

Cardiovascular manifestation and treatment in COVID-19

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Abstract: The novel coronavirus disease 2019 (COVID-19), with first presentation of atypical pneumonia, has spread rapidly from Wuhan, China, on December 12, 2019 to over 200 countries, caused 2 310 572 infected individuals and 158 691 mortalities, updated on April 19, 2020. Many studies have published timely to help global healthcare workers to understand and control the disease. Vulnerable patients with risk factors such as elderly, cardiovascular diseases (eg, hypertension, coronary disease, or cardiomyopathy), diabetes, and chronic kidney disease have worse outcomes after COVID-19 infection. COVID-19 could directly cause cardiovascular injuries such as pericarditis, myocarditis, myocardial infarction, heart failure, arrhythmias, or thromboembolic events, which urge cardiologists to be involved in the frontline to practice. Here, we provide a review of COVID-19 on cardiovascular system to assist clinical cardiologists to better understand the disease and being capable of providing comprehensive medical support.

Keywords: Cardiologists; Cardiomyopathy; Cardiovascular diseases; COVID-19

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2; also known COVID-19), which belongs to coronavirinae sub-family, is a single-strand RNA coronavirus, which enters human cells mainly by binding the angiotensin-converting enzyme 2 (ACE2) receptor.¹ ACE2 is mainly located at human oral pharynx, upper airway, heart, liver, kidney, intestine, neuron, and testis. After virus binding with ACE2 and entering the cell, receptor downregulation happens, which currently supposed to be host defense mechanism to limit further viral invasion or viral-induced mechanism to escape immune system.² After endocytosis, the virus leaves the endosome by PH-dependent cysteine protease and begins its replication. During above process, ACE2 receptor downregulation will significantly diminish the physiological functions of ACE2 in degrading angiotensin-2 (ANG2) into angiotensin 1-7 (ANG1-7). Physiologically, ANG2 can cause vasoconstriction, aldosterone secretion, increase inflammation and ROS production, thrombosis, and fibrosis; reciprocally, ANG1-7 can be considered as regulatory enzyme that opposes the effect of ANG2 and becomes cyto-protective (eg, anti-inflammation, anti-fibrosis). The downregulation of ACE2

leads to decreased ANG1-7 level and increased ANG2 level, which may induce uncontrollable cytokine storm and could lead to organ dysfunction in critical cases.³

2. CLINICAL FEATURES OF COVID-19

COVID-19 could cause viral pneumonia, which may lead to respiratory failure and other extrapulmonary complications. Among those extrapulmonary complications,⁴⁻⁶ the involvement of cardiovascular system has drawn the most attention.^{7,8} Not only patients with preexisting cardiovascular disease (CVD) have higher risk of adverse events, those without prior CVD are also vulnerable to the occurrence of cardiovascular complications.⁵ The estimated mean incubation period for COVID-19 is about 2 to 14 days, with about 15% asymptomatic carrier and 85% symptomatic patients. Among all patients with symptoms, 80% are mild cases and 20% are severe to critical cases. According to World Health Organization (WHO) as of March 3, the estimated mortality rate is about 3.4%, in which the comorbidity of cardiovascular disease may result in 10.5% mortality rate, much higher than diabetes (7.3%), chronic respiratory disease (6.3%), or no preexisting conditions (0.9%).⁹⁻¹³

The major symptoms of COVID-19 are fever, cough, and shortness of breath. Other symptoms such as headache, anorexia, malaise, sputum production, nasal congestion, diarrhea, or parageusia may also be presented initially. The viral transmission and spreading could occur in asymptomatic carriers. Typical chest compute tomography findings of COVID-19 are bilateral subpleural and peripheral ground-glass opacities and consolidations, which could be seen in 75% of the patients.¹⁴ The most common lab finding of COVID-19 is lymphopenia (83.2%). Other lab abnormalities similar to viral infections are noted such as leukopenia, thrombocytopenia, and elevated lactate dehydrogenase. Several biomarkers are linked to severe inflammatory response and could be used as poor prognostic

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factors such as ferritin, procalcitonin, C-reactive protein (CRP), D-dimer, troponin, and N-terminal pro-brain natriuretic peptide (NT-proBNP). About 8% to 28% patients with COVID-19 have elevated troponin levels, which indicate cardiac injury.¹⁵ Acute respiratory infections and respiratory system distress are recognized triggers for CVD and the underlying CVDs are also associated with increased severity of infectious diseases.^{6,16-18}

3. CARDIOVASCULAR INVOLVEMENT OF COVID-19

Many patients with COVID-19 have evidences of myocardial damage. Shi et al reported that among 416 hospitalized patients with confirmed COVID-19, 19.7% had myocardial injury which were manifested by elevated high-sensitivity troponin-I levels. Patients with myocardial injury had a significant higher in-hospital mortality rate (51.2%) compared with those without (4.5%).¹⁹ Guo et al²⁰ also presented a cohort of 187 hospitalized with confirmed COVID-19 and a total of 27.8% had myocardial injury as manifested by elevated troponin T levels. Similarly, mortality was significantly higher in those with elevated troponin T levels than those with normal troponin T levels (59.6% vs 8.9%, respectively; $p < 0.001$). Higher mortality was found in those with elevated troponin T levels in preexisting CVD (64.4%) and without prior CVD (37.5%), indicating that myocardial injury was correlated with the risk of mortality. Similar findings were also observed in western population. In a series of patients from Seattle, patients with evidence of cardiac involvement had a marked increase in mortality.²¹ In addition, during the internalization process of COVID-19 into human cell, activated macrophages can release cytokines, which will promote the expression of adhesion molecules for endothelial activation, inflammatory cell infiltration, and vascular inflammation. The dysfunctional endothelium becomes proadhesive and procoagulant. The activated macrophages can also release procoagulant factors, such as plasminogen activator that further accelerates vascular inflammation and enhances a prothrombotic state, and this is often seen with high D-dimer levels in COVID-19 infection. The presence of microangiopathy and microthrombi leads to micro-infarcts within the cardiac tissue and also contributes to plaque rupture and acute myocardial infarction.⁸

In addition to intracoronary plaque rupture, myocardial injury could result from other reasons. From a series of 18 patients with ST-segment elevation in New York with confirmed COVID-19, only six (67%) of nine patients who received coronary angiography had obstructive disease and five (56%) underwent percutaneous coronary intervention (one after the administration of fibrinolytic agents.²² Increased troponin value represents evidence of myocardial injury and these may come from cytokine storm, hypoxic injury, coronary spasm, microthrombi, myocarditis, or true plaque rupture.^{20,23} Severe infections could cause hypoxia and hypoperfusion to vital organs which predispose patient to thrombotic events.²⁴ Guo et al demonstrated additional insights that patients with high troponin T levels are associated with higher levels of CRP, procalcitonin, D-dimer, NT-proBNP, and greater leukocyte counts, indicating that myocardial injury was correlated with the severity of inflammation.²⁰ From previous influenza epidemics, more patients die of cardiovascular events than respiratory involvements.²⁵ Viral infections can trigger acute coronary syndrome, arrhythmias, and exacerbation of heart failure, owing to combination of systemic inflammatory response and localized arterial inflammation.^{26,27} Systemic inflammation or hypoxemia resulted from COVID-19 may also induce atrial/ventricular arrhythmia, most commonly atrial fibrillation, which may raise the issue of anticoagulants usage.²⁸

Severe inflammation could also cause hemostatic abnormalities including disseminated intravascular coagulation (DIC), pulmonary microthrombi formation, and intravascular coagulopathy.²⁴

Tang et al reported increased level of D-dimer and fibrin degradation products ([FDPs], ~3.5- and ~1.9-fold increase, respectively) and prothrombin time prolongation (by 14%, $p < 0.001$) in mortality cases than survivors after COVID-19.²⁹ In addition, 71% of COVID-19 patients who died fulfilled the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC, compared with only 0.6% among survivors.^{24,29} Furthermore, a small proportion of patients may have direct cardiac involvement including cardiomyopathy, myocarditis, or heart failure. One COVID-19 case was reported to have myocarditis with reduced systolic function and marked biventricular myocardial interstitial edema according to cardiac magnetic resonance images.³⁰ Sporadic autopsy cases also showed infiltration of interstitial mononuclear inflammatory within myocardium.³¹ Endomyocardial biopsy done in a COVID-19 patient with cardiogenic shock showed viral particles in the myocardium, suggesting the damages could either come from viremic phase or migration of infected macrophages.³²

The presence of cardiac injury and stress, as evidenced by altered biomarkers including troponin, natriuretic peptides, and coagulation parameters, indicates a poor prognosis of COVID-19. On the other hand, close monitoring of these biomarkers could help early detections of cardiac injury and possibly prevent further deterioration with appropriate management if available.

4. TREATMENT

Currently, many treatment strategies were ongoing, and we just reviewed treatment choices or consideration focus on treatment related to the cardiovascular field.

4.1. Antiviral therapies

Remdesivir (GS-5734), adenosine analogue, is a prodrug which is metabolized to its active form GS-441524 and thereafter interferes with the action of viral RNA-dependent RNA polymerase, resulting a in decrease in viral RNA production. Remdesivir was effective against various types of coronaviruses in cell culture and a mouse model of SARS. A preliminary data also showed that remdesivir also inhibited SARS-CoV-2 infection efficiently in a human cell line.³³ Remdesivir was provided on a compassionate-use basis to patients who were hospitalized for severe COVID-19. In this cohort, patients with severe COVID-19 received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. The results showed clinical improvement was observed in 36 of 53 patients (68%).³⁴ Gilead has initiated several trials in United States and China to evaluate the effect of remdesivir in COVID-19 patients with different disease severity (<https://www.gilead.com/purpose/advancing-global-health/covid-19/remdesivir-clinical-trials>).

Lopinavir and ritonavir were two protease inhibitor which was used to treat HIV infection. In a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed COVID-19 and high oxygen demand, patients were randomly assigned in a 1:1 ratio to receive either lopinavir-ritonavir (400 and 100 mg, respectively) twice a day for 14 days in addition to standard care or standard care alone. The primary endpoint was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital. Although the results showed no benefit on primary endpoint and the detectable viral load were also similar between the two groups, there were still some suggestions of potential benefit with lopinavir-ritonavir with a shorter intensive care unit (ICU) stay and a shorter time to hospital discharge.³⁵ One of the known adverse cardiac effects of lopinavir/ritonavir is hyperlipidemia and the potential prolongation of QT and PR intervals according to the warning of US FDA in 2009.

Antiviral drugs for influenza infection were also tested. Oseltamivir showed little effect on COVID-19 in an observational study.³⁶ Favipiravir, another Japanese antiviral drug for influenza, was shown to have more potent antiviral activity than lopinavir/ritonavir in a preliminary study.³⁷ Favipiravir showed better therapeutic responses on COVID-19 in terms of disease progression and viral clearance in an experimental trial.³⁸ In a prospective, randomized, controlled, open-label multicenter trial involving adult patients with COVID-19, patients were randomly assigned in a 1:1 ratio to receive conventional therapy plus umifenovir or favipiravir for 10 days. The primary outcome was clinical recovery rate of day 7. The results showed favipiravir, compared with umifenovir, did not significantly improve the clinically recovery rate at day 7 but favipiravir significantly improved the latency to relief for pyrexia and cough.³⁹

Antiviral therapies may have significant drug-drug interactions with antiplatelet agents and anticoagulants in patients with prior cardiovascular disease. Medications now in investigation of COVID-19 treatment such as lopinavir/ritonavir, remdesivir, tocilizumab, or sarilumab that were metabolized by CYP3A4 should be cautious when P2Y12 Platelet receptor inhibitors used simultaneously in patients with cardiovascular disease.²⁴

4.2. Chloroquine/hydroxychloroquine

Evidences suggested that the antimalarial drugs chloroquine and hydroxychloroquine might exert potent antiviral and anti-inflammatory effects.⁴⁰ Chloroquine and hydroxychloroquine are rapidly protonated and concentrated in endosomes and therefore increase the pH of the endosome, which prevents cathepsin-induced priming of the viral S protein. In vitro study showed both chloroquine and hydroxychloroquine decrease SARS-CoV-2 replication in cultured cells and hydroxychloroquine was more potent than chloroquine.^{33,41} In a small single-arm study of patients with confirmed COVID-19, treatment with hydroxychloroquine was associated with a significant difference in clearing of viral nasopharyngeal carriage of SARS-CoV2 within 3 to 6 days when compared with untreated controls. Moreover, combining hydroxychloroquine with azithromycin showed even more efficient virus elimination in present observation.⁴² Different trials were soon performed in China and the results showed acceptable safety against COVID-19-associated pneumonia.⁴³ The treatment was accepted worldwide and prophylactic usage had also been discussed recently.⁴⁴

Chloroquine and hydroxychloroquine can cause QT prolongation, and cautious monitoring was crucial especially in the combination usage with azithromycin. Chloroquine and hydroxychloroquine can also cause rare complications including cardiomyopathy, both systolic and diastolic, atrioventricular and bundle branch block.⁴⁵

4.3. Renin-angiotensin-aldosterone system inhibitors

ACE2 is an enzyme within the renin-angiotensin system (RAS) that is expressed on the cell surface of type 2 alveolar epithelial cells in the lungs and other tissues. It also acts as the receptor for the SARS-CoV spike protein. The affinity of SARS-CoV-2 for ACE2 is 10- to 20-fold higher than that of SARS-CoV. ACE2 is a crucial counter-regulatory component of the renin-angiotensin-aldosterone system (RAAS) and shares approximately 60% homology with ACE. ACE2 levels are increased following treatment with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which yield the concerns that using these medications might increase the severity of COVID-19, especially in patients with existing cardiovascular diseases. However, the experimental and clinical data showed conflicting results. Experimental models of acute lung injury, including a model of SARS-CoV infection, suggest that ARBs may mitigate COVID-19 by attenuating Ang II-mediated acute lung injury

by blocking AT1R.⁴⁶ RAAS inhibitors on ACE2 are complex and should not be assumed that changes in ACE2 levels reflect changes in ACE2 levels in the lung, which is the portal of entry for SARS-CoV2.⁴⁷ Currently, there is no evidence either from clinical or animal study showing that ACEI/ARB use increase cardiovascular complication. Therefore, the ACC/AHA statement suggested the ACEI/ARB use should continue in patients prescribing ACEI/ARB already (<https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>). Interestingly, Zhang et al just reported a retrospective, multicenter cohort of 1128 hospitalized patients with COVID-19 and hypertension. The results showed inpatient use of ACEI/ARB in COVID-19 patients with hypertension was associated with lower risk of all-cause mortality compared with non-users.⁴⁸ Paired trials of losartan as a treatment for COVID-19 are being conducted among patients who have not previously received treatment with a RAAS inhibitor and are either hospitalized (NCT04312009) or not hospitalized (NCT04311177).

4.4. Antiplatelet/anticoagulation

A large portion of patient with cardiovascular comorbidities in patient with COVID-19 and a significant number of patients would have received cutaneous coronary interventions. Thrombocytopenia, prolonged thrombin time, and elevated D-dimer levels were frequently observed in both SARS and COVID-19, suggestive of high likelihood of DIC. Also, diffuse alveolar hemorrhage (DAH) was reported as a common finding from lung pathology in SARS and COVID-19 patients. The safety concerns about antiplatelet therapy (DAPT) on life-threatening bleeding complications among COVID-19 should be addressed.

Evidences suggested that prehospital use of aspirin use was associated a lower risk of for developing ARDS and mortality in patients with community-acquired pneumonia. All P2Y12 inhibitors reduce platelet-leukocyte aggregates and platelet-derived pro-inflammatory cytokines. Ticagrelor is unique in having the most potent anti-inflammatory properties via dual inhibition of platelet P2Y12 receptor and equilibrative nucleoside transporter 1 (ENT1), which contributes to inhibition of cellular adenosine uptake. The XANTHIPPE trial, as well as post hoc analyses of PLATO study showed encouraging clinical benefit of ticagrelor in the management of pneumonia by preventing the complications of sepsis and reducing lung injury.^{49,50} However, P2Y12 inhibitors could aggregate DAH according to published literatures.⁵¹ Results from large randomized controlled trials provide evidence supports a net benefit of aspirin-free strategies (reduce aspirin duration to 1-3 months) after PCI for patients at low, intermediate, and high risk for both ischemia and bleeding.⁵² Zhou et al suggested among patients with COVID-19 who are currently on DAPT, maintaining P2Y12 inhibitor monotherapy (preferably ticagrelor) may be scientifically reasonable for patients with PCI performed ≥ 3 months. Due to the lack of converging evidence, for those with PCI performed < 3 months, DAPT should not be discontinued.⁵³

COVID-19 pathological mechanisms also contribute to increased venous thromboembolic risks which include endothelial damage, microvascular thrombosis/occlusion, and even autoimmune mechanisms. Coagulopathy is known to occur in the majority of patients who die of COVID-19. In a study of 449 patients with severe COVID-19, anticoagulant therapy mainly with low molecular weight heparin appeared to be associated with lower mortality in the subpopulation meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer. Currently statements suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation if indication is present.^{24,54}

Future research is needed to determine the optimal dose/duration of anticoagulation therapy.

4.5. Statins

Patients with comorbidities including hypertension, cardiovascular diseases, and diabetes tend to have higher risk for having severe COVID-19 which leads to acute respiratory distress syndrome (ARDS) and mortality.⁵⁵ Statins are commonly prescribed in most of the patients with CVDs according to current diabetes and cardiovascular guidelines. Statins are known to have anti-inflammatory effects which involved in Myd88 and downstream nuclear factor kappa B signaling pathways, which was highly activated in SARS-CoV infection. Several studies showed statins might have beneficial effect on influenza infection.^{56,57} Statin also showed potential therapeutic effects on hyper-inflammatory ARDS.⁵⁸ In JUPITER trial, a post hoc analysis showed a reduction in incident pneumonia with rosuvastatin.⁵⁹ Currently there is no evidence to determine whether statin usage could be beneficial in COVID-19. Farag et al screened more than 2000 Food and Drug Administration (FDA)-approved drugs against SARS-CoV-2 main protease enzyme substrate-binding pocket focusing using simulated structural analysis and the results showed rosuvastatin might be a promising target.⁶⁰ Large-scale observational or randomized trials would be needed to determine the effect of statins on COVID-19. For now, statin therapy should be continued in patients with suspected COVID-19 infection with existing cardiovascular comorbidities since no evidence show harmful and acute cardiac injury could also occur in COVID-19. Adverse effects of statin should still be monitored since myalgia, increased creatine phosphokinase, rhabdomyolysis, and acute kidney injury do occur in patients with COVID-19.¹⁵ Also, drug-drug interactions between statins and protease inhibitors had been described and should also be carefully accessed during clinical practice.⁶¹

4.6. Amiodarone

In a retrospective reviews of COVID-19 patients treated in China, Wang et al found that of the 138 patients analyzed, 23 (17%) had cardiac arrhythmias and the incidence was significantly higher among those requiring ICU care (44.4% vs 6.9%, $p < 0.001$).³⁶ Another study reported that cardiac arrhythmias were significantly more common in patients with critical forms of COVID-19 than in mild and moderate cases.⁶² Patient with COVID-19 would be like to be treated with anti-arrhythmic drugs whether due to disease progression or existing comorbidities. Amiodarone, a widely used antiarrhythmic drug, has been shown to inhibit in vitro spreading of SARS coronavirus. In vitro study showed amiodarone inhibited SARS-CoV infection and spreading via altering the late compartments of the endocytic pathway by acting after the transit of the virus through endosomes.⁶³ Extrapolating current evidence, administration of prophylactic intravenous amiodarone to mitigate the risk of late sudden cardiac arrest among patients infected with the novel COVID-19 had been suggested.⁶³

4.5. Colchicine

Patients with severe COVID-19 infection have higher serum levels of pro-inflammatory cytokines (tumor necrosis factor [TNF]- α , interleukin [IL]-1 and IL-6) and chemokines (IL-8) compared with individuals with mild disease or healthy controls. In experimental models, it has been shown that inflammasome NLRP3 is a major pathophysiological component in the development of ARDS and acute lung injury. The simulated structural models have shown that COVID-19 proteins (eg, viroporins E, 3a, and 8A) might provoke the activation of inflammasome NLRP3.

Colchicine was initially extracted from *Colchicum autumnale* (autumn crocus) and is an inexpensive, orally administered, potent anti-inflammatory medication that has been used for centuries. The mechanism of action is through the inhibition of tubulin polymerization and microtubule generation and affects the activities of cellular adhesion molecules, inflammatory chemokines, and the inflammasome.⁶⁴ Evidences showed colchicine counteracts the assembly of the NLRP3 inflammasome, thereby reducing the release of IL-1b and an array of other ILs, including IL-6.⁶⁵ Recently, colchicine has been successfully used in two cases of life-threatening posttransplant capillary leak syndrome, which mechanism also involves cytokine release.⁶⁶ Colchicine has been shown to limit IL-1b production as a response to various NLRP3 inflammasome inducers in a dose-dependent fashion.⁶⁷ Several trials have been performed for evaluating the effect of colchicine on the COVID-19 infection (NCT NCT04326790, NCT04322682).

In conclusion, the understanding of the diagnosis, prevention, spreading, and treatment for COVID-19 is rapidly evolving. CVDs may be precedent factors or incident complications in patients with COVID-19. Our clinical staff and physician should update latest information and be familiar with the possible complication related to COVID-19. Important considerations for the preventive and therapeutic use of treatment strategies should be kept in mind to mitigate the worse outcome, especially in these high-risk patients.

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