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COMPENDIUM ON COVID-19 AND CARDIOVASCULAR DISEASE

Interaction of COVID-19 With Common Cardiovascular Disorders

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ABSTRACT: The onset and widespread dissemination of the severe acute respiratory syndrome coronavirus-2 in late 2019 impacted the world in a way not seen since the 1918 H1N1 pandemic, colloquially known as the Spanish Flu. Much like the Spanish Flu, which was observed to disproportionately impact young adults, it became clear in the early days of the coronavirus disease 2019 (COVID-19) pandemic that certain groups appeared to be at higher risk for severe illness once infected. One such group that immediately came to the forefront and garnered international attention was patients with preexisting cardiovascular disease. Here, we examine the available literature describing the interaction of COVID-19 with a myriad of cardiovascular conditions and diseases, paying particular attention to patients diagnosed with arrythmias, heart failure, and coronary artery disease. We further discuss the association of acute COVID-19 with de novo cardiovascular disease, including myocardial infarction due to coronary thrombosis, myocarditis, and new onset arrhythmias. We will evaluate various biochemical theories to explain these findings, including possible mechanisms of direct myocardial injury caused by the severe acute respiratory syndrome coronavirus-2 virus at the cellular level. Finally, we will discuss the strategies employed by numerous groups and governing bodies within the cardiovascular disease community to address the unprecedented challenges posed to the care of our most vulnerable patients, including heart transplant recipients, end-stage heart failure patients, and patients suffering from acute coronary syndromes, during the early days and height of the COVID-19 pandemic.

Key Words: acute coronary syndrome ■ arrhythmia ■ cardiovascular disease ■ heart failure ■ pandemic

Coronavirus disease 2019 (COVID-19) caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in a period of intimidating uncertainty throughout the worldwide medical community.[1,2] Following a 3-year period that claimed the lives of 6.5 million people, including nearly 1 million Americans, there is now increased understanding of this unprecedented disease.[3] While there were innumerable unanswered questions early on, little time elapsed before a clear association between poor outcomes with COVID-19 in patients with preexisting cardiovascular diseases was established.[4–8] Similarly, it quickly became apparent that cases of severe COVID-19 resulted in cardiovascular injury, although the mechanisms for this were largely unclear at the time.[5,6,9]

Unfortunately, the onset of the pandemic coincided with an increase in the global burden of cardiovascular diseases and cardiovascular mortality, including in high-income countries in which rates were previously declining.[10] In 2019 alone, nearly 875 000 deaths attributable to cardiovascular disease occurred in the United States, which represented an ongoing upward trend beginning in 2010.[11] In contrast, COVID-19 death forecasts, which were accurately predicted in late 2020 to exceed 1 million in the United States by late 2022,[12] remained alarmingly high and resulted in strong public messaging early in the pandemic focused on social distancing with numerous "stay-at-home" orders put into place.[13] Therein, a unique challenge of providing necessary cardiovascular care to a fearful population of patients vulnerable to poor outcomes with COVID-19, in the face of limited resources and understanding, became evident.[13–15]

The aim of this review is to provide a comprehensive discussion of the interaction of COVID-19 and common cardiovascular disorders, examining the most current literature within the contextual vantage point of the challenges brought forth by this historic time.

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Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
ACS	acute coronary syndrome
CCL	cardiac catheterization laboratory
HF	heart failure
LVAD	left ventricular assist device
OHT	orthotopic heart transplant
PCI	percutaneous coronary intervention
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
STEMI	ST-segment elevation myocardial infarction

CORONAVIRUSES AND THE CARDIOVASCULAR SYSTEM—OVERVIEW

There are 7 identified coronavirus strains known to cause illness in humans, 4 of which account for 15% to 30% of common colds while the other 3 are further classified as causing severe acute respiratory syndrome (SARS).[16] SARS-CoV-2, like its predecessor SARS-CoV, the strain responsible for the 2002 pandemic, infects human cells by binding to the host cell receptor ACE2 (angiotensin-converting enzyme 2) via its spike protein; although SARS-CoV-2 does so with higher affinity.[17,18] After initial infection with SARS-CoV-2, the virus replicates in nasal and pulmonary epithelial cells, begins to circulate, and is then able to infect more distant cells that express ACE2 and other necessary cell-entry proteins such as proteases and integrin co-receptors.[17] Cardiac myocytes, fibroblasts, and pericytes express ACE2 along with the additional necessary cell-entry mediators.[19,20] Furthermore, there is increased expression of ACE2 in the setting of ventricular remodeling, a cardioprotective adaptation seen in response to acute and chronic cardiovascular conditions, providing a potential explanation for increased adverse outcomes of COVID-19 in patients with preexisting cardiovascular disease due to potential increased susceptibility to infection.[17,18,21] Following entry of SARS-CoV-2 into the host cell, ACE2 is subsequently downregulated, resulting in increased circulation of deleterious angiotensin II, which has been shown to result in cardiac dysfunction (Figure).[17,18,22–26]

Given this mechanism of cell entry, great concern arose surrounding the safety of continued use of chronic renin angiotensin system inhibitors, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, as use of these agents has been shown to increase ACE2 expression and presumably increase opportunity for viral cell entry.[6,27,28] Meanwhile, others proposed the use of these agents as possible COVID-19 therapeutics to combat the resultant downregulation of ACE2.[17,29,30] Numerous studies to evaluate these questions ensued and found no significant differences in all-cause mortality, intensive care unit admissions, or need for mechanical ventilation, among other adverse outcomes in patients receiving these drugs. There was also insufficient evidence for benefit, resulting in recommendations from professional societies to neither stop nor start these agents.[31–40]

Presence of myocardial injury, as defined by The Fourth Universal Definition of Myocardial Infarction based on elevations in troponin levels, was identified in the earliest COVID-19 patients in Wuhan.[4,41–47] This observation was accompanied by the finding that patients with preexisting cardiovascular disease were more likely to develop myocardial injury with COVID-19. Evidence of myocardial injury, irrespective of the presence of prior cardiovascular disease, significantly increased rates of morbidity and mortality.[41,48–57] During the interval of 3 years, extensive work has aimed to understand the pathophysiologic basis for this injury, and to extrapolate how injury at the level of the viral particle and endothelial cell or cardiac myocyte begets injury at the level of the cardiovascular organ system as a whole, with particular attention paid to venous and arterial thrombosis, arrhythmias, acute coronary syndromes, myocarditis, and systolic dysfunction.[24,25,50,58–68]

ARRHYTHMIA

Outside of elevated troponin levels, the most common cardiac manifestation of COVID-19 is arrhythmia, observed in 17% of hospitalized patients and up to 44% of patients admitted to the ICU in early reports from Wuhan.[47] Notably, the development of arrhythmia as a complication of infection in an early study was second only to development of acute respiratory distress syndrome.[47] A later study assessing incidence of dysrhythmias in hospitalized COVID-19 patients in New York City reported a rate of 7.4%, which again rose substantially to 18.5% when patients with more severe illness requiring mechanical ventilation were assessed.[69] Tachyarrhythmias, bradyarrhythmias, atrial arrhythmias, and ventricular arrhythmias have all been described with COVID-19.[70–72] Patients who developed arrhythmia unsurprisingly had high rates of cardiovascular comorbidities, despite low incidence of arrhythmia before infection.[72] In a large global retrospective analysis, 43% of patients who developed any arrhythmia were critically ill requiring mechanical ventilation, 41% of these critically ill patients survived to hospital discharge, and only 51% of all patients who developed an arrhythmia while hospitalized survived to hospital discharge.[72]

In patients who develop arrhythmia, atrial fibrillation is the most common.[70–81] Moreover, many cases of reported atrial fibrillation in these studies were new onset, and in patients with critical illness, new onset atrial fibrillation was found to occur with an incidence of 14.9%.[75,76,82,83] Development of atrial fibrillation has also been shown to

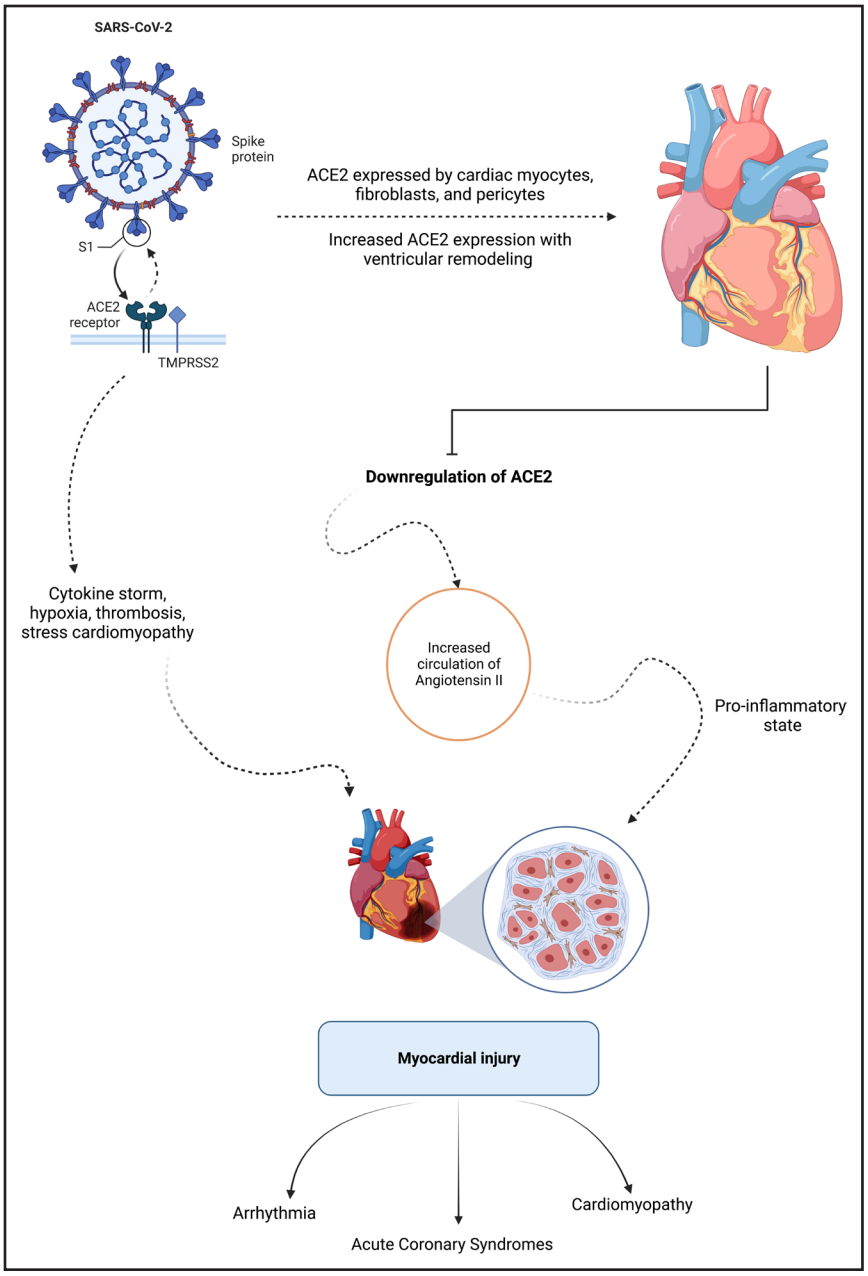

Figure. Proposed mechanisms of myocardial injury from COVID-19. ACE2 indicates angiotensin-converting enzyme 2; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

be an independent predictor of mortality in hospitalized patients with COVID-19.[83,84] In order of incidence following atrial fibrillation (61.5%), the relative proportion of arrhythmias seen in patients with COVID-19 worldwide were the following: bradycardia (12.8%), atrial flutter (10.4%), SVT (9.7%), AV block (8.6%), VT (8.1%), and VF (3.4%).[72] Proposed mechanisms of arrhythmogenesis are largely felt to be related to direct myocardial inflammation given the finding of greater degrees of troponin elevation in these patients as well as indirect effects from cytokine storm, hypoxia, and increased circulating angiotensin II resulting in a proinflammatory state (Figure).[71,75,77,79,83,85]

Similar to the trend seen in much of cardiovascular medicine at the onset of the pandemic, guidance on the management of patients living with preexisting electrical disturbances requiring ongoing electrophysiology care was put forth by the ACC/AHA/HRS in April of 2020. This guidance urged electrophysiology providers to avoid in-person visits, when possible, with a recommendation to perform device monitoring remotely as feasible. The guidance at this time was to postpone all elective procedures and gave clear recommendations on which procedures should be considered urgent versus semiurgent to help facilitate decision-making during this uncertain time.[86] Many electrophysiology providers highlighted the challenges they faced providing care to their patients, including the limitations of remote monitoring, the inability to utilize transesophageal echocardiography, and algorithms that were developed for QTc risk

management in the setting of hydroxychloroquine use in patients with borderline QTc intervals.[87] Updated recommendations from electrophysiology professional societies were made available regularly.[88]

HEART FAILURE AND MYOCARDITIS

Perhaps one of the most striking observations made early in the pandemic was the marked reduction in acute cardiovascular hospitalizations, many of which were nonelective, including those for heart failure (HF).[89–91] In a large academic hospital in Massachusetts, a 5.8% per day reduction in HF hospitalizations was identified throughout the month of March 2020, leading to concerns that this susceptible group of patients was intentionally avoiding necessary cardiovascular care due to the pandemic and public messaging.[89] This led to significant concerns that the national burden of HF incidence and undertreatment would rapidly grow due to delays in care.[92,93] Meanwhile, data became available revealing that patients with HF were particularly vulnerable with a 5- to 14.5-fold increase in mortality if hospitalized with COVID-19 as opposed to being hospitalized for a HF exacerbation.[94,95] Patients with HF hospitalized with COVID-19 in New York City between February and June 2020 had a mortality rate of 40%.[96] For patients with chronic HF, several pathophysiologic mechanisms for poor outcomes have been postulated. These include increased susceptibility to thrombosis, decreased cardiopulmonary reserve, baseline systemic inflammation characteristic of chronic HF syndromes, and interactions of COVID-19 with the rennin-angiotensin system.[92]

Given these findings, a rapid paradigm shift in delivery of chronic HF care took place, with emphasis placed on telehealth and alternate strategies to provide care outside of the inpatient and face-to-face arenas.[92] Two and a half years later, longer-term data are now available showing a modest increase in mortality among all hospitalized HF patients during the pandemic compared with prepandemic years regardless of infection status, albeit with a nearly 3-fold higher adjusted likelihood of death for patients with HF hospitalized with COVID-19.[97] Encouragingly, additional data are now becoming available showing relative stability in device related markers of HF status, such as thoracic impedance, over a 3-month period during the stay-at-home order in New York City and Minneapolis/Saint Paul.[98]

An additional high-risk population of interest is patients who have undergone advanced heart failure therapies, namely orthotopic heart transplant (OHT) and left ventricular assist device (LVAD) implantation. Early data with regards to OHT patients showed that most ultimately required inpatient admission with COVID-19 and at least 25% died. The authors highlight the challenges in management of posttransplant immunosuppression in the setting of acute infection.[99] Guidance from The International Society of Heart and Lung Transplantation released February 2021 advised that providers consider holding mycophenolate mofetil, mTOR inhibitors, or azathioprine in OHT patients with moderate to severe COVID-19.[100] Subsequent larger scale data in this population showed lower overall mortality rates although unchanged in OHT patients requiring hospitalization (24%).[101] This data set is further notable for a nearly 20% rate of requiring de novo renal replacement therapy in hospitalized patients, a 7-fold increased mortality risk for OHT patients receiving prednisone along with calcineurin inhibitor and antimetabolite immunosuppressive therapies, and a surprising trend of increased incidence of severe disease in patients who were further out from their transplant (10.9 versus 4.9 years—a finding which may be confounded by age and additional acquired comorbidities).[101] Similarly, LVAD patients had high hospitalization (60%) and case fatality (20%) rates with COVID-19.[102] A separate single-center analysis, however, showed that LVAD patients had lower case fatality rate than HF and OHT patients. While the authors highlight that most patients, including OHT (86.5%) and HF (69.8%) patients were on therapeutic anticoagulation, all LVAD patients were therapeutically anticoagulated and possibly conferred some benefit from this.[103] A few cases are available in the literature of LVAD pump thrombosis in the setting of COVID-19.[102,104,105]

Acute heart failure has also been described in COVID-19, dating back to the first cases in the United States from Washington state, where a third of patients developed acute cardiomyopathy within a cohort with an exceptionally high mortality rate of 67%.[106,107] In patients with severe COVID-19 who died in Wuhan, 49% developed acute heart failure during their course.[45] In concordance with this, elevated NT-pro BNP at time of admission, regardless of prior HF status, has been shown to be significantly and independently associated with COVID-19 inpatient mortality in a large nationwide cohort.[108]

While early hypotheses invoked myocarditis, defined by the presence of inflammatory infiltrate along with nonischemic myocyte necrosis, as the cause of this acute heart failure—the true incidence of COVID-19 myocarditis remains uncertain and debated, but lower than initially reported.[23,63,65,68,109–112] A large recent review of postmortem histopathologic data showed a high prevalence of myocardial necrosis and edema without myocarditis, owing to a lack of inflammatory infiltrate.[113] However, another up to date systematic review does show the presence of myocarditis, albeit infrequently, in available reported cases.[114] Current estimated rates of COVID-19 myocarditis are between 2.4 and 4.1 out of 1000 patients hospitalized for COIVD-19.[115]

Despite lack of clarity on true incidence of myocarditis, clinicians were, and continue to be, approached with important questions such as return to sport and physical activity with suspected myocardial inflammation

following COVID-19. Numerous return to play recommendations have been put forth by international organizations and include recommendations for symptomatic athletes to undergo additional testing before return to activity with laboratory testing (inflammatory markers, troponins), imaging, electrocardiography, and formal cardiology consultation.[116]

Imaging studies may help to shed some light on the myocardial injury that occurs in these patients.[117] In 100 patients with recovered mild to moderate COVID-19 who underwent cardiac MRI, 78 had evidence of cardiac involvement while ongoing myocardial inflammation was present in 60; 3 patients in the study had severe findings by imaging and underwent endomyocardial biopsy revealing active lymphocytic inflammation.[118] In order of frequency, imaging abnormalities were characterized by raised myocardial native T1 (representative of diffuse myocardial fibrosis and/or edema; when seen in isolation suggests a healed process with some residual diffuse myocardial damage), raised myocardial native T2 (specific for edema; suggestive of an active inflammatory process when seen along with raised native T1), nonischemic myocardial late gadolinium enhancement (defined anatomically by presence in the epicardium, the midwall, or at insertion points; proposed to be seen in patients with acute or healed myocarditis), pericardial enhancement (representative of regional damage due to myocardial inflammation; frequently seen with associated pericardial effusion attributed to fibrosis and/or edema due to an ongoing active pericarditis), and ischemic pattern late gadolinium enhancement (defined anatomically when present in a subendocardial or transmural pattern).[118] In a separate review of cardiac MRI studies involving 199 patients, the authors report myocarditis, diagnosed by Lake Louise criteria, in 40% of studies.[119] A review of the echocardiography literature in COVID-19 reveals low rates of LV systolic or diastolic dysfunction, modest rates of RV enlargement and systolic dysfunction, as well as modest rates of strain imaging abnormalities.[120] In another study examining echocardiograms performed within the first 24 hours of admission, 68% of studies were abnormal with the most common finding being RV dilation and dysfunction, followed by LV diastolic dysfunction, and then LV systolic dysfunction, which was present in 10% of studies.[121] A number of the patients in this study went on to clinically worsen and undergo repeat echocardiography, which predominantly showed deterioration in RV function followed by progressive LV systolic dysfunction.[121] RV dysfunction, present in large proportions of hospitalized patients with predictive value for poor outcomes, has been shown by other groups as well.[122,123]

While it is apparent that there is still no clear consensus, alternate explanations for acute myocardial injury resulting in myocardial dysfunction as identified on imaging studies, with associated poor outcomes, include injury at the level of the endothelial cell with subsequent microvascular and macrovascular thrombosis, stress cardiomyopathy, and toxic effects of angiotensin II.[62,109,124–130]

Albeit not an effect of COVID-19 and its pursuant syndrome, and therefore not discussed in this review, the discussion of myocarditis as related to COVID-19 vaccination is important and will be reviewed in detail separately within other articles included in this compendium.

ACUTE CORONARY SYNDROMES AND CARDIAC CATHETERIZATION LABORATORY CONSIDERATIONS

Similar to the observations made with HF hospitalizations at the onset of the pandemic, hospitalizations for chest pain and acute coronary syndromes (ACS) fell precipitously at the onset of the pandemic—including a marked reduction in ST-segment elevation myocardial infarction (STEMI) activations and primary percutaneous coronary intervention (PCI) volumes.[89,131–133] Furthermore, a significant fall in emergency transfers for acute cardiovascular conditions, including STEMI, was identified in Cleveland in March through May of 2020.[134] Despite this, interventional cardiologists prepared to adapt to a changing landscape in the delivery of cardiac catheterization laboratory (CCL) care through guidance put forth by professional societies on how to approach STEMI, non-ST-segment elevation myocardial infarction, and elective interventions.[135,136] These were updated regularly and, in April 2020, guidance was released indicating that primary PCI remained the standard of care for STEMI; as well as additional work flows to assist in navigation of situations such as receiving STEMI patients from referral hospitals and equivocal STEMI diagnoses.[137] Another adaptation to providing ACS care in the midst of the pandemic included consideration for utilization of risk scores for STEMI triage to identify patients who could be candidates for early discharge and non-ICU postprocedural care.[138] Early discussions regarding reintroduction of care were also put forward.[14] A thorough overview of best practices for CCL operations and periprocedural care in the face of pandemic has recently been made available.[139]

While these preparations were underway across the United States, early data became available from areas across the world that provided insight into the impact of COVID-19 on ACS presentations. During the initial COVID-19 surge in Northern Italy, a review of CCL activations over a month-long period highlighted that nearly 40% of typical STEMI presentations had no culprit lesion identified on angiography.[140] Given this unprecedented time, the North American COVID-19 Myocardial Infarction (NACMI) registry was created to assist in providing further guidance. Initial findings from the registry, involving data points from 1185 patients, of which 230

were confirmed to have COVID-19 and 495 were under investigation (and ultimately found to be negative), were made available in April 2021.[141] Again, a high incidence (23%) of CCL activations with no culprit lesion identified was observed in COVID-19 patients along with atypical presenting symptomatology.[141] This unique observation of STEMI without a culprit lesion on coronary angiography occurred more frequently in women (33% versus 18%).[142] In an effort to mitigate COVID-19 exposure risk and potentially unnecessary procedural risks, as well as data supporting diagnostic utility of coronary CT angiography in the acute setting, society recommendations included consideration of coronary CT angiography in place of angiography in select patients.[137,143]

Additional findings from the NACMI registry included high rates of cardiogenic shock, excess morbidity and mortality, and lower rates of invasive angiography in this group of predominantly ethnic minority patients.[141] Data from European registries showed similar findings including prolonged door to balloon times, significantly increased rates of in-hospital mortality, and suboptimal postprocedural TIMI flow in STEMI patients with active COVID-19 undergoing primary PCI.[144] Results from the International COVID-ACS registry were again consistent with the aforementioned registry data emphasizing increased in-hospital mortality, cardiogenic shock, and prolonged door to balloon times.[145,146] Using the NACMI registry, a weighted integer risk score was developed using readily available clinical data at time of STEMI presentation in patients with COVID-19 (respiratory rate >35, prePCI shock, hypoxia, age >55, infiltrates on chest x-ray, creatinine >1.5, diabetes, subjective dyspnea) to accurately predict in-hospital mortality.[147] Updated data from the NACMI registry showed that with the onset of vaccination in 2021, there was a reduction of in-hospital mortality, prePCI shock, and pulmonary manifestations, with an overall encouraging trend towards prepandemic STEMI outcomes in patients who present with STEMI and COVID-19.[148]

Immune system stimulation resulting in a hyperinflammatory state resulting in plaque rupture events as well as upregulation of procoagulants and platelet activation resulting in microvascular and coronary thrombosis is one of the proposed mechanisms for STEMI in COVID-19.[149] Interestingly, STEMI patients with COVID-19 were found to require higher doses of heparin intraprocedurally and had overall higher thrombus burdens requiring more aspiration thrombectomy use.[150] This is in line with the robust body of literature now available investigating the magnitude of the prothrombotic effects of COVID-19, and potential utility of anticoagulant treatments, highlighting these phenomena as a primary pathophysiologic mechanism for many of the cardiovascular clinical presentations encountered.[151–159]

Outside of ACS, life-prolonging and symptom-ameliorating procedures performed in the CCL, namely those performed for treatment of structural heart disease, required adaptation to the pandemic.[160] Again, professional society guidance on the triage of patients undergoing evaluation for or pending transcatheter valve therapies was put forth and of great utility to the interventional cardiology community.[161] Recommendations included navigating deferred procedure monitoring via telehealth, utilization of moderate procedural sedation, postprocedural care modifications to minimize ICU bed needs, and indications for preprocedural PCI before transcatheter aortic valve replacement.[161] Similar to the 55% reduction in PCI volume observed early in the pandemic, with many patients experiencing STEMI electing to stay-at-home rather than risk exposure to the virus, there was a 64% reduction in transcatheter aortic valve replacement volume felt to be due to an increase in preprocedure deaths while awaiting intervention.[162–165] In a 3-month period in early 2020, over 45 000 fewer cardiovascular procedures were performed as compared to prior years in England alone, which highlighted the far-reaching implications of the pandemic on all procedures performed in the CCL.[166]

When severe, the result of the aforementioned cardiovascular manifestations of COVID-19 is cardiogenic shock. Thankfully, this appeared to occur infrequently, but resulted in astonishingly high mortality rates when present.[167,168] In the context of STEMI, presentation with cardiogenic shock was increased with COVID-19 and delayed presentations resulted in an increase in mechanical complications and consequential shock physiology.[15,169] The approach to in-hospital resuscitation in critically ill COVID-19 patients, particularly those who suffered an in-hospital cardiac arrest with an observed survival rate of less than 6%, was scrutinized.[170,171] The need for mechanical circulatory support in COVID-19 STEMI patients who developed cardiogenic shock was also associated with excessive mortality rates.[133,172] The decision to pursue these aggressive interventions in this population should be highly selective and offered after consideration by a multidisciplinary team.[172–174]

DISPARITIES IN CARDIOVASCULAR CARE DURING THE PANDEMIC

While it was well understood that significant disparities existed in the delivery of cardiovascular care to certain racial, ethnic, and socioeconomic groups prior the pandemic, clear trends emerged early and persisted showing disproportionate cardiovascular morbidity and mortality during the pandemic, particularly among communities of color and historically marginalized groups.[175,176] The higher prevalence of both cardiovascular disease, as well as cardiovascular disease risk factors, in nonwhite populations has been

Table. Available Research by Study Type

	Strengths	Weaknesses	Impact	Future Needs
Epidemiological	Provide insight into overall burden of disease	Most have been single center or regional	Large number published early and often	Repetition to assess changes in trends to determine resolution of previously identified issues
	Foster formation of registries	Require ongoing re-examination as the disease evolves	Essential in identification of trends seen in early COVID (decreased cardiovascular admissions)	Ongoing focus on identified disparities after mitigation efforts are put into place
	Help to identify disparities			
Basic and translational science	Help foster understanding of underlying pathophysiology	Inconsistent conclusions have been drawn (myocarditis vs myocarditis-like findings at the cellular level due to alternate mechanisms such as microvascular thrombosis)	Although not specific to cardiovascular medicine, has been essential in the face of the pandemic for vaccine and development of novel therapeutics	Ongoing clarification of pathophysiologic mechanisms, specifically mechanisms of myocardial injury witnessed clinically, many of which remain unclear
Observational	Easy to perform with limited time and resources	Susceptible to confounding due to cross-sectional design (RV dysfunction could be related to direct cardiac effects or thrombotic complications or hypoxia)	Primary data type available throughout the pandemic, although requires cautious interpretation	Long-term impacts of COVID
Clinical trials	Gold-standard to provide definitive answers to important questions (impact of ACE inhibitor and ARB exposure)	Requires longer-study periods in a rapidly evolving disease process	Most have focused on exoneration of therapeutic hypotheses (hydroxychloroquine, ivermectin, etc)	Targeted treatments to identified high-risk groups (such as those with preexisting cardiovascular disease) and therapeutic impact
		Difficult to design in a way specifically relevant to cardiovascular impact of COVID	Anticoagulant strategy guidance	

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and RV, right ventricle.

well characterized. This, however, does not sufficiently explain why certain nonwhite populations (specifically Black, Hispanic, and Asians), experienced a 20% increase in cardiovascular death, while White individuals experienced only a 2% increase.[177,178] Disparities in treatment and care were noted both in the inpatient and outpatient settings. An institutional review from the United Kingdom demonstrated that nonwhite patients admitted with acute coronary syndromes during the pandemic had significantly longer times to reperfusion and were referred less frequently for invasive testing than matched white patients during the same time period.[179] In the outpatient setting, emphasis on a patient's age, race, and other social determinants with regard to their participation in the evolving world of telemedicine was scrutinized. A large single-center study from New England showed that older patients for whom English was not their primary language, patients from lower socioeconomic backgrounds, and Black patients were all less likely to be reached by providers via telemedicine platforms.[180] This is especially striking when considering the sharp rise in use and reliance on telemedicine observed during late 2019 through 2020.[181] The notable differences in the delivery of cardiovascular care, as well as the burden of cardiovascular morbidity and mortality as pertinent to social and racial constructs in the era of COVID-19, warrants further investigation.

CONCLUSIONS

As outlined throughout this review, the cardiovascular community has faced distinct and profound challenges throughout the COVID-19 pandemic. From an elevated risk of COVID-19 related complications in patients with preexisting cardiovascular disease, cardiovascular manifestations of COVID-19, and restrictions placed on the delivery of life-saving care, cardiologists across the globe have been called on to adapt quickly and diligently.[182] Cardiovascular professional societies responded quickly with frequently updated guidance and registries were formed to facilitate navigating this challenging time for the sake of our patients' health.[183] A primary challenge, from which the community is still recovering, involves the omissions and delays of care along with their downstream consequences for both acute and chronic cardiovascular conditions.[184] Without doubt, there were deep psychological and social impacts of the pandemic both affecting cardiovascular healthcare workers and their patients, with those most at risk suffering the greatest.[15,185]

Through these challenges, important lessons have been learned. Examples of these include the impact of public messaging on behaviors, the outcomes associated with these risk-aversion behaviors, strategies to tailor public messaging to mitigate associated poor outcomes due to these behaviors, and earlier recognition and intervention when unintended consequences of public health

efforts arise.[13,14,186,187] Alleviation of the impacts the pandemic has caused on the cardiovascular scientific community will be of utmost importance moving forward.[188]

As new data begin to emerge highlighting long-term impacts of COVID-19 infection on cardiovascular health, particularly increased incidence of nearly all cardiovascular disorders with prior history of COVID-19, the cardiovascular community must remain prepared and noncomplacent to tackle novel challenges that will continue to surface.[189,190] As should be evident through this review, a major limitation of our current understanding of cardiovascular manifestations of COVID-19 is the lack of high-quality research for clinicians to turn to and overall substandard for the level of evidence that the cardiovascular community has grown to expect (Table). The majority of the available literature, which has rapidly grown to an immeasurable collection, is largely observational and fraught with methodologic flaws, as highlighted by lack of consistency with frequent contradictory findings. Significant confounding cannot be excluded in many of these available studies, which is an inherent limitation to their cross-sectional design. While we appreciate that this work is an essential hypothesis-generating step in scientific discovery, follow-up studies investigating these hypotheses in rigorous scientific manner is necessary moving forward before conclusions can be made. A major focus moving forward should be on the production and dissemination of this high-quality reproducible evidence to guide our understanding and clinical practice in the face of this evolving pandemic.

ARTICLE INFORMATION

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