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COVID-19 for the Cardiologist: A Current Review of the Virology, Clinical Epidemiology, Cardiac and Other Clinical Manifestations and Potential Therapeutic Strategies

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Highlights
- Severe acute respiratory virus-2 (SARS-CoV2), the infection responsible for coronavirus disease-2019 (COVID-19), has spread globally leading to a devastating loss of life. In a few short months, the clinical and scientific communities have rallied to rapidly evolve our understanding of the mechanism(s) of disease and potential therapeutics.
- This review discusses the current understanding of the basis virology of SARS-CoV2 and the epidemiology, clinical manifestations, including cardiovascular, and mortality of COVID-19. A detailed review of the viral life cycle and putative mechanism(s) of injury frames the discussion of possible preventative and therapeutic strategies.
- The ongoing, unprecedented collective effort will, without a doubt, advance our ability to prevent the spread and optimally care for patients suffering from COVID-19.

Summary

The coronavirus disease-2019 (COVID-19), a contagious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), has reached pandemic status. As it spreads across the world, it has overwhelmed healthcare systems, strangled the global economy and led to a devastating loss of life. Widespread efforts from regulators, clinicians and scientists are driving a rapid expansion of knowledge of the SARS-CoV2 virus and the COVID-19 disease. We review the most current data with a focus on our basic understanding of the mechanism(s) of disease and translation to the clinical syndrome and potential therapeutics. We discuss the basic virology, epidemiology, clinical manifestation, multi-organ consequences, and outcomes. With a focus on cardiovascular complications, we propose several mechanisms of injury. The virology and potential mechanism of injury form the basis for a discussion of potential disease-modifying therapies.

Key words: COVID-19, SARS-CoV2, Cardiovascular, Virology, Treatments

Abbreviations
ACE2 – angiotensin-converting enzyme 2
ARDS – acute respiratory distress syndrome
CDC – Centers for Disease Control
CFR – case fatality rate
COVID-19 – coronavirus disease-2019
CoV – coronavirus
DIC – disseminated intravascular coagulation
ER - endoplasmic reticulum
hsCRP – high sensitivity c-reactive protein
ICU – intensive care unit
SARS-CoV1 or 2– severe acute respiratory syndrome coronavirus-1 or -2
SOFA – sequential organ failure assessment
TMPSS2 – trasmembrane serine protease-2

Introduction

The coronavirus disease-2019 (COVID-19), a contagious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), has reached pandemic status. As it spreads across the world, it has overwhelmed healthcare systems, strangled the global economy and led to a devastating loss of life. In the ongoing wake of COVID-19, the world's medical and scientific communities have come together to rapidly expand our knowledge of the pathogenesis, disease manifestations and possible preventive and therapeutic strategies. Virologists have looked to related diseases to understand the life cycle of this novel viral infection. Despite being overwhelmed, through conventional and historically unconventional mechanisms, clinicians managing patients with COVID-19 have made a concerted effort to rapidly educate colleagues in expectant regions of the world on lessons learned. The world's regulatory agencies and pharmaceutical industry are using emergency mechanisms to expedite access to and study of therapeutic options. These widespread efforts, drawn from many arenas, are driving a rapid expansion of collective experience and understanding of COVID-19.

Here, we review this body of work with a focus on our basic understanding of the mechanism(s) of disease and translation to the clinical syndrome and potential therapeutic options. Specifically, we discuss the basic virology, epidemiology and clinical manifestations, including presentation, progression, multi-organ consequences and outcomes. With a focus on the cardiovascular complications, we propose several potential mechanisms of injury. We discuss a range of possible therapeutic options in the context of the viral life cycle and possible mechanisms of injury. Finally, in recognition of the scale of this crisis, we address the ethical considerations around standards of care in the event of resource scarcity.

Basic Virology of SARS-CoV2

Genetics and Structure

Coronaviridae comprise a family of enveloped, single stranded, positive sense, RNA viruses with comparable genomic organization and functional mechanisms. Coronaviruses (CoV) are canonically divided into alpha- and beta-, gamma- and delta- genera predicated on genetic clustering. The alpha- and beta-CoV are known to cause human diseases, such as common respiratory infections. The SARS-CoV2 and SARS-CoV1 are beta-CoV (1-3). CoV are so-named because of the characteristic crown, or *corona*, of electron density that they exhibit on transmission electron micrographs. This appearance is thought to be caused by the densely packed protein that studs the viral membrane and is responsible for receptor binding on target-cell membranes.

The CoV genome is organized into two parts. Highly conserved with the CoV family, the 5' terminal end, encodes the *replicase* - the nonstructural proteins responsible for viral replication within the cell (1-3). It is translated as one peptide (~790 kDa) from which the constituent functional proteins are subsequently cleaved. CoV genomes encode 16 nonstructural proteins, as in SARS-CoV2, and they exhibit a multitude of functions required for viral replication (2,4,5). Critical proteins for viral replication include the main protease (nsp5), the papain-like protease (nsp3) and the RNA-dependent RNA polymerase (nsp12, RdRp). The other replicase constituent proteins repurpose the cellular machinery to facilitate viral replication and to blunt the intrinsic host immune functions (1,6).

The remaining third of the CoV genome encodes the structural proteins and a variety of accessory proteins (latter not discussed here). The structural proteins are the constituent proteins of the transmissible viral particle, or virion. The key structural CoV proteins are the nucleocapsid protein (N) and three transmembrane proteins: the spike protein (S), the membrane protein (M), and the envelope protein (E) (1-5)(Figure 1). The S protein is responsible for virus-cell receptor interactions (7-11)(Figure 1). The E and M proteins are responsible for membrane structure and fusion. The N protein binds viral RNA and mediates its interaction with the S, E, and M proteins for genome encapsulation (1,12).

Life Cycle

The life cycle of SARS-CoV2 has not been rigorously established; however, given the considerable sequence homology, it is presumed to be similar to that of SARS-CoV1 and other CoV (4,5). In general, the CoV life cycle consists of a series of steps that begins with viral binding to a target cell and culminates in viral reproduction. Knowledge of this process informs an understanding of viral physiology and also will serve as the basis for discussion of antiviral therapeutics (8)(Figure 1). The aim of evolving therapeutics will be to break the "links in the chain" of the viral life cycle in order to forestall the propagation of infection within the cells of an individual patient.

SARS-CoV2 is known to bind to cells via the same receptor as SARS-CoV1, the membrane-bound glycoprotein Angiotensin Converting Enzyme 2 (ACE2) (4). It has not been observed to bind other CoV receptors, namely dipeptidyl peptidase 4 (DPP4) or aminopeptidase N (APN) (4,13). After binding of ACE2, the virus is internalized via endocytosis without access to the

host intracellular compartment until a membrane fusion event occurs (4)(Figure 1). This process is mediated, at least in part, by another membrane bound protease known as transmembrane serine protease 2 (TMPRSS2), which cleaves the S protein as a necessary step of membrane fusion (7). Interestingly, the protease activity of the CoV receptors, ACE2, DPP4 and APN, does not seem necessary for membrane fusion (14).

Upon membrane fusion, the viral RNA genome enters the intracellular compartment. At this point, the viral RNA may be translated into its encoded structural and nonstructural proteins. The translation of the nonstructural proteins, or replicase, results in the production of a single massive polypeptide chain, from which the sixteen constituent nonstructural proteins are cleaved. This process is initially mediated by intracellular proteases, and then further propagated by the function of the CoV main protease and papain-like protease (1). Another replicase protein, the RNA-dependent RNA polymerase (RdRp) is responsible for the replication and amplification of the viral genome (15). During this process, mutations may be acquired by errors in replication and recombination events (1).

Upon amplification of the viral RNA, more viral structural and nonstructural proteins may be generated. Viral structural proteins, because of their transmembrane nature (with the exception of the N protein), are targeted to the ER membrane with appropriate signal sequences. Viral RNA, bound by N protein, interacts with the structural proteins on the membrane of the ER and Golgi apparatus before another membrane fusion event on these membranes results in viral budding and exocytosis (1,8,12).

Importantly, the precise molecular differences that account for the important clinical differences between SARS-CoV2 and SARS-CoV1 infections, such as prolonged latency, widely variable symptoms, a possible predisposition for individuals with pre-existing cardiovascular conditions, and a predilection for myocardial complications, remain unclear.

Pathogenesis: Angiotensin-Converting Enzyme 2

SARS-CoV2, SARS-CoV, and HCoV-NL63, a virus that causes a mild respiratory infection, are all known to employ ACE2 as a receptor (3,4,16,17). Given the functions of ACE2 in the cardiovascular system, the importance of angiotensin-directed pharmacology in cardiovascular disease and the apparent propensity for severe illness among patients with COVID-19 with cardiovascular comorbidity, the ACE2 molecule has been the subject of much attention (18). Indeed, major clinical societies have issued consensus statements on the use of ACE inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) in the setting of the COVID-19 pandemic, as discussed later (19).

Angiotensin-Converting enzyme 2 (ACE2) is a single-pass transmembrane protein with protease activity that cleaves the vasoconstrictor angiotensin II into the vasodilator angiotensin 1-7 (20-23). In doing so, it functions as a counter-regulatory enzyme to the functions of ACE1, which generates angiotensin II (20). In humans, the protein has a broad pattern of expression and has been found in the lung epithelium (in particular the type II pneumocyte), the myocardium, the endothelium, the GI tract, bone marrow, kidneys and spleen among other tissues; potentially explaining the multi-organ injury observed with SARS-CoV2 infection (24). Another relevant

feature of *Ace2* gene expression is its encoding on the X chromosome, which may account for possible sex differences observed in the epidemiology of COVID-19 (25).

In animal models of acute respiratory distress syndrome (ARDS), due to chemical pneumonitis, overwhelming sepsis, endotoxemia, or influenza, *Ace2*^{KO} mice have more severe acute lung injury (ALI) relative to their wild-type counterparts as evaluated histologically and by measures of elastance (26-28). The phenotype of increased elastance was rescued by administration of recombinant human ACE2, which affirms a causal link between *Ace2* deficiency and a more profound state of ALI (26,28). Additionally, the administration of losartan, an angiotensin II type-1 receptor (AT$_1$R) blocker mitigated the exacerbating effects of SARS-CoV spike protein in an animal model of ARDS (29). Losartan also abrogated the severity of ALI due to influenza in mice (27,28).

In regard to the counter-regulatory properties of ACE1 and ACE2, the effects of *Ace2*-deficiency appear to be rescued by *Ace1*-deficiency in mice. For example, the effects of *Ace2*-deficiency to result in more severe ALI are abrogated by *Ace1*-deficiency. *Ace2*^{KO} mice demonstrated more severe ALI than *Ace2*^{KO}*;Ace1*$^{+/-}$, with further reduction in severity observed in *Ace2*^{KO}*;Ace1*$^{-/-}$ (26). This dose-responsiveness also implies causation. Comparable effects were seen with myocardial dysfunction, as *Ace2*^{KO}*;Ace1*$^{+/-}$ *and* *Ace2*^{KO}*;Ace1*$^{-/-}$ had no evidence of the contractile deficit observed in *Ace2*^{KO} mice (30). Of note, in each of the above cases, however, the animal models were constitutive knockout systems (rather than lineage-specific or inducible knockout). Thus, the ACE2-expressing cell that mediates each phenotypic abnormality has not been determined.

SARS-CoV2 is able to utilize ACE2 isoforms from swine, bats, civets and humans suggesting a mechanism whereby the virus may have been initially transmissible from species to species and, with mutation, evolved into a novel pathogen (4). Notably, murine ACE2 is not a functional receptor for SARS-CoV2; thereby requiring transgenic expression of human *ACE2* if mice are to be used as a research model (4).

ACE2 undergoes cleavage by the membrane-bound protease ADAM17; resulting in the release of soluble ACE2 into the blood stream (31). The effects of soluble ACE2 are unclear in humans, however it appears to have favorable effects on lung function in models of ARDS, influenza, and RSV infection (26,28,32). Soluble ACE2 has been studied in a phase II trial of ARDS, but large-scale, well-powered clinical outcomes trials are needed (33). Research is ongoing to determine whether soluble ACE2 may act as a specific therapeutic to SARS-CoV2 in the role of a decoy receptor, as discussed later (34).

Finally, given the necessity of ACE2 for viral infection, the role of ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) in COVID-19 has drawn intense attention. Importantly, the ACE2 enzyme itself is not inhibited by ACEi/ARB use (21). ACEi or ARB exposure may result in ACE2 protein upregulation in animal models; however not all animal models exhibit this effect. The existing epidemiology of COVID-19 among patients taking ACEi or ARB is confounded by cardiovascular comorbidities which may alter ACE2 and angiotensin II expression (18). At this time, it is unclear if ACEi or ARBs use influences receptor expression and whether variable expression impacts the propensity for or severity of SARS-CoV2 infection.

Transmission

Exposure to the Huanan seafood market was common among the earliest cases contributing to the SARS-CoV2 epidemic in China suggesting that this was a zoonotic disease with an intermediate animal host (non-aquatic animals were sold in the market) (35). Genomic analyses have identified approximately 87% DNA sequence homology between SARS-CoV2 and two SARS-like CoV isolated from Chinese horseshoe bats, bat-SL-CoVZC45 and bat-SL-CoVZXC21, in the Zhejiang province in China (36). Notably, no bats are sold in the market and at the onset of the outbreak in December most bat species in Wuhan would be hibernating. Thus, similar to SARS-CoV1 and MERS-CoV, while bats may be the natural reservoir for SARS-CoV2, there is likely an unidentified intermediate animal host responsible for animal-to-human transmission. Despite closure of the Huanan market on January 1, 2020, the epidemic continued to expand and case clusters with no exposure to the market were reported indicating the occurrence of human-to-human transmission (37).

Akin to other respiratory viruses, SARS-CoV2 spreads primarily through small respiratory droplets that are expelled from infected individuals and can travel approximately 3-6 feet. The virus can exist in nature on surfaces and can last for up to 4 hours on copper, 24 hours on cardboard and up to 72 hours on plastic and stainless steel surfaces leading to fomite transmission (38). In fact, the Japanese National Institute of Infectious Disease reported detection of SARS-CoV2 RNA on surfaces in the cabins of symptomatic and asymptomatic passengers on the Diamond Princess up to 17 days after they were vacated (39). Live virus has also been isolated and cultured from fecal specimens raising the possibility of oro-fecal transmission,

though corroborating clinical evidence for this method of transmission is lacking (40). Airborne transmission may be facilitated in healthcare settings where aerosol-producing interventions are being performed including endotracheal intubation, bronchoscopy, suctioning, nebulizer treatment, non-invasive positive pressure ventilation and delivery of oxygen via a high-flow nasal cannula. These transmission data support the clinical recommendations that airborne precautions, including use of N-95 masks, should be implemented in these aerosol-producing settings whereas standard droplet precautions should be used during all other encounters with infected individuals (41).

In a fully susceptible population, reflected by early stages of the epidemic in China, studies have estimated a basic reproductive number (R_o) of 2.38 for SARS-CoV2, meaning that every infected individual is likely on average to spread the virus to 2 to 3 other individuals (42). An outbreak will continue to increase in size if the $R_o>1$. For context, seasonal influenza has an R_o of 1.5 (43). Substantial transmission from asymptomatic hosts has facilitated the widespread transmission of SARS-CoV2 and contributed to its pandemic potential (42). A study from Singapore with extensive contact tracing identified 7 clusters of cases where secondary spread of the infection occurred 1-3 days prior to symptom development in the source patient (44). Thus, containment measures aimed solely at isolating symptomatic individuals are inadequate. Furthermore, contact tracing efforts should take in to account the pre-symptomatic contagious period to comprehensively capture all potentially exposed individuals. R_o is not a static measure and interventions including self-quarantine, contact isolation, social distancing and enhanced hygiene measures have proven to be effective in China. Following implementation of such measures in

China, the R_o steadily decreased from 2.38 prior to January 23rd to 0.99 during the period of January 24-February 8, 2020 (42).

Epidemiology and Clinical Manifestations of SARS-CoV2

Epidemiology

The burden of the SARS-CoV2 virus has evolved rapidly since it first appeared in Wuhan, China in December 2019. What began as a few case reports of atypical pneumonia now spans the globe as a pandemic. At present, most published data come from China and form the basis for our understanding of the epidemiology of COVID-19. In the largest published registry to date, the Chinese Centers for Disease Control and Prevention (CDC) reported high-level details for patient characteristics, severity of manifestations and survival in 72,314 cases of putative (47%) and confirmed (63%) COVID-19 (45). In this population, predominantly identified by the presence of symptoms (~99%), <2% of cases occurred in children < 19 years of age suggesting that children either are either resistant to infection or rarely symptomatic. Of confirmed cases, most (87%) were mild, defined by no or mild pneumonia, 14% were severe with significant infiltrates or signs of respiratory compromise and 5% were critical with respiratory failure (e.g. mechanical ventilation), shock or multiorgan system failure.

The first confirmed case of COVID-19 in the US was identified on January 20, 2020 and the US has now surpassed all other countries in the absolute number of cases. However, given the rapid and recent onset of the burden, there are few published data reflecting the experience with COVID-19 in the US. In an early snap shot from the US CDC in 4,226 confirmed cases with symptoms or exposure, only 5% occurred in those under the age of 20 (46).

While data are rapidly accumulating, much of the epidemiology of this virus remains unknown. Most publications are small, single center studies, and detail the clinical characteristics, complications and outcomes in the subset of patients who were hospitalized. As a result of the limitations on testing and the data suggesting that many infected individuals may be asymptomatic, the true burden of infected individuals is unclear and underestimated (42,47). Not only does the variable manifestation of symptoms hamper public health initiatives to trace and isolate infected individuals, but also it limits our ability to accurately estimate infectivity, symptom burden, and non-fatal and fatal complication rates in the overall population of infected individuals. With that caveat, the published data provide insights into the more vulnerable, at-risk populations who require hospitalization. While the individual studies are small, the predictors of more severe manifestations and poor outcomes have been generally consistent as detailed below.

Clinical Presentation / Syndrome

In a multi-center case series of 1,099 hospitalized patients from China, the most common symptoms were fever in up to 90%, followed by cough, fatigue, sputum production, and shortness of breath (48). Less common symptoms included headache, myalgias, sore throat, nausea, vomiting, and diarrhea. The American Association of Otolaryngology has recently highlighted anosmia and dysgeusia as possible symptoms of disease as well (49). The median incubation period, or time from probable exposure to first symptom, was 4 days (IQR 2-7) (48). Another report detailed that 99% of infected patients develop symptoms within 14 days (50). Common lab derangements on admission included lymphopenia, elevations in c-reactive protein,

lactate dehydrogenase, liver transaminases and d-dimer (48). Notably, procalcitonin was rarely elevated (48). These data are generally consistent across multiple smaller studies, several of which noted elevations in other inflammatory markers, such as IL-6, ferritin and ESR (51-55). Evidence of cardiac or kidney injury at admission was variable across studies, but tended to be absent upon hospitalization (48,51-53,56). Chest computed tomography at the time of admission was abnormal in 87% of patients with ground glass opacities or local or patchy "shadowing" (48).

Disease Progression

Many of the more severe manifestations, such as ARDS, acute kidney injury (AKI) and myocardial injury, tend to occur as many as 8-14 days after the onset of symptoms and portend worse outcomes (53). Within a hospitalized population, rates of ICU admission range between 26-32% across most studies (35,48,51-53,57). Several studies have identified older age and baseline burden of comorbidity, such as diabetes, hypertension, prior coronary disease and prior lung disease, as predictors of more significant disease progression with higher rates of ARDS, AKI, cardiac injury, ICU admission and death (51-53,58,59). Increases in markers of inflammation, coagulation, and cardiac injury also correlate with disease severity and rise throughout the course of the disease (53,54,56). In hospitalized populations, the timing of death occurred at a median of 16-19 days after illness onset (53,58). The median time from symptom onset to discharge in survivors was around 3 weeks (53).

<u>*Non-Cardiovascular Clinical Manifestations*</u>

Respiratory Failure

The most prominent complication of COVID-19 is respiratory failure. As previously described, the majority of patients have no or mild symptoms (45). In hospitalized patients, respiratory symptoms are common and range in severity from cough (60-80%) or dyspnea (19-40%) to ARDS (17-42%) (51-53,56,57). ARDS rates were only 3.2% in the largest case series, but this may be an underestimate due to a short average follow up time of 12 days, with the vast majority of patients remaining hospitalized at the end of study (48). ARDS tends to occur ~1-2 weeks into illness and is often precipitous and protracted (51,53,57). For these reasons, and to avoid risk of provider infection with emergent intubation, professional societies recommend early intubation in the event of respiratory decline (41). Intubation was required in 10-33% in the various Chinese series; however, rates of high-flow nasal cannula and non-invasive mechanical ventilation also were high (35,51-53). These therapies are believed to result in aerosolization and are generally not recommended – consequently, more patients will be intubated when unable to be supported by nasal cannula or a non-rebreather mask (41). Older age, baseline hypertension, diabetes, high fever, lymphopenia, injury to other organs (e.g. AKI, ALI), and elevated d-dimer and inflammatory markers were predictors of ARDS; advanced age, neutropenia, elevated d-dimer and inflammation are associated with higher mortality in those with ARDS (51). Development of ARDS, along with acute cardiac injury, was an independent predictor of death (56). Importantly, hypoxemic respiratory failure is the leading cause of death in COVID-19, contributing to 60% of deaths (58).

Renal injury

Estimates vary as to the incidence of acute kidney injury in COVID-19, ranging between 0.5-15% (35,48,52,53,56,59). Among hospitalized patients the rates of proteinuria (43.9%) and

hematuria (26.7%) appear to be even higher (59). Acute kidney injury occurs in the first few days after admission in patients with baseline chronic kidney disease, and after 7-10 days in patients with normal baseline renal function (59). Mechanisms of renal injury have been hypothesized to include both acute tubular necrosis (ATN), direct cytotoxic effects of the virus itself, and immune-mediated damage (59).

Liver injury

Transaminitis is common with an incidence of 21-37%, and as high as 48-62% of patients who are critically ill or who do not survive (35,48,53). Acute liver injury, defined as either alanine aminotransferase or aspartate aminotransferase greater than three times the upper limit of normal, occurs less frequently, and was reported to occur in 19.1% (n=4) of 21 patients who were admitted to an ICU in Washington State (55).

Cardiovascular Manifestations

Cardiac injury

Numerous studies have reported acute cardiac injury as an important manifestation of COVID-19. In studies published to date, acute cardiac injury was variably defined as either cardiac troponin elevation >99th percentile alone or a composite of troponin elevation, ECG or echocardiographic abnormalities (52-56,58). Importantly, many aspects of this endpoint remain undefined including the frequency and severity of associated structural abnormalities. The reported rate of cardiac injury varies between studies, from 7% to 28% of hospitalized patients, a number which is likely partially dependent upon the definition used and the severity of cases at the hospital from which the data was drawn (52-54,56). Notably, patients with evidence of

cardiac injury tend to be older with more comorbidities, including baseline hypertension, diabetes, coronary heart disease, and heart failure (54,56). Across all studies, cardiac injury is associated with worse outcomes, including ICU admission and death (52-54,56). Based on serial assessment of troponin, researchers in China reported that the median time to the development of acute cardiac injury was 15 days (IQR 10 -17) after illness onset, occurring after the development of ARDS (53). Of note, early cardiac injury has been reported, even in the absence of respiratory symptoms (60). In a case series by Shi et al, the mortality rate for those hospitalized with subsequent evidence of cardiac injury was significantly higher than those without cardiac injury (51.2% vs 4.5%, p<0.001) and, along with ARDS, was an independent predictor of death (56). The magnitude of troponin elevation correlates modestly with the degree of hsCRP elevation (54). Dynamic increases in troponin were associated with a higher mortality rate (54,61). Importantly, the mechanism of cardiac injury may be multifactorial, including demand-ischemia, toxicity from direct viral injury, stress, inflammation, microvascular dysfunction or plaque rupture, as discussed later (Central Illustration).

Arrhythmia

Arrhythmias have been noted in several published reports. In a case series of 138 hospitalized patients with COVID-19, 16.7% (n=23) developed an unspecified arrhythmia during their hospitalization (52); higher rates were noted among patients admitted to the ICU (44.4%, n=16). A case series of 187 hospitalized patients provided insight into specific arrhythmias, reporting sustained ventricular tachycardia or ventricular fibrillation amongst 5.9% (n=11) of the patients (54). These findings are consistent with arrhythmias documented in influenza, which has been known to cause both AV node dysfunction and ventricular arrhythmias (62).

Heart failure, cardiogenic shock and myocarditis

Heart failure and myocardial dysfunction have been described in COVID-19 (53,55,58,60,63). In a case series of 191 patients, heart failure was noted as a complication of COVID-19 in 23% (n=44) of all patients and among 52% (n=28) of non-survivors, though the definition of heart failure was not clearly detailed (53). A smaller series of 21 elderly, critically-ill patients in Washington State reported incident systolic dysfunction and cardiogenic shock in 7 patients (33%).(55) Outside of this series, the incidence of cardiogenic shock has not been reported. Two case reports have documented cardiogenic shock in the setting of an elevated troponin, ST elevations, a reduction in left ventricular systolic function and no obstructive coronary disease in patients with COVID-19.(60,63) One report confirmed fulminant myocarditis by cardiac MRI.(60) Neither patient underwent endomyocardial biopsy. Both were treated with inotropes and steroids with recovery of LV function. The potential etiologies of the clinical myocarditis are discussed in detail below (Central Illustration). In one case series from China, myocardial damage or heart failure contributed to 40% of deaths overall with 7% attributed to solely to circulatory failure without respiratory failure.(58)

Thrombosis

One of the prominent findings replicated across most early studies of COVID-19 includes disarray of the coagulation and fibrinolytic system. Hospitalized patients with moderate and severe COVID-19 and those with poorer outcomes are noted to have prolonged prothrombin time (PT), elevated D-dimer, and activated partial thromboplastin time (APTT).(35,53,54,64) In the context of a clinical picture that is consistent with disseminated intravascular thrombosis, it is

reasonable to speculate that COVID-19 would be associated with venous or arterial thrombi, however the incidence has not been published. A pathology report from SARS-CoV1 demonstrated fibrin thrombi in 17 of 20 patients examined with 12 of them showing pulmonary infarcts (65). One preliminary case report, which has not been peer-reviewed, from a COVID-19 patient described autopsy findings of microthrombi in the pulmonary vasculature (66). While empiric anticoagulation is being used in some centers (Personal communication Lorenzo Grazioli, Papa Giovanni XXIII hospital in Bergamo, Italy), the absence of published data documenting thrombotic events in COVID-19, routine use of anticoagulation is not recommended without evidence a thrombotic indication (67).

Mortality

COVID-19 has a lower estimated case fatality rate (CFR) than its predecessors, SARS-CoV1 and MERS-CoV which were 9.4% and 34.4%, respectively (68). However, given the high global burden of infection seen in COVID-19 compared to SARS and MERS, the absolute number of fatalities is staggeringly high, crossing 70,000 fatalities at the time of this review (69). CFR estimates have been challenging with SARS-CoV2, as populations have not been widely screened for infection – leading to an underestimate of the denominator and probable overestimate of the CFR. Crude, unadjusted estimates for the global CFR are ~5% at the time writing with notable variation by country: Italy 11.9% (13,155 deaths), Spain 9.0% (9,387 deaths), South Korea 1.7% (169 deaths), China 4.1% (3312 deaths), Iran 6.4% (3036 deaths), Germany 1.2% (931 deaths) and the United States 2.3% (5,137 deaths) (69). Regional and national differences in CFR may be a result of multiple factors, including a) variable testing of the general and asymptomatic/mildly symptomatic population, b) differing age across countries,

c) variable health care system resources and preparedness as well as d) widely different public health measures for virus control. Importantly, as healthcare capacity is exceeded, a large number of deaths may occur because of limited availability of critical care resources, such as mechanical ventilation. When adjusted for underlying demography and under-ascertainment of cases, the CFR rate was estimated to be 1.4% in China.(70)

The general pattern of fatalities across the age groups appears to be consistent throughout the world. In general, greater age is associated with greater risk of severe disease as well as death. According to the Chinese CDC report of over 70,000 cases, the age-related CFR was as follows: <1% in age <50 years, 1.3% in age 50-59 years, 3.6% in age 60-69 years, 8% in age 70-79 years, and 14.8% in age 80 years and greater (45). This steep increase in age-related mortality was also observed in Italy, the US and South Korea (46,71,72). In fact, age, along with markers of disease severity (d-dimer and sequential organ failure assessment [SOFA] score) were the only independent predictors of mortality in one study (53).

Multiple associations have been reported between baseline characteristics and comorbid conditions with mortality in COVID-19. In univariate analyses of predictors of death, Zhou and colleagues reported that age, coronary heart disease, diabetes, hypertension, respiratory rate, SOFA score, elevated WBC, lymphocyte count, creatinine, lactate dehydrogenase, high sensitivity troponin I, D-dimer, and elevated inflammatory markers such as ferritin, IL-6 and procalcitonin were associated with death (53). However, in multivariable modeling only age (OR 1·10 [95% CI 1·03–1·17] per year increase), SOFA score (OR 5.7 [95% CI 2.6-12.2]) and elevated D-dimer (18.4 [95% CI 2.6 - 128.6]) remained independent predictors of mortality as

described above (53). In another multivariate analysis of 416 patients from Wuhan, after controlling for age, baseline cardiovascular, pulmonary, and renal disease, only presence of cardiac injury and development of ARDS were significantly associated with mortality (4.3 [95% CI, 1.9-9.5] and 7.9 [95% CI, 3.7-16.7], respectively).(56)   It should be noted, however, that both of these complications tend to occur in older individuals.(56,73)

Putative Mechanisms of Cardiovascular Manifestations in SARS-CoV2

As mentioned in prior sections, COVID-19 patients present with highly variable acuities of disease and disease progression. Cardiac injury is a common feature of the disease process, and 40% of patients die with myocardial injury as a proximate finding (58). While multiple therapies are currently under development and in trials for treatment of COVID-19, as discussed in a later section, understanding the mechanism(s) of cardiac disease will be vital to effective and timely targeted treatment of this syndrome and its devastating sequelae. Here we propose several putative mechanisms of COVID-19-induced cardiovascular disease (Central Illustration).

Direct viral myocardial injury

The presence of ACE2 receptors on the myocardium and vascular endothelial cells provides a theoretical mechanism for direct viral infection of the heart with resultant myocarditis. Reports have documented clear cases of myocarditis syndromes (60,63). However, to date there no reports of biopsy proven SARS-CoV2 viral myocarditis with viral inclusions or viral DNA detected in myocardial tissue. The closely related SARS-CoV1 has been documented to cause a viral myocarditis with detection of viral RNA in autopsied hearts (74,75). In light of the shared

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host cell entry receptor between SARS-CoV2 and CoV1, a direct viral myocardial entry and resulting injury is plausible with SARS-CoV2 as well (76).

Another hypothesized mechanism of direct viral injury to the myocardium is through an infection-mediated vasculitis. The ACE2 receptor is highly expressed in arterial and venous endothelial cells (24). There are pathologic data from SARS-CoV1 showing evidence of vasculitis with monocyte and lymphocyte infiltration, vascular endothelial cell injury and stromal edema in the heart (77). Either direct viral entry into myocardial endothelial cells could trigger a vasculitis or presence of virus could lead to an indirect immunological response and resulting hypersensitivity reaction (78,79). This insult would be associated with myocardial injury and perhaps even overt myocardial dysfunction in COVID-19.

Microvascular injury

Micro- and macro-thromboses were observed in autopsy evaluations of 3 patients who died from SARS-CoV1 (80). A prominent finding of SARS-CoV2 is disarray of the coagulation and fibrinolytic system, with >70% of non-survivors meeting criteria for DIC (81). It may be hypothesized that myocardial injury is a result of microthrombus formation in the myocardial vasculature in the setting of a hypercoagulable state like DIC.

Infections and sepsis are a leading cause of DIC in general (82). The exact mechanism of DIC in the setting of sepsis and ARDS is complex, but is generally thought to be related to an immune-mediated exhaustion of the coagulation and fibrinolytic systems promoting bleeding and thrombosis in the same patient (83). Endothelial injury and inflammatory cytokines, such as IL-

6 and TNF-alpha, upregulate tissue factor expression, driving a pro-thombotic state (84-87). Dysregulation of antithrombin III, plasminogen activator inhibitor type 1 (PAI-1) and protein C in the setting of significant inflammation and sepsis promote an anti-coagulated state (88-90). Furthermore, platelet activation also ensues in the context of sepsis and inflammation, further tipping the fine balance of the coagulation system (91-94). In summary, the hyperinflammation and immune activation seen in severe COVID-19 infection is likely sufficient to trigger DIC, microvascular dysfunction and myocardial injury.

Stress cardiomyopathy

The role of stress (Takotsubo) cardiomyopathy in COVID-19 related cardiac injury is not known at this time, with no cases in the literature currently. However, several of the proposed mechanisms of COVID-19 related cardiac injury detailed in this review are also thought to be implicated in the pathophysiology of stress cardiomyopathy, particularly those of microvascular dysfunction, cytokine storm and sympathetic surge (95).

Acute coronary syndrome

Any discussion of myocardial injury would be incomplete without addressing the issue of acute coronary syndrome (ACS) and myocardial infarction (MI). The current published experience does not detail the incidence of ACS or epicardial plaque rupture as a mechanism for the acute cardiac injury observed in COVID-19. However, there is historical precedent for an association between infection and an elevated risk of ACS. Epidemiologic studies have shown that hospitalization for pneumonia is associated with a higher risk for atherosclerotic events (96). Influenza infection has been well studied and shown to have a temporal association with

cardiovascular complications and acute coronary syndrome (97,98). Annual vaccination against seasonal influenza was associated with a 36% lower rate of major adverse cardiovascular events in a meta-analysis of clinical trials evaluating this question (97). Therefore, viral infection is associated with an increased risk for coronary events and prevention with a reduction in this risk. Therefore, it is plausible that ACS will also be an important cause of acute cardiac injury in patients with COVID-19. Accordingly, international societies have devised pathways and protocols to effectively treat COVID-19 patients with ACS, including appropriate and timely use of resources to ensure the best outcome for the patient while also maintaining provider safety (99).

There are multiple pathophysiologic mechanisms by which systemic viral infection (by influenza or SARS-CoV2, for example) may lead to a higher risk of plaque destabilization and ACS (100). The role of inflammation in the development and progression of atherosclerosis is well established (101,102). The immune response to acute viral infection and the accompanying surge of cytokines and inflammatory mediators can lead to localized arterial inflammation which is more pronounced within coronary plaques (61,103). Entry of viral products into the systemic circulation, also known as pathogen-associated molecular patterns (PAMPs), can cause innate immune receptor activation which can cascade into activation of immune cells resident in pre-existing atheromata driving plaque rupture.(104) Viral PAMPs are also believed to activate the inflammasome, resulting in conversion of pro-cytokines into the biologically active cytokines (105). In addition, dysregulation of coronary vascular endothelial function by infection and inflammation may lead to a more vasoconstricted coronary bed (106). All of these changes are

putative mechanisms by which COVID-19 infection could lead to destabilization of pre-existing atherosclerotic plaque driving an acute coronary event.

Myocardial injury secondary to oxygen supply and demand mismatch

Periods of severe physiologic stress in the setting of sepsis and respiratory failure can be associated with elevations in biomarkers of myocardial injury and strain in some patients, an entity that confers poorer prognosis.(107-109) The mechanism of such myocardial injury is thought to be related to a mismatch between oxygen supply and demand, without acute atherothrombotic plaque disruption, and consistent with a diagnosis of type 2 myocardial infarction (MI) (100,110). Indeed, patients who suffer from type 2 MI compared to type 1 MI have higher mortality rates, which may in part be explained by a higher burden of acute and chronic comorbid conditions in the type 2 MI population (111). Furthermore, type 2 MI on the background of coronary artery disease (CAD) has a worse prognosis than those patients without CAD. Given the age and comorbidity profile of patients hospitalized with severe COVID-19, it is reasonable to assume that this population has a higher risk of underlying non-obstructive CAD, and therefore the presence of type 2 MI in this population is likely a marker of and contributor to the poor outcomes of COVID-19 patients with troponin elevations (56).

Systemic hyperinflammatory response with resulting myocardial injury

Perhaps one of the more intriguing mechanisms for cardiac injury in severe COVID-19 patients stems from the significant systemic inflammatory response. Early reports have demonstrated severely elevated levels of inflammatory biomarkers and cytokines, including IL-6, C-reactive protein (CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-2R and ferritin (112). Higher

levels of these biomarkers are associated with more severe COVID-19 manifestations and worse outcomes. A proposed theoretical model of COVID-19 disease progression divides the course into three overlapping yet distinct stages. In this staging framework, stage I represents early viral infection with associated constitutional symptoms. In stage II, direct viral cytotoxicity of the pulmonary system with associated inflammatory activation leads to prominent respiratory system compromise, associated with dyspnea and ultimately acute respiratory distress syndrome (ARDS) and hypoxia. With ACE2 receptors serving as an entry-point for viral replication in type II pneumocytes, the pulmonary system becomes the maiden organ of injury. If the host is unable to clear the virus via a productive and protective immune response, COVID-19 progresses to stage III - a hyperinflammatory state associated with profound elevations in inflammatory biomarkers. Patients who reach stage III have severe COVID-19 manifestations with multiorgan dysfunction and cytokine storm, with immune dysregulating akin to that seen in cytokine release syndrome (CRS) associated with chimeric antigen receptor T-cell (CAR-T) therapy (112-116). This observation is basis for several investigational therapies in COVID-19, including steroids and anti-inflammatory agents, as discussed later.

Prior studies have shown that cardiomyopathy in sepsis is partially mediated by inflammatory cytokines such as TNF-α, IL-6, IL-1β, INF-γ and IL-2 (73). Recombinant TNF-α resulted in an early and sustained LV systolic dysfunction in canines (117). Cultured rat cardiomyocytes demonstrated reduced contractility when exposed to IL-6 (118). The mechanism may be through modulation of calcium channel activity with resultant myocardial dysfunction (119-121). Additionally, nitric oxide (NO) is also believed to be a mediator of myocardial depression in hyperinflammatory states such as sepsis. Seminal studies found that medium from LPS-activated

macrophages suppressed myocyte contractility, a finding reversed with the NO synthase inhibitor, L-N-monomethyl arginine (122). Finally, recent understanding of the key role of mitochondrial dysfunction in septic states has raised questions about the role of this entity in sepsis associated cardiomyopathy (123). Indeed, similar mechanisms are thought to possibly underly the pathophysiology of stress (Takotsubo) cardiomyopathy as well.

Potential Targeted or Disease Modifying Treatments in SARS CoV2

The preceding review of the viral physiology of SARS-CoV2 and the various potential mechanisms of injury to the host, serve as the basis for considering specific targeted treatment and prevention. The following section outlines several current candidate classes of agents, including a brief discussion of vaccine development (Figure 1).

Nucleotide Analogs - Inhibitors of Viral Genome Replication

The antiviral mechanism of nucleotide analogs is to interfere with RdRp function and viral genome replication and amplification (Figure 1). There are no CoV-specific drugs available at this time and so ongoing efforts to employ this drug class against SARS-CoV2 are reliant on pre-existing agents designed for other viral illnesses (124).

The most widely-applied agent in this class against SARS-CoV2 has been remdesivir (125). Remdesivir functions as a chain terminator of RNA replication, initially designed for use against Ebola (124). Addition of remdesivir to the growing RNA strand by RdRp blocks the incorporation of additional nucleotides, thereby halting genome replication (126,127). The agent has been shown to have *in vitro* activity against SARS-CoV2, leading to off-label and

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investigational use around the world (4,125). Multiple randomized-controlled trials are ongoing in China and the United States for moderate, severe and critical COVID-19 (NCT04292730, NCT04292899, NCT04252664, NCT04252664, NCT04292730).

Another nucleotide analog for the disruption of RdRp-dependent viral replication is favipiravir, which has investigational approval in several countries (128,129). Additional agents that are under study include emtricitabine/tenofovir and ribavirin (128,130).

Protease Inhibitors - Inhibitors of Nonstructural Protein Generation

The antiviral mechanism of action of protease inhibitors is to block viral proteases which cleave the non-structural proteins from the large, monomeric, replicase as detailed above (Figure 1). As the maturation of non-structural proteins, such as RdRp, is necessary for viral reproduction, the pharmacologic impairment of the protease should be effective to stop viral replication.

A randomized control trial of lopinavir-ritonavir, a combination protease inhibitor designed for HIV treatment, in 199 patients with at least moderate COVID-19 did not significantly alter clinical improvement or viral clearance (131). While the results of this trial were met with disappointment, this negative study should not forestall trials and drug development of protease inhibitors as a therapeutic class, given that this drug was not specifically designed for SARS-CoV2 (128).

Indeed, the development of inhibitors specific to SARS-CoV2 main protease is underway. A class of agents identified using structure-based drug design, α-ketonamide inhibitors, has demonstrated *in vitro* efficacy and favorable pharmacokinetics (132). Other candidate protease

inhibitors for SARS-CoV2 include danoprevir, a drug originally intended for HCV therapy (133).

Inhibitors of Membrane Fusion

In order for the viral genome to gain access to cellular machinery for replication, a membrane fusion event must occur between the viral and endosomal membranes, which are noncovalently bound by the interaction between the S protein and ACE2. The exact mechanism of membrane fusion is unknown but appears to be dependent on endosomal maturation and a membrane-bound host protease, TMPRSS2 (7).

Chloroquine (CQ) / Hydroxychloroquine (HCQ)

The antiviral properties of chloroquine (CQ) were previously observed in HIV and other viruses (134,135). CQ and HCQ are thought to inhibit endosomal maturation, a process by which endosomes are translocated from the perimembrane regions of the cell to central hubs (136,137) (Figure 1). CQ prevented viral replication of SARS-CoV1 *in vitro* (138). A follow-up study demonstrated comparable efficacy of HCQ, a less toxic derivative, and suggested that the mechanism of impaired endosomal maturation indeed applied to SARS-CoV2 infection *in vitro* (139). Only poor-quality, non-randomized, unblinded data exists assessing the benefit of HCQ in COVID-19 (140). While HCQ is being widely used with an FDA emergency authorization, more data are needed to prove efficacy against SARS-CoV2 in humans. Notably, CQ and HCQ prolong the QT and may induce arrhythmia; significant caution should be used in starting these agents in patients with a QTc>500 ms. Concomitant use of other QT prolonging agents is not recommended.

Camostat

Camostat is a protease inhibitor approved for the treatment of chronic pancreatitis. Camostat appears to inhibit TMPRSS2 in proteomic and *in vitro* studies (7,141). A randomized, placebo-controlled trial is underway for this agent in COVID-19 (NCT04321096) (Figure 1).

Neutralizing Antibodies and Decoy Proteins

Neutralizing antibodies are designed to bind virions, preventing viral exposure or binding to host cells (Figure 1). Plasma from patients who have recovered from SARS-CoV2 may contain anti-SARS-CoV2 IgG antibodies. In a small, single-arm trial of convalescent plasma in COVID-19 patients with ARDS, all had clinical improvement with 3/5 patients weaning from the ventilator (142). Additional trials are ongoing to better define the safety and efficacy of this strategy.

Isolation of SARS-CoV2 specific neutralizing antibodies with clonal techniques is an appealing strategy to provide targeted therapy, potentially with lower risk of adverse events. Strategies currently under investigation include antibodies cloned from convalescent serum of individuals recovered from SARS-CoV2 or SARS-CoV1 and synthetic antibodies. It is unclear whether differences in the S proteins of SARS-CoV1 and SARS-CoV2 may limit the effectiveness of antibodies cloned from patients convalescent to SARS-CoV1 (9). Synthetic antibodies represent an exciting, novel therapeutic avenue. One strategy being explored is to fuse ACE2 to Fc IgG, with the hypothesis that this synthetic antibody would serve as a decoy receptor, preventing cellular binding of the virion (143).

In a similar vein, studies are ongoing of decoy proteins that are designed to act as viral "sinks". There is preliminary success with this strategy using soluble human ACE2 (34) (Central Illustration).

Anti-Inflammatory Therapy

Advanced stages of COVID-19 have been likened to cytokine storm syndromes with non-specific widespread immune activation (114). Elevated levels of inflammatory biomarkers, such as IL-6 and hsCRP, identify patients at high risk of progressing to severe disease and death (53). Immunomodulatory and anti-inflammatory therapy have been used, despite limited data, in patients with evidence of hyperinflammation in an effort to curb pathologic immune activation.

Corticosteroids

Corticosteroids have been used in several, severe viral respiratory infections including influenza, SARS-CoV and MERS-CoV with limited benefit and, in some instances, evidence of delayed viral clearance and increased rates of secondary infection and mortality (144). A retrospective analysis of 84 patients with ARDS secondary to SARS-CoV2 observed an association with improved survival in patients who received solumedrol (51). In the absence of robust evidence, major professional society guidelines do not recommend routine use of corticosteroids in treatment of COVID-19 but rather restricting its use to patients with other indications for steroids, such as refractory shock or advanced ARDS (41). Clinical trials are ongoing to examine the safety and efficacy of corticosteroids in hospitalized non-critically ill COVID-19 patients (Clinical Trials.gov ID: NCT04273321) and in those with ARDS (Clinical Trials.gov ID: NCT04323592).

IL-6 Inhibitors

Elevation of IL-6 in patients with severe COVID-19 has prompted consideration of use of IL-6 inhibitors (Tocilizumab, Siltuximab) extrapolating from treatment of cytokine release syndrome (145). Tociluzimab, a recombinant humanized monoclonal antibody, and Siltuximab, a chimeric monoclonal antibody, both bind soluble and membrane bound IL-6 receptors resulting in inhibition of IL-6-mediated signaling. In one preprint case series from China, 21 patients with severe or critical COVID-19 treated with tocilizumab experienced a salutary effect with resolution of fever, improved oxygenation, improvement in lung opacities on chest CT, resolution of lymphopenia and a reduction in CRP levels within a few days of therapy in the absence of any significant reported adverse events (146). In this preliminary report, 19 patients were discharged alive and 2 remained hospitalized at the time the case series was published. Several randomized clinical trials of tocilizumab in treatment of severe COVID-19 infection are ongoing (NCT04317092; NCT04306705).

Azithromycin

Azithromycin, a macrolide antibiotic, has long been touted for its anti-inflammatory effect and has been used as adjunctive therapy in treatment of community acquired pneumonia and chronic obstructive pulmonary disease exacerbations (147). Limited data suggest that adjunctive azithromycin in moderate-severe ARDS is associated with improved outcomes (148). A small non-randomized study showed that combination azithromycin and hydroxychloroquine was associated with more effective SARS-CoV2 clearance in COVID-19 patients compared with either monotherapy with hydroxychloroquine or standard of care; however, numerous limitations

of this study render the data uninterpretable (140). QT interval monitoring is prudent especially when used in combination with hydroxychloroquine. Several randomized clinical trials assessing the combination of hydroxychloroquine/chloroquine with azithromycin across the severity spectrum of COVID-19 are ongoing or about be launched (NCT04321278, NCT04322396, NCT04322123, NCT04324463).

Other Anti-Inflammatory Therapies

JAK-2 inhibitors inhibit receptor mediated-endocytosis leading to the hypothesis that it might prevent cellular entry of the SARS-CoV2 (Figure 1). Additionally, this class of agents have anti-inflammatory effects by inhibiting cytokine release (149). An agent in the class, baricitinib, is being studied in an open-label non-randomized pilot study in patients with COVID-19 (NCT04320277). Currently, a 3-arm randomized control trial is being launched to compare anakinra monotherapy, emapalumab monotherapy and standard of care (NCT04324021). Anakinra is a recombinant monoclonal antibody that blocks IL-1 receptors. It has been used to treat autoimmune conditions including juvenile idiopathic arthritis as well as recurrent pericarditis. Emapalumab is a fully human anti-gamma interferon monoclonal antibody that has been approved by the FDA for treatment of primary hemophagocytic lymphohistiocytosis, a disease reminiscent of the hyperinflammatory state seen in advanced COVID-19. Finally, colchicine, a microtubule polymerization inhibitor and anti-inflammatory drug, is being tested in a large randomized clinical trial of ambulatory COVID-19 patients (NCT04322682).

Other Therapies

Angiotensin Converting Enzyme Inhibitors & Angiotensin Receptor Blockers

ACE-2 receptor mediated endocytosis of SARS-CoV2 is central to the viral life cycle. Conflicting data exist regarding the effect of renin-angiotensin-aldosterone-inhibitors (RAASi), including ACE-I and ARB, on ACE2 activity/levels in various human tissues and the resultant susceptibility to infection with SARS-CoV2 (18). The totality of the available data is insufficient to recommend cessation of ACE-I/ARB in individuals with an existing indication for life-prolonging therapy with these drugs and major societies have strongly recommended continuation of ACE-I/ARB therapy. An open label randomized trial is on the way to examine the effect of prophylactic ACE-I/ARB withdrawal in COVID-19 naive individuals with essential hypertension as the sole indication for treatment on the risk of infection and subsequent complications (NCT04330300). Based on the pre-clinical data described earlier in this review, two paired trials are currently underway examining losartan therapy in COVID-19 who are ambulatory (NCT04311177) and hospitalized (NCT04312009).

Statins

The anti-inflammatory pleiotropic effects of statins have been cultivated in different pathologic states. Statins have been shown in murine models of acute lung injury and in humans to attenuate the inflammatory component of acute lung injury (150,151). A multi-center randomized trial of simvastatin in patients with versatile causes of ARDS showed no difference as compared to placebo in ventilator free days, multi-organ failure and mortality (152). A subsequent study, subphenotyping the trial population in to hyper vs. hypoinflammatory ARDS, found a statistically significant improvement in survival with simvastatin in the hyperinflammatory group (153). A post-hoc analysis of the JUPITER trial observed a reduction

in incident pneumonia with rosuvastatin (154). The benefit of statin therapy in the hyperinflammatory state in advanced COVID-19 is unknown.

Vaccines Against SARS-CoV2

As discovery of a safe and efficacious vaccine again SARS-CoV2 is clearly the aspiration for preventative strategies, intense efforts are ongoing employing numerous approaches with accelerated testing. It is believed that all 4 structural proteins, E, M, N and S proteins, may serve as antigens for neutralizing antibody and $CD4^+CD8^+$ T cell responses (155). Based on the experience with SARS-CoV1 vaccine development, it seems that the most promising candidates target the S protein, which induces humoral and protective cellular immunity (8). Encouragingly, administration of full-length or the ACE2-receptor binding domain of the S protein of SARS-CoV1 induced highly potent neutralizing antibodies that conveyed protective immunity in animal models (156,157).

Potential delivery strategies include inactivated or attenuated virus, subunit vaccines, viral vectors, DNA or RNA-based vaccines (158). Live attenuated viral vaccines are likely to induce significant immune response but may carry risk of disease, particularly in immunosuppressed individuals. Inactivated "whole" viral or subunit vaccines are relatively easy to develop, but do not induce immediate or complete immunity, typically requiring multiple doses to promote humoral, but often not cellular, immunity. Immunity may also wane over time, requiring booster dosing. Viral vector-based vaccines would employ other viruses, such as the vaccina virus (a poxvirus used for the smallpox vaccine) or adenovirus, to display SARS-CoV2 antigens. This strategy can promote robust cytotoxic T cell responses but may fail in the face of the pre-existing

immunity to or toxicity of the viral vector (159). Nucleic acid-based strategies, which work through delivery of DNA or RNA that are translated by host machinery to produce viral protein antigens, are relatively simple to design but may be limited by toxicity and/or stability concerns. Of note, at this time, there are no approved DNA or RNA vaccines for humans. Most approaches to SARS-CoV2 are in pre-clinical development, with several early trials of RNA (NCT04283461) and viral-vector (NCT04299724, NCT04313127, NCT04276896) vaccine strategies ongoing.

Crisis Standards of Care and Ethical Resource Allocation

Estimates suggest that, as has happened in Italy and Spain, the burden of COVID-19 will far outstrip the healthcare capacity in the US and globally with insufficient availability of hospital and ICU bed capacity, healthcare providers and specific therapeutic or supportive interventions, such as mechanical ventilation and renal replacement (160). For this reason, organizations, such as the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) and individual healthcare institutions are developing guidance for allocation of resources in the event that adequate, additional resources cannot be obtained (161). These efforts are building off of a set of principles established in the wake of the 2009 H1N1 pandemic.

At that time, the US Department of Health and Human Services commissioned the Institute of Medicine (IOM) to provide expert guidance on implementing alternative standards of healthcare in the setting of a disaster. In their report, the IOM defined the principles of "crisis standards of care", defined as a substantial change in usual healthcare operations, including the level of care possible to deliver, in the setting of a pervasive or catastrophic disaster.(162) Notably, this

framework recognizes that "the formal declaration that crisis standards of care are in operation enables specific legal/regulatory powers and protection for healthcare providers in the necessary task of allocating and using scarce medical resources." Appreciating the distress associated with allocation of scarce medical resources, the IOM recommend that the process be guided by seven ethical principles: fairness, duty to care, duty to steward resources, transparency, consistency, proportionality and accountability (162).

Working with these principles, ethicists have come to a general consensus that the goal is to maximize benefit while maintaining equity, objectivity and transparency (160,163). Maximizing benefit ideally involves preserving the most lives as well as the most life-years, acknowledging the importance of prognosis. While the practical application of these principles is challenging, there appears to be general agreement across the literature on a number of concepts (160,163,164)   Most recommend development of a triage or scoring system that accounts for acute and pre-morbid prognosis in order to allocate scarce resources to those who are most likely to benefit. The scoring system should utilize objective clinical information, in order to minimize the need for clinical judgement and the risk of introducing inconsistency and bias. The use of the system - and the determination that stems from it - should be transparent to providers, patients and families. Triage should be applied broadly to all patients requiring a particular resource, not just those suffering from the pandemic disease (e.g. applies to decision to use VA ECMO in patients with myocarditis due to COVID-19 and cardiogenic shock from a non-COVID-19 etiology). A random system (e.g. lottery) should be used to break "ties" in cases with a similar estimated prognosis, rather than a first-come-first serve approach. Importantly, many advocate that an independent triage physician make the determination to remove the

burden from the bedside healthcare team. The triage physician may be supported, as necessary, by a triage committee, comprised of experts in the area of ethics and relevant medical fields.

Areas of controversy include whether there should be priority allowed for healthcare providers. Some ethicists argue that they should not be prioritized as that are unlikely to recovery in a time frame that would allow them to continue their professional responsibilities.(163) Others argue that granting priority recognizes the assumption of risk and also encourages ongoing participation in patient care (160). Along the same line, an argument has also been made to prioritize research participation (160).

The optimal tool for prognostication also remains elusive. The sequential organ failure assessment (SOFA) score has been suggested as quantitative assessment of acute illness severity; however, there is a recognition that this tool may not be well calibrated to all populations and could lead to inaccurate assessments of prognosis (165,166).

The value of pre-determination of this framework with community and provider engagement, establishment of legal authority and logistic and operational preparedness is clear. Nevertheless, acknowledging the prospect of large-scale rationing of healthcare is heartbreaking and foreign to most civilian healthcare providers in developed countries.

Summary

In just a few short months, SARS-CoV2 has spread across the world with distressing speed, threatening global economic and individual health and well-being. Many regional healthcare

systems are overwhelmed and under-resourced, forcing clinicians and administrators to make previously unthinkable decisions regarding allocation of medical care. However, in the wake of this devastation, clinicians and scientists have rallied together to rapidly evolve our understanding of all aspects of SARS-CoV2 infection, from the basic virology, to the human manifestations to therapeutic and preventative strategies. This unprecedented collective effort will, without a doubt, advance our ability to prevent the spread and optimally care for patients suffering from COVID-19.

Acknowledgments

Figure Legends

Figure 1: Putative SARS-CoV2 Life Cycle and Therapeutic Targets.

The SARS2-CoV2 virus binds to the ACE2 receptor on the host cell membrane. Endocytosis is believed to be mediated, in part, by JAK-2. Membrane fusion occurs between the mature endosome and virion with facilitation by the transmembrane serine protease 2 (TMPRSS2) resulting in release of the SARS-CoV2 RNA into the intracellular space. The RNA is translated by host machinery to produce the replicase and structural proteins. Host and SARS-CoV2 proteases cleave the replicase to in non-structural proteins, including the RNA-dependent RNA polymerase (RdRp). RdRp mediates SARS-CoV2 RNA replication and amplification. SARS-CoV2 transmembrane proteins (S, E and M) are shuttled via the endoplasmic reticulum and Golgi apparatus to the forming viral capsids. Viral assembly occurs with addition of the viral RNA and N protein through association with the transmembrane viral proteins. Exocytosis results in release of the newly synthesized viral particle.

Central Illustration: Potential Mechanisms of Myocardial Injury in COVID-19

MI denotes myocardial infarction; ASCVD, atherosclerotic cardiovascular disease; DIC, disseminated intravascular coagulation.

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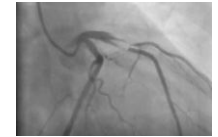
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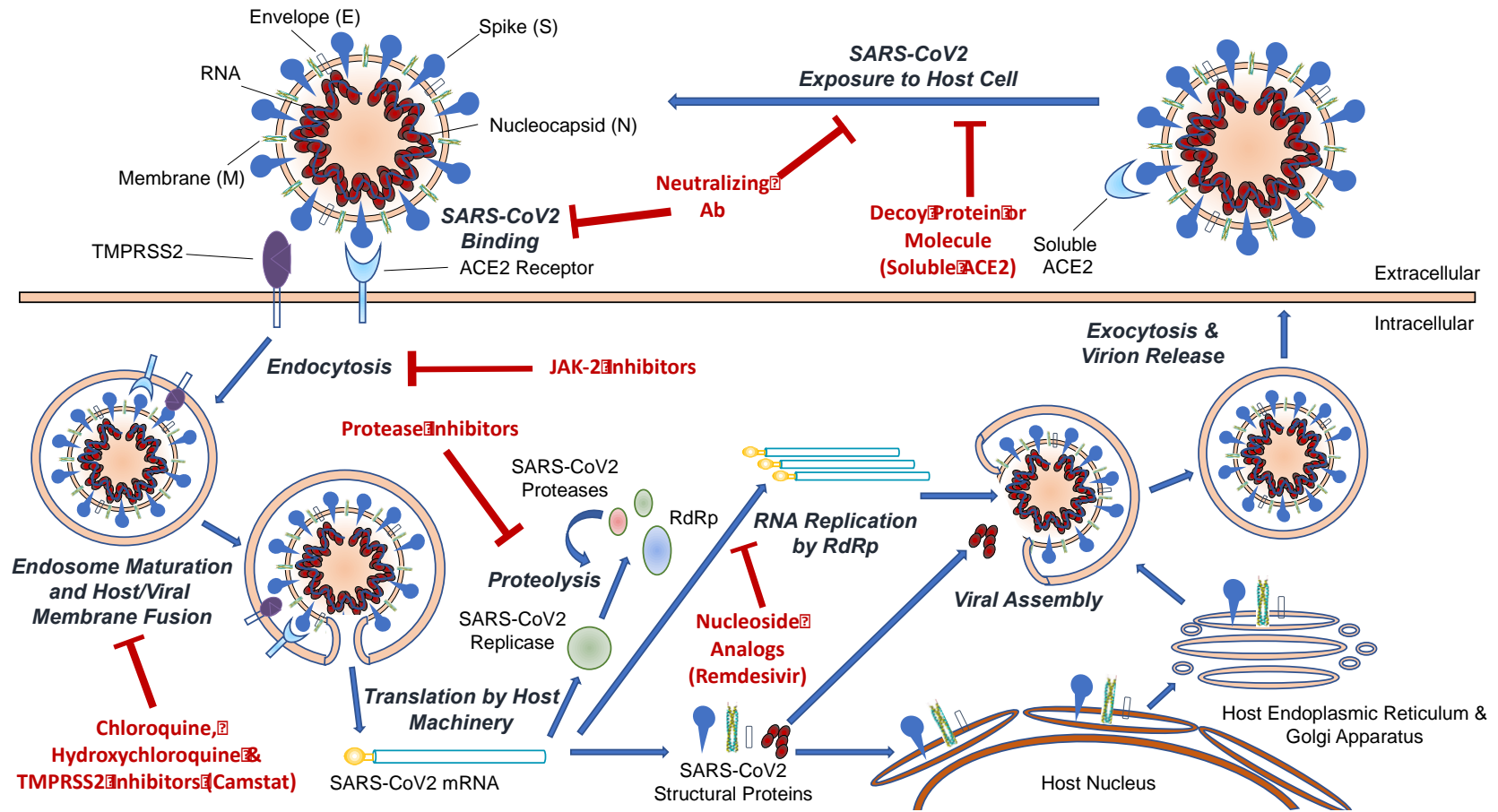
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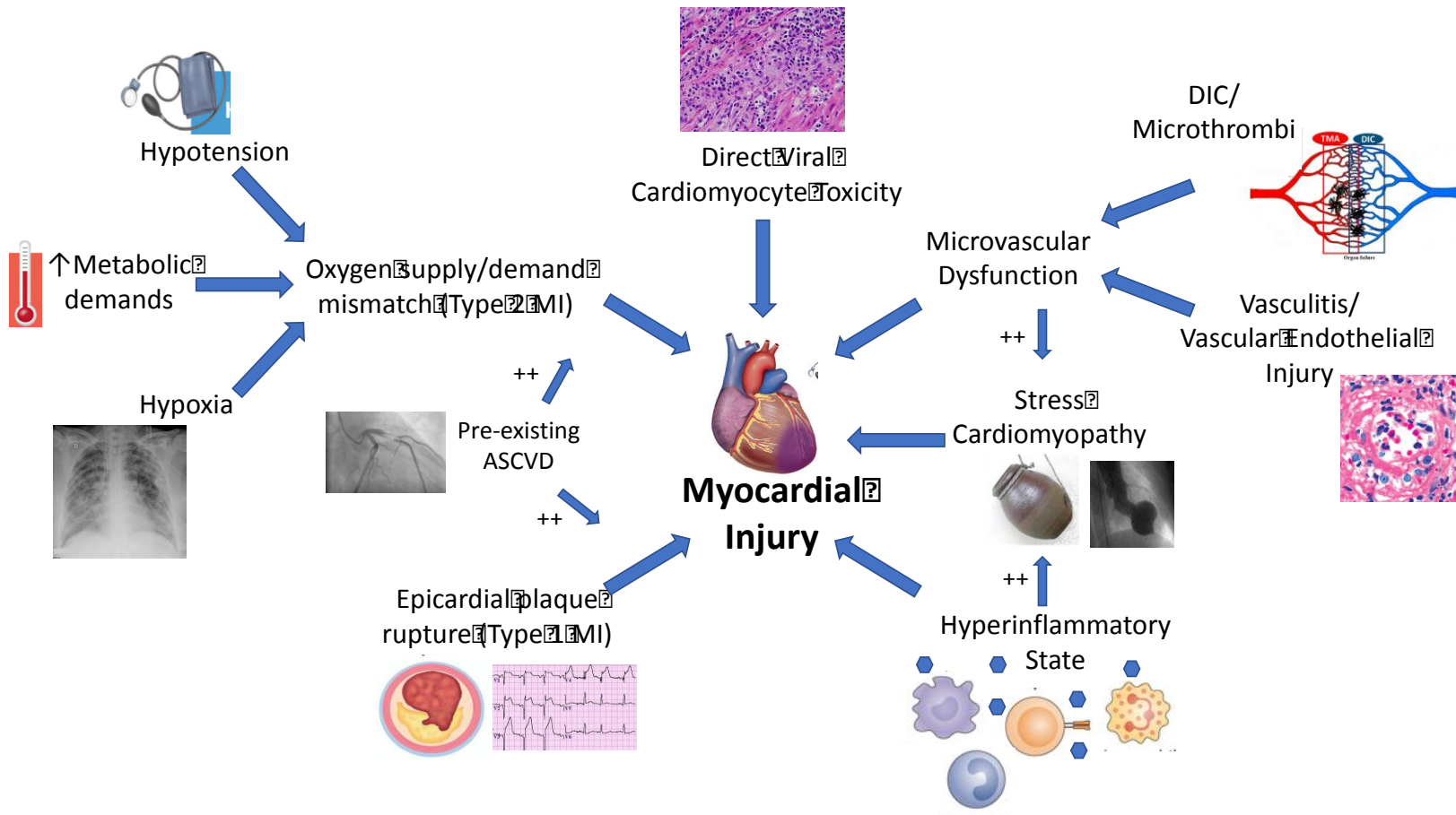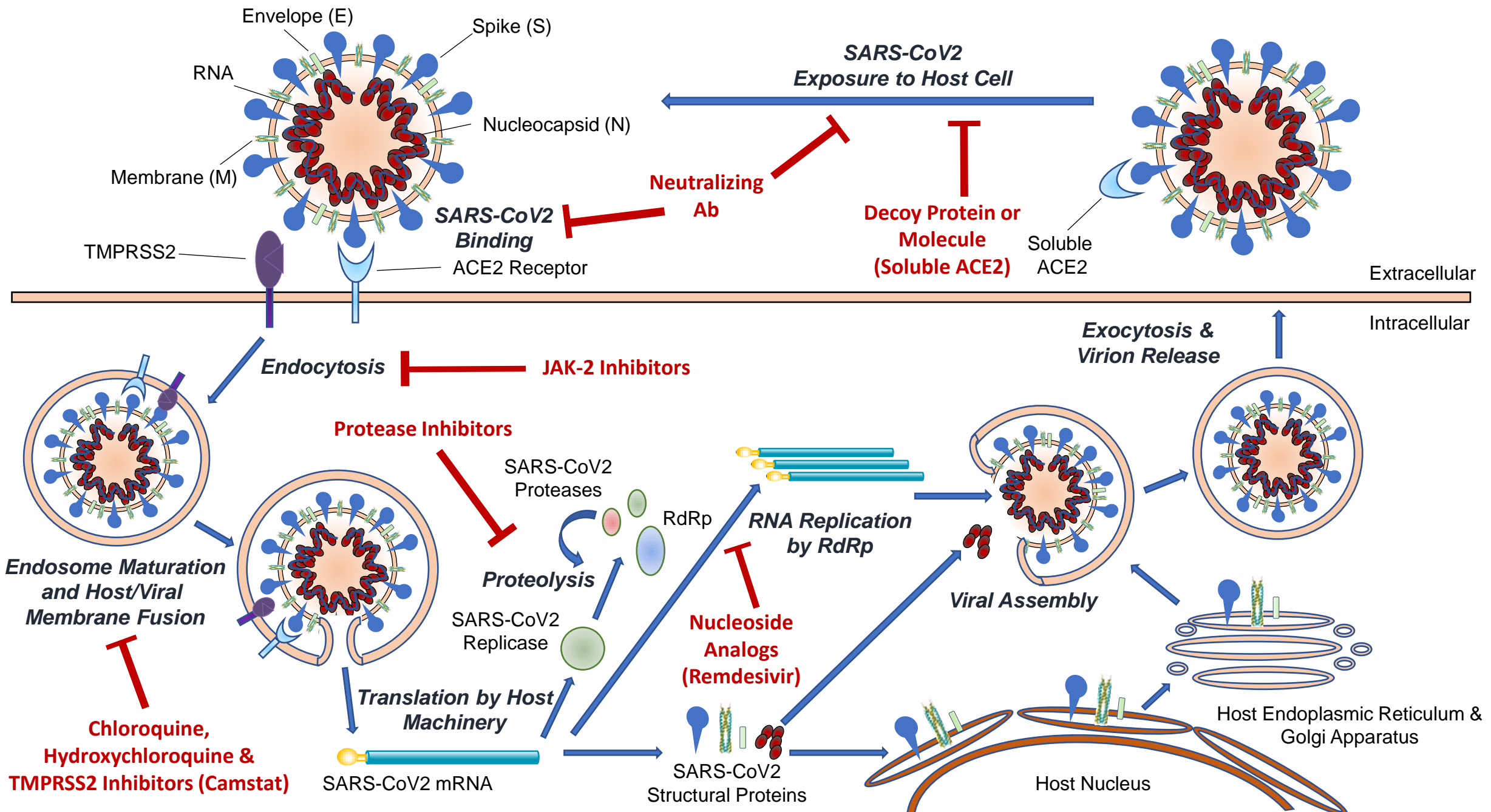
Hypotension

↑Metabolic demands
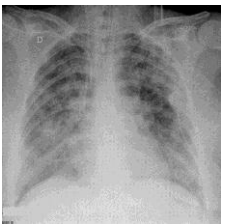
Hypoxia

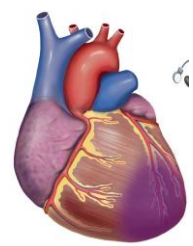Oxygen supply/demand mismatch (Type 2 MI)

Direct Viral Cardiomyocyte Toxicity

DIC/ Microthrombi

Microvascular Dysfunction
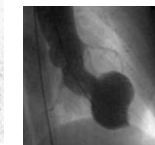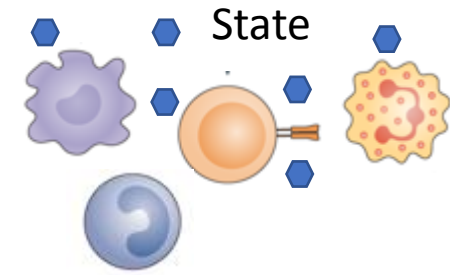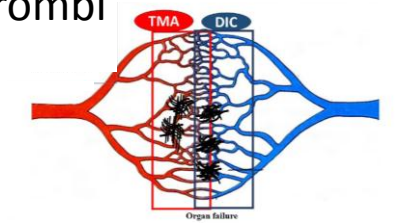
Vasculitis/ Vascular Endothelial Injury

Pre-existing ASCVD

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Myocardial Injury

Stress Cardiomyopathy

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Epicardial plaque rupture (Type 1 MI)

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Hyperinflammatory State

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