

IN DEPTH

The Science Underlying COVID-19

Implications for the Cardiovascular System

ABSTRACT: The coronavirus disease 2019 (COVID-19) pandemic has affected health and economy worldwide on an unprecedented scale. Patients have diverse clinical outcomes, but those with preexisting cardiovascular disease, hypertension, and related conditions incur disproportionately worse outcome. The high infectivity of severe acute respiratory syndrome coronavirus 2 is in part related to new mutations in the receptor binding domain, and acquisition of a furin cleavage site in the S-spike protein. The continued viral shedding in the asymptomatic and presymptomatic individuals enhances its community transmission.

The virus uses the angiotensin converting enzyme 2 receptor for internalization, aided by transmembrane protease serine 2 protease. The tissue localization of the receptors correlates with COVID-19 presenting symptoms and organ dysfunction. Virus-induced angiotensin converting enzyme 2 downregulation may attenuate its function, diminish its anti-inflammatory role, and heighten angiotensin II effects in the predisposed patients.

Lymphopenia occurs early and is prognostic, potentially associated with reduction of the CD4+ and some CD8+ T cells. This leads to imbalance of the innate/acquired immune response, delayed viral clearance, and hyperstimulated macrophages and neutrophils. Appropriate type I interferon pathway activation is critical for virus attenuation and balanced immune response. Persistent immune activation in predisposed patients, such as elderly adults and those with cardiovascular risk, can lead to hemophagocytosis-like syndrome, with uncontrolled amplification of cytokine production, leading to multiorgan failure and death.

In addition to the airways and lungs, the cardiovascular system is often involved in COVID-19 early, reflected in the release of highly sensitive troponin and natriuretic peptides, which are all extremely prognostic, in particular, in those showing continued rise, along with cytokines such as interleukin-6. Inflammation in the vascular system can result in diffuse microangiopathy with thrombosis. Inflammation in the myocardium can result in myocarditis, heart failure, cardiac arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death.

Aggressive support based on early prognostic indicators with expectant management can potentially improve recovery. Appropriate treatment for heart failure, arrhythmias, acute coronary syndrome, and thrombosis remain important. Specific evidence-based treatment strategies for COVID-19 will emerge with ongoing global collaboration on multiple approaches being evaluated. To protect the wider population, antibody testing and effective vaccine will be needed to make COVID-19 history.

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The coronavirus infection coronavirus disease 2019 (COVID-19) first presented as an outbreak of atypical pneumonia in Wuhan, China, on December 12, 2019.^{1,2} Since then, it has spread globally to infect >1 963 943 individuals and killed >123 635 in >200 countries as of April 14, 2020. This infection has affected health and the economy worldwide on an unprecedented scale.

Whereas COVID-19 is primarily a respiratory infection, it has important systemic effects including on the cardiovascular and immune systems. Patients with preexisting cardiovascular conditions represent large proportions of patients with symptomatic infection, and experience disproportionately worse outcomes at between a 5- and 10-fold increase in mortality (World Health Organization).³

Although we are learning constantly about the changing epidemiology, the rapidly evolving underlying science, together with insights from previous coronavirus infections, such as severe acute respiratory syndrome (SARS), can help us to better understand COVID-19, and, in turn, diagnose and treat our patients more insightfully.

CLINICAL SPECTRUM OF CARDIOVASCULAR INVOLVEMENT IN COVID-19

In addition to increased propensity and worse outcomes for COVID-19 in patients with preexisting cardiovascular diseases (Table 1), patients with new COVID-19 infections can also develop cardiovascular complications, such as heart failure, myocarditis, pericarditis, vasculitis, and cardiac arrhythmias.^{4,5}

Between 8% and 28% of patients with COVID-19 infections will manifest troponin release early in the course of the disease, reflecting cardiac injury or stress.^{6–9} The presence of troponin elevation, or its dynamic increase during hospitalization, confers up to 5 times the risk of requiring ventilation, increases in arrhythmias such as ventricular tachycardia/ventricular fibrillation, and 5 times the risk for mortality (Figure 1).⁵ A similar proportion of patients also manifest elevations of brain natriuretic peptides. Troponin and brain natriuretic peptides, together with the presence of underlying cardiovascular diseases or cardiovascular risk factors, are highly prognostic of the requirement for intensive care unit admission, ventilation, and death.

UNIQUE PROPERTIES OF THE VIRUS AND THE DISEASE PHENOTYPE

SARS coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, is a novel betacoronavirus (large RNA virus) that shares 80% sequence homology with the earlier

SARS coronavirus (SARS-CoV) that caused the SARS outbreak in 2003.¹ The coronavirus surface features multiple spike glycoproteins (S) consisting of homotrimers protruding far from the viral surface, giving it a halolike appearance (or corona). The spike S protein is used by the virus to engage its target cell receptor, angiotensin converting enzyme 2 (ACE2) (Figure 2). The S protein has 2 subunits: S1 and S2, facilitating target cell internalization.

SARS-CoV-2 has evolved several features that make it a more efficient virus for infection than SARS-CoV. The most critical receptor binding domain of SARS-CoV-2 preserved the overall configuration of the SARS-CoV binding domain, including 8 of the 14 residues being completely identical.¹⁰ However, the 3-dimensional structure of the SARS-CoV-2 binding site shows that it is more compact, has improved binding stability, and potentially enhanced ACE2 receptor binding affinity.¹¹

Another difference is that SARS-CoV-2 contains a polybasic (furin) cleavage site inserted at the boundary of the S1/S2 subunits of the spike S protein.¹² This furin binding site is unique, can enhance the virus' ability to internalize into cells, and is a feature shared by several recent highly pathogenic viruses, including avian influenza.

In general, RNA viruses are prone to higher mutation rates, and viruses are known to continue to mutate during an epidemic. Viruses continue to adapt to local environments to facilitate their transmission. The ability to track changes over geography and time can help us to better understand the disease pathogenesis, clinical phenotype variation, and its molecular epidemiology.¹³

Clinical Implications

The high replication rate of the virus, especially in the human oral pharynx and upper airway where the ACE2 receptors are located, likely enhances its ability for efficient person-to-person transfer.¹⁴ This allows shedding of the virus just with normal speaking or singing, without the need for coughing or sneezing, which may partially explain its infectivity.

The ability of the virus to proliferate and shed in completely asymptomatic individuals, including children and young adults, and also before symptoms occur (presymptomatic shedding), further increases its ability to transmit between individuals (Figure 1).¹⁵ In a series of 191 inpatients from Wuhan with COVID-19, the median duration of viral shedding was 20 days in survivors, with the longest viral shedding being 37 days, beyond symptom resolution, and SARS-CoV-2 was detectable until death in nonsurvivors.¹⁶

Because of the efficiency of SARS-CoV-2 in viral transmission, aggressive control measures are critical for attenuating the COVID-19 pandemic. But with 25% to 50% of infections being asymptomatic, traditional containment measures based on symptoms alone are

Table 1. Death Rate to Date of Patients With COVID-19 Infection and Specific Preexisting Conditions (World Health Organization Data)

Preexisting Condition	Death Rate, %
Cardiovascular disease	10.5
Diabetes mellitus	7.3
Chronic respiratory disease	6.3
Hypertension	6.0
Cancer	5.6
No preexisting conditions	0.9

COVID-19 indicates coronavirus disease 2019.

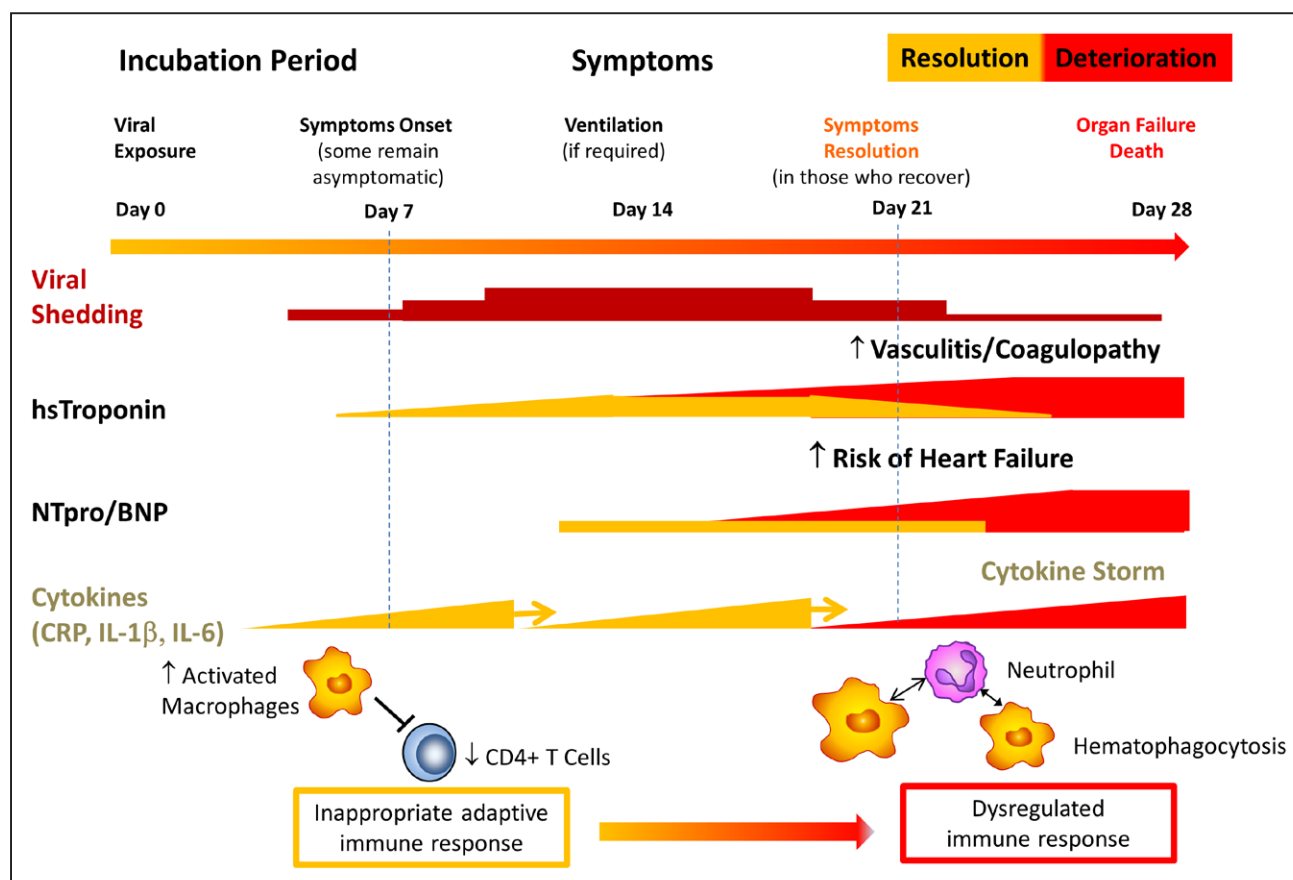
less effective. Contact tracing that is based on accurate and rapid diagnostic tests will be necessary. When deployed effectively, these measures can avert hundreds of thousands of cases.¹⁷

Patients with cardiovascular diseases are more prone to viral illness, in general, and thus constitute an already high-risk group. This is consistent with documented increases of acute myocardial infarction after influenza epidemics,^{18,19} even though this trend has not been consistently observed with COVID-19.

Whether the virus can directly proliferate in the heart is unknown. There are very few pathology studies on patients who have COVID-19. Previous analysis of human hearts in patients who died of SARS demonstrated that 7 of 20 (35%) hearts harbored virus in the myocardium.²⁰ Direct viral entry into the myocardium and blood vessels can certainly enhance the risk for myocardial injury, and subsequent inflammatory response, as well. It is not known whether the observed cardiac damage is attributable to viral injury or to an immunologic response affecting the myocardium and related structures, such as the pericardium and conduction system.

VIRAL RECEPTOR ACE2 AND TRANSMEMBRANE PROTEASE SERINE 2 CONTRIBUTE TO THE DISEASE PHENOTYPE

ACE2 has been confirmed recently as the SARS-CoV-2 internalization receptor causing COVID-19,²¹ in concert with the host's transmembrane protease serine 2

**Figure 1.** Clinical course of COVID-19 infection.

The incubation period averages 7 days, but can be up to 14 days. There can be asymptomatic, presymptomatic, or postsymptomatic viral shedding, likely contributing to its rapid transmission. Cardiac biomarkers such as high-sensitivity troponin (hsTroponin) can be detectable in patients at symptom onset and are prognostic. Continued increases in troponin together with rising cytokines predict the need for intensive care unit stays, ventilation, and vascular complications. Together with cytokine rise, NTproBNP rise can predict the risk of myocarditis or heart failure. Lymphopenia, with suppression of T cells and inefficient viral clearance, set the stage for overstimulated macrophages, cytokine amplification, and hemophagocytosis with organ failure, including the heart. COVID-19 indicates coronavirus disease 2019; CRP, c-reactive protein; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; and NTproBNP, N-terminal pro-brain natriuretic peptide;

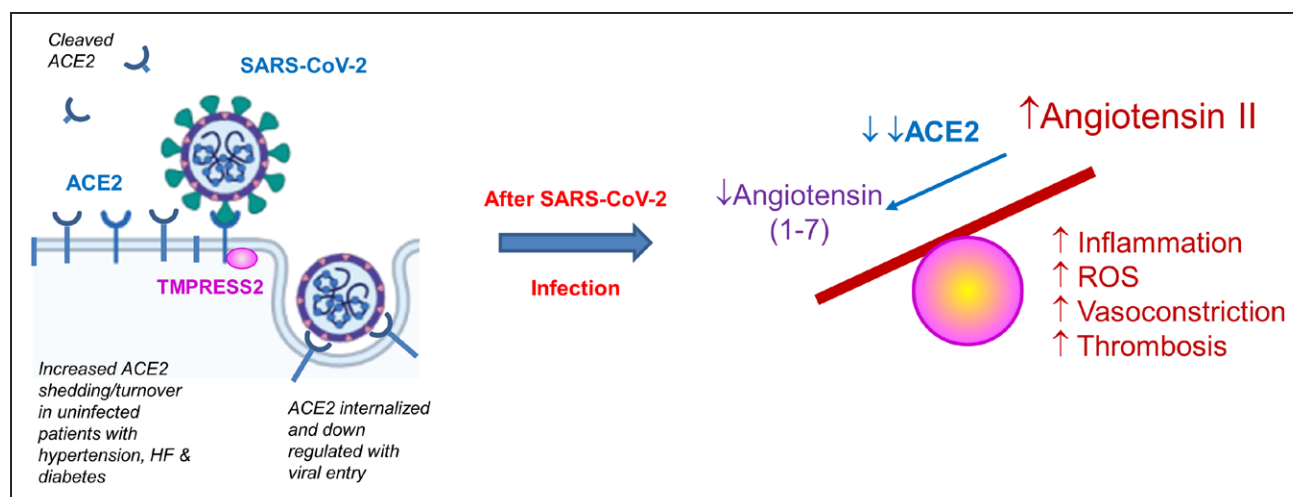


Figure 2. SARS-CoV-2 uses the ACE2 internalization receptor, facilitated by TMPRSS2 protease.

ACE2 can be shed in the circulation, and ACE2 is increased in patients with hypertension, heart failure, or diabetes mellitus. ACE2 can be downregulated following viral entry. This partial decrease in ACE2 function leads to dominant angiotensin II effects, including enhanced inflammation, vasoconstriction, and propensity for thrombosis. This can also worsen heart failure. ACE2 indicates angiotensin converting enzyme 2; HF, heart failure; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; and TMPRSS, transmembrane protease, serine 2.

(TMPRSS2) membrane protease that primes the spike S protein of the virus to facilitate its cell entry.²² ACE2 is the same functional receptor of the earlier SARS-CoV.²³ The presence of TMPRSS2 significantly enhances viral infectivity.²⁴ Protease inhibitors against TMPRSS2 appear to block effectively viral entry and infection of lung cells in vitro.

ACE2 is a type 1 transmembrane protein, with its enzymatic domain located on the external surface of cells where it performs its function of converting angiotensin II (1–8) to angiotensin 1–7.^{25,26} The latter is a vasodilator, and a counterregulator of the renin-angiotensin system (RAS). In stress states or proinflammatory conditions, membrane-bound ACE2 protein can be cleaved by the transmembrane disintegrin ADAM17 (a disintegrin and metalloproteinase 17), releasing ACE2 into the interstitium or circulation, without depleting intracellular ACE levels.²⁷ The latter conditions are found more commonly in patients with heart failure and diabetes mellitus. Loss of ACE2 enhances susceptibility to heart failure, and increasing ACE2 levels prevent and reverse the heart failure phenotype. In established heart failure, the expression of ACE2 is downregulated, although the function may be upregulated. There is reduced expression on the cell surface, but increases in circulating ACE2 levels.

ACE2 is expressed in the airway and type 2 pneumocytes in the lung. In models of diabetes mellitus, ACE2 can be found to be increased in renal tubules.²⁸ In humans, circulating ACE2, shed from endothelial cells, is a biomarker of hypertension and heart failure,^{29,30} and of diabetes mellitus, as well,³¹ reflecting increased ACE2 activity (Figure 2).

In addition, ACE2 has important immune modulation roles, acting through at least 2 mechanisms. ACE2

can directly interact with macrophages in the setting of vascular and lung inflammation,³² as demonstrated by genetic manipulation in a model of SARS, and by the salutary anti-inflammatory effects of the infusion of recombinant ACE2.^{33,34} In addition, ACE2 reduces the levels of angiotensin II, which is directly proinflammatory and pro-oxidant. Therefore, ACE2 is important in controlling excess inflammation in the presence of danger signals.³⁴

Clinical Implications

TMPRSS2 and ACE2 facilitate SARS-CoV-2 entry, and the copresence of these 2 molecular entities in tissues to a large extent explains the tropism of viral proliferation. TMPRSS2 and ACE2 are coexpressed in lung, heart, gut smooth muscle, liver, kidney, neurons, and immune cells.³⁵ Their distribution may help to explain patient symptoms or laboratory findings in COVID-19 (Table 2).

Circulating ACE2 levels in patients are sex dependent, being 50% higher in men than in women in heart failure.^{29,30} Whereas circulating levels do not directly reflect tissue levels, ACE2 is shed as part of the tissue response to stress, thereby upregulating ACE2 function. Of note, the ACE2 gene is located on the X chromosome, such that females have 2 copies of the ACE2 gene, in comparison with a single copy in men. Whether this ACE2 gene polymorphism is functionally relevant is unknown. Another intriguing association is the fact that, in COVID-19 infections, the death rate of males in comparison to females is much higher (Table 3), despite adjustment for differences in risk factor profiles.³⁶

Previous investigations of ACE2 polymorphism in SARS susceptibility or outcomes did not reveal significant linkages. However, this attribute is still unknown

Table 2. Distribution of ACE2 and TMPRSS2 in Organs and Symptoms of COVID-19

ACE2/TMPRSS2 Distribution	Symptoms/Laboratory Findings
Lymphocytes/dendritic cells	Fever (>99%), fatigue (70%), myalgia, lymphopenia
Lung (type 2 pneumocytes, bronchial epithelium)	Dyspnea (31%), dry cough (60%), respiratory failure
Gastrointestinal smooth muscle	Nausea (30%), diarrhea
Myocardium	Myocarditis, heart failure, arrhythmias
Vasculature (smooth muscle)	Vasculitis, thrombosis, microangiopathy
Neurons	Anosmia, hypogeusia, encephalopathy, seizures, myopathy
Liver	Abnormal liver function
Kidney	Renal dysfunction

Percentage indicates estimated frequency in patients with COVID-19. ACE2 indicates angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; and TMPRSS2, transmembrane protease, serine 2.

in the setting of COVID-19 infection. There appear to be different population outcomes observed to date (eg, higher mortality in Italy versus lower mortality in Germany), but this may be related to many other factors, such as age, health system organization, virus testing, social behavior, etc. Whether this may be related to different distributions of functional ACE2 polymorphism in different populations awaits further studies.³⁷

VIRUS-RECEPTOR INTERACTION AND POTENTIAL CONSEQUENCES

During virus engagement of the ACE2 receptor in the presence of TMPRSS2, the virus can enter the target cell through endocytosis or membrane fusion. The positive strand viral RNA is then transcribed by the host cell ribosome while also being transported to the endoplasmic reticulum to mediate transcriptional activation and production of viral component proteins. These are ultimately assembled into intact viruses and discharged from the cell. This process can disable or destroy the host cell, leading to the release of potential danger signals to activate the host's innate immune responses.

There is also evidence in preclinical models using the SARS-CoV virus of significant downregulation of ACE2 in the heart as a result of virus engagement of the ACE2 receptor during infection.²⁰ This is likely part of the host defense mechanism in response to the

infection to limit continued viral proliferation. However, the potential consequence of this interaction is that the biologically essential role of ACE2 is also significantly diminished. This can lead to unopposed angiotensin II effects, including proinflammatory, prothrombotic, and pro-oxidant risks.

This virus does proliferate, likely at low levels, in the host's heart, possibly involving inflammatory responses, because troponin can be released very early during disease presentation and portends poor prognosis.⁷ This may lead to further release of potential danger signals to the immune system to trigger downstream exaggerated responses. However, no replicable SARS-CoV-2 virus has been recovered in blood; thus, the quantity of replicated virus in the circulation is not high, in contrast with that present in the oral and respiratory systems.¹⁴

There has been much controversy regarding the role of RAS-interfering agents, such as ACE inhibitors or angiotensin receptor blockers, on the levels of ACE2 expression, hence susceptibility to SARS-CoV-2 infection. There have been good review articles on this controversy and will not be repeated here.^{38,39}

Clinical Implications

The initial phase of this virus infection can be marked by evidence of cardiac injury with the release of troponin. This portends a poor prognosis. Whereas the release of troponin is relatively modest, this may be an indication of either viral- or immune-mediated cardiac injury. The release of danger signals from the heart in patients with heightened immune response can further amplify myocardial damage. Patients with continued increases in biomarker release are usually marked by an amplified inflammatory response and worse outcomes. Thus, patients with cardiac injury or stress marker release warrant more careful monitoring and institution of cardioprotective agents to minimize ongoing damage.

Downregulation of ACE2 with viral infection may predispose to relatively unopposed angiotensin II effects, such as hypertension, enhanced inflammation, and thrombosis (Figure 2).³⁴ Although there are no definitive data on the risk versus benefit of ACE inhibitors or angiotensin receptor blockers in COVID-19, most cardiac professional organizations have recommended continuation of RAS inhibitors in patients who have been prescribed them. In fact, there is cautious emerging data to suggest that the benefit may outweigh the risk in patients with COVID-19 and hypertension when prescribed ACE inhibitors or angiotensin receptor blockers. However, ongoing randomized trials will help to provide definitive answers to these questions.

The virus-receptor interaction step also provides many opportunities for potential intervention, and a number of therapeutic trials are currently ongoing. Infusion of recombinant human ACE2 may act as a decoy

Table 3. Mortality in Confirmed Cases, or in All Cases, by Sex Distribution in Patients With COVID-19

Sex	Death Rate, %	
	Confirmed Cases	All Cases
Male	4.7	2.8
Female	2.8	1.7

COVID-19 indicates coronavirus disease 2019.

to interfere with viral replication. Chloroquine or hydroxychloroquine may interfere with cellular endocytosis of the virus, and viral proliferation can be blocked at multiple stages, including inhibition of RNA polymerase with remdesivir, among many others.

VIRUS-RECEPTOR AND THE IMMUNE SYSTEM INTERACTIONS

The SARS-CoV-2 infection can generate a diverse range of responses in patients, ranging from completely asymptomatic virus shedding to a severe inflammatory response including cytokine stormlike outcomes that are accompanied by high mortality. Current epidemiology suggests that 81% of infected individuals have mild symptoms, 14% have severe symptoms requiring hospitalization, whereas 5% become critically ill requiring ventilation. The differences in response are likely the result of degree of viral load, host immune response, age of the patient, and the presence of comorbidities. This is similar to many types of respiratory infections, including the flu.

In terms of cardiac manifestations of infection, the spectrum is also similar to conditions such as viral myocarditis. After infection with common RNA viruses such as coxsackievirus, most exposed patients may experience only a transient viral syndrome with no significant cardiac dysfunction. However, those with an exuberant immune response can manifest acute myocarditis with heart failure or cardiogenic shock, accompanied by hypercytokinemia and inflammatory cell infiltration of the heart.⁴⁰ With support, the patients can recover, but some persist with inflammatory cardiomyopathy.⁴¹

Analysis of the inflammatory response to SARS-CoV-2 is relatively limited. A consistent finding is lymphopenia that occurs in >80% of patients. The degree of lymphopenia is a very important prognostic indicator early in the course of infection. Among the most prominent findings in early analyses of patients succumbing to COVID-19 are marked reductions in circulating levels of CD4+ and CD8+ T lymphocytes, and a relative dominance of mononuclear cells (monocytes and macrophages) in target injury tissues, where the lung was primarily assessed (Figure 1).^{42,43}

In parallel with the SARS infection, in which lymphopenia was also observed to be highly prognostic, reports showed an early reduction in T cells, in particular, a reduction in CD4+ more than CD8+ T cells.⁴⁴ Recovery of lymphocyte count coincided with clinical improvement. Pathology in select patients with SARS revealed the spleen featuring atrophic white pulp with lymphoid depletion (without local viral signatures), whereas the bone marrow appeared to show normal activity.⁴⁵ This suggests that T cells (possibly CD4+) are selectively destroyed, possibly by the immune system, although one

cannot rule out the possibility of direct viral infection of T cells.

The important role of CD4+ T cells was further delineated in a primary infection model with SARS-CoV in senescent mice. CD4+ T cells were found to enable the production of neutralizing antibodies and a balanced immune response. Without CD4+ T cells, there was much more severe interstitial pneumonitis. When both CD4+ and CD8+ T cells were depleted, there was a predominance of neutrophils and innate immune macrophages in the lesions.⁴⁶

Accompanying the loss of CD4+ T cells, there is an unusual macrophage predominance in SARS lung infiltration. This can be accompanied by hemophagocytosis in lung and spleen, compatible with severe immune cytokine dysregulation.⁴⁷ This syndrome results from the ineffective activation of cytotoxic CD8+ T lymphocytes and Natural Killer T lymphocytes, resulting in ineffective viral clearance and weak antibody production. This, in turn, stimulates further macrophage activation and the loop of self-amplification can be uncontrolled, leading to cytokine-storm syndrome and multiorgan failure. Indeed, patients who died of COVID-19 infection show continued virus shedding at the time of death.¹⁶

Other indications that SARS-CoV-2 induces a relatively mild immune response is the fact that there is prolonged virus shedding in many individuals. Virus proliferation is extremely rapid in COVID-19, yet many patients are asymptomatic. This suggests that, although the immune system is mounting a response, it is not adequate to attenuate viral replication potential. In 1 study of serial viral and immunologic monitoring in hospitalized patients, the virus was capable of inducing immunoglobulin M and immunoglobulin G. But viral proliferation is not affected, suggesting lack of neutralizing effect and ineffective early viral clearance.¹⁴

To gain insight into the successful attenuation of the virus without severe disease, we may search for clues in nature. In bats, where the virus may have originated, it is able to reside at low levels chronically without severe disease. The bat immune system has much lower NLRP3 (NOD-like receptor protein 3) inflammasome activation, thus limiting an excessive inflammatory response, with lower levels of interleukin-1 β (IL-1 β). It also has a Natural Killer cell repertoire with dominant inhibitory signaling. Furthermore, bats manifest an enhanced response to infection with 22 interferon- ω genes,⁴⁸ in coordination with a continuously activated interferon regulatory factor 3 leading to interferon regulatory factor 7 upregulation,⁴⁹ providing an adequate amount of type I interferons. This overall general anti-inflammatory milieu, while effectively controlling infections, has been invoked to explain the extraordinary lifespan of bats (30–40 years) for their body size.

Type I interferon production is important for innate defense against SARS-CoV, as demonstrated by

protection in a rhesus macaque infection model,⁵⁰ and in limited clinical studies, as well. Several studies of SARS and related Middle East respiratory syndrome, also the result of a coronavirus infection, have illustrated the importance of type I interferon to potentiate effective antiviral immunity. Murine modeling and clinical evidence suggest that interferon- α production, mainly by plasmacytoid dendritic cells, is necessary for control of viral infection.⁵¹ In Middle East respiratory syndrome studies, type I interferons were found to be rapidly up-regulated,⁵² whereas one study suggested that successful clearance of Middle East respiratory syndrome depended on appropriately rapid induction of high levels of type I interferons.⁵³

Conversely, in the ageing immune system, there is progressive lymphopenia with CD4+ T-cell attrition and decreased regulatory T-cell function, leading to homeostatic lymphocyte proliferation, with propensity for autoimmune and excessive inflammatory responses.⁵⁴ This can be compounded by decreased capacity to phagocytose apoptotic cells by senescent macrophages, leading to a general proinflammatory state. The imbalanced aged immune system is then exacerbated by infection such as COVID-19, which further exacerbates the depletion of CD4+T cells and inflammatory macrophage response. The net consequence of inadequate interferon response and inefficient viral clearance therefore is detrimental to the patient, with development of inappropriate cytokine storm, inadequate sustained immune response, and lack of effective formation of immunologic memory. Consistent with this phenomenon, studies in an aged mouse model showed that mice produced increased levels of immunosuppressive prostaglandin D₂, leading to impairment of dendritic cell recruitment and reduced T-cell function.

Clinical Implications

In patients with COVID-19 infection, in addition to lymphopenia, there appears to be a heightened level of IL-1 β inflammatory response, in particular, in those with a poor prognosis. As the infection progresses, building on IL-1 β elevation, there is also increasing production of interleukin-6 (IL-6), which can presage an impending cytokine storm.

In patients with potential dysfunctional immune responses, there are early warning signals, such as lymphopenia, troponin release, elevated brain natriuretic peptides, rising inflammatory markers such as c-reactive protein, IL-1 β , and IL-6; these patients should be followed closely, monitored for organ failure, with efforts made to restore immune balance. If viral proliferation is still continuing, strategies to attenuate the virus may be critical. The ability to restore immune balance, with approaches such as type I interferon, immunoglobulin,

and recovered serum, may be considered. Utility of anti-inflammatory strategies, whether anti-IL-1 or anti-IL-6 approaches, will be best determined in time through randomized trials. However, intervention will likely need to be instituted early, before the immune amplification process is fully underway.

THE EFFECT OF ADVANCED DISEASE ON THE MICROVASCULAR SYSTEM AND COAGULATION

Vascular smooth muscle has both ACE2 receptor and TMPRSS2 protease to facilitate local viral entry and proliferation. Pathological evaluation of lung tissue and other affected organs has uncovered evidence of microvascular inflammation together with microvascular thrombi. There have also been clinical observations of distal vasculitis with acrosyndrome and dyshidrosis in terminal digits of patients with COVID-19. These cutaneous vasculitis signs have been discussed as early indications of SARS-CoV-2 infection.

Activated macrophages can release cytokines, including IL-1 β and IL-6, which will promote the expression of adhesion molecules for endothelial activation, inflammatory cell infiltration, and vascular inflammation. This may be locally enhanced if there is smooth muscle cell harboring of viral proliferation and cellular damage. Endothelial cells release proinflammatory cytokines that contribute to propagation of microcirculatory lesions.⁵⁵ The dysfunctional endothelium becomes proadhesive and procoagulant.⁵⁶

Localized macrophages can also release procoagulant factors such as plasminogen activators. With the retreat of ACE2 and activation of angiotensin II, the production downstream of plasminogen activator inhibitor-1 is also enhanced. This combination further accelerates vascular inflammation and enhances a prothrombotic state. This is often seen in patients with advanced disease with laboratory evidence of increases in IL-6 together with D-dimer elevation.

The presence of microangiopathy and microthrombi can also predispose the patient to microinfarcts within multiple organs, such as the liver, heart, or kidney, further exacerbating the state of multiorgan injury and failure.

Clinical Implications

The presence of vasculitis and prothrombotic state can lead to increased frequency of pulmonary embolism, which worsens hypoxemia by increasing shunting in these already highly hypoxemic patients with acute respiratory distress syndrome. This, in combination with systemic inflammatory or cytokine storm, can worsen cardiac injury, heart failure, and the prognosis.

Patients with clinical evidence of vasculitis, or laboratory indicators of progressive inflammation, such as rising IL-6 and D-dimer levels, should be considered early for anti-inflammatory measures. Many of these patients should also be considered for full anticoagulation, such as heparin, depending on individual risk versus benefit. Patients can also be enrolled in ongoing clinical trials evaluating different mitigation strategies.

THE EFFECT OF COVID-19 ON THE HEART

Between 8% and 28% of patients with COVID-19 infections show evidence of cardiac injury with elevated troponin.⁷ In a series of patients from Seattle, the first major COVID-19 center in the United States, several patients presented with cardiomyopathy.⁵⁷ Patients with evidence of cardiac involvement had a marked increase in mortality, confirming the major effect of the cardiovascular system in the prognosis of these patients.

Many patients with COVID-19 infections die of cardiac arrest, probably as a result of a combination of primary cardiac involvement, or manifestation of systemic involvement such as severe hypoxia, multiorgan dysfunction syndrome, or systemic inflammatory response syndrome, among others.

In the 2003 SARS outbreak, Oudit from our group demonstrated SARS-CoV viral presence in 7 of 20 hearts of patients with SARS on autopsy.²⁰ Viral proliferation was likely enabled by ACE2 and TMPRSS2 receptor expressions. However, there was also reduced expression of ACE2 following infection, likely contributing to the enhanced inflammation.

We have demonstrated previously that viral infection of the heart, modeled with another RNA virus, coxsackievirus, can activate the intrinsic innate immune system very rapidly.^{58,59} However, the balance of the immune response determined the ultimate outcome.^{60–62} Downstream activation of toll-like receptor signal regulators, such as IRAK4 (interleukin-1 receptor associated kinase 4) leading to TRAF6 (tumor necrosis factor receptor-associated factor 6)–nuclear factor- κ B activation, can modify monocyte migration and accelerate myocarditis.^{63,64} On the other hand, early enhancement of interferon regulatory factor 3–interferon regulatory factor 7–type I interferon production can mediate more viral attenuation while reducing overall inflammation.⁶⁴ This can also be enhanced by augmenting the regulatory T-cell population, while allowing adequate interferon production.⁶⁵ Therefore, the balance of nuclear factor- κ B– versus interferon regulatory factor 3–related signal amplification and that between the innate and acquired immunity are critical to outcome and recovery.⁶⁴

Clinical Implications

The early presence of cardiac injury and stress, as evidenced by biomarkers of elevated troponin and natriuretic peptides, are important to ascertain especially in higher-risk patients, and appropriate expectant treatments to monitor and prevent cardiac and systemic complications are warranted. Enrolling these high-risk patients into therapeutic trials will be the vital next step.

A small proportion of patients may have direct cardiac involvement including cardiomyopathy, myocarditis, or heart failure. Again these features have a major influence on the patient's overall outcome. Because the inflammatory response is self-amplifying, the early recognition and attenuation can have a potentially important effect on outcomes.

In patients with suspected acute myocarditis or inflammatory cardiomyopathy, appropriate investigations, such as magnetic resonance imaging where feasible and safe to perform, can be helpful.^{4,66} In patients with heart failure, appropriate heart failure medications, including RAS inhibitors, should be considered.

Arrhythmias, such as atrial fibrillation, are also more frequent in COVID-19 cardiomyopathy, occurring in up to half of patients admitted to an intensive care unit, because inflammation is a substrate for atrial arrhythmias.⁶⁷ Ventricular arrhythmias are also observed and may accompany cardiac arrest in these patients. QT prolongation will need to be monitored, because this may occur as a combination of myocarditis and also concomitant side effects from medications such as chloroquine and hydroxychloroquine. Appropriate use of anticoagulants evaluating risk versus benefit will be important.

POTENTIAL THERAPEUTIC OPPORTUNITIES

Because COVID-19 is a new disease, there are currently no proven treatments. There are good evidence-based websites collating up-to-date information: <https://covdb.stanford.edu/search/?study=clinical-studies&virus=SARS-CoV-2>. The medical community, biotechnology, and pharmaceutical partners have already come together and proposed >500 ongoing clinical trials to date, such as [<https://www.transparimed.org/single-post/2020/03/27/COVID-19-clinical-trials-information-sources>] or <https://clinicaltrials.gov>.

The most important public health solution is an effective vaccine for the broad population remaining at risk. The spike glycoprotein S of SARS-CoV-2 is an ideal antigenic target for vaccine development, and there are multiple candidates now beginning to enter clinical trials.

A very partial list of potential targeted processes and examples of candidate agents now entering clinical trials is provided in Table 4.

POTENTIAL LONG-TERM CONSEQUENCES AND REMAINING QUESTIONS

While the pandemic is evolving its course, there will be a growing population of recovered patients. The majority will do well. However, many unanswered questions remain. Will exposed patients have adequate long-term immunity? Does the immunoglobulin G produced have adequate neutralization capacity?

Those with complications may have a more challenging course of recovery and long-term sequelae. The immune activation and dysfunction can lead to target tissue fibrosis and microangiopathy, as was observed in some patients after SARS. This can affect long-term lung function, or if the heart is involved, residual cardiomyopathy. There was also increased cardiometabolic risk reported in patients who recovered from SARS, possibly related to steroid treatment and ongoing RAS imbalance.⁶⁸

From an epidemiological point of view, an important question is how many people in the population

ultimately acquire immunity to SARS-CoV-2 as antibody testing becomes more available. Will there be an effective vaccine for the remaining unexposed population? Will there be continued mutation of the virus? Does the virus have a natural reservoir? Are there enough asymptomatic carriers that can restart another infectious cycle?

GLOBAL COLLABORATION TO ADVANCE SCIENCE AND MEDICINE ON COVID-19

These are unprecedented times in health and medicine worldwide. However, the pandemic has also brought together the medical community to share information and seek rapid solutions for so many patients. It has also underscored the critical importance of science and data-driven decision making in times of uncertainty.

Much more will be learned about COVID-19 in the ensuing months and years. We are only at the beginning of this journey together.

ARTICLE INFORMATION

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Table 4. Potential Processes in COVID-19 Infection Amenable to Therapeutic Targeting, With Examples of Candidate Agents

Potential Targeted Process	Candidate Agent
Antiviral/anti-inflammatory general	Convalescent serum (patients with COVID-19), type I interferon, immunoglobulins, mesenchymal stem cells
ACE2 entry	Soluble recombinant ACE2
TMPRSS2 protease S priming	Protease inhibitor (camostat mesylate)
Receptor endocytosis	Chloroquine or hydroxychloroquine
RNA polymerase for replication	Remdesivir, favipiravir
Viral proteases	Lopinavir/vitonavir
Importin nuclear transport	Ivermectin
Interleukin-1 excess activation	Anakinra, canakinumab, colchicine
Angiotensin II excess	ACE inhibitors/angiotensin receptor blocker, recombinant ACE2
Cytokine storm	Tocilizumab, sarilumab, or siltuximab (interleukin-6 inhibitors) or baricitinib (JAK inhibitor), lenzilumab (granulocyte-macrophage colony-stimulating factor inhibitor)
Oxidative stress	Deferoxamine, vitamin C
Fibrosis	Nintedanib
Bacterial infection/inflammation	Azithromycin
Coagulopathy	Normal or high-dose anticoagulation regimen
Severe acute respiratory syndrome coronavirus 2	Multiple vaccine candidates, including Bacille Calmette-Guérin

ACE2 indicates angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; and TMPRSS2, transmembrane protease, serine 2.

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