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Cardiovascular Changes in COVID19

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Abstract

The COVID19 pandemic has become a new challenge for doctors and patients. Cardiovascular changes often accompany the disease caused by the SARS-CoV-2 virus. Many researchers are proving the connection of COVID-19 with myocardial damage. Acute myocarditis (acute inflammatory cardiomyopathy) can be caused by direct or indirect exposure to the SARS-CoV-2 virus. The effect of COVID-19 on atherosclerosis of blood vessels, primarily coronary, is also known. SARS-CoV-2 can cause endothelial dysfunction, an independent factor in the development of myocardial and cerebral infarction. Disseminated endotheliopathy caused by COVID-19 triggers a hyperinflammatory reaction and hypercoagulation, resulting in vascular thrombosis and thromboembolism. Many cases of various types of heart rhythm disturbances in COVID-19 have been described, including exposure to antiviral and other drugs. Most of the direct and indirect mechanisms of action of SARS-CoV-2 on the host lead to hypertension or hypotension. Troponin level research should be considered an ally and essential diagnostic and prognostic assistance in providing medical care worldwide in the context of COVID-19.

Keywords: SARS-CoV-2; COVID-19; Cardiovascular Changes

Introduction

The spread of heart failure (HF) is steadily showing an upward trend around the world. There has also been an increase in the number of people with various risk factors for cardiovascular complications. High mortality rates and cardiovascular disease have long been directly linked. But most deaths from acute heart failure or chronic decompensation occur in less developed countries, as well as for low- or middle-income groups [1]. The COVID-19 pandemic has become a new challenge for doctors and patients.

There is a lot of evidence that COVID-19 infection has the highest mortality rates in the elderly, as well as in patients with a history of concomitant cardiovascular disease [2,3]. According to a meta-analysis, the mortality rate in patients with concomitant cardiovascular diseases infected with SARS-CoV-2 is 20 times higher, and the risk of entering the intensive care unit has increased by 13.5 times [4].

Many researchers have proven a link between COVID-19 and myocardial damage [5]. However, the mechanisms of damage are not fully understood. According to the international registry CAPACITY-COVID, created to determine the role of cardiovascular disease during the COVID-19 pandemic, cardiovascular complications were diagnosed in more than 11% of patients. At the same time, the most common was atrial fibrillation, then heart failure, acute coronary syndrome, ventricular arrhythmias, bacterial endocarditis, myocarditis, pericarditis [6].

Consider the main cardiovascular changes that can occur with COVID-19, as well as after the disease.

Acute myocarditis (acute inflammatory cardiomyopathy)

Acute myocarditis is one of the most difficult diagnoses, because it is characterized by a variety of clinical manifestations and course, as well as the complexity of verifying the diagnosis. Consider the direct and indirect effects of SARS-CoV-2 on the myocardium, epicardium, and pericardium.

Direct effect of the virus on the myocardium with the development of viral myocarditis [7,8]. When the virus is exposed to cardiomyocytes, the authors of the study note an increase in wall thickness with diffuse biventricular hypokinesis and severe left ventricular dysfunction. Pronounced biventricular interstitial myocardial edema is described, as well as circumferential pericardial effusion. Damage to cardiomyocytes recorded in the laboratory. All of these results corresponded to acute myopericarditis in a patient who tested positive for SARS-CoV-2 when analyzing a real-time reverse transcriptase polymerase chain reaction [8]. There is a description of 39 autopsies of COVID-19 patients that confirms the presence of SARS-CoV-2 infection in myocardial tissue with the greatest activity in interstitial cells in addition to invading macrophages [7].

However, there is also an indirect effect of the virus on cardiomyocytes. Indirect effects include several mechanisms: hyperinflammatory syndrome, binding of SARS-CoV-2 to receptors of angiotensin-converting enzyme 2 (ACE2) in human tissues, multisystem inflammatory syndrome and the accession of bacterial infection.

One study noted a group of patients with severe left ventricular dysfunction and vasoplegia caused by hyperinflammatory syndrome. There was a rapid development of multi-organ dysfunction [9]. In other studies of hyperinflammatory reaction, diffuse signs of edematous myocarditis have been recorded [10]. Cases of toxic cardiomyopathy with a decrease in the ejection fraction are also described [11]. However, levels of highly sensitive troponin and brain natriuretic peptide (NT pro BNP) were elevated without ischemic changes on the ECG, as were biomarkers of inflammation [8-11]. Most of the above studies pointed to delayed myocarditis. Damage to the pericardium and myocardium may be associated with specific profiles of immune cells, especially an increase in the level of cytotoxic T cells [12].

It should also be noted the role of angiotensin-converting enzyme 2 (ACE2) receptors on cardiomyocytes in the development of myocarditis. SARS-CoV-2 is known to bind through its spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor of the host. It is part of the renin-angiotensin-aldosterone system (RAAS), which mediates the virus's entry into host cells, and is expressed in the lungs, heart, vessels, and gastrointestinal tract. Overexpression of the ACE2 receptor by the SARS-CoV-2 virus may lead to an increased likelihood of myocarditis and mortality in patients with heart failure [13]. Theoretically, the presence of angiotensin-converting enzyme 2 (ACE2) receptors on cardiomyocytes may be the mechanism by which SARS-CoV-2 causes lymphocytic myocarditis [14]. Relation between angiotensin-converting enzyme 2 (ACE2) and renin-angiotensin system (RAS) is shown in figure 1.

Figure 1: Relation between angiotensin-converting enzyme 2 (ACE2) and renin-angiotensin system (RAS).

Multisystem inflammatory syndrome can be considered as a cause of heart damage. The first cases of new multisystem inflammatory syndrome in children (MIS-C) [15] and in adults (MIS-A) [16] were identified a few months after the onset of the COVID-19pandemic. Clinical signs included elevated markers of inflammation, heart dysfunction and others.

Another indirect mechanism of heart damage is the attachment of bacterial superinfection. Bacterial endocarditis, myocarditis, and pericarditis are less common complications among patients infected with SARS-CoV-2 compared to other comorbidities of the heart. Bacterial endocarditis is more commonly initiated by Staphylococcus aureus, Streptococcus viridians, Enterococcus faecalis, Klebsiella pneumoniae, and Enterococcus faecium [17,18]. At the same time, bacterial endocarditis is difficult to notice in patients with COVID-19, because acute respiratory distress syndrome and inflammatory syndrome can mask symptoms.

With myocarditis caused by COVID-19, manifestations typical of angina pectoris can be observed, such as discomfort behind the sternum, chest pain with irradiation in the left arm, shortness of breath, left ventricular dysfunction and others. On an echocardiogram in severe myocarditis, global dysfunction of wall movement can be detected [2]. Moreover, on an electrocardiogram (ECG) there may be signs of ACS (changes in ST and T), but most often they are not. But quite often there is an increase in the level of isosensitive troponin and brain natriuretic peptide (NT pro BNP).

As we can see, determining the level of highly sensitive troponin and brain natriuretic peptide (NT pro BNP) can play an important role in the timely diagnosis of myocardial damage during the COVID-19 pandemic. It has also been suggested that a combination of immunoglobulins and corticosteroid therapy may be useful to patients with myocarditis initiated by COVID-19 [9]. The inclusion of this study in routine medical practice may be promising.

In the absence of convincing histological data indicating the presence of myocarditis, today the term «acute inflammatory cardiomyopathy» can be more appropriate, but less specific [19].

Atherosclerosis

Type 1 myocardial infarction caused by atherothrombosis can be triggered by a pro-inflammatory and prothrombotic condition. The development of atherosclerosis can be influenced by many factors, such as the protein and lipid components of native and modified low-density lipoproteins, angiotensin II, smoking, visceral adipose tissue and dysmetabolism. Infectious processes and products of the endogenous microbiome can also affect atherosclerosis and its complications directly and indirectly, causing local and systemic reactions [20].

Pneumonia can accelerate the progression of atherosclerosis [21]. Of course, this mainly concerns bacterial infection [20]. But as we know, it's not uncommon for a bacterial superinfection to join COVID-19 [6,17].

Low HDL levels have been associated with a higher risk of contracting SARS-CoV-2 and more severe disease, and increases the risk of mortality from COVID-19 [22]. However, SARS-CoV-2 has not yet been detected in coronary plaques [21].

In severe COVID-19, a cytokine storm develops. It arises as a result of an imbalance in the activation of T cells with dysregulated release of interleukin-6, 7, 17, 22, chemokine 10 of the C-X-C motif (CXCL10), MCP-1, macrophage inflammatory protein 1α (MIP-1α), tumor necrosis factor (TNFα) and other cytokines. Activation of the immune system itself can lead to plaque instability, contributing to the development of acute coronary events [3,23].

Endothelial dysfunction

A known independent risk factor for myocardial and cerebral infarction is endothelial dysfunction. Many studies indicate that cardiovascular complications caused by COVID-19 are strongly associated with endothelial damage. Thus, it can be considered as a potential mechanism of myocardial damage. However, endothelial damage can be caused by the direct ingress of the virus [24], as well as the influence of circulating inflammatory factors on the vascular endothelium [25].

In severe COVID-19, there is a risk of sepsis, which in this case is characterized by acute respiratory distress syndrome (ARDS). In parallel with ARDS, patients develop multiple organ failure due to disseminated vascular micro thrombotic disease. In response to viral septicemia, the body activates the complement system, which synthesizes the C5b-9 complement terminal complex to neutralize the pathogen. However, C5b-9 causes endothelial cell damage, leading to endothelial dysfunction [25]. Disseminated endotheliopathy caused by COVID-19 triggers a hyperinflammatory reaction and hypercoagulation.

Hyperinflammatory reaction is accompanied by dysregulation of pro-inflammatory cytokines [3,23]. Damaged cells and the virus can be molecular patterns that are recognized by pattern recognition receptors (PRRs) on the endothelium. When these endothelial PRRs are activated, an inflammatory response is stimulated, which causes a loss of vasoconstrictor factors such as nitric oxide (NO) and prostacyclin. The loss of these factors contributes to the adhesion of platelets and leukocytes. The expression of endothelial

adhesion molecules, chemokines and inflammatory cytokines accelerates the local inflammatory response, which aggravates the interaction of blood elements with the vessel wall [24].

Hypercoagulation initiates endothelial exocytosis of von Willebrand factor (VWF) and factor VIII from Weibel-Palade bodies, as well as P-selectin [25,26]. SARS-Cov-2 causes a unique endothelial reaction – endothelial exocytosis. Exocytosis is a rapid secretory response to damage in which various agonists bind to surface cell receptors, causing endothelial granules to fuse with the endothelial membrane and release the contents of the granules into the bloodstream [27]. Von Willebrand factor (VWF) attaches to the damaged endothelium and then collects circulating platelets, thereby triggering micro thrombogenesis, culminating in micro- and macro thrombotic syndrome [25]. At the same time, a reduced number of platelets, as well as a low level of fibrinogen, may be associated with an increased risk of venous thromboembolism [28]. Patients with severe COVID-19 often have a state of hypercoagulation, indicating widespread thrombosis and fibrinolysis. In laboratory studies, there is an increase in the level of D-dimer, von Willebrand factor (VWF) and factor VIII [25,27]. Autopsy studies have shown that there is both endothelial inflammation and microvascular thrombosis. In this case, inflammatory cells attach to the endothelium of small vessels in the lungs, heart, kidneys and liver. Therefore, it can be assumed that the combination of high levels of VWF, P-selectin, as well as microvascular thrombosis and microvascular inflammation may be a common trigger for inflammatory and thrombotic complications of COVID-19.

In severe COVID-19, arterial and venous thromboembolism is common [21]. The incidence of venous thromboembolic complications in COVID-19 patients admitted to intensive care units ranges from 20% to 35%, and deep vein thrombosis has been detected in 70-100% of patients who died from COVID-19 [29]. A case of a 65-year-old male patient infected with SARS-CoV-2 with acute myocardial infarction, in which stent thrombosis has been documented,» has been described [30]. Overall, among patients infected with SARS-CoV-2 with cardiovascular complications, pulmonary embolism was diagnosed in more than 6% of patients [6]. Cases of extensive coronary thrombosis of patients infected with SARS-Cov-2 have been repeatedly described. However, do not forget that in the severe course of COVID-19, most patients are with limited mobility. Accordingly, factors of infection and immobilization may increase the risk of thromboembolism [31].

Anticoagulant therapy with low molecular weight heparin has reduced mortality in patients with severe COVID-19 infections [32].

Arrhythmia

Many cases of the development of various types of heart rhythm disturbances have been described [23]. Possible causes of arrhythmias in the context of COVID-19 can be myocarditis, systemic inflammation, electrolyte imbalance, concomitant diseases, as well as taking medications [33]. The most common is sinus tachycardia [2], which is mainly associated with inflammation, fever, mental disorders, hypoxia, as well as reduced adherence to continuous therapy of patients with chronic heart failure, hypertension [34], coronary heart disease and others. In addition to sinus tachycardia, there are supraventricular tachycardia, atrial fibrillation, fluttering, stable ventricular tachycardia, ventricular fibrillation and ectopia of the atria or ventricles [5,6,33].

It is very important to consider the characteristics of certain medicines in the treatment of COVID-19. For example, the widely used antibacterial agents of the fluoroquinolones group have the side effect of prolonging the QT interval [35]. Do not forget about the combination of the antimalarial drug hydroxychloroquine and antibacterial azithromycin, which was originally used in the treatment of COVID-19 [36]. But it is no longer used due to cardiotoxicity, and a high risk of heart failure and arrhythmia. There is also evidence of cardiotoxic and proarrhythmic effects of the antiviral drug remdesivir, especially in the form of bradycardia [37].

Hypertension

Hypertension is present in more than one billion people among the adult population of the world. There are many known factors contributing to the pathogenesis of hypertension, including the role of the immune system. Consider the association of hypertension with COVID-19. It is known that hypertension can increase the risk of mortality from COVID-19.

Let's return to the role of angiotensin-converting enzyme 2 (ACE2) receptors of the renin-angiotensin-aldosterone system (RAAS) in COVID-19. SARS-CoV-2 binds by adhesions to the ACE2 receptor of host cells.

The main treatments for hypertension are angiotensin-converting enzyme (ACE inhibitors) or angiotensin receptor blockers (ARBs). However, studies have shown that these drugs do not affect the outcome of COVID-19disease [38]. Of course, there are studies that indicate an improved prognosis with the use of ACE inhibitors/ARBs on the outcome of the disease caused by SARS-CoV-2 [39]. However, these data are not enough to summarize the role of ACE inhibitors/ARBs in the treatment of COVID-19.

Increased cardiovascular risks are also associated with social factors. The change in daily stress associated with restrictions during the pandemic has led to an increase in average daily blood pressure. The phenomenon of the white coat has become particularly entrenched [34]. Patients have also become less likely to seek medical care on time, which has led to an increase in mortality rates [40]. Public pressure caused by the COVID-19 pandemic has reduced the effectiveness of family medicine [41]. There is even a case of suicidal acute alcohol intoxication that led to the death of a person who could no longer tolerate restrictions due to the COVID-19 pandemic. However, no significant cardiac injuries were found after autopsy [42]. Although public health approaches have changed throughout the pandemic, the clinical characteristics and outcomes of patients with heart failure have been similar in different waves. This suggests that the health care system should pay more attention to family medicine and the media.

Hypotension

The development of hypotension and COVID-19 can be associated with capillary leakage syndrome and vasoplegia [10].

Systemic capillary leakage syndrome is a very rare and fatal disease characterized by hemoconcentration and hypoalbuminemia, frequent episodes of shock, anasarca [43]. The syndrome may be idiopathic or secondary to the underlying cause, which may include viral infections. Cases of systemic capillary leakage syndrome in patients with COVID-19 have been described, more often leading to a state of shock [44]. However, the relatively small number of cases described does not allow us to draw conclusions. But further observation of such cases will help to study the pathogenesis of COVID-19 more deeply, as well as the etiology of systemic capillary leakage syndrome.

Vasoplegia is a syndrome of pathological low systemic vascular resistance, the dominant clinical feature of which is a decrease in blood pressure with normal or increased cardiac output. The causes of vasoplegia can be sepsis, conditions after surgery, injuries, systemic inflammation, predisposing to organ dysfunction [45]. The body's hyperinflammatory response in COVID-19 could theoretically cause vasoplegic syndrome. Elevated levels of pro-inflammatory cytokines, in particular IL-6, positive IgG serology indicate an immunological mechanism of heart damage and vasoplegia [46]. This is especially true of multisystem inflammatory syndrome in both children and adults [8-10].

Coronary vasospasm

Coronary vasospasm can be a cause of myocardial infarction in the absence of obstructive changes in the coronary arteries. Spasm of the coronary vessels can be caused by a systemic inflammatory process.

A case of focal spasm of the coronary artery, simulating myocardial infarction with ST segment elevation, successfully treated exclusively with intracoronary nitroglycerin in an accidentally positive patient with COVID, is described. At the same time, the patient did not have sepsis, which makes us think about the unusual manifestation of COVID-19 [47].

The role of troponin

Troponin should be seen as an ally and essential diagnostic and prognostic aid in the provision of health care worldwide in the context of COVID-19. An increase in troponin levels may indicate latent coronary heart disease [9]. Elevated levels of highly sensitive troponin (hs-TNT) in the context of COVID-19 infection are associated with a significantly increased risk of mortality [3]. According to some reports, approximately 20% of hospitalized patients show signs of heart damage, as evidenced by elevated levels of highly sensitive troponins (hs-cTnI) [48].

However, the American College of Cardiology recently published a brief overview of the role of biomarkers in COVID-19 patients. It states that clinicians are advised to measure troponin only if the diagnosis of acute myocardial infarction is considered on a clinical basis. This approach was recommended on the basis that an increase in troponin levels in patients with COVID-19 may be multifactorial, and less likely to be associated with atherothrombotic coronary occlusion [49].

But there are numerous studies supporting the need to measure troponin levels in hospitalized patients. For example, one study involved 416 hospitalized COVID-19 patients. In 1 out of 5 patients,

there was an increase in the concentration of cardiac troponin. Such patients were more likely to require invasive and non-invasive ventilation, developed acute respiratory distress syndrome more often, and had a mortality rate 10 times higher [50].

Clinicians should measure troponin levels in hospitalized COVID-19 patients. Ignoring this study can lead to myocardial damage. Early diagnosis can facilitate proper triage in intensive care units, and determine the use of inotropes, vasopressors, and diuretics for significant cardiac dysfunction.

Conclusion

Patients with cardiovascular disease are vulnerable to COVID-19, which can cause many complications. Against the background of the body's hyperinflammatory reaction, the manifestation of cardiovascular events can be erased. More frequent examination of the level of highly sensitive troponin and cerebral natriuretic peptide (NT pro BNP) will avoid cardiovascular complications caused by COVID-19, which is confirmed by many studies.

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