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COVID-19 and cardiovascular diseases: from epidemiology to rehabilitation

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Abstract

The article is devoted to a review of data on the prevalence and impact of cardiovascular diseases on the course and outcomes of the new coronavirus infection COVID-19. The review examines the relationship between COVID-19 and the functioning of the renin-angiotensin-aldosterone system, the pathophysiological mechanisms of their mutual influence. The analysis of the latest literature data on the safety of taking angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers is presented. The causes and pathophysiological mechanisms of the development of acute myocardial damage in COVID-19 are discussed. The issue of organizing rehabilitation assistance for patients who have undergone COVID-19 is being considered. The main components and features of the COVID-19 rehabilitation program are presented.

Key words: coronavirus, COVID-19, SARS-CoV-2, cardiovascular diseases, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, arterial hypertension, acute myocardial injury, rehabilitation.

Conflict of interests. The authors declare the absence of conflict of interests.

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COVID-19 и сердечно-сосудистые заболевания: от эпидемиологии до реабилитации

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Резюме

Статья посвящена обзору данных о распространенности и влиянии сердечно-сосудистых заболеваний на течение и исходы новой коронавирусной инфекции COVID-19. В обзоре разбирается связь между COVID-19 и функционированием ренин-ангиотензин-альдостероновой системы, патофизиологические механизмы их взаимного влияния. Приведены результаты анализа последних данных литературы о безопасности приема ингибиторов ангиотензинпревращающего фермента и блокаторов рецепторов к ангиотензину II. Обсуждаются причины и патофизиологические механизмы развития острого миокардиального повреждения при COVID-19. Рассматривается вопрос организации реабилитационной помощи больным, перенесшим COVID-19. Представлены основные компоненты и особенности программы реабилитации при COVID-19.

Ключевые слова: коронавирус, COVID-19, SARS-CoV-2, сердечно-сосудистые заболевания, ингибиторы ангиотензинпревращающего фермента, антагонисты рецепторов ангиотензина, артериальная гипертензия, острое миокардиальное повреждение, реабилитация.

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Coronavirus infection COVID-19 (COronaVIrus Disease 2019) caused by novel coronavirus species – SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has led to high morbidity and mortality all over the globe [1]. Despite SARS-CoV-2 tropism in lungs, COVID-19 results in a high risk of multiple organ failure, including due to cardiovascular system (CVS) involvement.

Epidemiological aspects

Approximately 50% of SARS-CoV-2 patients have multiple morbidity and its rate rises to 72% in severe COVID-19 [2, 3]. Very often COVID-19 patients have cardiovascular diseases (CVD) and cardiovascular risk factors e.g. obesity and diabetes mellitus (DM).

According to one retrospective analysis (n = 1,590 from 575 Chinese hospitals), 25% of COVID-19 patients had comorbidities [4]. Arterial hypertension (AH) was recorded in 16.9%, other CVS – in 53.7%, and DM – in 8.2%. In an Italian cohort of COVID-19 patients (n = 22,512, including 355 lethal cases) comorbid ischemic heart disease (IHD) was recorded in 30%, atrial fibrilation – in 24.5%, a history of stroke – in 9.6%, and DM – in 35.5% [5]. An analysis of the database of 5,700 COVID-19 patients hospitalised to 12 New York hospitals showed AH in 56.6%, IHD in 11.1%, obesity in 41.7%, and DM in 33.8% [6].

A retrospective analysis of clinical and demographic parameters of 1,007 COVID-19 patients hospitalised to in-patient clinics (resuscitation and intensive care unit, ICU) in the Russian Federation with acute respiratory distress syndrome (ARDS) demonstrated that 61.4% of patients had CVD [7]. Most common were AH (56.3% of patients) and IHD (16.3%), followed by a history of stroke (7.1%) and atrial fibrillation (9.3%). Obesity and type 2 diabetes were recorded in 26.1% and 25% of patients, respectively. The incidence of CVD was age-dependant, reaching 80% in the group of patients > 60 years old.

Impact of comorbid CVD on the course and outcome of COVID-19

Patients with CVD and/or standard cardiovascular risk factors (elderly age, men, AH, DM, obesity) are the most vulnerable cohort; they usually have severe COVID-19 and high hospital mortality [8, 9]. A meta-analysis of 6 trials (n = 1,558) allowed identifying independent predictors of severe COVID-19 (with ARDS) [9]. These are the following comorbid diseases: AH (hazard ratio (HR) 2.29, $p < 0.001$), other CVD (HR 2.93, $p < 0.001$), cerebrovascular disease (HR 3.89, $p = 0.002$), DM (HR 2.47, $p < 0.001$), and chronic obstructive pulmonary disease (HR 5.97, $p < 0.001$). With IHD the probability of severe COVID-19 rises 2.5-fold [10].

S.Tai et al. studied the impact of CVD on the risk of severe COVID-19 in patients (n = 332, mean age: 51 years) with mild infection [11]. Comparison of two groups of patients "with CVD" (n = 48, 14.5%) and "without CVD" (n = 284, 85.5%) demonstrated that patients with CVD were older (mean age: 56 years *vs* 50 years, $p = 0.007$), they complained of fatigue (28.3% *vs* 11.1%, $p = 0.002$), chest tightness (40.0% *vs* 6.0%, $p < 0.001$) and myalgia (13.0% *vs* 2.6%, $p = 0.001$) more often; they had DM (8.3% *vs* 2.5%, $p < 0.05$) and pulmonary diseases (8.3% *vs* 1.1%, $p < 0.05$), and were hospitalised to ICU more often (47.9% *vs* 12.4%, $p < 0.001$). Intensive care was required for patients with AH (44.7% *vs* 13.9% with other CVD, $p < 0.001$) and IHD (90.9% *vs* 15.0%, $p < 0.001$, respectively). A multivariate analysis demonstrated that comorbid CVD are an independent risk factor for severe COVID-19 (odd ratio (OR) 2.652, 95% confidence interval (CI) 1.019 – 6.899) [11].

A viral infection can de-stabilise the heart condition, significantly increasing the risk of comorbid CVD. In the trial [12] the risk of death with CVD was 2.4-fold higher ($p = 0.019$). An analysis of 44,672 cases with confirmed COVID-19 from the Chinese Centre for Disease Control and Prevention showed high mortality in patients with CVD (10.5%), AH (6.0%), and DM (7.3%), whereas the overall mortality was 2.3% [13].

A multivariate Cox regression analysis of 1,590 patients hospitalised with COVID-19 showed the following predictors of death: patient age > 75 years (HR 7.86; 95% CI 2.44 – 25.35) and 65 – 74 years (HR 3.43; 95% CI 1.24 – 9.5), coronary artery disease (HR 4.28; 95% CI 1.14 – 16.13), cerebrovascular diseases (HR 3.1; 95% CI 1.07 – 8.94), dyspnea (HR 3.96; 95% CI 1.42 – 11.0), procalcitonin level > 0.5 ng/mL (HR 8.72; 95% CI 3.42 – 22.28), and aspartate transaminase activity > 40 U/L (HR 2.2; 95% CI 1.1 – 6.73) [14].

Thus, very often concomitant CVDs are associated with severe COVID-19 with patient hospitalisation to ICU and worse prognosis. Therefore, all patients, even with moderate and even mild COVID-19 should be subject to a cardiac examination and follow-up.

COVID-19, arterial hypertension and renin-angiotensin-aldosterone system

According to various studies, AH is recorded in 15 – 40% of COVID-19 patients [15, 16]. AH is prevailing in patients with severe COVID-19; e.g. in the study by *W.J.Guan et al.* 23.7% of patients had AH (*vs* 13.4% with mild disease) [17]. It is reported that COVID-19 mortality in patients with AH is 2.6 times higher [10]. Possible mechanisms of AH correlation with poorer COVID-19 outcome can relate to the role of type 2 angiotensin converting enzyme (ACE2) [18].

ACE2 is an essential component of the renin-angiotensin-aldosterone system (RAAS) participating in pathogenesis of AH and other CVDs. It is known that ACE2 is a type I transmembrane protein expressed in lungs (high ACE2 expression is seen on the surface of type II alveolar cells), heart, kidneys, vascular endothelium, liver, testicles, and intestine [19]. ACE2 can be present in a free form as well (in blood).

The physiological role of ACE2 is primarily related to angiotensin I (ATI) cleavage to inactive AT 1 – 9 peptide, which then turns into AT 1 – 7 with the help of ACE or other peptidases, and to ATII degradation to AT 1 – 7 binding to Mas receptors (Figure 1). AT 1 – 7 ensures vaso- and cardioprotection, antiproliferative, antiinflammatory and natriuretic effect. When cleaving ATII, ACE2 mitigates negative effect of the latter (vasoconstriction, cytokine-like activity, sodium retention and development of fibrosis).

SARS-CoV-2 virus binds to ACE2 receptors on target cell surfaces with the help of glycoprotein (peplomer), known as a spike protein (S-protein) [20]. S-protein of SARS-CoV-2 virus mimics ACE2. Then the virus and ACE2 transmembrane domain penetrate cells (endocytosis). SARS-CoV-2 virus causes imbalance in the ACE2 system associated with reduction in AT 1 – 7 levels together with increase in ATII and ACE-ATII-AT_1-receptor path activation. As a result, acute damages to lungs, myocardium, vessels and other organs initially caused by SARS-CoV-2 can worsen.

Another possible mechanism of AH association with severe COVID-19 is related to synergistic immune response [16]. Poor blood pressure (BP) control promotes overactivation of the immune system causing chronic inflammation in the vessel walls and tissues of kidneys. In a study with "mendelian randomization", patients with AH had a correlation between AH and circulating lymphocytes and monocytes [21]. Experimental, prospective and intervention studies demonstrated interaction of some cytokines with AH regulating systems (RAAS, sympathic nervous system) and AH develop-

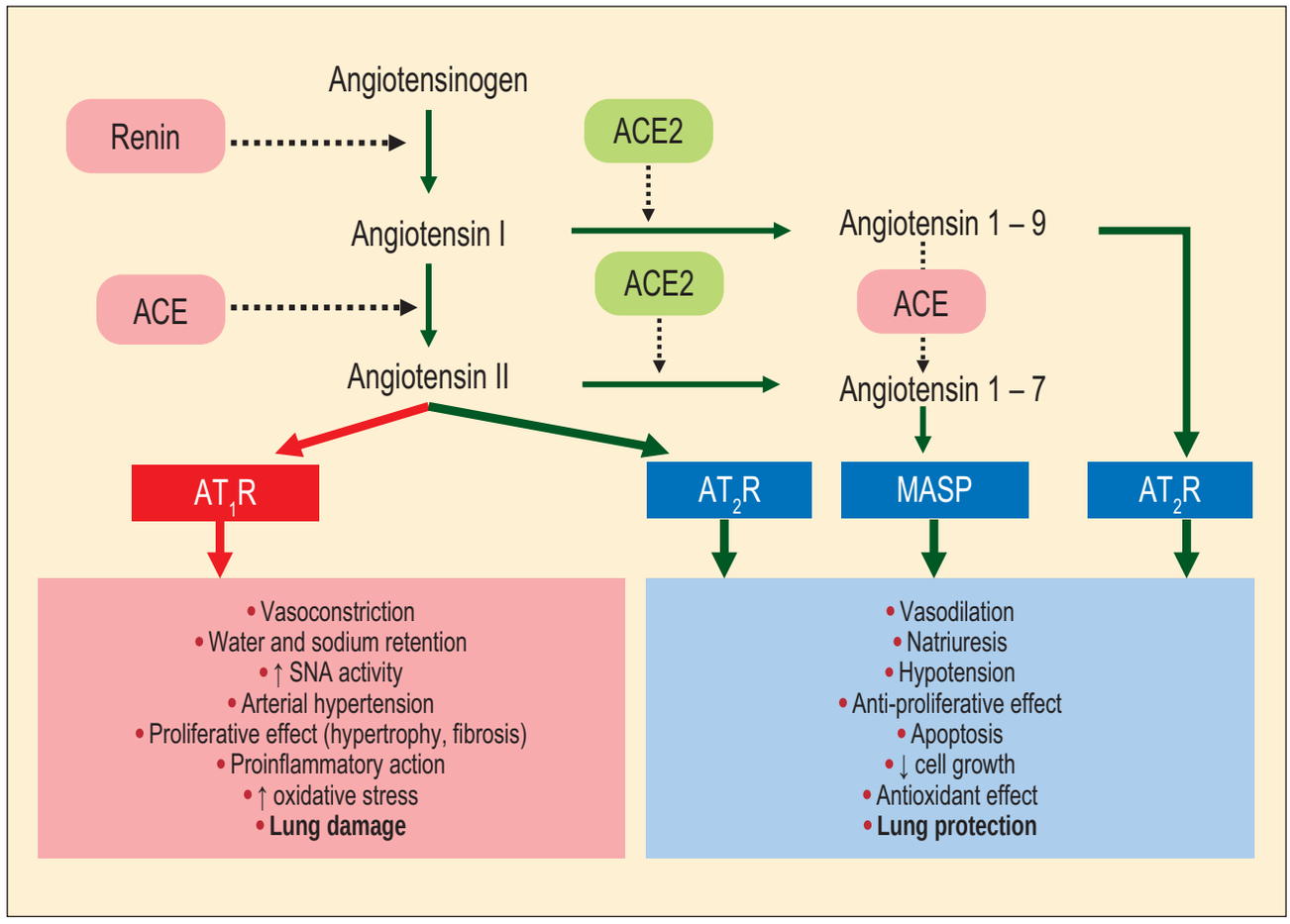

Figure 1. The role of angiotensin-converting enzyme 2 (ACE2) in the rennin-angiotensin-aldosterone system
Note: ACE, angiotensin-converting enzyme; ATR, angiotensin receptors; MASP, Mas protection; ↓ – decrease; ↑ – increase.

Рис. 1. Роль ангиотензинпревращающего фермента-2 в ренин-ангиотензин-альдостероновой системе
Примечание: ↓ – снижение; ↑ – повышение.

ment. For instance, interleukin-6, a predictor of poor COVID-19 outcome, is one of the key cytokines in initiation of inflammatory immune response in AH [18]. In another study on animal models, the relation between AH and circulating $CD8^+$ T-cells was identified [22]. In SARS-CoV-2 infection, a high rate of circulating cytotoxic $CD8^+$ T-cells facilitates hyperproduction of proinflammatory cytokines [18].

It can be believed that, while ensuring better AH control, RAAS inhibitors can mitigate immune system imbalance in AH [16]. During a virus infection, patients with AH should have their AH and cardiovascular risk monitored.

COVID-19 and RAAS inhibitors

The main activity of ACE inhibitors (ACEi) is related to reduction in ATII formation, while ATII receptor inhibitors (ARI) inhibit the interaction between ATII and type 1 angiotensin receptors (AT_1 receptors). ACE2 is not the target for RAAS inhibitors, despite the fact that an experiment on animals demonstrated that administration of RAAS inhibitors can increase ACE2 expression on cell surface [23, 24]. Therefore, there appeared a hypothesis: administration of RAAS inhibitors will promote SARS-CoV-2 internalization to lungs, heart, etc., thus increasing the risk of COVID-19 infection and severity [25]. It provoked a hot discussion.

Unlike experimental studies, COVID-19 patients did not demonstrate sound evidence of increase in ACE2 expression on target cell surface, therefore no increase in the viral load with ACEi/ARI administration [26]. It is obvious that increase in ACE2 activity with RAAS inhibitor therapy does not necessarily cause an increase in patient's susceptibility to infection [18, 27]. To penetrate the host cell, SARS-CoV-2 uses other receptors as well, e.g. transmembrane glycoprotein CD147, transmembrane protease serine 2 (TMPRSS2), acting as a co-factor of S-protein activation for efficient cell invasion by the virus [28]. After virus internalization in the cell and virus RNA release in the cell cytoplasm, ACE2 expression on the cell surface reduces (including alveolar cells). Loss of functional ACE2 (and reduced AT 1 – 7) associated with excessive ATII accumulation promotes lung damage [29]. Studies demonstrated a direct correlation between ATII blood level, viral load and lung damage severity [30]. The protective action of ACE2 in acute lung and myocardium damages has been proven on animal models [31].

It can be assumed that increase in ACE2 expression together with inhibition of proinflammatory ACE2 activ-

ity and "ACE2/AT1 – 7-Mas-receptor" signalling associated with administration of RAAS inhibitors will have a protective effect in SARS-CoV-2 infection [32].

In their study of 1,178 patients hospitalised with COVID-19 in China, *J.Li et al.* demonstrated the lack of correlation between ACEi/ ARI administration and severe infection and mortality [33]. *G.Mancia et al.*, who conducted a case-control analysis on an Italian cohort of COVID-19 patients (n = 6,272, mean age: 68 ± 13 years), did not find any negative impact of ACEi/ARI on the risk of complications, including severe cases [34].

There are first evidences of declining hospital mortality when using RAAS inhibitors in COVID-19 patients [35, 36]. According to a retrospective analysis [36], 2,877 (29.5%) patients with AH hospitalised with COVID-19 had higher mortality rates than patients without AH (4.0% *vs* 1.1%, HR 2.12, 95% CI 1.17 – 3.82, p = 0.013) and needed invasive lung ventilation (4.6% vs 1.3%, $p < 0.001$). Hospital mortality in patients with AH who did not take any antihypertensive medications was 2.17 times higher than in those who took medications (95% CI 1.03 – 4.57, p = 0.041). There are no differences between hospital mortality with administration of RAAS inhibitors and other medications (betablockers, calcium antagonists and diuretics).

Currently, global communities are unanimous: withdrawal from ACE inhibitors or ARI in COVID-19 patients can increase the risk of cardiovascular complications, especially in patients with AH, chronic cardiac failure (CF) and/or a history of myocardial infraction (MI) [37, 38]. Further studies will allow clarifying some mechanisms of RAAS activation and inhibition in COVID-19.

Cardiological manifestations of COVID-19

We have an evidence that COVID-19 negatively impacts de novo cardiovascular pathology development [12]. *N.S.Hendren at el.* proposed a new term to describe cardiological manifestations of COVID-19: **acute COVID-19-associated cardiovascular syndrome** (ACovCS), describing a wide range of cardiovascular and thrombotic complications from coronavirus infection [39]. Acute COVID-19-associated cardiovascular syndrome includes arrythmia (atrial fibrillation, ventricular tachycardia and ventricular fibrillation), acute myocardial injury, fulminant myocarditis (a risk factor for cardiac failure), pericarditis with effusion, cardiac tamponade, arterial and venous thrombotic disorders – acute coronary syndrome (ACS), stroke, pulmonary artery thromboembolia (PATE), deep venous thrombosis (Table). A majority of patients have signs of pulmonary hypertension.

Cardiac manifestations can be a primary phenomenon in COVID-19 (according to some researchers, this is a "cardiac phenotype" of the disease); however, they can be secondary to pulmonary damages (mixed pulmonary and cardiac phenotype) [41]. Of note, symptoms of CVD can be diagnosed at any stage of patient hospitalisation, but usually the risk increases from day 15 after fever initiation (or manifestation of other symptoms of a viral infection). Cardiovascular complications often appear after stabilisation and/or improvements in patient's respiratory status [41].

There are no clear explanations of the variability of cardiological manifestations of COVID-19 and it is unknown why some patients have their cardiovascular system affected. Possible mechanisms of SARS-CoV-2-induced myocardium damages are associated with increased ACE2 expression in heart and vascular endothelium (Figure 2) [20]. Various pathophysiologic mechanisms of cardiovascular complications in COVID-19 [8, 39] have been discussed:

- direct noci-influence of SARS-CoV-2 virus on pericapillary cells (high ACE2 expression on their surface), cardiomyocytes and fibroblasts [42];
- indirect influence of SARS-CoV-2 virus on myocardium during a "cytokine storm" (release of excessive inflammatory mediators and cytokins/chemokines) [42, 43];
- direct noci-influence of SARS-CoV-2 virus on vascular endothelium causing its dysfunction [44, 45];
- hypercoagulation resulting from endothelial dysfunction, increased activity of platelets and von Willebrand factor, increased expression of type 1 antioxidant tissue-type plasminogen activator inhibitor, and reduced tissue-type plasminogen activator production which causes thrombolysis, blood flow disturbances and micro- and macrothrombosis [44];
- marked hypoxaemia resulting in anaerobic processes activation, intracellular acidosis and oxidative stress (direct influence of virus on hematoglobulin causing reduction in blood oxygen capacity) [44];
- imbalance between myocardium oxygen demand and oxygen supply caused by virus-induced inflammation, hypoxia, oxidative stress, endothelial involvement and hypercoagulation, resulting in acute myocardium damage, atheroma instability and rupture associated with coronary artery thrombosis [16];
- sympathic nervous system activation and stress-induced release of catecholamines into the blood flow, causing vasospasm, myocardium hypoperfusion/ischemia and life-threatening arrythmias [46];
- electrolyte imbalance (in severe COVID-19) promoting tachyarrythmia; hypokalaemia is a result of SARS-CoV-2 impact for RAAS [44].

However the exact mechanism of acute myocardium damage in COVID-19 needs further elaboration. Therefore, COVID-19 can provoke acute myocardium damage with poor prognosis for the patient. Prompt myocardium damage identification upon patient admission into hospital and inpatient management is of great importance. Autopsy results demonstrated that cardiotropic viruses, like SARS-CoV-1, can remain in myocardium tissue for several weeks and even months [47]. The information on previous infection caused by SARS-CoV-1 virus makes it possible to assume that COVID-19 survivors may have more cardiovascular complications in future.

COVID-19 and myocardial/cardial damages. Acute myocardial damage in COVID-19 can be associated with a non-ischemic cause (myocarditis, cytokine- or stress-induced cardiomyopathy, etc.) or with myocardial ischemia resulting from coronary artery atherothrombosis [40].

Table
Cardiac manifestations in COVID-19 (acute COVID-19 cardiovascular syndrome) and possible mechanisms (ad. [39, 40])
Таблица
Кардиальные проявления COVID-19 (острый COVID-19-ассоциированный сердечно-сосудистый синдром) и возможные механизмы развития (адапт. из [39, 40])

Pathology	Symptoms	Mechanisms/Comments
Acute myocardial injury (without intracoronary thrombosis)	Increased cardiac troponin I, including additional clinical symptoms and instrumental test results	Mechanisms:
		• direct viral damage to myocardium
		• systemic inflammation
		• imbalance between myocardium oxygen demand and supply
		Possesses prognostic value
Acute coronary syndrome (STEMI and non-STEMI)	Precordialgia, increased troponin, typical ECG changes	Mechanisms:
		• atheromatosis plaque rupture (bursting) (also resulting from inflammation)
		• intracoronary thrombosis; intramural hematoma in damaged atheroma
		• attack of previous IHD
Cardiac failure	De novo left ventricular systolic dysfunction, myocarditis or pericarditis, cytokine-/stress-induced cardiomyopathy	Mechanisms:
		• hypoxaemia, dehydration, hypoperfusion
		• abnormal response to a cytokine storm
		• direct effect of virus
		Any cause of myocardium dysfunction causing acute cardiac failure
		Chronic cardiac failure decompensation resulting from increased metabolic needs
Arrythmia	Supraventricular arrhythmia, ventricular tachycardia or conduction trouble	Mechanisms:
		• hypoxia
		• hypokalaemia
		• disturbed metabolism
		• sympathic nervous system activation and increased blood catecholamines

Note: STEMI, *ST* elevation myocardial infarction; Non-STEMI, non-*ST* elevation myocardial infarction; IHD, ischemic heart disease, ECG, electrocardiography; CF, cardiac failure.

Manifestations of acute myocardial damage are increase in specific cardiobiomarkers, typical abnormal ECG changes or instrumental test results. T- and I-troponins are known risk factors of poor outcomes in acute cardiovascular pathology. Highly-specific cardiac troponin I levels of over 99th percentile of the upper reference limit are an evidence of acute myocardium damage in COVID-19 [8, 40].

In a series of COVID-19 patients from China, acute myocardium damage was recorded in 10 – 30% [2, 10, 48]. In 20 – 40% of cases, symptoms of acute myocardium damage are chest pain (myocardial ischemia), CF augmentation (also caused by myocarditis), arrythmia, and cardiac death [16, 49]. Increased myocardial damage markers in COVID-19 are a sign of severe disease and poor outcome [2]. A meta-analysis of 6 trials (n = 1,527) demonstrated a high probability of severe COVID-19 (with ARDS) associated with acute myocardial injury (risk ratio (RR) 13.48, 95% CI 3.60 – 50.47, p = 0.0001) [50].

In a study of 187 COVID-19 patients by *T.Guo et al.*, 35% had concomitant CVD (AH, IHD or cardiomyopathy), 28% were diagnosed with acute miocardial damage (troponin T > 99th percentile of the upper limit) after contact with the virus [51]. Hospital mortality with normal troponin T in patients without CVD was 7,62%, while where patients had concomitant CVD, hospital mortality was 13.33%; with increased troponin T, the value was 37.50% and 69.44%, respectively (the highest value in this group).

In a study by *S.Shi et al.* (n = 671), 75.8% of casualties had acute myocardium damage (*vs* 9.7% in COVID-19 survivors, p < 0.001) [52]. Where troponin I was > 0.026 mg/mL (a cut-off point), the risk of hospital mortality was 4.56 higher (95% CI, 1.28 – 16.28, p = 0.019). A multivariate analysis demonstrated that the risk of acute myocardial damage in COVID-19 increased: a 10-year increase in the age – 1.64-fold (95% CI 1.28 – 2.10, p < 0.001), concomitant AH – 3.3-fold (95% CI 1.77 – 6.14, p < 0.001), chronic IHD – 2.92-fold (95% CI 1.32 – 6.48, p = 0.008), and chronic obstructive pulmonary disease – 4.01-fold (95% CI 1.28 – 12.61, p = 0.018).

In a series of studies of COVID-19 patients, acute myocardial damage was associated with high levels of

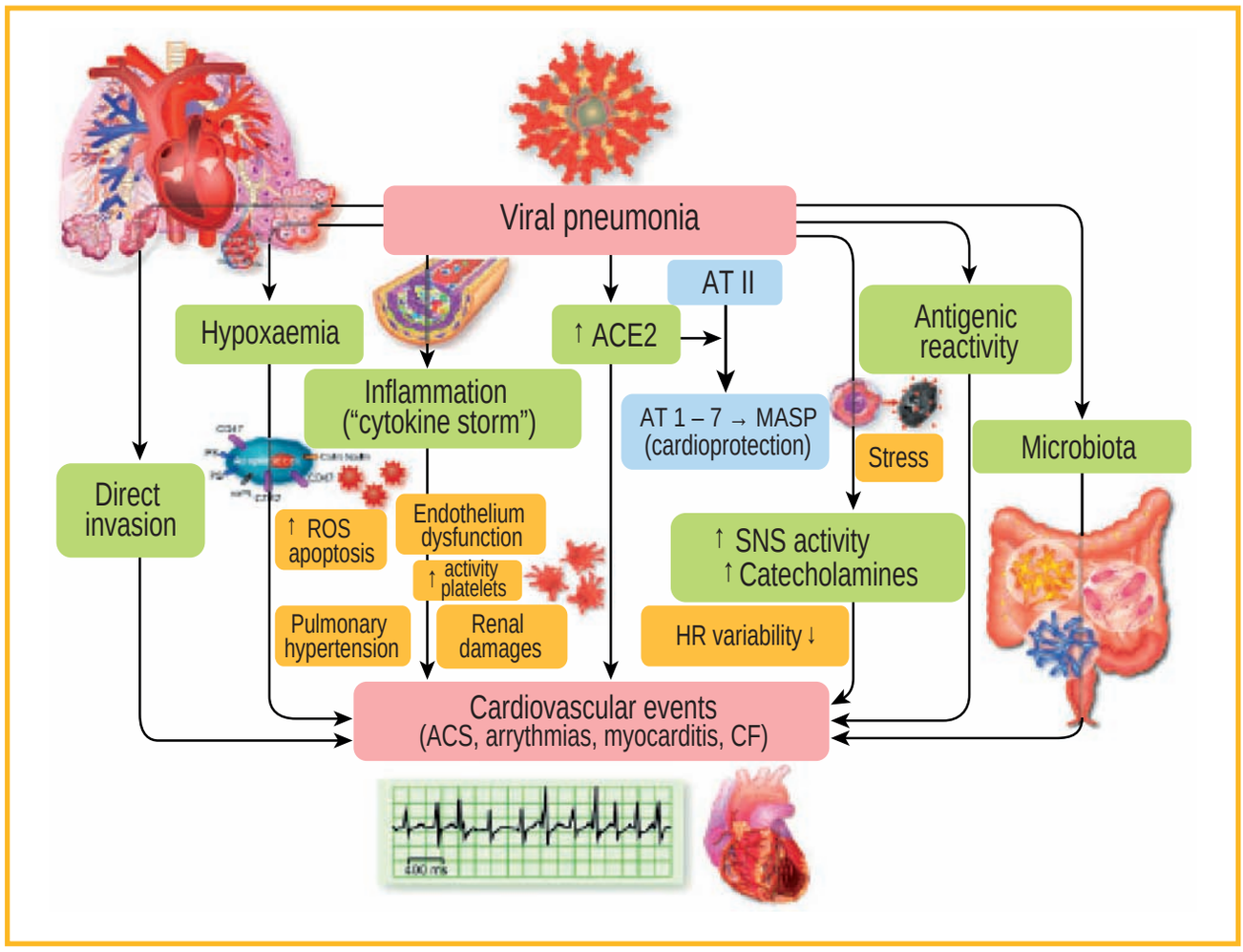

Figure 2. Possible mechanisms for the effect COVID-19 disease on the cardiovascular system (ad. [20])
Note: AT, angiotensin; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; SNS, sympathetic nervous system; HR, heart rate; ROS, oxygen free radicals; MASP, MAS protection; CF, cardiac failure; ↓, decrease; ↑, increase.

Рис. 2. Возможные механизмы воздействия COVID-19 на сердечно-сосудистую систему (адапт. из [20])
Примечание: ↓ – понижение; ↑ – повышение.

D-dimer, N-thermal pro-B-type natriuretic peptide (NT-pro-BNP), C-reactive protein and interleukin-6 [42, 48, 51, 52]. It proves the association between acute myocardial injury in COVID-19 and marked inflammation and cardiac dysfunction.

COVID-19 and cardiac failure. Viral infection can provoke decompensation of chronic CF, if the patient has comorbidies, and a shock. The incidence of CF in patients who died of COVID-19 was 52%, while in survivors this value was 12% ($p < 0.0001$) [10]. The incidence of new CF cases in COVID-19 patients was aprox. 23% [10].

Acute CF associated with viral infection seems to be a consequence of a prior systolic dysfunction, ARDS and cardiovascular pathology *de novo* (acute myocardial ischemia, MI, tachyarrythmia, myocarditis or cardiomyopathy). First COVID-19 cases in the USA described cardiomyopathy in 33% cases [49]. *E.Argulian et al.* found that right ventricle dilatation seen at echocardiography is associated with a high risk of hospital mortality in COVID-19 patients [53]. COVID-19-associated pulmonary hypertension caused by lung damage and hypoxia or PATE leads to increased right ventricle load and cardiomyocyte damage.

Daily diuresis monitoring, reasonable water schedule, continued scheduled base therapy, including ACEi and ARI, are all very important for COVID-19 patients with chronic CF decompensation [8].

COVID-19 and myocarditis. The incidence of myocarditis in COVID-19 patients is about 8 – 12% [16]. In a high viral load, cases of fulminant myocarditis were recorded (approx 7% of patients) [54]. Myocarditis patients can complain of moderate chest discomfort and palpitations; clinical manifestations are systolic cardiac dysfunction, conduction trouble and tachyarrythmia [16]. Clinically, miocarditis is diagnosed 2 weeks after coronavirus symptoms appear.

COVID-19, acute and chronic coronary syndrome. COVID-19 can trigger atheromatosis plaque instability and cause MI [39, 51], significantly increasing the risk of mortality among infected patients. Acute MI mortality is 40% of the overall COVID-19 mortality rates [2].

Patients with COVID-19-associated pneumonia can have acute type 1 MI (resulting from coronary atherothrombosis associated with atheroma rupture (bursting), epicardial coronary artery occlusion); but usually they have type 2 acute MI (because of imbalance between

myocardium oxygen need and oxygen supply, metabolic stress) [39, 40]. Acute myocardial damage interpreted as acute type 2 MI is recorded in 7 – 30% COVID-19 patients [2].

In pathogenic terms, ACS in SARS-CoV-2 is associated with marked microvascular inflammation, endothelial dysfunction, thrombothic disorders, and haemodynamic changes [39]. It is known that circulating interleukin-6, a biomarker of high COVID-19 mortality, is one of the key inflammatory factors of atherothrombosis [16]. ACS can be promoted by inadequate control of associated cardiovascular risk factors. To verify the diagnosis of ACS in COVID-19 patients, a thorough examination is required [8].

In patients with chronic IHD, SARS-CoV-2 aggravates the disease because of atheroma destabilisation and high risk of atheroma rupture [8, 39, 51]. COVID-19 patients who underwent invasive cardiovascular procedures or surgery are at higher risk of stent or bypass thrombosis.

L.N.Fovino et al. conducted a retrospective analysis of clinical COVID-19 outcomes (a combined endpoint was hospital mortality and need in intensive care) (n = 45, mean age: 65.3 ± 14.6 years) with subclinical coronary artery disease. They assessed coronary calcium score (CCS) levels using chest high-resolution computed tomography (HRCT) [55]. The combined endpoint was recorded in 75% of patients with marked atherosclerosis (CCS ⩾ 400 Agatston units) *vs* 20% of patients (p = 0.004) with minimal/moderate signs of atherosclerosis (CCS < 400 Agatston units); hospital mortality was 50% *vs* 8.9%, respectively (p = 0.003). CCS ⩾ 400 units was a marker of poorer outcomes in patients hospitalised with COVID-19: OR was 7.86 (95% CI 1.16 – 53.01, p = 0.034) in an age- and gender-adjusted model, OR 10.7 (95% CI 1.19 – 68.01, p = 0.035) in a model with age and oxygenation.

In pandemic settings, an exact routing and transportation of patients with suspected ACS should be strictly followed. In general, a widely accepted strategy for management of such patients should be adhered to [8]. In severe COVID-19 and lung damage, when the patient is hospitalised to with respiratory support, conservative strategy is preferable, including in MI1 cases (if an invasive procedure is contraindicated).

COVID-19 and arrythmia. In a series of observations of COVID-19 patients (n = 138) in China, supraventricular and ventricular arrythmia was diagnosed in 16.7% [2]. In severe COVID-19, arrythmia was recorded ≈ 5 times more often than in mild cases. Recurrent paroxysmal atrial fibrillation was found in 23 – 33% of patients with severe COVID-19 (sepsis or ARDS), newly diagnosed paroxysm were diagnosed in 10% [2]. In a recent report from Italy, atrial fibrillation was recorded in 24.5% of 355 deaths (mean age: 79.5 years, including 30% of women) [56].

Prognosis depends on the type of heart rhythm disorder and COVID-19 severity (more favourable prognosis with mild or moderate infection) [8]. There have been reports of arrythmia in COVID-19 patients resulting from proarrhythmic effect of medications (prolonged QT interval and a higher risk of torsade de pointes) [8]. Therefore, standard 12-lead ECG, transthoracic echocardiography, and blood potassium level measurement are mandatory.

ECG monitoring should be started next day after antiviral therapy initiation. In initially congenital or acquired long QT-syndrome, brachycardia (< 50 bpm), ECG monitoring is required 4 hours after first antiviral medication administration. Prior to antiviral medication prescription, plasma potassium should not be < 3.5 mmol/L. In patients with atrial fibrillation, heart rhythm and ventricular contraction rate should be monitored and thromboembolic disorders should be prevented with anticoagulants, taking into account possible interaction of oral anticoagulants with antiviral therapy.

Cardiopulmonary rehabilitation in COVID-19 patients

COVID-19 survivors with cardiovascular complications, especially in moderate and severe cases, need medical rehabilitation. Currently rehabilitation programs are being prepared for such patients. Then these programs will be tested in randomised clinical trials. As COVID-19 is a multi-system disease, rehabilitation programs should be based on syndromic-pathogenetic approach. It will ensure that an adequate number of rehabilitation methods/techniques will be used to correct pathological changes in a specific patient.

Rehabilitation of COVID-19 survivors aims at recovery of functions of external respiration, oxygen transport and utilization by functioning tissues/organs; reduction in dyspnea; cardiovascular system support and minimisation of the risk of cardiovascular complications; improved quality of life; psychological status normalisation; daily activities recovery, and active life.

Key principles of medical rehabilitation of COVID-19 patients: staggered and personalised approach, early initiation (when acute COVID-19 is over and after patient's clinical condition has stabilised), multidisciplinarity, continuous monitoring of patient's condition during rehabilitation (first of all, respiratory and cardiovascular parameters), comprehensive approach to the rehabilitation program.

Any rehabilitation intervention should take into account disease severity, rate of cardiorespiratory decompensation and other organs involvement (kidneys, neurocognitive, psychiatric, musculoskeletal systems), fatigue, asthenia, risk of thromboembolic disorders, and comorbidities. For patients who had severe COVID-19, rehabilitation should consider nutrition status, total body weight and muscle mass. Most promising for pulmonary rehabilitation are first two months after acute coronavirus infection; this is a therapeutic window [57]. During physical rehabilitation COVID-19 patients should have access to oxygen therapy (as required), especially patients with clinical indications or those patients who did not have any respiratory support.

In the novel coronavirus infection, rehabilitation starts in and continues in a specialised inpatient unit – **this is stage 1 of early rehabilitation**. This is an important stage because it allows preventing or minimising com-

plications of a viral disease and detrimental effect from immobilisation; ensuring prevention of critical conditions, joint stiffness and contractions, thrombotic complications; and, if possible, recovery of physical and psychological state of the patient. For patients with severe COVID-19 early rehabilitation is not recommended; it can be considered only after the acute stage, vital functions stabilisation, with positive dynamics evidenced by computer-aided tomography or ultrasound examination [58].

Attention should be paid to exercises of weakest and most important muscles involved in verticalization and locomotion of the patient. Methods of physical rehabilitation comprise: patient positioning ("positioning" rehabilitation, also with the help of the prone position), early mobilisation (passive, partially passive and active motions in all joints with more and more physical activity), verticalization, respiratory manoeuvres, neuromuscular electrical stimulation of lower limbs (for certain groups of patients), dynamic physical activities with low-intensity, low amplitude and slow pace (a bedside stationary bike can be used), moderate resistance exercises (to reduce muscle mass losses and to strengthen the muscles), physical exercises for imbalance correction (if any) [59].

In one therapeutic exercise session (either passive, or passive-active mode) should last for 5 to 15 minutes 3 and more times daily (with the overall duration of at least 30 minutes a day). Once the patient is moved to inpatient setting, therapeutic exercises should last for 10 – 15 minutes 2 – 3 times daily.

Stage 2 of rehabilitation (early inpatient rehabilitation in a specialised inpatient rehabilitation unit) should be arranged in accordance with the antiepidemic provisions. It includes in-ward patient isolation, no group therapy, minimum staff involved into rehabilitation, remote communication between the patient and multidisciplinary team members, use of video, booklets and other telerehabilitation techniques for patient education [60]. At stage II, rehabilitation procedures should last for at least 3 hours 5 times a week.

Physical rehabilitation at stage II means early activation of patient's physical activity, use of various methods of pulmonary and cardiological rehabilitation: diaphragm breathing, exercises for inhale muscles (inspiratory training devices can be used), vibration and compression therapy and acoustic exercises together with drain-activating exercises (where indicated), exercises for general strength, dynamic physical exercises with low intensity (including aerobic exercises on a statutory bike), low-intensity resistance loads (to train main groups of muscles).

Physical exercises in COVID-19 patients with CVD has some features:

- they start with low-intensity loads (exercise stress intensity ⩽ 3 points on modified Borg Dyspnoea Scale or laboured breathing ⩽ 3 on Borg Dyspnoea Scale);
- intensity increases gradually, initially at the account of exposition (duration), then at the account of more intensive exercises (with adequate response to exercises);
- strict state monitoring during exercises.
- power loads in COVID-19 should be based on MRC, UK Medical Research Council.

Special attention should be paid when prescribing physical exercises to patients, whose coronavirus infection was complicated with acute myocarditis, cardiomyopathy, postinfectious cardiac failure [61]. In such cases, rehabilitation should be started after acute period (taking into account contraindications), when the clinical condition is stable and CT, ECG and ultrasonic cardiography results demonstrate positive dynamics.

Stage 3 of rehabilitation is late outpatient rehabilitation (in outpatient settings). Physical rehabilitation of COVID-19 survivors with CVD involves continuation of exercise therapy in order to recover respiratory and cardiovascular system, and transition to more lengthy exercises (statutory bike and/or step exercises). Physical exercises are supervised by medical professionals (also via telerehabilitation). Then patients are recommended to do exercises at home. At home, patients can walk on a flat surface, step up, etc. At this stage it is very important to teach the patient to self-control the condition and ensure safe exercises.

A significant aspect of rehabilitation of COVID-19 patients at all three stages is awareness of the healthy life style (no bad habits, anti-atherosclerotic diet and stress tolerance), explanation why it is important to follow doctor's recommendations, take medications and participate in rehabilitation. Psychological support should be offered almost to all patients with coronavirus infection [62]. Anxiodepressive disorders are managed as required.

Three-stage cardiorehabilitation of COVID-19 patients complicated with ACS (myocardial infraction) or coronary artery bypass grafting should be based on the recommendations of the Russian Society of Cardiosomatic Rehabilitation and Secondary Prevention [63, 64].

Conclusion

The impact from SARS-CoV-2 and other pathogens with toxic, proinflammatory and procoagulation effects can cause decompensation of concomitant CVD and increase hospital mortality rates. The new role of ACE2 as a receptor for SARS-CoV-2 can partially explain the pathophysiological association between the viral infection, immune system and CVD. The novel coronavirus infection can provoke acute myocardial damage and other cardiological complications. As some medications used to treat COVID-19 have cardiotoxic effect, continuous haemodynamic monitoring, ECG and ultrasonic cardiography (as indicated) are mandatory.

As the association between administration of RAAS inhibitors (ACEi and ARI) and a higher risk of infection with more severe COVID-19 has not been yet proven, patients with CVD should keep on taking these medications. COVID-19 survivors should take part in rehabilitation programs for faster and better recovery of their functions (first of all, of respiratory and cardiovascular systems), better quality of life and lower risk of disability.

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