antiplatelet therapy continues unless contraindicated or adverse effects appear. Conservative use of i.v. fluids aiming to maintain tissue perfusion but a negative fluid balance aids lung recovery. Extracorporeal membrane oxygenation (ECMO) may be required in severe cases, but should be considered early. Similarly, broad-spectrum antibiotics/antifungal treatments are needed. Atorvastatin therapy did not reduce risk for venous or arterial thrombosis or all-cause death among patients with COVID-19 admitted to the ICU compared with placebo, according to data from the INSPIRATION-S study.

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19 since March 2020. This is the world's largest clinical trial of treatments for patients hospitalised with COVID-19, taking place in 177 hospital sites across the UK and with over 33,000 patients recruited so far. No convincing evidence was found for the the convalescent plasma-since January 2021 (1873 reported deaths among 10,406 randomised patients, no significant difference in the primary endpoint of 28-day mortality-18% convalescent plasma vs.18% usual care alone; RR 1.04 [95% confidence interval 0.95-1.14]; p=0.34). No convincing evidence was seen for colchicine, anti-inflammatory drug that is commonly used to treat gout, on clinical outcomes and mortality benefit in patients admitted to hospital with COVID-19 (2178 reported deaths among 11,162 randomised patients, no significant difference in the primary endpoint of 28-day mortality, 20% colchicine vs. 19% usual care alone; RR 1.02 [95% confidence interval 0.94-1.11]; p=0.63). Hydroxychloroquine and chloroquine had received a lot of media attention in early 2020 and was used widely to treat COVID patients, despite the absence of any good evidence (1542 patients were randomised to hydroxychloroquine compared with 3132 on usual care - 25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10, there was also no evidence of beneficial effects on hospital stay duration or other outcomes).

RECOVERY trial has demonstrated that an anti-inflammatory treatment, tocilizumab, an intravenous drug used to treat rheumatoid arthritis, a recombinant humanized anti-IL-6 receptor monoclonal antibody reduces the risk of death in all patient subgroups of hospitalised patients with severe COVID-19 (29% of the patients in the tocilizumab group died within 28 days compared with 33% in the usual care group RR 0·86; [95% confidence interval [CI] 0·77 to 0·96]; p=0·007), shortens the time until patients are successfully discharged from hospital (within 28 days from 47% to 54% - RR 1·23, [95% CI 1·12 to 1·34], p<0·0001) and reduces the need for a mechanical ventilator (from 38% to 33%- RR 0·85, [95% CI 0·78 to 0·93], p=0·0005). In June 2020, the trial found that the inexpensive steroid dexamethasone (corticosteroids) reduces death for patients with severe COVID-19. This rapidly became part of standard-of-care given to all such patients. The data suggest that in COVID-19 patients with hypoxia (requiring oxygen) and significant inflammation, treatment with the combination of a systemic corticosteroid plus tocilizumab reduces mortality (REMAP-CAP trial). Azithromycin, widely-used antibiotic that also reduces inflammation, a key feature of severe COVID-19, showing that has no significant effect on clinical outcomes in COVID-19.[9] Baricitinib, an anti-inflammatory treatment for rheumatoid arthritis, may block the signalling activity of cytokine molecules which contribute to the hyper-inflammatory state seen in severe COVID-19 is under investigation. The Adaptive Covid-19 Treatment Trial (ACTT-2), a randomised clinical trial involving over 1,000 patients with moderate to severe COVID-19 (tested baricitinib with remdesivir against remdesivir with a placebo) showed that baricitinib with remdesivir was superior to remde-

sivir alone (particularly those receiving oxygen or non-invasive ventilation) in reducing recovery time and accelerating improvement in clinical status among COVID-19 patients. The numbers were too small to provide a clear answer. The ACTT-2 trial did not look at the effect of baricitinib in addition to corticosteroids, which is now standard of care for severe COVID-19 worldwide.[3] Recruitment to all other treatment arms – aspirin, baricitinib, Regeneron's antibody cocktail and dimethyl fumarate continues. Regeneron Pharmaceuticals' investigational antiviral antibody cocktail, REGN-COV2, is the first specifically designed COVID-19 therapy to be evaluated by the trial. The current evidence on the use of ivermectin, broad spectrum anti-parasitic agent, to treat COVID-19 patients is inconclusive (independent, international panel of experts reviewed pooled data from 16 randomized controlled trials - total enrolled 2407 including both inpatients and outpatients with COVID-19 and determined that the evidence on whether ivermectin reduces mortality, need for mechanical ventilation and for hospital admission and time to clinical improvement in COVID-19 patients is of "very low certainty").The panel did not look at the use of ivermectin to prevent COVID-19, which is outside of scope of the current guidelines (World Health Organization - WHO, 31 March 2021). The drugs also to be tested are infliximab, used to treat autoimmune conditions, including Crohn's disease and rheumatoid arthritis. It blocks tumour necrosis factor alpha (TNF-α). Cancer drug imatinib and also artesunate, an anti-malaria drug with potential anti-inflammatory effects. Researchers hope that it will target both the coronavirus and inflammation, blocking viral infiltration of human cells and reducing the activity of pro-inflammatory proteins.[9] Bamlanivimab, SARS-CoV-2 neutralizing antibodies, 700 mg injection is authorized for use under EUA (FDA) for treatment of mild to moderate COVID-19 patients, not hospitalized (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progressing to severe COVID-19 and/or hospitalization (BLAZE 4 trial). The old antiplatelet acetylsalicylic acid is always on the road, concidering its mechanism of actions and known cascade of COVID-19 prothrombotic inflammation. We need to keep pushing to find better treatments.

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Sažetak

COVID -19 kardiovaskularni aspekti i pregled terapije

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Virus SARS-CoV-2 vezuje se za transmembranski angiotenzin-konvertujući enzim 2 (ACE2), homolog ACE-a i na taj način ulazi u različite tipove ćelija, mehanizmima direktnog citotoksičnog efekta, disregulacije RAAS-a, oštećenjem endotelnih ćelija tromboinflamacijom i poremećenim imunološkim odgovor. Stalnom aktivacijom RAAS nastaje disbalans hiperprodukcije Ang II i inhibicije stvaranje Ang-$^{1-7}$, što povećava zapaljenje, vaskularnu propustljivost, protrombogenezu i smanjuje antiinflamatorna i antitrombogena svojstva. Ova endoteliopatija započinje oštećenim endotelom i posledičnom aktivacijom koagulacione, trombocitne i fibrinolitičke kaskade. COVID-19 utiče na kardiovaskularni sistem ishemijskim komponentama (oštećenje miokarda, endotelna disfunkcija, mikrovaskularna disfunkcija, nestabilnost plaka, ACS), neishemijskim komponentama (citokinska oluja, stres kardiomiopatija, metabolička disfunkcija, simpatička neuronska aktivacija, elektrolitska neravnoteža) i komorbiditetima (starost, hipertenzija, dijabetes, gojaznost, KAB, HOBP, karcinomi). Posledično nastaju KV komplikacije: aritmije, miokardna nekroza (20–40% hospitalizovanih slučajeva, uključujući MINOCA), miokarditis, srčana insuficijencija, kardiogeni šok (multiorganska disfunkcija), perikardijalni izliv, plućna embolija, diseminovana intravaskularna koagulacija. STEMI u sklopu COVID-19 imali su više tromboza stenta i višesudovne tromboze, veće opterećenje trombom, upotrebu inhibitora glikoproteina IIb IIIa.

Standardne kardiovaskularne terapije treba koristiti prema potrebi (uključujući ACE inhibitore / ARB). Nisu pronađeni uverljivi dokazi za korišćenje rekonvalescentne plazme, kolhicina, hidroksihlorokina, hlorokina, azitromicina, a postoje dokazi smanjenog mortaliteta za upotrebu kortikosteroida, tocilizumaba (anti-IL-6R At) u teškim oblicima COVID-19 i bamlanivimaba (SARS-CoV-2 neutrališuća At) za lečenje blagih do umerenih oblika bolesti sa rizikom od ozbiljnog pogoršanja.

Ključne reči: COVID-19, kardiovaskularne komplikacije, RAAS, disfunkcija endotela, ishemijska kardiomiopatija, inflamacija