REVIEW ARTICLE

What should a cardiologist know about coronavirus disease 2019?

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ABSTRACT
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19). The most common symptoms of COVID-19 are: fever (81.8%–100%), cough (46.3%–86.2%), myalgia and fatigue (11%–50%), expectoration (4.4%–72%), and dyspnea (18.6%–59%). The most common laboratory abnormalities in COVID-19 include decreased lymphocyte count (35%–82.1%), thrombocytopenia (17%–36.2%), elevated serum C-reactive protein (60.7%–93%), lactate dehydrogenase (41%–76%), and D-dimer concentrations (36%–46.4%). Among comorbidities in patients with COVID-19, cardiovascular disease is most commonly found. In addition, patients with concomitant cardiovascular diseases have worse prognosis and more often require admission to the intensive care unit (ICU), compared with patients without such comorbidities. It is estimated that about 20% of patients with COVID-19 develop cardiac injury. Cardiac injury is more prevalent among patients with COVID-19 who require ICU care. In a group of critically ill patients, 27.5% had an elevated N-terminal pro-B-type natriuretic peptide concentration, and increased cardiac troponin level was found in 10% of patients. One of the life-threatening cardiac manifestations is coronavirus fulminant myocarditis, which may also occur without accompanying symptoms of pulmonary involvement. Early recognition and treatment is crucial in these cases. So far, data on the incidence of arrhythmias in patients with COVID-19 are limited. Coronavirus disease 2019 impacts patients with cardiovascular comorbidities and affects daily practice of cardiologists. Thus, it is important to know typical COVID-19 symptoms, possible clinical manifestations, complications, and recommended treatment.

Introduction First cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were recorded in September 2019. Subsequently, pneumonia and other respiratory infections were reported in some Chinese hospitals in Wuhan (Hubei Province). Finally, the new viral genome was isolated on January 7, 2020, and it was called the new coronavirus (2019-nCoV). Coronaviruses are enveloped, single-stranded, positive-strand RNA viruses, with the largest genome among RNA viruses (approximately 30 kb).[1,2] On February 11, 2020, the International Committee on Taxonomy of Viruses decided to change the name of the new virus to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), due to its genetic similarity to the coronavirus responsible for the severe acute respiratory syndrome (SARS) outbreak in 2003. On the same day, the World Health Organization announced coronavirus disease (COVID-19) as the clinical manifestation of SARS-CoV-2 infection.

The most common symptoms of COVID-19 include fever (81.8%–100%), cough (46.3%–86.2%), myalgia and fatigue (11%–50%), expectoration (4.4%–72%), and dyspnea (18.6%–59%). Less common are headache and dizziness (6.5%–50%), hemoptysis (0.9%–5.1%), nausea or vomiting (1%–5%), and diarrhea (2%–14%).[3-11] These symptoms are similar to those caused by other coronaviruses. There is also data on the neurological manifestation of COVID-19, which include acute cerebrovascular disease and impairment of consciousness.[12]

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The most common laboratory abnormalities found in COVID-19 include decreased lymphocyte count (35%–82.1%), thrombocytopenia (17%–36.2%), elevated serum C-reactive protein (60.7%–93%), lactate dehydrogenase (41%–76%) and D-dimer concentration (36%–46.4%). Elevated concentrations of serum creatine kinase (7%–13.7%), transaminases (21%–28%), or total bilirubin (10.5%–18%) have been rarely reported.[6,7,10,13]

Current evidence indicates that at least 25.1% of patients with COVID-19 have one or more comorbidities, with diabetes, hypertension, and cardiovascular diseases being the most common.[8,14]

Similarly, SARS-CoV-2-like coronaviruses (also SARS coronavirus) use angiotensin-converting enzyme 2 (ACE2) protein as a cell entry receptor. This protein is expressed on pulmonary alveolar epithelial cells: type I alveolar and, mainly, type II alveolar cells. Type II alveolar cells are best known for their role in synthesizing and secreting pulmonary surfactant which is affected by virus infection. To a lesser extent, ACE2 is also present in other tissues: the heart, kidneys, vascular endothelium, and intestines.[15-19] Autopsy studies in patients who died of COVID-19 revealed that also the heart, kidneys, spleen, bone marrow, liver, pancreas, stomach, intestines, thyroid, and skin can be affected by SARS-CoV-2[20]; however, the mechanism is different from that in the lung tissue, since the presence of virus RNA has only be found in the lungs so far.

Are patients with cardiovascular comorbidities at higher risk? Cardiovascular diseases are the most common comorbidities in patients with COVID-19. Available data indicate that these patients are often diagnosed with hypertension (15%–30.4%), diabetes (7.3%–18.8%), coronary artery disease (2.5%–8%), or other cardiovascular disease (4%–14.6%). In addition, patients with concomitant cardiovascular diseases have a worse prognosis and more often require admission to the intensive care unit (ICU) compared with patients without such comorbidities.[8,10,21-23] In a meta-analysis by Li et al,[24] which included 1527 patients with COVID-19 from China, it was shown that hypertension was twice as common in the ICU / severe cases when compared with the non-ICU / severe patients.

There are several hypotheses about the worse prognosis of COVID-19 in patients with diabetes or hypertension. First, higher plasma plasminogen levels are found in patients with diabetes or hypertension.[25] It is postulated that plasminogen may increase the pathogenicity of SARS-CoV-2 by increasing its ability to bind to ACE2 and thereby facilitate its penetration into host cells.[26] However, according to the theory of Fang et al,[27] in diabetic or hypertensive patients who are treated with ACE inhibitors (ACEIs) or angiotensin II type 1 receptor antagonists, ACE2 expression may be increased, which may promote SARS-CoV-2 infection. In the literature, there are data available indicating that patients with cardiovascular diseases, including hypertension or diabetes, have higher ACE2 activity.[28-30]

In the literature, 2 cases of patients after a heart transplant and affected with COVID-19 have been reported, and with similar clinical presentation as in nontransplant patients (with the main symptoms of fever and fatigue). The first reported patient was treated successfully with antiviral drugs (ganciclovir and arbidol) and antibiotics (ceftriaxone sodium and moxifloxacin). The second patient was initially treated with moxifloxacin and ganciclovir, but as his condition worsened, human γ-globulin and methylprednisolone were given, which resulted in recovery and discharge from the hospital after 1 month after admission.[31]

May coronavirus disease 2019 mimic other cardiovascular diseases? Some symptoms in patients with COVID-19 pneumonia suggest cardiovascular diseases. Fatigue, dyspnea, cough are typical in COVID-19, but these symptoms may also result from exacerbation of chronic heart failure. Chest computed tomography (CT) has been shown to be a very useful tool in differentiating these 2 conditions. In a patient with heart failure, the ratio of central and gradient distribution of ground-glass opacity and thickening of interlobular septum is higher, as is the ratio of the expansion of small pulmonary veins.[32] It should be emphasized, however, that severe cases of pneumonia or acute respiratory distress syndrome may be complicated by heart failure, which makes interpretation of CT changes difficult. Therefore, when interpreting the CT scans, the clinical context and laboratory findings are extremely important.

The most characteristic CT findings in patients with COVID-19 are shown in TABLE 1.

Results of cardiac troponin measurements should be interpreted with caution in differentiating COVID-19 and myocardial infarction, as their increased levels have been found in 8% to 12% of COVID-19 cases.[8,40] Thus, this laboratory finding has to be interpreted in the clinical context and electrocardiography recording as well as the result of echocardiography. Chest pain was reported by 1% to 6% of COVID-19 patients, but with no features of typical angina, and most likely resulted from the inflammatory pleural involvement.[6,41,42]

Elevated D-dimer levels are observed in 36% to 46.4% of patients with COVID-19, which may suggest pulmonary embolism.[6,10] It seems that CT angiography plays a key role in these cases. It has been shown by Danzi et al[43] that bilateral COVID-19 can act as a precipitant factor in acute pulmonary embolism. It has been

TABLE 1 Most characteristic features for coronavirus disease 2019 in chest computed tomography

Parameter	Zhou et al[33]	Bernheim et al[34]	Ai et al[35]	Chung et al[36]	Pan et al[37]	Bai et al[38]	Liu et al[39]
Feature							
Ground-glass opacity	62.9%	76%	46%	57%	75%	91%	89%
Crazy-paving pattern[a]	22.6%	5%	1%	19%	25%	5%	38%
Consolidation	33.9%	43%	50%	29%	42%	69%	11%
Linear opacities	ND	7%	ND	14%	ND	51%	ND
Air bronchogram	72.6%	ND	ND	ND	ND	14%	7%
Multiple lesions	83.9%	ND	90%	ND	ND	61%	60%
Single lesion	16.1%	ND	ND	ND	ND	7%	ND
Localization							
Unilateral	ND	ND	ND	ND	ND	19%	20%
Bilateral	ND	60%	ND	75%	75%	75%	75%
Peripheral	77.4%	52%	ND	33%	54%	80%	ND
Peripheral and central	22.6%	ND	ND	ND	ND	14%	ND
Central	0%	0%	ND	ND	ND	1%	ND

a A reticular shadow on the background of ground-glass opacity and thickening of the interlobular septum and interlobular septum, showing paving stone sign

Abbreviations: ND, no data

reported that viral infection with subsequent systemic inflammatory response may lead to imbalance between procoagulative and anticoagulant mechanisms.[44] In addition, increased levels of plasminogen are found in bronchoalveolar lavage in patients with acute respiratory distress syndrome.[26,45] Thus, elevated levels of D-dimers appear to be the result of both excessive systemic inflammatory response and increased fibrinolysis due to increased plasmin concentration. Patients with COVID-19 also present other coagulation abnormalities such as increased levels of fibrinogen and fibrin and fibrinogen degradation products, and reduced levels of antithrombin, when compared to the healthy control population. This indicates that COVID-19 is associated with a risk of developing disseminated intravascular coagulation, which in turn is linked with a worse prognosis.[46,47] Due to the hypercoagulability observed in some patients with COVID-19, some authors postulate the use of low-molecular-weight heparin, which additionally shows anti-inflammatory effect by reducing the concentration of interleukin (IL) 6 and increasing the lymphocytes' count.[48-50]

What about cardiovascular complications in the course of coronavirus disease 2019?

It is estimated that about 20% of patients with laboratory-confirmed COVID-19 develop cardiac injury, and there are several possible mechanisms that may lead to this. The first one is related to ACE2 expression in cardiomyocytes. Binding SARS-CoV-2 to ACE2 could result in alteration in ACE2-related signaling pathways and subsequently cause local inflammation.[24,51] The second possible mechanism is acute cardiac injury due to the cytokine storm, which is triggered by an imbalance between type 1 and type 2 helper T cells. In most cases of severe course of COVID-19, elevated serum levels of pro-inflammatory cytokines were reported, including IL-6, IL-1β, IL-2, IL-8, IL-17, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon γ-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and tumor necrosis factor.[8,52,53] As a result of this systemic inflammatory response, not only cardiac injury, but also multiorgan failure syndrome may occur.[8,21] Another effect of systemic inflammation is increased coronary blood flow which can lead to myocardial infarction due to atherosclerotic plaque rupture. Other important factor is hypoxemia as a result of acute lung injury. This leads to impairment of myocardial oxygen demand-supply relationship, oxidative stress, intracellular acidosis, and eventually to myocardial cells damage.[51] Finally, electrolyte imbalance may play a role in COVID-19, especially hypokalemia due to SARS-CoV-2 interaction with the renin-angiotensin-aldosterone system.[54] This condition may result in life-threatening ventricular arrhythmias, especially in patients with underlying cardiac disease.

Cardiac injury is more prevalent among patients with COVID-19 referred to the ICU (22% vs 7.2%).[11] These patients more often require

noninvasive and invasive mechanical ventilation, and their mortality is higher than in patients without cardiac injury.[55] It has been shown that patients with severe or critical course of COVID-19 are at high risk of myocardial injury, as indicated by increased serum cardiac troponin levels, and subsequently at higher risk of in-hospital mortality.[55] Among the patients who died, as reported by the National Health Commission of China, there were almost 12% of patients without any cardiovascular disease who experienced cardiac injury, with significant increase of troponin concentration or cardiac arrest during hospitalization.[51]

Among the 120 critically ill patients infected with SARS-CoV-2, 27.5% had an elevated N-terminal pro-B-type natriuretic peptide concentration, and in 10% an increase in cardiac troponin level was found.[56] These findings indicate that cardiovascular injury may affect systemic stability and should not be ignored.

One of the life-threatening cardiac manifestations is coronavirus fulminant myocarditis, which can occur without the associated symptoms of pulmonary involvement. Early recognition and treatment is crucial in these cases. Viral fulminant myocarditis may mimic an acute ST-segment elevation myocardial infarction, with high levels of cardiac troponins, creatine kinase isoenzyme MB, and N-terminal pro-B-type natriuretic peptide, and with regional wall motion abnormalities, left ventricular ejection fraction impairment in echocardiography, but with no coronary stenosis in coronary angiography. Cardiac magnetic resonance imaging is a useful tool to confirm acute myocarditis in such cases, showing typical abnormalities: diffuse edema and slow gadolinium washout.

Data on treatment of fulminant myocarditis in SARS-CoV-2-infected patients include mainly case reports.[57,58] Hu et al[57] used treatment regimen based on sufficient doses of immune-modulation drugs, for example, steroids (methylprednisolone 200 mg daily for 4 days) and intravenous immunoglobulins (20 g/d for 4 days). Inciardi et al[58] administered lopinavir and ritonavir (200 and 50 mg twice daily, respectively), hydroxychloroquine (200 mg twice daily) and steroids (methylprednisolone 1 mg/kg/d for 3 days). Both regimens were effective in the myocarditis treatment. However, as we know from myocarditis with a different etiology, some patients may require active mechanical life-support therapy, and the application of mechanical respirators and circulatory support systems, such as intra-aortic balloon pulsation, Impella implantation, or extracorporeal membrane oxygenation. In the case of life-threatening cardiac tamponade in patients with COVID-19-associated myocarditis, pericardiocentesis is required. Interestingly, in the case reported by Hua et al,[59] a nasopharyngeal swab was positive for SARS-CoV-2, while pericardial fluid testing was negative.

There is limited data on the incidence of arrhythmias in patients with COVID-19. One study showed that this problem may occur in almost 17% of patients with laboratory-confirmed COVID-19, but the type of arrhythmia has not been clarified.[11]

What about cardiac complications associated with coronavirus disease 2019 treatment? It is estimated that about 90% of patients with COVID-19 receive antiviral drugs, such as ribavirin, lopinavir, or ritonavir. Complications related to this treatment include angina, myocardial infarction, and arrhythmias. In the context of arrhythmias, one of the serious side effects of antiviral drugs may be QT interval prolongation and polymorphic ventricular tachycardia (torsades de pointes).[60] In patients treated with chloroquine or hydroxychloroquine, apart from the torsades de pointes risk, the occurrence of conduction abnormalities, and left ventricular diastolic and systolic dysfunction have also been reported.[61,62] The beneficial effects of combined chloroquine and azithromycin treatment have recently been reported in patients with COVID-19; however, azithromycin may cause QT prolongation.[63,64] According to the position paper of 2 scientific committees of the Polish Academy of Sciences and 4 Polish scientific societies on the use of chloroquine in the treatment of patients with COVID-19 infected with SARS-CoV-2, the use of chloroquine is justified in the treatment of COVID-19, while it is unjustified and potentially dangerous in the prophylaxis of infection.[65] Therefore, electrocardiography recordings should be repeated and cardiac function monitored in these patients.[31,66]

Does cardiovascular treatment affect the risk of coronavirus disease 2019? Since the ACE2 protein has been reported as a cell entry receptor for SARS-CoV-2, there was a concern that ACEIs or angiotensin II receptor blockers (ARBs), which are commonly used to treat heart failure and hypertension, may facilitate COVID-19 development, due to increased expression of ACE2.[27] It should be emphasized that the name ACE2 is the result of partial homology with ACE (40% identity, 61% similarity). In contrast, ACE2 cannot converse angiotensin I into angiotensin II, because homology does not involve its active site. Therefore, ACEIs and ARBs treatments do not affect ACE2.[67]

There is evidence from animal studies that ARBs (but not ACEIs) may upregulate ACE2; however, the results are conflicting and differ depending on the type of analyzed tissue and drug dosage. Currently, we have no data confirming

that the use of ACEIs or ARBs facilitates virus entry into human cells.[67,68] Major cardiological scientific societies, such as the European Society of Cardiology Council on Hypertension, American College of Cardiology, American Heart Association, and Heart Failure Society of America, European Society of Hypertension, International Society of Hypertension, British Cardiovascular Society, British Society for Heart Failure, Canadian Cardiovascular Society, Canadian Heart Failure Society, Polish Society of Hypertension, and other national cardiological societies have recently published their position in which, according to current knowledge, they do not recommend discontinuing ACEI or ARB treatment in patients with cardiovascular diseases to prevent SARS-CoV-2 infection.[69]

Conclusion: does coronavirus disease 2019 have an impact on cardiologist daily practice?

The coronavirus disease 2019 pandemic forced tremendous changes in the functioning of the healthcare systems of all countries. Implemented safety protocols that aim to prevent the spread of the disease also have an impact on management of patients without COVID-19. As reported by Tam et al,[70] at the end of January 2020, the median time from the occurrence of chest discomfort in patients to the first medical contact was almost 4-fold longer compared with 2018 to 2019 (318 min vs 82.5 min). Also the median time between arrival at hospital to successful wire crossing for reperfusion during primary percutaneous coronary intervention has increased by the end of January 2020 (110 min vs 84.5 min). Moreover, in patients with acute aortic syndromes, time is of the essence. Fast diagnosis of coexisting COVID-19, safe and effective transport, implementation of the intervention procedure, as well as—and maybe above all—protection of the team of healthcare workers as well as further management and treatment of patients are still a great challenge.[71] Our own observations indicate that the COVID-19 pandemic significantly impeded patients' access to routine cardiac diagnostics, such as echocardiography or control of cardiac implantable electronic devices, and prevented previously planned invasive cardiac procedures from being performed. It cannot be excluded that after the COVID-19 pandemic, we will have to deal with the treatment of patients with more advanced heart diseases, which may result in worse treatment results.

In conclusion, COVID-19 is a disease that has a huge impact on patients with cardiovascular diseases and will have a significant impact on the daily practice of cardiologists. That is why it is so important to know the typical symptoms and course of COVID-19, clinical complications, management, and recommended treatment.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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