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Expert Review

# Severe Acute Respiratory Syndrome Coronavirus-2 Cardiovascular Complications: Implications for Cardiothoracic Anesthesiology

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CORONAVIRUSES, so named for the crownlike spikes on their surfaces under electron microscopy, are enveloped, single-stranded positive-sense RNA viruses that have high propensity for mutation and recombination.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the causative agent of coronavirus disease-2019 (COVID-19), which emerged rapidly—with catastrophic global consequences—as a pandemic since its initial appearance in Wuhan, China, in early December 2019.[2] As of the writing of this article, there were more than 4 million persons infected with COVID-19, and more than 280,000 deaths worldwide had been attributed to the disease.[3]

In many parts of the world, a rapid increase in patients with COVID-19 who require hospitalization has been noted. Anesthesiologists have been tasked with caring for patients with COVID-19 in preoperative, intraoperative, and postoperative states and for patients in critical care units. Because of the broad perioperative "footprint" of the cardiovascular anesthesiologist, it is imperative to have a robust familiarity with the manifestations, therapies, and relevant considerations of COVID-19. Much of the early contributions to the medical literature addressed the respiratory-related issues of COVID-19 and for understandable reasons. There now are concerns for cardiovascular manifestations in patients with COVID-19. Malignant arrhythmias, ST elevations, and myocarditis all have been diagnosed in COVID-19 patients, even in individuals without previous cardiovascular disease.[4] Not surprisingly, patients with COVID-19 in whom cardiac injury occurs have been shown to have increased risk of mortality more than those

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who do not have this presentation.[5] In addition, an unusual degree of coagulopathy (mainly favoring hypercoagulability) has been associated with COVID-19 infection, with implications for considerable morbidity and mortality. Moreover, although many elective surgeries have been deferred during the surge of SARS-CoV-2, anesthesiologists must be prepared to care for patients with COVID-19 who require intraoperative care on an emergency basis.

The present review addresses cardiovascular-specific factors in COVID-19 and the implications of the disease that are relevant for cardiothoracic anesthesiologists caring for patients during the current pandemic.

## Structural Cardiac Injury

It is well- established in retrospective data that elderly patients with comorbid conditions are at the highest risk of severe COVID-19 infection, with associated complications of acute respiratory distress syndrome (ARDS), cardiogenic or distributive shock, or multiorgan failure.[6,7] In early studies, cardiac and metabolic comorbidities in particular were associated with higher rates of death.[8] Even though these data are difficult to interpret because of sampling bias, testing scarcity, and reporting variability, these comorbidities also are closely related to advancing age.[9,10] One study of 8,910 patients from 169 hospitals in North America, Asia, and Europe revealed that independent risk factors that increased mortality were age greater than 65 years (mortality of 10.0%), coronary artery disease (10.2%), heart failure (15.3%), cardiac arrhythmia (11.5%), chronic obstructive pulmonary disease (14.2%), and current smoker (9.4%).[11] Unsurprisingly, patients with immune system dysfunction also are at high risk for severe COVID-19 infection, and it is likely that existing metabolic and cardiac diseases impair the ability to prevent either SARS-CoV-2 infiltration or the sequelae of an uncontrolled inflammatory response.[9]

SARS-CoV-2 gains entry to host cells via a spike protein with binding affinity for angiotensin-converting enzyme 2 (ACE2),[12,13] a transmembrane protein widely expressed in the lung, heart, vasculature, kidney, and intestine.[14-16] This spike protein is nearly identical to that of the SARS-CoV-1 responsible for the 2002–2003 outbreak, but has an even greater affinity for ACE2, likely promoting the higher transmission rate seen in SARS-CoV-2.[17-20] The likeliest route of viral inoculation follows the observation that ACE2 is highly expressed in enterocytes of the small intestine and type II alveolar epithelial cells of the apical lung, which also offer a reservoir for viral replication and local tissue damage.[16] The ACE2 expression within the cardiovascular system is concentrated on the surfaces of myocytes, coronary endothelial cells, and arterial smooth muscle, which explains the potential for direct organ damage, and SARS-CoV-2–induced attenuation of ACE2 supports evidence for indirect cardiovascular damage via an unregulated systemic inflammatory response.[16,19,21-23]

In healthy physiology, ACE2 counterbalances the proinflammatory angiotensin-converting enzyme 1 pathway of the renin-angiotensin-aldosterone system (RAAS).[15] It does this by cleaving proinflammatory angiotensin II to form angiotensin-(1-7), which suppresses inflammation, vasoconstriction, apoptosis, and thrombosis while imparting cardioprotective effects against heart failure, arrhythmia, and atherogenesis.[22] The cardiopulmonary protective role of ACE2 has been demonstrated in several ACE2 knockout studies in which the absence of ACE2 worsened ARDS as a result of SARS-CoV-1, and genetically absent ACE2 study groups developed severe left ventricular dysfunction and showed impaired ventricular remodeling.[14,24,25]

Infection with SARS-CoV downregulates ACE2 expression.[14,26] This decrease in ACE2 and derangement of RAAS are likely important mechanisms for the inflammation and cardiac dysfunction seen in severe COVID-19 patients .[10,19,22,23] The resultant proinflammatory state is caused by unopposed angiotensin II and RAAS activation, with associated vasoconstriction, bronchoconstriction, and increased vascular permeability.[10,20] In fact, angiotensin II levels are strongly correlated with the viral load and the degree of lung injury sustained by SARS-CoV-2 patients.[27] This illustrates that ACE2 likely serves a dual purpose as both receptor and arbiter of immune response and is crucial to the determining of the virulence of SARS-CoV-2. It not only acts as an entry point for SARS-CoV-2 but, upon binding, SARS-CoV-2 decreases ACE2 expression and prevents its protective effect.[10,23] Some in vivo and animal studies have suggested that higher ACE2 expression could place a patient at greater risk of SARS-CoV-2 infection, although whether this clinically results in a greater infection rate or increased morbidity and mortality is unknown and controversial.[10,20,22,28] Several authors theorized that angiotensin-converting enzyme inhibitors (ACEi) and angiotensin- receptor blockers (ARB) hypothetically could increase susceptibility to SARS-CoV-2 by increasing ACE2 receptor sites for the virus.[29,30] Momentum to discontinue ACEi/ARB followed, which led to several publications reiterating the duality of ACE2 and the cardioprotective nature of ACEi/ARB; many medical societies issued statements supporting continuing ACEi/ARB in patients with and without COVID-19 until contrary evidence arises.[10,11,20,22]

Clinical manifestations of COVID-19 are varied; some patients test positive for the presence of SARS-CoV-2 but remain asymptomatic. However, the development of a severe infection has the following 3 phases of illness: an inoculation/incubation phase; a pulmonary phase; and an acute, exaggerated, systemic inflammatory phase.[9,23] The definitive cardiac pathophysiology of SARS-CoV-2 is unclear and currently is hypothesized to be a combination of 2 direct mechanisms and 2 indirect mechanisms. Viral entry via cellular ACE2 expression, with direct toxicity to cells, has some supporting evidence but is yet to be proven and was observed in the SARS-CoV-1 outbreak.[23,26] Because of the high level of ACE2 surface expression in pericytes and endothelial cells, viral-induced vasculitis and microthrombosis may be other sources of direct cardiac injury.[31] Indirect cardiac tissue damage can result from stress demand or hypoxia and immune-mediated cytokine storm.[9,22,23] Appreciating the cardiac sequelae of COVID-19 patients is paramount to triage and treatment of this highest-risk cohort who can experience myocardial injury or myocarditis, heart failure, and arrhythmia.[9,23,32,33]

*Myocardial Injury, Myocarditis, and Heart Failure*

Elevated troponin levels are pathognomonic for myocardial injury and, despite a connotation of acute coronary syndrome (ACS), should reinforce ischemic and non-ischemic differentials in all patients, particularly those with SARS-CoV-2.[34] Because of its sensitivity, the troponin level is the earliest and most accurate indication of end-organ damage.[34] Interestingly, elevated troponin levels were more closely associated with COVID-19 mortality than age, diabetes, and chronic cardiopulmonary disease; however, this is confounded by the fact that troponin can remain elevated with the impaired renal function often seen in critical illness. In a study of 416 patients hospitalized with SARS-CoV-2, 1 in 5 patients were found to have elevated troponin levels upon admission.[5,35] These patients were significantly more likely to develop ARDS and acute kidney injury, and they experienced a mortality rate 10 times higher than patients without evidence of myocardial injury (51% *v* 5%).[35]

The incidence of ACS, or type I myocardial infarction (MI), in COVID-19 patients is unknown, perhaps in part because of overlap of symptomatology in both conditions and difficulty in obtaining an angiographic diagnosis in an unstable and highly infectious patient population.[9,23,33] There are multiple case reports of COVID-19 patients with MI signs and symptoms absent of actual obstructive coronary disease.[33,36] The predilection for thrombosis and disseminated intravascular coagulation demonstrated by elevated D-dimer levels in COVID-19 nonsurvivors lends evidence to the role of microvascular thrombosis in myocardial ischemia.[7,23,36] Inflammation-induced macrophage and platelet activation also are likely to be significant in patients with unstable atheromatous plaque, particularly because a significant portion of patients with severe COVID-19 have comorbid risk factors for ACS.[7] Paradoxically, a study from China found that blood pressure was significantly greater in intensive care unit (ICU) patients than in non-ICU patients (mean systolic blood pressure 145 mmHg *v* 122 mmHg), although hypotension requiring vasopressors also is typical.[6] Type II MI is also an important consideration for myocardial injury in these patients because hypoxia, elevated pulmonary afterload, hypermetabolic state, and hemodynamic deregulation combine to unbalance myocardial oxygen consumption and supply.[9] In addition, it should be noted that after recovery from viral illnesses, including coronaviruses, patients have been found to be at greater risk for acute MI, although it remains to be seen whether this will be true for SARS-CoV-2.[37]

Myocarditis as a product of systemic inflammation in SARS-CoV-2 is supported by the deregulation of cytokine cascades and histopathologic findings. Lymphocytopenia is a hallmark of critical COVID-19 patients and is correlated to mortality.[7] Specifically, this lymphocytopenia is manifested as decreases in helper and regulatory T cells, which further impairs the regulation of the immune response in addition to the mechanism of ACE2, as already discussed.[23] Inflammatory markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP), have been shown to be correlated with increased SARS-CoV-2 mortality but also with troponin levels and electrocardiographic abnormalities.[5] Autopsy studies of the heart have demonstrated both cell necrosis and acute right ventricular dilation and did not report direct viral infiltration, reiterating the hypothesis of microvascular dysfunction as a possible cause.[21] Acute fulminant myocarditis is described, with one patient presenting 1 week after resolution of pulmonary symptoms, suggesting a persistently elevated inflammatory state even upon convalescence.[4] Myocardial injury can present as acute heart failure in COVID-19 patients (23% in one study), with both reduced and preserved left ventricular ejection fraction.[7,33] In the setting of severe ARDS, development of right-sided heart failure, pulmonary hypertension, and right ventricular dilation all are possible when progression of cardiogenic pulmonary edema creates a dangerous positive feedback loop of increasing pulmonary arterial afterload.[9] When distinguishing between cardiogenic and pulmonary or mixed causes of respiratory failure, serial brain natriuretic peptide levels, echocardiographic studies, and pulmonary arterial pressures can be instructive.[9,38]

*Arrhythmias*

SARS-CoV-2–positive patients can develop cardiac arrhythmias such as tachycardia, bradycardia, heart block, malignant ventricular arrhythmias, and asystole.[23,39] Palpitations were a presenting symptom in 7.3% of admitted patients in a Chinese study, and arrhythmia was present in 16.7% of hospitalized patients and 44.4% of ICU patients, although the type of arrhythmias prevalent in these populations has not been described.[40,41] Again, the mechanistic genesis of these arrhythmias is unknown but likely is related to myocarditis, metabolic derangements, inflammatory stress, high sympathetic tone, hypoxia-induced apoptosis, or even direct viral toxicity.[9,23,39] Increasingly, attention also is being brought to the side effect profile of off-label drug therapy as a possible nidus for QT prolongation and arrhythmogenicity.[39] Many of these drugs, including chloroquine and hydroxychloroquine, antivirals ritonavir plus lopinavir, azithromycin, and even remdesivir, directly or indirectly via drug metabolism interactions, have the potential for QTc prolongation.[39] There also is the consideration that many critically ill patients receive proton pump inhibitors and medications commonly administered in cardiothoracic anesthesia, such as atropine, sevoflurane, and antiemetics like droperidol and ondansetron, which all can further potentiate prolonged QTc.[42] Unsurprisingly, there are anecdotal and case reports of complete heart block, ventricular fibrillation/tachycardia, and pulseless electrical activity in these highly critically ill patients, underscoring the need for providers well-versed in acute cardiothoracic pathophysiology.[33,43,44]

## Coagulopathy in COVID-19

Historically, coronaviruses have caused infections that have been associated with (and generally limited to) respiratory symptoms of the following varying ranges: 4 common coronaviruses cause signs and symptoms of the common cold, whereas severe acute respiratory syndrome, Middle East

respiratory syndrome, and SARS-CoV-2 potentially may cause much more severe respiratory distress. Unique to SARS-CoV-2 (which causes COVID-19) is considerable cardiovascular pathology, including profound aberrations in the coagulation system. These coagulation anomalies are reflected in laboratory testing derangements and appear to result in an increased incidence of deep vein thrombosis, pulmonary embolism, and ischemic cerebrovascular accidents.[45-47] This pathologic change has been named "COVID-19- associated coagulopathy" (CAC) and appears to be predominantly prothrombotic and hypercoaguable.[48] At present, it appears that a combination of SARS-CoV-2–generated inflammation and endothelial cell abnormalities are paramount to CAC.

*Inflammation*

Descriptions of clinical features of COVID-19 patients consistently have reported abnormalities in several laboratory results including decreased levels of white blood cells—in particular decreased lymphocytes—and elevations in blood urea nitrogen, creatinine, CRP, D-dimer, ferritin, erythrocyte sedimentation rate, fibrinogen, and IL-6.[48-50] CRP, ferritin, erythrocyte sedimentation rate, and IL-6 all are markers of inflammation, and it may be the robust increase in inflammation that contributes most to the CAC that has been described.[48]

Coagulopathy as a related factor of inflammation associated with infection is not unique to COVID-19; "sepsis-induced coagulopathy" and thromboinflammation are described entities in the literature that are not solely attributed to COVID-19.[51,52] Mechanistically, inflammation gives rise to a procoagulant environment via complement system activation, cytokine release, and platelet activation.[48] Decreased fibrinolysis. as a result of increased plasminogen activator inhibitor-1 activity. impairs the natural systems designed to prevent thrombosis in patients with sepsis and may have a role in the prothrombotic states in CAC.[48]

*Endothelial Cell Abnormalities*

In the normal coagulation cascade, endothelial cells play a key role in initiating thrombus generation. In COVID-19 patients, there appears to be a derangement in the vascular endothelial cells themselves, contributing to CAC. Varga et al. described an "endothelitis" found on postmortem tissue analysis of patients with COVID-19, in which they noted evidence of direct viral infection of endothelial cells and cell inflammation attributed to SARS-CoV-2 infection. This pathologic finding is presumed to be a result of the fact that the ACE2 receptor is widely expressed throughout the body, and it is this receptor that SARS-CoV-2 uses to enter host cells. Endothelial cell inflammation begets endothelial cell dysfunction; this dysfunction may manifest itself with both imbalanced vasoconstriction and vasodilation and a procoagulant state.[53]

*Clinical Manifestations of CAC*

As with much of the evidence in the novel coronavirus pandemic, case reports, case series, and retrospective reports of patient cohorts serve as the foundational knowledge of the clinical manifestations of CAC.

The aforementioned laboratory anomalies may serve as markers of risk for clinical outcomes. Elevated D-dimer values in patients with COVID-19 upon admission to the hospital were associated with both an increased likelihood of necessitating critical care support during the hospital course and increased in-hospital mortality.[54] In a cohort of 171 patients in Wuhan, China, an admission D-dimer level of >1.0 μg/mL (normal value <0.5 μg/mL) was associated with an 18-fold increase in risk of mortality compared with patients with lower admission values. Similarly, increasing D-dimer levels over the course of hospitalization were associated with increased mortality.[48,55] Elevations in the acute phase reactants and markers of inflammation of serum ferritin >1,297 ng/mL (normal value 21-275 ng/mL), IL-6 >11.4 pg/mL (normal value 0-7 pg/mL), and CRP >126.6 mg/L (normal value 0-5 mg/L) were associated with mortality.[49]

Oxley et al. reported a series of large-vessel occlusive ischemic strokes in 5 patients with COVID-19, all of whom were younger than 50. Even though stroke in young persons is rare, but not unheard of, the authors noted the aforementioned 5 patients presented within a 2-week period in early 2020; the same hospital averaged 0.73 patients younger than 50 with large-vessel occlusive stroke per 2-week period for the prior 12 months. Venous thromboembolism (VTE) (deep vein thrombosis and pulmonary embolism) are reported in increased frequency in COVID-19. Cui et al. reported on a cohort from Wuhan, China, in which 25% of patients in an ICU developed VTE[56]; these findings were similar to those reported in Dutch and French reports (31% and 16.7% of ICU patients, respectively).[45,57]

There is no current standard of care for VTE prophylaxis or treatment in the COVID-19 population. In many ICUs across the world, VTE prophylaxis for patients is routine.[58,59] Given the proinflammatory and procoagulant milieu of CAC, standard pharmacologic VTE prophylaxis. with unfractionated heparin or low-molecular–weight heparin (LMWH), is recommended for patients with COVID-19. It must be noted that case series have described VTE developing in patients despite the administration of standard doses of appropriate VTE prophylaxis medications.[45,57] Treatment of diagnosed thrombosis or thromboembolism is guided mainly by pre-COVID-19 era literature. A group of Chinese experts released a consensus statement on the treatment of COVID-19–associated VTE, recommending parenteral LMWH as first-line therapy and the use of "rescue thrombolytic therapy" for patients with clinical signs and symptoms of massive/high-risk PE.[60] This guidance was similar to that issued in a document with multinational society endorsements, including the International Society on Thrombosis and Hemostasis, which recommended LMWH, intravenous unfractionated heparin, or direct oral anticoagulants, with judicious consideration of the risks and benefits of each specific regimen.[61] A retrospective analysis of a large cohort of hospitalized patients with COVID-19 in New York City who received systemic anticoagulation suggested an overall decreased mortality compared with that of patients who did

not receive systemic anticoagulation (29.1% in-hospital mortality in patients with anticoagulation *v* 62.7% in those without anticoagulation).[62] Formation and dissemination of formal guidelines will take time as data emerge and are reviewed. Several areas of controversy exist in the management of CAC-related VTE, including the use of bivalirudin versus unfractionated intravenous heparin for anticoagulation during continuous renal replacement therapy and whether patients who have recovered from COVID-19 require anticoagulation therapy after hospital discharge.[61]

## Interventions for COVID-19–Related Cardiovascular Disease

Various investigators have shown that patients with coronavirus-related cardiac disease (CoVCD) or preexisting cardiovascular disorders are more likely to experience severe manifestations of COVID-19 and a greater mortality.[11,63] Hence, early identification of patients at risk and expected management may help mitigate the adverse outcomes associated with CoVCD. Known manifestations of CoVCD include heart failure (right or left ventricular failure), ACS, and arrythmias.[33,64] Patients also may present with worsening of preexisting cardiac disease.[33] Diagnostic and management strategies primarily are driven by standard guidelines specific to each presentation from the pre-COVID-19 era.[64]

### *Principles of Management*

The cornerstone for treatment is supportive care because therapies specific to CoVCD are limited. COVID-19 is a morbid disease, with a high risk of viral transmission. Hence, management strategies should prioritize interventions that minimize the risk of viral transmission to healthcare personnel. This is especially important because there are reports of patients without respiratory signs and symptoms presenting with CoVCD. Fried et al. reported on a patient who presented with ST elevation MI and cardiogenic shock without the typical respiratory presentation seen in COVID-19.[33] Cardiovascular presentations, even in the absence of typical presentation of COVID-19, therefore should generate a high index of suspicion for SARS-CoV-2.

The vast majority of patients with CoVCD also are likely to have concomitant severe respiratory illness.[63] CoVCD in this scenario presents significant diagnostic challenges because clinical presentations of heart failure overlap with respiratory failure. Moreover, frequent physical examination of patients necessary for the diagnosis and management of heart failure (eg, jugular venous distention, capillary refill, perfusion to extremities) comes with an increased risk to the provider. This risk can be mitigated by increasing reliance on invasive monitoring. Patients at high risk for CoVCD, or associated heart failure, would benefit from an invasive arterial catheter for blood pressure monitoring and a central venous line for central venous pressure monitoring. In addition, routine measurement of laboratory parameters, including central venous oxygen saturation, D-dimer, serum troponins, and N-terminal pro B-type natriuretic peptide, will facilitate early diagnosis of CoVCD.

There should be a very high threshold for transporting patients from their room for diagnostic or therapeutic procedures. Need for imaging studies should be weighed against risk of exposure to additional providers and challenges with decontamination of essential equipment (eg, computed tomography scan, echocardiography). A reasonable tradeoff might be to use point-of-care ultrasound examination and focused echocardiography to elucidate the etiology of undifferentiated shock, especially when other diagnostic data are equivocal. Point-of-care ultrasound has various advantages. Intensivists, either certified through the National Board of Echocardiography or institutionally credentialed, are often experts in critical care echocardiography.[65] With portable, hand-held point-of-care ultrasound, it is easier to contain the entire equipment in a barrier sheath, minimizing the risk of contamination to the equipment. A formal diagnostic transthoracic or transesophageal echocardiogram (TEE) rarely is indicated and should be avoided.

### *Supportive Care*

The most commonly reported serious manifestation of CoVCD is cardiomyopathy leading to cardiogenic shock. Supportive echocardiographic findings on point-of-care ultrasound are useful for initial diagnosis. Reliance on pulmonary artery catheter–based therapy would be beneficial in the presence of cardiogenic shock, especially to avoid repeated physical examinations and echocardiograms. Standard heart failure measures need to be instituted, specifically preload optimization and diuresis, afterload reduction, and inotropic support.[66] These therapies should be titrated to optimize end-organ perfusion. Although noninvasive positive- pressure ventilation typically is used for management of acute pulmonary edema from cardiogenic shock, these interventions must be balanced against possible viral transmission to healthcare personnel from aerosolization. Considerations for extracorporeal membrane oxygenation (ECMO) need to be discussed early so that decision- making and ECMO cannulation, if needed, can be done in a controlled fashion.[67] Emergency ECMO cannulation increases the risk of exposure to involved personnel.

Heart failure related to CoVCD also may be primarily right ventricular failure. Right-sided heart dysfunction can occur because of increased pulmonary vascular resistance from ARDS and may be managed by optimizing ventilation strategies. The hyperinflammatory cytokine response associated with COVID-19 has been associated with a prothrombotic state, increasing the risk of pulmonary emboli and associated right-sided heart strain. These patients need to be anticoagulated.[45] A failing right ventricle would need preload optimization, inotropic support, and inhaled pulmonary vasodilators to minimize right ventricular afterload.

Patients presenting with markedly elevated serum troponin and electrocardiogram changes suggestive of ACS present a significant diagnostic challenge. Some authors reported myocarditis from CoVCD presenting with typical signs and symptoms of ACS without coronary artery disease on cardiac

catheterization.[33,68] On the other hand, viral pneumoniae increase the risk of acute MI.[69] Coronary angiogram would be diagnostic and therapeutic in case of acute MI but would increase the risk of exposure to various personnel. Hence, the decision to perform cardiac catheterization is not trivial and needs to be made after multidisciplinary deliberation. Endomyocardial biopsy and cardiac magnetic resonance imaging, which were standards for diagnosis of viral myocarditis in the pre-COVID era, currently are discouraged because their findings will not change management but increase risk of exposure to personnel and equipment. Patients with viral myocarditis or myocardial ischemia might be at a greater risk for arrhythmias, which may be managed with typical antiarrhythmic agents.

*Specific Therapies*

As previously noted, ACEi and ARB increase the quantity of ACE2 receptors. One of the pathways by which SARS-CoV-2 enters cells, including cardiac myocytes, is by binding to ACE2 receptors on the cell membrane. Hence, it was postulated that patients on ACEi or ARB might be at risk for more severe disease. On the other hand, there is enough supportive evidence stating that discontinuation of ACEi or ARB could be detrimental because of propagation of excessive angiotensin II–mediated acute lung injury.[70] Because there is clinical equipoise, professional societies and experts recommend that infection with SARS-CoV-2 should not influence management of ACEi or ARB until more data are available from randomized controlled trials. Data from 3 retrospective studies supported this recommendation.[71]

Case reports of viral myocarditis from SARS-CoV-2 reported improvement after treatment with steroids and intravenous immunoglobulin.[4,68] This should be interpreted with caution because of a high risk of publication bias. A Cochrane review evaluating the effect of steroids on acute viral myocarditis in the pre-COVID era showed no benefit.[72] However, certain studies have reported increased mortality and higher viral loads among patients with SARS-CoV-1 treated with steroids, despite reports of improved oxygenation in some studies.[73] Hence, to the best of the authors' understanding of available published literature at this point, steroids reasonably may be avoided in non-severe COVID-19 cases but reserved as a salvage therapy for severe cases after interdisciplinary deliberation. Because cardiomyopathy from viral illnesses may be related to autoantibodies, intravenous immunoglobulin has been used as a treatment strategy, although supporting evidence is minimal. At least one study in the pre-COVID era did not show any benefit in mortality or recovery of heart failure.[74] Because no specific harm was reported and data on SARS-CoV-2 are not available, it might be reasonable to consider intravenous immunoglobulin in patients with the most severe manifestations of CoVCD.

Although various therapeutic agents are being studied for COVID-19, the effect of these agents on CoVCD is unknown. Some of them are worth discussion. Hydroxychloroquine was widely prescribed by clinicians for off-label use against COVID-19. However, a retrospective evaluation showed no benefit; nevertheless, additional data are awaited from randomized trials.[75] Although hydroxychloroquine is relatively safe, it increases the QT interval and thus increases the risk of torsades de pointes. This risk may be greater in patients with CoVCD.[75]

The National Institutes of Health reported that a large multicentric, randomized, controlled trial evaluating remdesivir (an antiretroviral medication) for treatment of COVID-19 reduced time to recovery by 30%.[76] Currently, remdesivir is the only drug that has shown a favorable effect against SARS-CoV-2 in a randomized, controlled trial, but its effect on CoVCD is unknown. The other antiretroviral medication evaluated for COVID-19, lopinavir-ritonavir, did not show any benefit in a small randomized, controlled trial.[77] Because cytokine storm is an important feature of COVID-19 and potentially of CoVCD, various inhibitors of IL-6 are being studied. The results of those trials may give more insight into its effect on CoVCD.

*Mechanical Circulatory Support Considerations*

When a patient develops refractory cardiac, pulmonary, or cardiopulmonary dysfunction, the only hope for continued survival may be the initiation of mechanical circulatory support. The choice of support depends on the underlying organ dysfunction and the patient's prognosis. In the absence of substantial outcome data on patients with CoVCD, providers are obliged to follow consensus guidelines and experience from other illnesses. Currently, mechanical support is a reasonable option for patients with CoVCD who do not have significant underlying comorbidities. The choice of which type of mechanical support depends on the patient's clinical manifestations.

A significant subset of patients with COVID-19 who are admitted to the hospital will develop severe ARDS, necessitating mechanical ventilation. Despite maximal supportive care (low- tidal- volume ventilation, prone positioning, and inhaled pulmonary vasodilators), refractory hypoxia/hypercapnia may persist, which can lead to cardiovascular compromise. This cardiovascular dysfunction likely is related to stress from circulating catecholamines and increased right ventricular afterload from poor pulmonary function. Cardiac function in these patients may recover with the initiation of venovenous ECMO in order to restore adequate oxygenation delivery and correction of severe respiratory acidosis. If these patients continue to have signs of cardiogenic shock or require significant inotropic support during the initiation of ECMO, they potentially may benefit from a hybrid circuit configuration—venoarterial-venous ECMO. In this configuration, blood is drained from the inferior vena cava, oxygenated, and then the return to the patient is divided between an arterial limb (to support blood pressure) and a venous limb (commonly in the internal jugular vein) to "pre-oxygenate" blood before it flows through the lungs. The ratio of the flow returning venous versus arterial is determined by the degree of cardiogenic dysfunction; once the heart has adequately recovered, the patient can be converted to a venovenous ECMO configuration.[78]

A smaller subset of COVID-19 patients present with a different phenotype—profound cardiogenic shock with minimal

respiratory involvement. For patients with signs of cardiogenic shock refractory to pharmacologic support, the initial support strategy likely will be venoarterial (VA) ECMO. This will allow for support to be initiated at the bedside, minimizing the need for transport and hopefully reducing the risk of exposure to other providers. Unfortunately, VA ECMO has its own complications that will need to be addressed, such as leg ischemia, infection, and need for anticoagulation.[79] It remains to determine the relative incidence of these complications in COVID-19 and whether they are more common in this patient population. In addition, the left ventricle must be unloaded to prevent the development of pulmonary edema and lung injury. There are multiple ways to accomplish this, each with their own benefits and drawbacks. One method is to use lower ECMO flows to allow the heart to have a more native ejection; however, in the setting of profound shock, this may not provide adequate support. Another option is to place a percutaneous ventricular assist device, such as an Impella (Abiomed, Danvers, MA), to unload the left ventricle. This option is attractive because it may facilitate weaning from ECMO.[80,81] Once the patient has been stabilized with VA ECMO, support may be "upgraded" to individual biventricular support. This strategy will allow for independent weaning of the support of the right ventricle, left ventricle, and respiratory system.

There are many unknowns regarding mechanical support for patients with COVID-19. Their recovery trajectories, candidacy for durable therapies or transplantation, and survival on mechanical support remain to be elucidated. Based on current information, however, mechanical support is a reasonable strategy in patients who meet institutional criteria. Finally, it is important to consider that the decision to implement mechanical circulatory support in patients with COVID-19 disease should not be taken lightly. Interventions such as ECMO are very resource- intensive and in a pandemic setting may not be feasible in crisis standards of care.

## Implications for the Cardiovascular Anesthesiologist

### *Anesthesiologists' Risk of Infection and Personal Protective Equipment*

All healthcare workers (HCWs) are at high risk of infection with SARS-CoV-2. As of April 9, 2020, in states with more thorough reporting, HCWs accounted for 11% of SARS-CoV-2 infections in the United States. This number is expected to grow as the duration of the pandemic increases.[82] Notably, one of the first physicians in China to speak out about this new virus, Li Wenliang, an ophthalmologist, died of SARS-CoV-2 infection in January 2020.[83] Even though the total number of HCWs who will be infected by the current pandemic is unknown, evidence from the past may provide some insight. During the original SARS outbreak in 2003, HCWs made up 51% of the total number of people infected.[84] An international registry has been created at intubateCOVID.org to collect information on exposures to HCWs from SARS-CoV-2. This registry has been endorsed by organizations including the International Anesthesia Research Society and the American Society of Anesthesiologists (ASA).[85]

Among HCWs, anesthesiologists are at particularly high risk of infection. This is because of the procedures they perform and the proximity of their work to their patients, both of which increase their likelihood of exposure and subsequent infection. It is believed that the majority of SARS-CoV-2 infections occur via droplet (particles 5-10 μm in size) transmission when respiratory secretions containing viral particles are emitted by infected patients and either land directly on other individuals or on objects that then serve as fomites. However, infection via aerosols (particles <5 μm in size) is possible and particularly concerning because standard surface cleaning of equipment does not decrease this route of transmission. Aerosolization is especially relevant to anesthesiologists because they regularly perform procedures known to generate aerosols, such as intubation, bronchoscopy, and airway suctioning.[86]

In light of the high risk of transmission to HCW, multiple organizations have issued recommendations and guidelines specifying appropriate personal protective equipment (PPE) to be used when caring for confirmed or suspected SARS-CoV-2 patients. The US Centers for Disease Control and Prevention (CDC) has published recommendations that are based on the modes of transmission of the virus (ie, droplet and aerosol); the differences among various types of healthcare settings; and the shortage of ideal PPE in certain geographic areas. When performing aerosol-generating procedures, such as intubations, the CDC specifically recommended that the number of HCWs present be limited to the fewest necessary to perform the procedure; that these procedures take place in an airborne infection isolation room; and that the proceduralist wear, at a minimum, an N95 respirator along with eye protection, gloves, and a gown.[87] The Anesthesia Patient Safety Foundation (APSF) also released recommendations for the perioperative care of patients during the coronavirus pandemic. Similar to the CDC, the APSF advised that a gown, goggles, gloves, footwear, and a minimum of a fit-tested N95 mask be worn when caring for known or suspected SARS-CoV-2 patients. However, they also noted that a powered air-purifying respirator (PAPR) provided superior protection to an N95 mask and its use should be considered when possible.[88] Going further, a joint statement from the ASA, APSF, American Academy of Anesthesiologist Assistants, and American Association of Nurse Anesthesiologists recommended that PPE appropriate for aerosol-generating procedures (ie, an N95 mask or PAPR) be used when caring for all patients near their airway because it cannot be known with certainty who is infected with SARS-CoV 2.[89] Adherence to these recommendations obviously will create a much greater need for high-level PPE than was required before the emergence of SARS-CoV-2. Accordingly, lack of sufficient supplies of PPE has become a major issue worldwide. In the event that appropriate PPE is not available from employers of HCWs, the ASA has released a statement supporting the rights of anesthesiologists to purchase and use their own approved respirators.[90] The use of these specific pieces of PPE and the protocols introduced at various healthcare institutions to reduce the transmission of SARS-CoV-2

likely will be new to many. For this reason, both the APSF and a joint task force of the Chinese Society of Anesthesiology and Chinese Association of Anesthesiologists specifically recommended preparatory training for HCWs before caring for patients with SARS-CoV-2.[88,91]

*Concepts for Intubation, Transesophageal Echocardiography , and Bronchoscopy*

As already mentioned, the routine work of anesthesiologists places them at high risk of infection when caring for patients infected with SARS-CoV-2. This risk is greatest when performing aerosol-generating procedures such as intubation. Of particular relevance to the cardiothoracic anesthesiologist, TEE and bronchoscopy represent additional risks for SARS-CoV-2 through frequently performed procedures. The size of an infectious particle is inversely related to the velocity of air flow that produced it, so procedures that result in the rapid flow of air across respiratory mucosa are potentially high risk. The World Health Organization has defined which procedures fall into this category, including those performed regularly by anesthesiologists, such as manual ventilation, intubation, suctioning, bronchoscopy, and cardiopulmonary resuscitation.[92] There is general agreement that these procedures only should be performed when proper PPE (discussed previously) is available. However, various groups have advocated additional measures, with the goal of further reducing the infectious risk to HCW.

Anesthesiologists are experts in airway management and will be relied on to perform this task at various sites within the hospital during the novel coronavirus pandemic. The World Health Organization guidelines recommend that intubation be performed by an experienced provider, and the APSF similarly recommends that the most experienced provider perform the intubation. Both organizations also advocate preoxygenation with 100% oxygen for 5 minutes and performance of a rapid-sequence intubation to reduce the risk of coughing.[93] Video laryngoscopy is a tool that was not widely available during the first SARS outbreak in 2003. These devices allow the intubator to keep his/her face farther away from the patient's mouth and may reduce the number of failed intubations.[94] Both of these resources theoretically could decrease the risk of infectious transmission. Accordingly, the APSF suggests using video laryngoscopy when intubating patients known or suspected to have SARS-CoV-2-infection. Finally, after successful intubation is performed, a heat and moisture exchange filter rated to remove ≥99.97% of airborne particles ≥0.3 μm in size should be placed between the face mask and the breathing circuit or between the face mask and reservoir bag to help prevent viral transmission to future patients.[88] Additional techniques have been advocated to reduce the risk of transmission, such as clamping the endotracheal tube during circuit disconnections and the use of "intubating boxes" made of a variety of materials. However, at this time, there is not adequate evidence to support the use of these techniques above and beyond the guidelines already discussed.

Like intubation, bronchoscopy is an aerosol-generating procedure and as such represents an increased risk to proceduralists. The American Association for Bronchology and Interventional Pulmonology recommends that elective bronchoscopy be postponed in any patient with risk factors for SARS-CoV-2 infection. For patients with known or suspected infection necessitating urgent or emergency bronchoscopy, it is recommended to perform the procedure in designated airborne isolation rooms or negative- pressure rooms and with

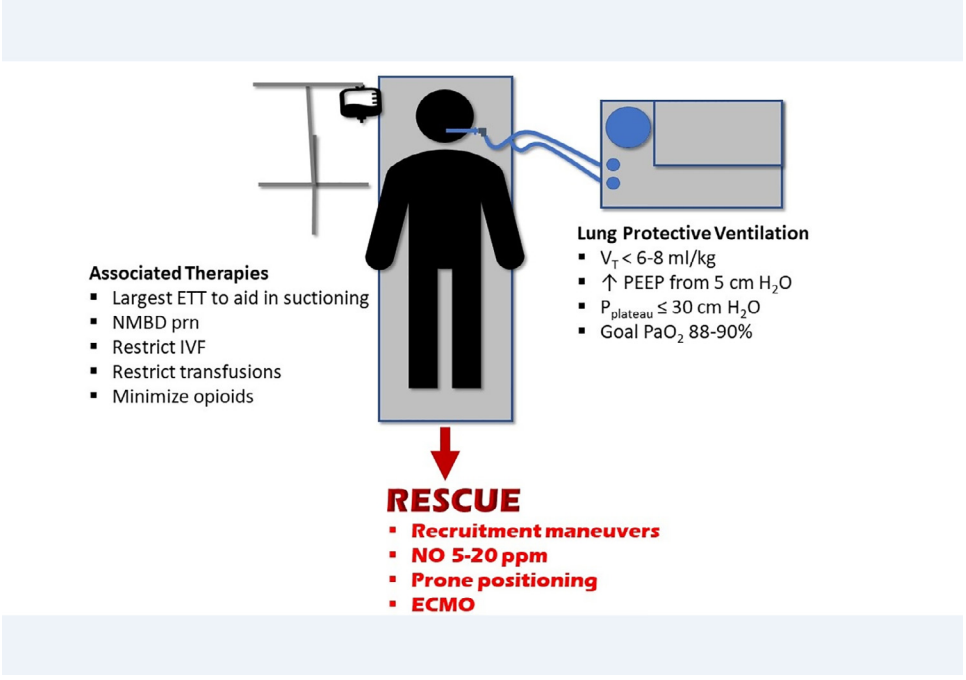


Fig 1. Coronavirus ventilation principles. ECMO, extracorporeal membrane oxygenation; ETT, endotracheal tube; IVF, intravenous fluids; NMBD, neuromuscular blocking drugs; $PaO_2$, partial pressure of oxygen; NO, nitrous oxide; PEEP, positive end-expiratory pressure, $V_T$, tidal volumes.

the use of an N95 mask with eye protection or a PAPR, standard PPE, and the use of disposable bronchoscopes if available.[95]

TEE is another procedure with the potential to generate aerosols. This is particularly true when TEE is performed in patients breathing on their own with a natural airway, during which coughing is common. It is recommended that the necessity of a TEE examination versus another imaging modality (ie, transthoracic echocardiography) be considered carefully and only truly necessary examinations that likely are to provide immediately needed data be performed. When these criteria are met, the echocardiographer should use airborne precaution PPE (gown, gloves, shoe covers, head cover, face mask, eye shield, and an N95 or PAPR) while performing the TEE.[96] Additional recommendations include limiting the extent of the examination, limiting trainee involvement to reduce the number of HCWss at risk and to reduce the time to complete the examination, and strict adherence to institutional protocols on the cleaning of echocardiography equipment after the examination.[96] Whether there is a lower risk of viral transmission from TEEs performed in intubated patients (as is common in the operating room) versus nonintubated patients currently is unknown. It is believed that general anesthesia and an endotracheal tube reduce the likelihood of generating infectious aerosols.[97] Nevertheless, the American Society of Echocardiography makes no distinction between TEEs in intubated versus nonintubated patients when recommending the use of airborne precaution PPE.[96]

### *Review of Intraoperative Treatment and Rescue Therapies for Hypoxia*

Patients with severe SARS-CoV-2 infections may develop hypoxia, ARDS, and respiratory failure. ARDS is a syndrome of acute, diffuse, bilateral lung injury, with increased pulmonary vascular permeability, leading to hypoxia.[98] The severity of ARDS is based on the partial pressure of oxygen/fraction of inspired oxygen ratio, with a value $<100$ indicating severe disease. The care of patients with hypoxia and ARDS from SARS-CoV-2 is challenging, and the interventions recommended for use in the operating room primarily are derived from those used in the ICU. These recommendations include lung-protective ventilation (LPV) strategies (discussed in the following), restrictive fluid management, judicious use of blood products, minimization of opioids, and the use of neuromuscular blocking drugs to help with patient-ventilator asynchrony and high peak airway pressures (Fig 1).[99,100]

For patients with persistent hypoxia, advanced therapies may be needed. Prone positioning should be considered in moderate- to- severe ARDS.[99] Clearly, the position of the patient intraoperatively primarily is dictated by the surgical procedure. However, prone positioning has been used as a rescue therapy intraoperatively immediately after surgery requiring supine positioning.[101] Inhaled nitric oxide (5-20 ppm) is another intervention that can improve oxygenation and is used regularly in the operating room. Finally, for hypoxia that fails to improve with these therapies, ECMO is an option that can be used readily in the operating room, given resource availability.[99]

### *Review of LPV*

In the past few decades, it has become increasingly clear that the primary therapy for respiratory failure, mechanical ventilation, itself causes injury to the lungs. It should be noted that ventilator-induced lung injury may be particularly robust and destructive to patients with COVID-19; reports regarding the specific variations in the pathophysiology and manifestations of COVID-19 respiratory failure are just now beginning to emerge.[102] To the best of the current understanding, classic "low- lung- compliance" ARDS is best treated with LPV strategies. These strategies include a number of ventilator settings and practices that have been shown to reduce ventilator-induced lung injury. Adherence to these practices in the operating room has been sporadic, likely because most patients presenting for elective surgery have healthy lungs.[103] However, patients infected with SARS-CoV-2 who present for surgery will, at the very least, be at increased risk of postoperative pulmonary complications and at worse be experiencing full-blown ARDS. Hence, LPV strategies should be considered for all patients with SARS-CoV-2 who require mechanical ventilation. The most important recommendation is to maintain a tidal volume $\leq$6- to- 8 mL/kg of predicted body weight.[100,104] For patients with definitive ARDS, a tidal volume of 4- to- 6 mL/kg predicted body weight is recommended.[99] Positive end-expiratory pressure is beneficial, but the exact amount is not agreed on. In general, starting with a low level (ie, 5 $cmH_2O$) and gradually increasing the amount in an individualized fashion to improve oxygenation is recommended.[99,100,104] Maintaining plateau pressures as low as possible also is important, with a goal of $\leq$27- to- 30 $cmH_2O$. Recruitment maneuvers generally should be used only as a rescue therapy when other interventions have failed.[99,100] The end goal of these interventions is to maintain an oxygen saturation of 88% to 90%.[99]

## Conclusion

COVID-19 has created a pandemic and a global crisis that has infected millions and killed hundreds of thousands and has frequently overwhelmed healthcare systems in the hardest hit areas. Cardiothoracic anesthesiologists are routinely charged with caring for the most gravely ill patients admitted to hospitals and therefore likely are to be called on to care for critically ill patients with COVID-19. It is clear that COVID-19 creates devastating clinical derangements beyond the respiratory system; the cardiovascular system is profoundly affected in patients with COVID-19.

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## Conflict of Interest

None.

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