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 (WHO) 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 400000 deaths worldwide as of June 12, 2020 (1).

A 2020 report by the China Medical Treatment Expert Group for Coronavirus disease 2010 (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 drugs therapies have yet shown clear benefit in COVID-19. Nevertheless, understanding the mechanisms underlying the infection course complications is critical.

Interplay between COVID-19, Inflammation and the cardiovascular system

It has been hypothesized that the viral infection course is characterized by 2 pathways: one related with the virus inoculation and multiplication in the upper respiratory tract with or without pulmonary involvement, and one related with the host response showing an extra-pulmonary 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 (CRP), 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 a long-term multi-organ damage for those that survive.

Subjects at high risk also present a significant burden of cardiovascular (CV) comorbidities with hypertension being the most common (30-35.8%), followed by diabetes (19-26.9%) and

coronary artery disease (8-9%) (2,4). On the contrary, healthy subjects including children and young adults are more often asymptomatic, probably given the low immune response and inflammation burden. Whether underlying CV disease can aggravate infectious complications and amplify the inflammatory response need 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 (MERS- CoV) and SARS-CoV-2 (5). Cardiac injury has an incidence of around 20% during the infection course and it is associated with an increased risk of mortality, more impaired radiographic findings and elevate laboratory markers, such as C-reactive protein, NT-proBNP, d-dimer and troponin (6). Similarly, there have been increasing evidence of arterial and venous thromboembolic events associated with an increase of laboratory markers, underlying CV injuries. Thus, SARS-CoV-2 may represent 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 over activation 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, ACE2 enzyme is over-expressed in patients with prevalent cardiac disease, thus potentially increasing the availability for the virus binding/entry and easing larger viral burden into cells. To date, however, no SARS-CoV-2 genome was detected inside the myocardial cells but only inside macrophages (9). There is no evidence, that prescription of ACE inhibitors or angiotensin receptor blockers increases this risk and stopping these agents can be hazardous for patients (10). Hence, given the absence of clinically harmful evidence, international societies and experts opinion have recommended continued use of these medications. The inflammatory activation that many patients with cardiovascular disease already have 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 SARS-CoV-2.

Viral infection may further amplify the inflammatary burden carried by patients with atherosclerotic CV disease. This amplification, in turn, may potentially mediate lung 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 down-regulation 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 CRP or IL-6, is strongly associated with future CV events in subjects with and without prevalent heart disease and independent of usual CV 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 trial where canakinumab, a monoclonal antibody targeting interleukin-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 interleukin plasma levels, inducing complement activation, oxygen radicals, and immune complex deposition, leading to endothelial dysfunction, a hypercoagulable state, plaque destabilization and rupture and thus contributing to acute coronary syndrome (ACS) 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 has also 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 ARDS, as well as in the hallmark histological changes related with massive interstitial and alveolar edema, SARS-CoV-2 can mediate potential myocardial injuries as shown in some rare cases of SARS-related HF onset due to acute myocarditis. Although this hypothesis needs to be confirmed, about 35% 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 period. Although the deleterious effect of inflammation potentially leading to HF takes place over long periods of time, in subjects with underlying heart disease this process may be triggered in acute or subacute phases. As previously described for SARS-CoV and influenza infection, a transient impairment in cardiac function followed by a progressive recovery, characterized the clinical course of infection (14). Systematic study of affected SARS-CoV-2 patients 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 for SARS-CoV-2 infection include antiviral therapy as well as immunomodulatory agents. Although no specific anti-viral 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 MERS-CoV, 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) and its use is under investigation in controlled studies (NCT04273321, NCT04381936). On one hand, the use of corticosteroids may be justified in order to attenuate the excessive inflammation burden, especially when there is no evidence of active viral replication, and on the other by directly suppressing inflammatory cytokines such as IL-10 and IL-6 secreted by macrophages and monocytes (17). Based on a promising case series from Wuhan, 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 (ChiCTR2000029765, 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, represent the main unmet medical need. Alternative immunomodulators such as the complement inhibition and janus kinase (JAK) inhibitors (NCT04288713 and NCT04320277), affecting both inflammation and cellular viral entry, and the vascular endothelial growth factor (VEGF) inhibition (NCT04305106), to reduce lungs inflammatory exudation and vascular permeability, are under examination. Moving upstream, it is logical that trials of IL-1β inhibition [canakinumab (NCT04362813, NCT04365153) and anakinra (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 derive from the use of intravenous immunoglobulin (IVIg) and monoclonal antibodies. Given their efficacy in improving passive immunity and modulating immune inflammation on one side and targeting vulnerable sites on viral surface proteins on the other, their use is under investigation in controlled trials (NCT04411667, NCT04350580, NCT04354766) as potential options at the early stage of patents with 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 public health emerging outbreak. It is already clear that myocardial injury during COVID-19 identifies patients at high risk of death and hospital complications. Protection from cardiac injury may therefore be a further potential target, although this is likely to occur with effective agents

among those outlined above. Hard trial evidence demonstrating that anti-viral and anti-inflammatory agents can improve outcomes in COVID-19 is urgently needed.

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