ABSTRACT
Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has far-reaching impacts on human health. First identified as a disease of the respiratory system, COVID-19 also causes gastrointestinal, renal, neurological, and/or cardiovascular symptoms. This article elucidates biological relationships between COVID-19 and the cardiovascular system. It postulates molecular and physiological mechanisms behind COVID-19–related cardiovascular ailments and examines intersections among the cardiovascular system, SARS-CoV-2, COVID-19, and certain medications. New scientific information on COVID-19 and the cardiovascular system accumulates weekly. In recognition of such rapidity, this paper offers a framework in which the reader will be able to place the growing and evolving field of knowledge.

EFFECTS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION ON THE CARDIOVASCULAR SYSTEM
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells through an interaction between the virus' s spike (S) protein and angiotensin-converting enzyme (ACE) 2 in host cells.1-5 Within the cardiovascular system, ACE2 is reportedly located on heart muscle cells,6-11 endothelial cells (ECs) that line the interior of blood vessels and regulate blood clotting and blood pressure,12,13 pericytes that surround and aid ECs,6-8 and arterial smooth muscle cells (SMCs) that control vascular diameter and thereby blood pressure and flow.7,12,13 SARS-CoV-2 infection of these cells hinders their health-promoting work.

Cardiovascular health is also threatened when SARS-CoV-2 invades noncardiac areas and triggers immune responses. To fight the “intruder,” local white blood cells activate, recruit other white blood cells, and produce pro-inflammatory chemicals, which increases inflammation. Interestingly, a source of these chemicals may be direct SARS-CoV-2 infection of macrophages—a type of white blood cell that expresses ACE2.14 As the immune system battles the virus, the affected body organ may (temporarily) malfunction. These malfunctions and the pro-inflammatory chemicals released into the blood may elicit negative effects on blood vessels and the heart.15

Cardiovascular conditions induced by these direct and indirect effects of SARS-CoV-2 infection include myocarditis (inflamed heart tissue), blood pressure irregularities, abnormal blood clot (thrombus) formation, hypoxia, arteriosclerotic heart disease (ASHD), myocardial infarctions (MIs; heart attacks), arrhythmias, and heart failure (Figure 1).16-29 If left unchecked or if severe enough, these ailments could be fatal.

Myocarditis
Myocarditis compromises contractility of the heart muscle. As a result, the heart compensates in order to insure proper delivery of blood (and O2) to the body. Compensation occurs by one of at least 2 methods: (1) thickening of the heart muscle layer (hypertrophy), and (2) heart rate elevation (tachycardia). Both choices could progressively worsen the heart’s already precarious condition.

Blood Pressure Irregularities
Some patients with coronavirus disease 2019 (COVID-19) present with hypertension.19 The causal link between this elevated blood pressure and SARS-CoV-2 may be ACE2. Besides being the binding target of SARS-CoV-2’s S protein, ACE2 is part of the renin–angiotensin system (RAS) pathway (Figure 2). The RAS pathway controls SMC contraction and relaxation and thereby influences blood pressure. SMC contraction narrows vessels’ diameter (vasoconstriction) and raises blood pressure. SMC relaxation widens vessels’ diameter (vasodilation) and lowers blood pressure. SMC contraction and relaxation are controlled by the RAS pathway’s angiotensin II and angiotensin (1-7), respectively. ACE1 converts relatively inactive angiotensin I into angiotensin II, a highly active vasoconstrictor. ACE2 converts angiotensin II into angiotensin (1-7), a vasodilator (Figure 2).30 ACE2 levels likely decline in SARS-CoV-2–infected
Figure 1. Confirmed and plausible mechanisms by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes cardiovascular symptoms. Several cell types and organs (indicated by the spiked star symbol) are reported targets for SARS-CoV-2 infection. Some of these host cells are part of the cardiovascular system, macrophages may lie within or outside of the cardiovascular system, and other sites lie outside of the cardiovascular system. (The cardiovascular system is defined by the thin–dashed enclosure.) Infections initiate a variety of cardiovascular symptoms (shaded boxes) that, if prolonged and severe enough, cause arrhythmias and heart failure (shaded boxes with thick outline). Viral infection of other organs may also affect the cardiovascular system in ways not specified here. Related schematics can be found in Guzik et al.\textsuperscript{17} and Atri et al.\textsuperscript{16} ASHD, arteriosclerotic heart disease.

Figure 2. The renin–angiotensin system (RAS) pathway and sites of angiotensin–converting enzyme (ACE) inhibitor (ACEI) and angiotensin receptor blocker (ARB) inhibition. In the RAS pathway, renin (produced by the kidneys) converts angiotensinogen (produced by the liver) into angiotensin I. Angiotensin I is modified into angiotensin II, an active vasoconstrictor, by ACE1. ACE2 (the target for SARS–CoV–2 infection) produces the vasodilator angiotensin (1–7) from angiotensin II. The ACEI and ARB high–blood–pressure medications work by preventing vasoconstriction. They inhibit ACE1 and binding of angiotensin II to its receptors, respectively.
cells. Without ACE2, levels of angiotensin (1-7) would decrease, and angiotensin II levels would likely increase. These events would tip the scales toward vasoconstriction and elevated blood pressure. This mechanistic explanation for hypertension, although plausible, needs to be strengthened with additional research.

Another explanation for hypertension development in patients with COVID-19 lies in direct viral infection of ECs and perhaps pericytes. Both of these cell types impact blood vessel diameter (Figure 1). A deficit of vasodilation or a prevalence of vasoconstriction likely causes hypertension.

Some patients with COVID-19 develop low blood pressure (hypotension) rather than high blood pressure. Hypotension is a symptom of acute respiratory distress syndrome (ARDS), so it is likely the result of SARS-CoV-2 infection of lung cells.

**Thrombi Formation and Hypoxia**

Another blood-related condition found in some patients with COVID-19 is the presence of thrombi. These abnormal blood clots form in arteries or veins. Interference of arterial blood flow jeopardizes delivery of O₂ and nutrients to areas downstream of the blockage, whereas impedance of blood flow through a vein may cause swelling in the body upstream of the clot.

Besides blood-flow alteration, thrombi pose an additional risk to patients: pieces may break off the clot, travel through the bloodstream, and lodge in another blood vessel. These traveling clots (emboli) endanger other organs. When an embolus in a large systemic artery flows to a narrower artery within an organ, it may get stuck, hinder blood flow, and deprive downstream organs—or areas within an organ—of O₂.

Emboli in veins pose a significant risk to the lungs. Such emboli could migrate through the right heart chambers, lodge in the lungs’ narrow arterial branches, and impede blood flow to the pulmonary capillaries. Complications of pulmonary emboli include right ventricular hypertrophy, swelling (edema), and low O₂ levels in the blood (hypoxia) (Figure 1).

Right ventricular hypertrophy and edema are indirect effects of a pulmonary embolism. To force blood past the pulmonary embolism, the heart’s right ventricle hypertrophies in an attempt to strengthen its pumping power. At best, this adjustment is a temporary fix. Persistence of the embolism increases blood pressure in the right side of heart, and by extension, in the body’s veins. This elevated vascular pressure induces edema. Gravity causes the swelling to be most prominent in the lower limbs.

Such edema also occurs in the lungs. This fluid buildup impedes the diffusion of O₂ from the lungs’ alveoli to the blood in the pulmonary capillaries. It also reduces alveolar ventilation (O₂ entry into the alveoli), as fluid-filled sacs fail to remain open. Diminished blood flow to alveoli on account of pulmonary emboli may also prevent the blood from picking up adequate O₂. Collectively, these emboli-initiated events cause hypoxia.

Two culprits induce thrombi formation: injured ECs and pro-inflammatory chemicals (Figure 1). ECs may be damaged by direct SARS-CoV-2 infection. Such damaged cells activate platelets and make them more “sticky”; thus, they adhere to the vessel wall and to each other. Clotting factors in the blood set off a chain reaction that culminates in the modification of fibrinogen to fibrin. Fibrin threads attach to the mass of platelets to form the clot. If ECs are undamaged, a clot may still form: pro-inflammatory chemicals may activate platelets and clotting factors (Figure 1).

**Preexisting hypertension, ASHD, arrhythmias, MIs, and heart failure seem to increase the severity of COVID-19 symptoms in patients.**

**ASHD, MIs, and Arrhythmias**

Thrombi may form in the coronary arteries of some patients with COVID-19, a condition known as ASHD. Coronary arteries carry O₂-rich blood to the heart tissue. Such O₂ helps fuel the heart’s vital blood-pumping actions. Partial or complete blockage of these coronary vessels is life-threatening. Whether through blocked delivery or through hypoxia, insufficient O₂ causes heart muscle cells to malfunction and die. The likelihood of MIs increases (Figure 1). MIs in a small number of patients with COVID-19 have been reported.

Arrhythmias have also been reported in some patients with COVID-19. In the general population, these altered heart rhythms are caused by ASHD, MIs, myocarditis, and heart hypertrophy. Therefore, these cardiovascular conditions are the current “suspects” for reported arrhythmias in COVID-19–related cases.

**Heart Failure**

Persistence of these aforementioned cardiovascular problems gradually weakens the heart, compromises its pumping ability and effectiveness, and can lead to heart failure (Figure 1). The heart becomes progressively more incapable of delivering O₂– and nutrient-rich blood to the body. Preexisting heart failure appears to increase the likelihood of death from the disease in patients with COVID-19.
MEDICATIONS AND HEALTH (COVID-19 AND CARDIOVASCULAR) RISKS
COVID-19 impacts the cardiovascular system, but the inverse may also be true. Percentages of patients with COVID-19 and cardiovascular conditions are not higher than the prevalence of these conditions in the general population.\textsuperscript{18-20,40-46} Therefore, these cardiovascular illnesses do not appear to increase one’s risk of developing COVID-19. However, preexisting hypertension,\textsuperscript{18-20,40-41} ASHD,\textsuperscript{18,19,40-41} arrhythmias,\textsuperscript{19,20,41} MIs,\textsuperscript{26} and heart failure\textsuperscript{19,20,41} seem to increase the severity of COVID-19 symptoms in patients. This observation led scientists to examine whether certain cardiovascular related medications alter patients’ risk of SARS-CoV-2 infection and/or COVID-19 severity. (It is worth noting that classifications of “severity” vary among studies. Distinctions include normal vs high protein (troponin) concentrations in the blood, nonsevere vs severe disease, nonhospitalized patients vs hospitalized patients, non-intensive care unit (ICU) patients vs ICU patients, and survivors vs nonsurvivors.\textsuperscript{17,20}

ACE Inhibitors and Angiotensin Receptor Blockers
Some antihypertensive medications are the focus of such research. Many Americans (13% to nearly 50%, depending on definitions and the data source) have hypertension.\textsuperscript{42,45,46} This percentage increases as one ages.\textsuperscript{45} To lower high blood pressure, physicians may prescribe ACE inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs). These medications minimize production of angiotensin II and block angiotensin II’s interaction with receptors, respectively (Figure 2), thereby preventing the vasoconstriction that elevates blood pressure (Figure 2).

However, certain ACEIs and ARBs likely increase levels and activity of ACE2 throughout the body.\textsuperscript{47-49} Because ACE2 is the receptor for SARS-CoV-2 binding, it is important to ascertain whether ACEIs and ARBs alter patients’ risk of contracting SARS-CoV-2 and/or developing COVID-19. Mackey et al\textsuperscript{50} provide regular updates on newly published research articles pertaining to this topic. Articles sampled from this compilation show wide variability in the study design.\textsuperscript{44,50-54} Differences include variations in comparison groups, ethnic groups, statistical analyses, sample sizes, dates of studies (before or after widespread COVID-19 testing), lengths of time on ACEIs or ARBs, attention levels paid to confounding health issues, and definitions of “severe COVID-19.” Some articles are retrospective observational studies. Such studies are subjective to selection bias; for example, a cohort of hypertensive patients tested for COVID-19 leaves out hypertensive patients who did not get tested because they were asymptomatic. Identification of patients prescribed ACEIs or ARBs also assumes that the patients take these medications as prescribed, which may not be the case.

Nevertheless, most studies come to the same conclusion: use of ACEIs or ARBs does not increase one’s risk of SARS-CoV-2 infection or development of severe COVID-19.\textsuperscript{55,56} Currently, the Centers for Disease Control and Prevention (CDC) and other cardiovascular health organizations advise patients to continue their ACEI or ARB prescriptions, unless advised otherwise by a physician.\textsuperscript{57,58} Clinical trials concerning ACEIs, ARBs, and COVID-19 are ongoing.\textsuperscript{29}

Interestingly, the ACEI- and ARB-induced increase in ACE2 expression levels may be advantageous to patients.\textsuperscript{52,54} It may counteract virally induced reduction of ACE2 levels and thereby preserve the production of angiotensin (1-7), which lowers elevated blood pressure, promotes structural health of blood vessels and ECs, protects against cardiac hypertrophy, and may enhance blood cell production.\textsuperscript{60,61}

COVID-19 Treatments and Cardiac Health Risks
Some medications—lopinavir/ritonavir, hydroxychloroquine (HCQ), favipiravir, remdesivir, and tocilizumab—were originally developed for other uses but demonstrate various levels of efficacy in treating patients with COVID-19. Lopinavir/ritonavir and HCQ reportedly disrupt SARS-CoV-2’s entry into host cells.\textsuperscript{62} Favipiravir and remdesivir likely prevent the replication of the virus’s genome.\textsuperscript{62} Tocilizumab reduces inflammation by limiting the effectiveness of pro-inflammatory chemicals.\textsuperscript{52} Last year, a multinational study of more than 10,000 patients examined the effects of some of these drugs on the mortality of patients with COVID-19.\textsuperscript{63} The tests using HCQ (low doses) and lopinavir/ritonavir were halted prematurely, as no improvements were seen.\textsuperscript{64} Currently, the National Institutes of Health (NIH) recommends against their use as a treatment for COVID-19.\textsuperscript{65,66}

These drugs have been linked to cardiovascular side effects. Lopinavir/ritonavir, HCQ, favipiravir and remdesivir may cause arrhythmias.\textsuperscript{29,67-69} Lopinavir/ritonavir may trigger MIs.\textsuperscript{70} Furthermore, lopinavir/ritonavir and tocilizumab may compromise the effectiveness of cardiovascular medications.\textsuperscript{29,71} These cardiovascular risks are inferred primarily from a small number of studies with a small number of subjects without COVID-19. A more robust examination of these drugs’ cardiovascular effects in patients with COVID-19 has begun in several clinical trials funded by the NIH.\textsuperscript{29}

CONCLUSION
Approximately 1.5 years have passed since SARS-CoV-2 and COVID-19 were identified.\textsuperscript{1,72,73} In this time, much scientific understanding of SARS-CoV-2 infection patterns and COVID-19 comorbidities has been acquired. Improved treatment procedures enhance patients’ prognoses, and awareness of drug side effects likely reduces health complications. This article
illuminates the landscape of SARS-CoV-2 and COVID-19 in relationship with the cardiovascular system and provides a biological foundation to support readers as they engage with the burgeoning quantity of scientific studies on this topic. Indeed, the necessity of continued research remains. Some current information is conjecture, drawn from studies on the first severe acute respiratory syndrome coronavirus or in patients without COVID-19. Other knowledge is based on only a few small studies and needs stronger support. Longitudinal studies are necessary to determine the long-term effects of SARS-CoV-2 and COVID-19 on human health. Regardless, the approval of effective SARS-CoV-2 vaccines, enhancements to patient care, and funded clinical trials provide hope for a future in which SARS-CoV-2 infection rates decline, patient mortality decreases, and life without social-distancing restrictions resumes.

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References


