SPECIAL REPORT

Cardiac emergencies during the coronavirus disease 2019 pandemic in the light of the current evidence

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Introduction As a result of healthcare reorganization, restrictions concerning social behaviors and fear of becoming infected, the coronavirus pandemic is dangerous not only to patients with coronavirus disease 2019 (COVID-19), but to all people who will face an imminent threat to their life and health during this time. It particularly pertains to cardiac patients, in whom delays in receiving medical help may result in irreversible changes and, in the worst case scenario, death. Providing quick access to professional healthcare and maintaining high standards of treatment, considering the safety of patients and medical personnel as well as hospital capacity, are among the greatest challenges encountered by medicine in the time of the pandemic.[1]

Pathogenesis of cardiovascular complications in severe acute respiratory syndrome coronavirus 2 infection Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects the host organism through angiotensin-converting enzyme 2 (ACE2), which is mainly present in the lungs, heart, kidneys and gastrointestinal tract.[2] The course of the infection can be divided into 3 stages. The early infection, during which the virus enters the lung parenchyma and begins to replicate, might be accompanied by mild symptoms, such as fever, dry cough, myalgia, and diarrhea. Prolonged prothrombin time, increased level of D-dimer and lactate dehydrogenase in serum as well as lymphopenia, particularly concerning T lymphocytes, can also be observed. In most patients, the infection is limited to this stage, and in some younger it may be clinically silent.[3,4] During the second, pulmonary stage, dyspnea and gas exchange disturbances, accompanied by radiological abnormalities of the lungs, do occur. There is an increased inflammatory response, dysfunction of the endothelium and further damage to the pulmonary tissue, hypoxia, and additional involvement of the cardiovascular system. The third stage is the period of an increased inflammatory response associated with developing acute respiratory distress syndrome and systemic inflammatory response syndrome, shock, and multiorgan failure. The triggered inflammatory cascade leads to cytokine storm and systemic disorders. The increased concentration of several biomarkers is detectable, such as interleukins (IL-2, IL-6, IL-7), tumor necrosis factor α, interferon γ, C-reactive protein, procalcitonin, lactate dehydrogenase, D-dimer, and ferritin. These are indicators of disease severity and activate the differentiation and migration of the immune cells both locally and systemically, causing damage to the pulmonary tissue and other organs, including the heart. To a certain extent, the phenomenon is similar to the organ damage in hemophagocytic syndromes with a rapid release of cytokines. This dependence is confirmed by a positive correlation between the concentration of inflammatory and heart damage markers, electrocardiographic abnormalities, and worse prognosis.[5-8]

The endothelium plays a crucial role in the pathophysiology of SARS-CoV-2 infection.

The virus enters the host organism through ACE2, penetrates the endothelial cells, and causes their apoptosis.[9] Dysfunction of the microvascular endothelium leads to vasoconstriction and organ ischemia, tissue edema, and enhanced prothrombotic processes. Histological examination confirmed endotheliitis with focal necrosis in various vascular regions: lungs, heart, kidneys, liver, and intestines.[10] Binding with ACE2 enables the virus to penetrate the cell and plays an important regulatory role.[11] Extrapolating the results of studies conducted on severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), we may conclude that the infection causes ACE2 suppression, which may underlie myocardial dysfunction.[12] An experimental decrease in the activity of ACE2 in animal models causes disturbances in heart muscle contractility, increased angiotensin II concentration, and activation of anaerobic processes.[13] It is a mechanism that—accompanied by endothelial dysfunction—may lead to cardiac damage. It should be emphasized that myocardial involvement is associated with a greater risk of death than factors such as age, diabetes, chronic lung disease, and cardiovascular disease.[7,14]

Myocarditis and heart failure Cardiac troponin (cTn) concentration constitutes a quantitative marker of cardiomyocyte damage. In patients with COVID-19, cTn should be assessed in the context of cardiac comorbidities and the potential acute damage caused by SARS-CoV-2 infection. Elevated troponin levels can be detected in 5% to 25% of patients, especially in the group treated in the intensive care unit (ICU), in the case of the development of acute respiratory distress syndrome, and is associated with higher mortality.[7,14] A moderate increase of cTn (less than 2- to 3-fold higher than the upper limit of normal), particularly in elderly patients with a history of cardiac disease, does not necessarily indicate acute coronary syndrome (ACS) if it is not associated with clinical or electrocardiographic features of myocardial ischemia. A significant increase in the concentration of cTn (more than 5-fold higher than the upper limit of normal) may directly stem from COVID-19 complications, such as shock, severe respiratory failure, hypoxia, and cardiac damage in the course of myocarditis, stress cardiomyopathy (Takotsubo syndrome) or myocardial infarction caused by COVID-19. The exact mechanism explaining increased troponin levels in some patients with COVID-19 remains unclear. Direct or indirect myocardial injury, by systemic inflammation and cytokine storm, hypoxia due to lung damage or simultaneously increased metabolic demand, is regarded as a possible pathophysiological mechanism.[7,15] Single cases of myocarditis in the course of SARS-CoV-2 infection have been reported.[16] In those cases, cardiac magnetic resonance imaging revealed diffuse tissue swelling, and inflammatory infiltrations from T cells with edema and necrosis were found on cardiac biopsy. However, the presence of viral RNA was not confirmed in the samples.[17] Based on the observations concerning SARS-CoV-1 infection, indicating that viral RNA was found on postmortem examination of the heart in 35% of patients who had died of severe acute respiratory syndrome, it may be presumed that the cardiac muscle may also be directly infected in the course of COVID-19.[12] Cardiac magnetic resonance imaging may be considered in patients with suspicion of myocarditis or Takotsubo syndrome in the course of COVID-19, when accompanied by severe arrhythmia or myocardial dysfunction and elevated levels of troponin, if the expected finding is critical for further clinical management and patients are stable enough to be scanned.[18]

The impact of the previous cardiovascular disease on the clinical course of the infection is also a relevant issue. In elderly patients, diabetes and hypertension frequently coexist with heart failure with preserved left ventricular ejection fraction. Increased left ventricle filling pressure and secondary pulmonary hypertension is observed in these patients. Meanwhile, fluid therapy as well as nonsteroidal anti-inflammatory drugs and insulin are frequently applied in the treatment of COVID-19. This management promotes water and sodium retention, especially in patients with renal dysfunction, which may further lead to respiratory deterioration and even to pulmonary edema.[19-21] Natriuretic peptides, the concentration of which should be interpreted in the context of previously diagnosed heart failure (HF), are potential quantitative markers of cardiac wall stress.[22] It is known that elevated natriuretic peptide levels are a predictor of death in pneumonia or pulmonary embolism (PE). The assessment of their concentration may help to stratify the risk and imply diagnostic decisions.[23] An increased natriuretic peptide concentration may be a result of previous, undiagnosed cardiac disease, whereas its low concentration makes it possible to rule out cardiac dysfunction with a high probability.[24] Physicians should follow the 2016 European Society of Cardiology (ESC) guidelines concerning diagnosis and treatment of acute and chronic HF.[24] The model of outpatient treatment of acute HF with the use of intravenous infusions of loop diuretics, minimizing the necessity of hospitalization, constitutes a potential solution for patients without COVID-19 who develop HF decompensation.[25] In patients with chronic HF, the therapy improving the prognosis should be continued. It must be emphasized that patients with HF are at a greater risk of infection and severe course

of COVID-19 due to frequently observed numerous comorbidities and advanced age. Therefore, efforts should be made to educate patients on how to prevent the infection and the development of acute HF. Patients in stable condition should be, if possible, cared with the use of telemedicine tools in order to limit the number of outpatient visits during the pandemic. Such solutions indicate the necessity to invest in remote care, including home nursing visits, access to a 24-hour helpline service for patients, and protocols of clinical and laboratory control.[26-28]

Acute coronary syndromes Observations conducted in small patient groups in Hong Kong have clearly indicated that, during the COVID-19 pandemic, the time between the onset of angina and the performance of primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) has become significantly longer. The median time of delay depending on the patient and emergency medical services was approximately 3.5-fold higher during the pandemic than in the year preceding it.[29,30] There is also a risk that some patients with ACS will not seek medical help owing to fear of coronavirus nosocomial infection. This may lead to the development of HF, cardiac arrest, or death.[29]

In Poland, patients infected with SARS-CoV-2 and suffering from ACS are treated at special cardiology centers designated for given provinces and cooperating with single-specialty hospitals. Other patients should be treated at the cardiac centers closest to their place of residence.[31]

According to the ESC position statement, the pandemic should not affect the timely performance of reperfusion treatment in patients

TABLE 1 Treatment strategies in patients with ST-segment elevation myocardial infarction depending on the concurrence of coronavirus disease 2019

Recommendation source	STEMI		
	COVID-19 (+) (or undergoing diagnosis)		COVID-19 (-) or low probability
	High-risk MI	Low-risk MI	
European Society of Cardiology[33]	Primary PCI. Patients with COVID-19 and those with an unknown result of SARS-CoV-2 tests should be treated in catheterization laboratories prepared for treating patients with COVID-19. Fibrinolysis is the first-choice therapy only when it is not possible to perform PCI within the recommended time frame (<120 minutes) because of circumstances accompanying the pandemic and no contraindications exist.		
	–		Patients with a negative result of the SARS-CoV-2 test should be treated according to the current ESC guidelines.
Canadian Association of Interventional Cardiology[31]	Primary PCI or a pharmacoinvasive strategy (adopting the appropriate protection measures)		Primary PCI or pharmacoinvasive strategy
	Pharmacological strategy (fibrinolysis in STEMI or pharmacological treatment in NSTEMI and unstable angina) when PCI cannot be performed owing to complete lack of access to advanced medical procedures		
American College of Cardiology[34]	Primary PCI (adopting appropriate protection measures)	Primary PCI (adopting appropriate protection measures) Fibrinolysis can be considered in stable patients	
Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship[38]	Primary PCI (adopting appropriate protection measures)	Primary PCI (adopting appropriate protection measures) Fibrinolysis can be considered[a] in the case of limited access to reference centers (however, the necessity of extended hospitalization in the ICU should be considered). In particular cases, conservative treatment may be considered.	Primary PCI
	In patients with coexisting severe pneumonia, conservative treatment, possibly including fibrinolysis, can be considered.		
Peking Union Medical College Hospital[32]	Fibrinolysis Conservative treatment if fibrinolysis is contraindicated		Fibrinolysis and / or invasive treatment

a Low-risk ST-segment elevation myocardial infarction: ST-segment elevation myocardial infarction of the inferior wall, no involvement of the right ventricle, or infarction of the lateral wall without hemodynamic deterioration

Abbreviations: –, absent; COVID-19, coronavirus disease 2019; MI, myocardial infarction; NSTEMI, non–ST-segment elevation infarction; PCI, percutaneous coronary intervention; +, present; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STEMI, ST-segment elevation myocardial infarction

with STEMI. A test for SARS-CoV-2 should be performed immediately at first medical contact, regardless of the diagnosis (STEMI or non–ST-segment elevation infarction [NSTEMI]) and the adopted treatment strategy. A higher level of personal protective equipment should be used by medical staff for any suspected COVID-19 patient until the infection is excluded. The maximum delay of 120 minutes between the diagnosis of STEMI and reperfusion should remain the goal of the therapy. Primary PCI constitutes the preferred treatment strategy as long as the time frame allows for it and the procedure can be performed at a catheter laboratory prepared for the treatment of patients with COVID-19. However, the observations made so far showed that, during the pandemic, primary PCI may be delayed even up to 60 minutes because of hindered access to medical care and the introduction of additional protective measures. If the recommended time frame cannot be achieved and there are no contraindications to fibrinolysis, pharmacotherapy should constitute the first-line treatment. Treatment of nonculprit lesions in stable patients with ACS should be delayed for the time after the COVID-19 pandemic peak.

According to the ESC, the therapeutic management of NSTEMI should depend on risk stratification (very high, high, moderate, and low risk). Only in very high-risk patients with NSTEMI, who should be treated as patients suffering from STEMI, it is not recommended to delay the implementation of an invasive strategy, while waiting for the results of SARS-CoV-2 tests. Other patients, if their test result is positive, should be transported to the hospital prepared for the treatment of patients with COVID-19. In very high-risk patients with NSTEMI, pharmacotherapy (antiplatelet and antithrombotic agents, nitrates, β-blockers, and opiates when needed) should be applied while planning an early invasive strategy (at a time <24 hours) in order to stabilize their clinical status. It is, however, acceptable to withhold the performance of the invasive procedure according to the timing of SARS-CoV-2 testing. Moderate-risk patients should be thoroughly diagnosed for alternative diseases such as: type 2 myocardial infarction, stress cardiomyopathy (Takotsubo syndrome), myocarditis, myocardial damage in the course of respiratory failure or multiorgan failure.[32-34] In such situations and in low-risk STEMI, it is preferred to adopt a noninvasive diagnostic strategy, with cardiac computed tomography angiography (CTA) as the first-choice method.

The Canadian Association of Interventional Cardiology developed 3 proposals for the management of patients with ACS depending on the probability of SARS-CoV-2 infection, current staff capacity, and availability of medical procedures at a given center. In the case of STEMI, the choice of the procedure (primary PCI or a pharmacoinvasive strategy) is at the discretion of the treating team, with permission to apply pharmacotherapy (fibrinolysis) when PCI cannot be performed owing to complete lack of access to advanced medical procedures.[32] In the case of moderate and low-risk NSTEMI and unstable angina, pharmacological treatment is acceptable in most cases, except for centers adopting mild restrictions concerning the performance of regular medical procedures, at which invasive treatment should be considered.[32,35]

The researchers of the Peking Union Medical College Hospital proposed a completely different procedure scheme and recommended clinicians to perform fibrinolysis if there are no contraindications, in all STEMI patients with confirmed or suspected COVID-19, in order to avoid reperfusion delay. After the infection has been ruled out, it may be considered to complement pharmacotherapy with invasive treatment. Only in cases in which SARS-CoV-2 infection can be ruled out within an hour or there is a low risk of infection, referring the patient with STEMI for primary PCI can be considered. In the case of NSTEMI, invasive treatment is preferred only in patients at high and very high risk, especially those with hemodynamic instability.[33,36] Differences in the proposed strategies of treatment in STEMI and NSTEMI patients depending on the coexistence of COVID-19 are presented in TABLES 1 and 2.

Observational data concerning the duration of in-hospital stay of patients with uncomplicated course of STEMI or NSTEMI show that hospitalization exceeding 48 hours is not associated with a decrease in mortality after discharge.[20,37,38] Therefore, it is important to shorten the duration of hospitalization in stable patients with ACS in order to reduce the risk of nosocomial infection and increase the availability of hospital beds.[35]

The safety of medical personnel is crucial in all invasive procedures. Due to the risk of contracting COVID-19, special recommendations concerning the use of personal protection equipment, proper preparation for procedures as well as organization of work at catheter laboratories have been introduced.[35,39,40]

Acute pulmonary embolism—diagnosis and prevention Venous thromboembolism (VTE) is a common complication in COVID-19, as it is present in around 25% of patients hospitalized at the ICU and around 7% on general wards, including also those on anticoagulant treatment at prophylactic doses.[41-44]

Patients with COVID-19 frequently suffered from dyspnea (19%–59%), cough (46%–86%), and hemoptysis (8%).[45-48] These symptoms are also typical of PE, in which dyspnea occurs in 50% of cases, cough in 23%, and hemoptysis in

TABLE 2 Treatment strategies in patients with non–ST-segment elevation myocardial infarction depending on the concurrence of coronavirus disease 2019

Recommendation source	NSTEMI		
	COVID-19 (+) (or undergoing diagnosis)		COVID-19 (-) or low probability
	High-risk MI	Low-risk MI or unstable angina	
European Society of Cardiology[34]	Patients at very high risk[a]: an urgent invasive strategy at a catheterization laboratory prepared to treat patients with COVID-19	Transfer to a hospital for cardiac patients with COVID-19	In the groups of high and very high-risk treatment according to the current ESC guidelines
	Patients at high risk[b]: transfer to a hospital for cardiac patients with COVID-19, followed by an early invasive strategy (preferably within 24 hours)	In the case of moderate[c] and low-risk[d] patients, noninvasive diagnostic workup should be considered (cardiac CTA).	
Canadian Association of Interventional Cardiology[32]	Invasive strategy (adopting appropriate protection measures)[e]	Invasive strategy or pharmacotherapy	
	Pharmacological strategy (fibrinolysis in STEMI or pharmacological treatment in NSTEMI and unstable angina) when PCI cannot be performed owing to complete lack of access to advanced medical procedures		
American College of Cardiology[35]	Invasive strategy in hemodynamically unstable patients (adopting appropriate protection measures)	Pharmacotherapy should be sufficient.	–
Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship[39]	Invasive strategy In patients at very high risk[f]: coronary angiography within 2 hours, further treatment depending on the coronary artery status (PCI, CABG,or pharmacotherapy)	Pharmacotherapy may be considered.	Coronary angiography within 24 hours
Peking Union Medical College Hospital[33]	Invasive treatment is preferable	Pharmacotherapy	Invasive strategy or pharmacotherapy depending on the risk

a Very high-risk non–ST-segment elevation myocardial infarction: hemodynamic instability; cardiogenic shock; recurring or persisting angina despite pharmacotherapy; life-threatening arrhythmia or cardiac arrest; mechanical complications of infarction; acute heart failure; recurring transient elevations of ST segment on electrocardiography

b High-risk non–ST-segment elevation myocardial infarction: diagnosed based on changes in cardiac troponin levels and the dynamics of changes in the ST / T-segment on electrocardiography and / or recurring symptoms.

c Moderate-risk non–ST-segment elevation myocardial infarction: diagnosed based on troponin dynamics in patients with concurrent diabetes and / or chronic kidney disease and / or left ventricular ejection fraction <40% and / or congestive heart failure and / or early postinfarction angina and / or a history of percutaneous coronary intervention or coronary artery bypass grafting

d Low-risk non–ST-segment elevation myocardial infarction: no criteria met for non–ST-segment elevation myocardial infarction of very high, high, or moderate risk

e High-risk non–ST-segment elevation myocardial infarction: persisting symptoms, hemodynamic instability, severe dysfunction of the left ventricle, suspected involvement of the left main coronary artery or severe proximal coronary stenosis, Global Registry of Acute Coronary Events scale >140 points

f Very high-risk non–ST-segment elevation myocardial infarction: persistent angina, hypotension, heart failure, cardiogenic shock, life-threatening arrhythmia

Abbreviations: CABG, coronary artery bypass grafting; CTA, computed tomography angiography; ECG, electrocardiography; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; others, see TABLE 1

8%.[49] The overlapping clinical presentation of both diseases may result in underrecognition of PE. If sudden deterioration of ventilation, tachycardia, and hypotension occur in a COVID-19 patient, thromboembolic complications should be considered in differential diagnosis. It is recommended to follow the algorithm that takes into consideration the clinical pretest probability of PE (the revised Geneva rule and the Wells rule) and D-dimer concentration.[50] Increased levels of D-dimer may be secondary to an infection and inflammation, which significantly decreases the specificity of the result. In most patients with COVID-19, the concentration of D-dimer is lower than 1000 ng/ml, and the results are normal in 32% to 53%.[8,46,51] The use of compression ultrasound of the lower extremities, echocardiography, and CTA is of paramount importance. If the results of thoracic computed tomography do not provide explanation for respiratory failure, CTA of the pulmonary arteries should be considered.

Treatment of PE should be conducted in accordance with the ESC guidelines, based on risk assessment. Patients in cardiogenic shock should undergo immediate reperfusion, whereas those who are hemodynamically stable can be treated with heparin or non–vitamin K antagonist oral anticoagulants (NOACs). Of note, some medications applied in the treatment of SARS-CoV-2 infection inhibit cytochrome P450 3A4 (lopinavir-ritonavir), and thus may increase the activity of NOACs and the risk of bleeding. Chloroquine, on the other hand, inhibits glycoprotein P, which may result in reducing NOAC concentration and this effect may persist for a long time owing to a long half-life of chloroquine. As it is necessary to control the international normalized ratio,

vitamin K antagonists are not recommended, except in patients with mechanical heart valves or antiphospholipid syndrome.[50]

Considering the current reports on the occurrence of VTE in patients with COVID-19, a generalized inflammatory process and immobilization, anticoagulation at a prophylactic dose should be applied in each patient hospitalized for COVID-19, considering the risk of hemorrhagic complications.[52,53] Some institutions suggest considering higher prophylactic doses of anticoagulant agents; however, VTE can occur in the ICU setting even when a therapeutic dose of anticoagulants is used.[15,42,43]

Summary Coronavirus disease 2019 affects the cardiovascular system, and cardiac damage is associated with poor patient prognosis. Its pathomechanism is complex and includes an excessive inflammatory response with endothelial damage and activation of the coagulation cascade. Patients with suspected ACS and acute HF require special medical attention. Despite the fact that the number of scientific reports has been rapidly increasing since January 2020, the current recommendations are based on limited evidence or constitute only expert opinions. Therefore, it is necessary to follow the available literature and conduct further clinical studies.

ARTICLE INFORMATION

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