VIEWPOINT

Cardiology and COVID-19

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The initial reports on the epidemiology of coronavirus disease 2019 (COVID-19) emanating from Wuhan, China, offered an ominous forewarning of the risks of severe complications in elderly patients and those with underlying cardiovascular disease, including the development of acute respiratory distress syndrome, cardiogenic shock, thromboembolic events, and death. These observations have been confirmed subsequently in numerous reports from around the globe, including studies from Europe and the US. The mechanisms responsible for this vulnerability have not been fully elucidated, but there are several possibilities. Some of these adverse consequences could reflect the basic fragility of older individuals with chronic conditions subjected to the stress of severe pneumonia similar to influenza infections. In addition, development of type 2 myocardial infarction related to increased myocardial oxygen demand in the setting of hypoxia may be a predominant concern, and among patients with chronic coronary artery disease, an episode of acute systemic inflammation might also contribute to plaque instability, thus precipitating acute coronary syndromes, as has also been reported during influenza outbreaks.

However, in the brief timeline of the current pandemic, numerous publications highlighting the constellation of observed cardiovascular consequences have emphasized certain distinctions that appear unique to COVID-19.[1] Although the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains entry via the upper respiratory tract, its affinity and selective binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is abundant in the endothelium of arteries and veins as well as in the respiratory tract epithelium, create a scenario in which COVID-19 is as much a vascular infection as it is a respiratory infection with the potential for serious vascular-related complications. This may explain why hypertension is one of the cardiovascular conditions associated with adverse outcomes. In the early stages of the pandemic, the involvement of the ACE2 receptor as the target for viral entry into cells created concerns regarding the initiation or continuation of treatment with ACE inhibitors and angiotensin receptor antagonists in patients with hypertension, left ventricular dysfunction, or other cardiac conditions. Subsequently, many studies have shown that these drugs do not increase susceptibility to infection or increase disease severity in those who contract the disease,[2] thus supporting recommendations from academic societies that these drugs should not be discontinued in patients who develop COVID-19 infections.

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Thrombosis, arterial or venous, is a hallmark of severe COVID-19 infections, related both to vascular injury and the prothrombotic cytokines released during the intense systemic inflammatory and immune responses.[3] This sets the stage for serious thrombotic complications including acute coronary syndromes, ischemic strokes, pulmonary embolism, and ischemic damage to multiple other organ systems. Such events can complicate the course of any patient with COVID-19 but would be particularly devasting to individuals with preexisting cardiovascular disease.

Another unique aspect of COVID-19 infections that is not encountered by patients with influenza is myocardial injury, manifested by elevated levels of circulating troponin, creatinine kinase-MB, and myoglobin. Hospitalized patients with severe COVID-19 infections and consequent evidence of myocardial injury have a high risk of in-hospital mortality.[4] Troponin elevations are most concerning, and when accompanied by elevations of brain natriuretic peptide, the risk is further accentuated. Although myocardial injury could reflect a COVID-19–related acute coronary event, most patients with troponin elevations who undergo angiography do not have epicardial coronary artery obstruction. Rather, those with myocardial injury have a high incidence of acute respiratory distress syndrome, elevation of D-dimer levels, and markedly elevated inflammatory biomarkers such as C-reactive protein and procalcitonin, suggesting that the combination of hypoxia, microvascular thrombosis, and systemic inflammation contributes to myocardial injury. Myocarditis is a candidate explanation for myocardial injury but has been difficult to confirm consistently. However, features of myocarditis have been reported in case reports[5] based on clinical presentation and results of noninvasive imaging, but thus far confirmation of myocarditis based on myocardial biopsy or autopsy examinations has been a rare finding.[6] Instead, myocardial tissue samples more typically show vascular or perivascular inflammation (endothelialitis) without leukocytic infiltration or myocyte damage.

There remain important unknowns regarding the intermediate and long-term sequelae of COVID-19 infection among hospital survivors. In an autopsy series of patients who died from confirmed COVID-19 without clinical or histological evidence of fulminant myocarditis,[7] viral RNA was identified in myocardial tissue in 24 of 39 cases, with viral load of more than 1000 copies/μg of RNA in 16 cases. A cytokine response panel demonstrated upregulation of 6 proinflammatory genes (tumor necrosis factor, interferon γ, *CCL4*, and interleukin 6, 8, and 18) in the 16 myocardial samples with the high viral RNA levels.

Whether a subclinical viral load and associated cytokine response such as this in survivors of COVID-19

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could translate into subsequent myocardial dysfunction and clinical heart failure require further investigation. However, the results of a recent biomarker and cardiac magnetic resonance (CMR) imaging study provide evidence to support this concern.[6] Among 100 patients who were studied by CMR after recovery from confirmed COVID-19 infection, of whom 67 did not require hospitalization during the acute phase, left ventricular volume was greater and ejection fraction was lower than that of a control group. Furthermore, 78 patients had abnormal myocardial tissue characterization by CMR, with elevated T1 and T2 signals and myocardial hyperenhancement consistent with myocardial edema and inflammation, and 71 patients had elevated levels of high-sensitivity troponin T. Three patients with the most severe CMR abnormalities underwent myocardial biopsy, with evidence of active lymphocytic infiltration.[6] It is noteworthy that all 100 patients in this series had negative COVID-19 test results at the time of CMR study (median, 71 days; interquartile range [IQR], 64-92 days after acute infection). The results of these relatively small series should be interpreted cautiously until confirmed by larger series with longer follow-up and with confirmed clinical outcomes. But the findings do underscore the uncertainty regarding the long-term cardiovascular consequences of COVID-19 in patients who have ostensibly recovered. Of note, a randomized clinical trial of anticoagulation to reduce the risk of thrombotic complications in the posthospital phase of COVID-19 infection is under development through the National Institutes of Health's set of ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) initiatives.

In addition, the indirect effects of COVID-19 have become a major concern. Multiple observations during the COVID-19 pandemic confirm a sudden and inexplicable decline in rates of hospital admissions for ST–segment elevation myocardial infarction and other acute coronary syndromes beginning in March and April 2020. This has been a universal experience, with similar findings reported from multiple countries around the world in single-center observations, multicenter registries, and national databases. A concerning increase in out-of-hospital cardiac arrests has also been reported.[8] These data suggest that COVID-19 has influenced health care–seeking behavior resulting in fewer presentations of acute coronary syndromes in emergency departments and more out-of-hospital events. Failure to seek appropriate emergency cardiac care could contribute to the observations of increased number of deaths and cardiac arrests, more than the anticipated average during this period[8,9] with worse outcomes among those who ultimately do seek care.[10] Recent data suggest that admission rates for myocardial infarction may be returning to baseline,[10] but outcomes will improve only if patients seek care promptly and hospital systems are not overwhelmed by COVID-19 surges.

Given the ongoing activity of COVID-19, very clear messaging to the public and patients should include the following: heed the warning signs of heart attack, act promptly to initiate emergency medical services, and seek immediate care in hospitals, which have taken every step needed to be safe places. And especially, the messaging should continuously underscore the most important considerations that have been extant since this crisis began—wear a mask and practice physical distancing. In the meantime, the generation of rigorous evidence to inform best practices for diagnosis and management of COVID-19–related cardiovascular disease is a global imperative.

ARTICLE INFORMATION

Conflict of Interest Disclosures: None reported.

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