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VIEWPOINTS

Coronavirus 2019 Disease (COVID-19), Systemic Inflammation, and Cardiovascular Disease

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Acute respiratory failure, associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread worldwide and presents critical challenges for the public health and medical communities. The World Health Organization has declared SARS-CoV-2 a public health emergency of international concern, with a global estimate of over 7 million human infections and more than 400 000 deaths worldwide as of June 12, 2020.[1]

A 2020 report by the China Medical Treatment Expert Group for Coronavirus Disease 2019 (COVID-19)[2] showed that the clinical spectrum of the viral infection is dominated by fever (up to 88.7% of patients during hospitalization) and cough (67.8% of patients), followed by symptoms such as headache, fatigue, or shortness of breath. Rapid deterioration of lung function, disproportionate to the magnitude of pneumonia, has implicated the cytokine storm as a major life-threatening complication of COVID-19 infection. To date, other than antibiotic therapy and ventilator support, no drug therapies have shown clear benefit in patients with COVID-19. Nevertheless, understanding the mechanisms underlying the complications from the infection is critical.

INTERPLAY BETWEEN COVID-19, INFLAMMATION, AND THE CARDIOVASCULAR SYSTEM

It has been hypothesized that the viral infection's course is characterized by 2 pathways: (1) the virus inoculation and multiplication in the upper respiratory tract with or without pulmonary involvement, and (2) the host response showing extrapulmonary systemic hyperinflammation syndrome.[3] Subjects developing this abnormal response, usually in the advanced stages of infection, present a cytokine storm characterized by marked elevations of interleukin- (IL-) 2, IL-6, IL-7, tumor necrosis factor-α, C-reactive protein, ferritin, d-dimer, and high-sensitivity cardiac troponin I. This inflammatory response is associated with a far higher risk of adverse outcomes and potentially with long-term multiorgan damage for those who survive.

Subjects at high risk also present a significant burden of cardiovascular comorbidities with hypertension being the most common (30%–35.8%), followed by diabetes mellitus (19%–26.9%) and coronary artery disease (8%–9%).[2,4] Healthy subjects, including children and young adults, are more often asymptomatic, probably given the low immune response and inflammation burden. Whether underlying cardiovascular disease can aggravate infectious complications and amplify the inflammatory response needs to be proven. Nevertheless, cardiac involvement, including acute myocarditis and heart failure (HF), as a complication of viral infection has been reported for both the Middle East respiratory syndrome-related coronavirus and SARS-CoV-2.[5] Cardiac injury has an incidence of around 20% over the course of the infection; it is associated with an increased risk of mortality, more impaired radiographic findings, and elevated laboratory markers, such as C-reactive protein, NT-proBNP

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(N-terminal pro-B-type natriuretic peptide), d-dimer, and troponin.[6] Similarly, increasing evidence of arterial and venous thromboembolic events has been associated with an increase in laboratory markers underlying cardiovascular injuries. Thus, SARS-CoV-2 may be an example of adverse neurohormonal activation and inflammation as major pathogenic mechanisms.

This concept may explain why specific subsets of patients seem so susceptible to coronavirus infection. One potential mechanism relates to the upregulation of the renin-angiotensin system with overactivation of angiotensin-converting enzyme-2 (ACE2), a receptor for coronavirus entry into cells.[7] Although the main target is the respiratory system, it has been hypothesized that the virus may use the ACE2 receptor to directly invade the cardiovascular system through the cardiomyocytes, the arterial and venous endothelial cells, and the arterial smooth muscle cells.[8] Moreover, the ACE2 enzyme is overexpressed in patients with prevalent cardiac disease, thus potentially increasing virus binding/entry and easing a larger viral burden onto cells. To date, however, no SARS-CoV-2 genome has been detected inside myocardial cells—only inside macrophages.[9] There is no evidence that ACE inhibitors or angiotensin receptor blockers increase this risk; stopping these agents can be hazardous for patients.[10] Hence, given the absence of clinically harmful evidence, international societies and experts have recommended continued use of these medications. The inflammatory activation, which many patients with cardiovascular disease already experience, may be a more general cause of increased susceptibility to coronavirus infection, and once it has taken place, of more severe respiratory failure and end-organ damage occurring in patients with SARS-CoV-2.

Viral infection may further amplify the inflammatary burden carried by patients with atherosclerotic cardiovascular disease. This amplification, in turn, may potentially mediate lung injury, as well as myocardial and vascular injury, caused by COVID-19. Ultimately, after gaining initial entry through ACE2, the viral infection process leads to a downregulation of ACE2 that has a well-recognized role in myocardial recovery and injury response.[10] Consequently, it may theoretically attenuate its cardioprotection role in the context of myocardial and vascular involvement in COVID-19. A critical issue for the cardiovascular community is thus to better understand potential interactions between atherosclerosis, myopathy, and the hyperinflammation syndrome associated with SARS-CoV-2 infection.

Epidemiologic and vascular biology data clearly indicate that high inflammation burden, as measured either by C-reactive protein or IL-6, is strongly associated with future cardiovascular events in subjects with and without prevalent heart disease and independent of usual cardiovascular risk factors.[11] Inflammatory pathway activation is known to play a major role in the pathogenesis of atherosclerosis, hypertension, and coronary artery disease. Proof-of-principle that inflammation inhibition can improve cardiovascular outcomes was provided in the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial where canakinumab, a monoclonal antibody targeting IL-1β, significantly reduced the rate of recurrent cardiovascular events in subjects with previous myocardial infarction and a high-inflammatory burden measured by sensitivity C-reactive protein plasma levels.[11]

Acute and chronic infections may promote the inflammatory process increasing IL plasma levels, inducing complement activation, oxygen radicals, and immune complex deposition, leading to endothelial dysfunction, a hypercoagulable state, plaque destabilization and rupture, thus contributing to acute coronary syndrome events or thromboembolic events. The recognition of such complications during COVID-19 infection will increase our understanding of this emerging outbreak, potentially providing novel therapeutic strategies.

Inflammation also has a major role in the pathogenesis of HF. This has been shown in HF and reduced ejection fraction (HFrEF), but likely to a higher degree when EF is preserved (HFpEF).[12]

In HFpEF, a systemic proinflammatory state has been proposed to promote microvascular endothelial cell inflammation, increase oxidative stress, impair endothelial formation of nitric oxide, and eventually cause myocyte hypertrophy, apoptosis, and interstitial fibrosis replacement with consequent cardiac remodeling and dysfunction.[12] Given the role of inflammation in the pathogenesis of pneumonia and acute respiratory distress syndrome, as well as in the hallmark histological changes related to massive interstitial and alveolar edema, SARS-CoV-2 can mediate potential myocardial injuries as shown in some rare cases of SARS-related HF onset caused by acute myocarditis. Although this hypothesis needs to be confirmed, about 35% of autopsies of patients who died from SARS-CoV revealed the presence of viral RNA associated with reduced ACE2 protein expression.[10,13] Hence, it can potentially explain the mechanisms by which the infection process can mediate cardiac injuries, at least in the short-term. Although the deleterious effect of inflammation potentially leading to HF takes place over long periods, in subjects with underlying heart disease this process may be triggered in acute or subacute phases. As previously described for SARS-CoV and influenza infections, a transient impairment in cardiac function followed by progressive recovery characterized the clinical course of infection.[14] Systematic study of affected patients with SARS-CoV-2 and

epidemiological surveillance will address whether the acute and long-term effect of the immune response to the viral infection contribute to cardiac remodeling and to the incidence of HF hospitalizations, with a potential long-term reversibility.

POTENTIAL THERAPEUTIC APPROACHES

Hypothesized therapeutic approaches to SARS-CoV-2 infection include antiviral therapy as well as immunomodulatory agents. Although no specific antiviral drugs have been developed for COVID-19, multiple existing antiviral drugs are being tested.

The cytokine storm syndrome is also a promising therapeutic target, especially in patients with symptomatically worsening disease. There are still controversies about the efficacy of glucocorticoids during the clinical course of major viral infection, given prior observational data suggesting potential harmful effects for influenza, SARS-CoV, and Middle East respiratory syndrome-related coronavirus, resulting in potential delayed viral clearance.[15] However, recent observational data showed a use of steroids in a variable proportion of COVID-19 patients with some potential beneficial effect for those who developed acute respiratory distress syndrome[16] its use is under investigation in controlled studies (ClinicalTrials.gov Identifiers: NCT04273321 and NCT04381936). The use of corticosteroids may be justified to attenuate the excessive inflammation burden, especially when there is no evidence of active viral replication, and to directly suppress inflammatory cytokines, such as IL-10 and IL-6 secreted by macrophages and monocytes.[17] Based on a promising case series from Wuhan, China, multiple trials are now underway evaluating the potential benefits and risks of targeted IL-6 inhibition using recombinant monoclonal antibodies such as tocilizumab and sarilumab (Chinese Clinical Trial Register: ChiCTR2000029765; ClinicalTrials.gov Identifiers: NCT04317092 and NCT04315298, respectively). As the main hypothesis is to obtain a reduction of worse events by reducing the host inflammation response causing the main clinical course complications, the selection and identification of the patients with a high inflammation burden, potentially before the hyperactivation of the cytokines storm, are the main unmet medical need. Alternative immunomodulators, such as the complement inhibition and Janus kinase inhibitors (ClinicalTrials.gov Identifiers: NCT04288713 and NCT04320277), affecting both inflammation and cellular viral entry, and vascular endothelial growth factor inhibition (ClinicalTrials.gov Identifier: NCT04305106), to reduce lungs inflammatory exudation and vascular permeability, are under examination. Moving upstream, it is logical that trials of IL-1β inhibition (canakinumab [ClinicalTrials.gov Identifiers: NCT04362813 and NCT04365153] and anakinra [ClinicalTrials.gov Identifier: NCT04364009]) and colchicine are also being initiated. However, these latter approaches may require much earlier intervention if they are to successfully inhibit the downstream IL-6–mediated cytokine storm. Finally, promising results may derive from the use of intravenous immunoglobulin and monoclonal antibodies. Given their efficacy in improving passive immunity and modulating immune inflammation, as well as targeting vulnerable sites on viral surface proteins, their use is under investigation in controlled trials (ClinicalTrials.gov Identifiers: NCT04411667, NCT04350580, NCT04354766) as potential options in patients in early-stage COVID-19.

Ultimately, the recognition of potential cardiovascular complications related to COVID-19 infection may be helpful for monitoring affected patients and for improving our knowledge of this emerging public health outbreak. It is already clear that myocardial injury in patients with COVID-19 identifies high risk of hospital complications and death. Protection from cardiac injury may therefore be a further potential target, although this is likely to occur with the effective agents among those outlined above. Hard trial evidence demonstrating that antiviral and anti-inflammatory agents can improve outcomes in cases of COVID-19 infection is urgently needed.

ARTICLE INFORMATION

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Disclosures

None.

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