Cardiovascular Disease Complicating COVID-19

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Cardiovascular disease (CVD) is the leading cause of death worldwide. Its incidence increases sharply with age, and the elderly bear a disproportionate burden of CVD morbidity and mortality. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), has also caused significant mortality, specifically amongst the elderly, who are the most likely patient population to be hospitalized and die from the infection. Pre-existing CVD is a known risk factor for poor outcome in Covid-19 patients and, in our efforts to preserve life, attention must be paid to the adverse impact of the virus on the cardiovascular system. The emergence of novel SARS-CoV-2 pathogenic variants with greater transmissibility is prolonging the pandemic and sustaining the threat to life and health. An understanding of the pathogenic mechanisms that underlie the CVD-Covid-19 interaction can lead to improved treatment and reduced sequelae in the midst of this global health crisis.

COVID-19 atherosclerosis cardiovascular disease hypertension inflammation cytokines

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1][2]. Its incidence increases sharply with age, and the elderly bear a disproportionate burden of CVD morbidity and mortality [3][4][5]. Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), the causal agent of Coronavirus disease 2019 (COVID-19), has a single-stranded RNA genome. It is able to invade cells through attachment of the spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor. This highly infectious virus has spread globally, causing significant mortality. A poor prognosis is observed amongst the elderly who are the most likely patient population to be hospitalized and die from the infection [6][7][8].

Factors that likely contribute to a complicated course and higher death rate in COVID-19 patients with underlying CVD are the hypercoagulable state that can result from COVID-19 infection, as well as polypharmacy (an indicator of comorbidities) [9][10][11][12]. Furthermore, the pandemic can disrupt lifestyle, leading to poorer diet and inactivity [13]. Another obstacle for older CVD patients is the avoidance of medical care from fear of contracting COVID-19. Hypertension, diabetes, and obesity, which often accompany CVD, are themselves established risk factors for severe COVID-19 that require careful management [14]. There is also a higher prevalence of cancer within the elderly population [15]. In addition to being immunocompromised from the cancer itself, cancer patients are frequently treated with immunosuppressants and cardiotoxic chemotherapies, making them especially susceptible

to both viral illnesses and secondary cardiovascular complications. A particularly high risk of poor outcome is seen in those who have undergone recent bone marrow or stem cell transplantation and those exposed to poly ADP ribose polymerase (PARP) inhibitors [16][17]. The aforementioned conditions are more prevalent in those over age 65 and extremely common in those over age 85. Low vitamin D levels, common in the obese state, may add further risk [18].

Excess production of cytokines and cytokine storms are central to many of the sequelae of COVID-19, including damage to the cardiovascular system via pathways that involve direct cardiotoxicity and through inflammation-induced myocarditis and pericarditis [19][20]. The effects of cytokines, particularly of interleukin (IL)-6, will be discussed in the sections to follow.

Since persons with CVD are susceptible to poor COVID-19 outcomes, targeted treatment and removal of barriers to care are crucial for this population [21]. These may include the use of telemedicine, adjusting antihypertensive regimens, and online activity tracking.

2. Coagulopathy in COVID-19: Mechanisms, Manifestations, and Treatment

A state of hypercoagulability frequently accompanies COVID-19, especially in severe disease [22][23]. Coagulopathy leaves patients vulnerable to thrombotic complications, including venous thromboembolism, pulmonary embolism, and disseminated intravascular coagulation [24][25][26][27][28].

Pro-inflammatory mediators produced during COVID-19 infection cause the release of tissue factor, an initiator of blood coagulation, from mononuclear cells [29][30]. IL-6, a key mediator elevated in the COVID-19 setting, can raise tissue factor levels and may also stimulate platelet production in bone marrow and lungs [31][32][33]. The panoply of inflammatory factors also activates endothelial cells, increasing their expression of adhesion molecules and leading to the release of the von Willebrand factor, thus promoting a procoagulant endothelial phenotype, excessive activity in the coagulation cascade, and multiple thrombotic complications.

Coagulation abnormalities are detected in laboratory tests as increased serum concentrations of the procoagulants fibrinogen and D-dimers as well as decreased antithrombin and prolonged prothrombin time (**Table 1**) [34][35].

Table 1. Early Markers Associated with Poor Outcomes in COVID-19 Patients.

Marker	Mean Level	Time of Measurement	Definition of Poor Outcome	Reference
IL-6	7.39 pg/mL	On admission	ARDS	[20]
Fibrinogen	5.16 g/L	On admission	Death	[26]
D-dimer	≥1 µg/mL	Outpatient	Death	[32]

Marker	Mean Level	Time of Measurement	Definition of Poor Outcome	Reference
LDH	445 µg/mL	On admission	Ventilation	[34]
CAC score	≥400	During hospitalization	Death	[36]
CRP	>40 mg/L	On admission	Death/ARDS	[37]
Ferritin	>950 ng/L	On admission	ARDS	[38]

ARDS: acute respiratory distress syndrome; CAC: coronary artery calcium; CRP: C-reactive protein; LDH: lactate dehydrogenase; IL-6: interleukin-6.

As a result of vascular injury, the propeptide fibrinogen is cleaved to fibrin, and high circulating fibrin levels are common in the early phase of COVID-19 infection. Either hyper- or hypofibrinolysis can occur in the setting of COVID-19, with hyperfibrinolysis causing susceptibility to bleeding and hypofibrinolysis creating susceptibility to thrombus formation [39]. The hypofibrinolytic state may be attributed to the elevated production of plasminogen activator inhibitor 1 (PAI-1) by epithelial and endothelial cells in the inflamed lung [40]. D-dimers, produced during the degradation of crosslinked fibrin, are below 0.5 µg/mL under normal physiologic conditions. An increase in fibrinogen and D-dimers is associated with the risk of microthrombus formation in COVID-19 patients and subsequent emboli and/or organ failure [41][42]. Fibrinogen levels were, on average, higher in patients who developed severe versus less severe illness (5.16 vs. 4.51 g/L) [43]. D-dimer levels over 1 µg/mL can identify patients with poorer prognoses early in the course of disease and may signal the need for admission to critical care. Elevated D-dimer appears to be an independent risk factor for death [43][44]. In evaluating D-dimer levels, the implementation of age adjustment instead of a fixed cutoff may increase the accuracy of clinical assessment [45].

Sepsis-induced coagulopathy due to COVID-19 infection can lead to thrombotic stroke and myocardial infarction (MI) [46][47][48][49]. Losartan, previously mentioned for its ability to normalize levels of ACE2, is believed to be protective against strokes, offering another reason for its use in place of ACEIs [50].

Addressing the hypercoagulability risk at all levels of COVID-19 severity and in different age groups is challenging. Hypercoagulability may worsen in the setting of this pandemic via decreased activity, decreased exercise, and less movement in general under quarantine restrictions. Particularly affected are the elderly, with more limited movement capability due to age and co-morbidities. Venous stasis that accompanies inactivity, combined with hypercoagulability, sets the stage for two of three predisposing factors described in Virchow's triad for vascular thrombosis (blood flow alterations, endothelial injury, and hypercoagulability) [51]. Hypertension predisposes to endothelial injury, the last remaining factor in Virchow's triad. As discussed above, ACEIs should be used cautiously in COVID-19 patients. Anti-inflammatory drugs, cytokine inhibitors, and statins may be considered to protect the endothelium while simultaneously working against viral replication. Thromboprophylaxis with low molecular weight heparin could decrease D-dimer levels, and heparin can decrease fibrosis in those suffering from COVID-19-induced ARDS [43]. At this time, there are different approaches to coagulopathy in the field, with the

evaluation of efficacy still ongoing. We await the results of major clinical trials regarding the dosage, class, and timeline of the use of anticoagulation therapy [52].

3. Myocardial Injury: Subclinical Atherosclerosis and Acute Coronary Syndrome

COVID-19 cardiac manifestations may include myocarditis, cardiac arrhythmias, and new or worsening heart failure, which may be particularly damaging to patients with a history of CVD [53][54]. The mechanisms underlying cardiac injury may be multifactorial (**Figure 1**). Inflammation and thrombosis are known culprits [55]. Infection increases overall metabolic demand and heart rate. This intensifies oxygen expenditure while shortening the filling time in the diastole and limiting coronary perfusion. Infection-mediated vasoconstriction and ventilation/perfusion mismatch negatively affecting blood oxygenation can exacerbate the oxygen deficit, leading to myocardial ischemia [56][57]. Internalized virus loads within cardiomyocytes may directly damage the heart.

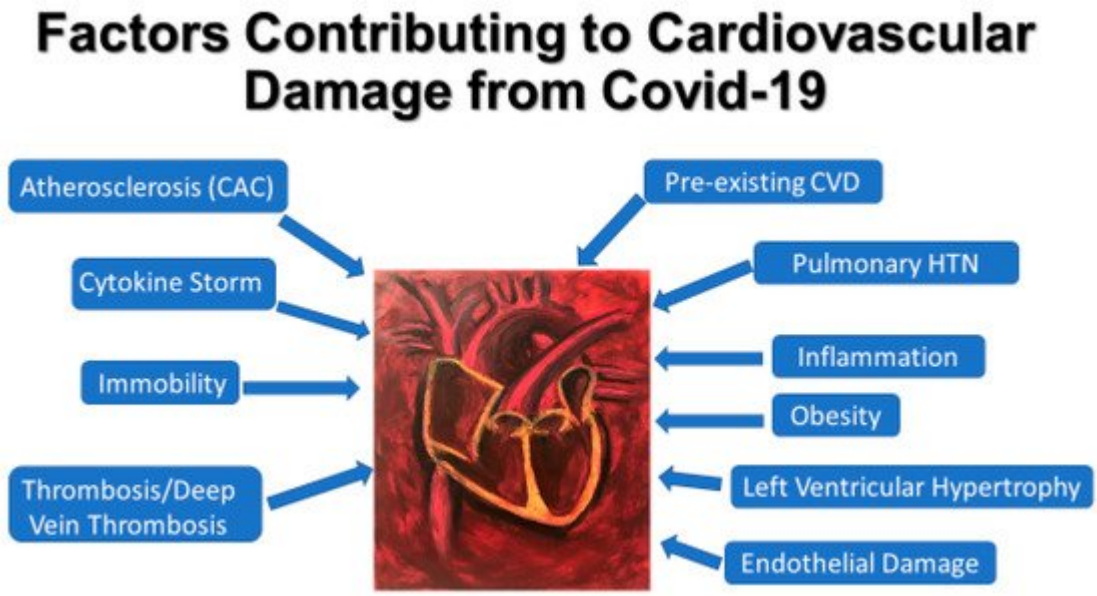

Figure 1. Factors contributing to cardiovascular damage in COVID-19. The white text in blue bubbles represents some of the pathologies that are associated with CVD in patients with COVID-19. Arrows are drawn from each factor to the central image of the heart and associated vasculature to emphasize their effect on the cardiovascular system specifically. CAC—Coronary Artery Calcium score; IL-6: interleukin-6; CVD: cardiovascular disease.

Immune-inflammatory-mediated injury to the heart from COVID-19 is more likely in severe cases and in those with high blood pressure and can be monitored via the release of certain injury biomarkers, including cardiac-specific troponin and creatine kinase-MB [58][59][60][61]. Elevated lactate dehydrogenase (LDH) may be of cardiac origin but is nonspecific and can result from damage to other organs [62]. In COVID-19, LDH may be released from the lung since this is a key site for inflammatory processes [63]. LDH levels above 445 µg/mL on admission can be predictive of more severe COVID-19 [46][64][65][66]. An analysis of 353 COVID-19 patients, 79 (22.4%) of whom presented with myocardial injury, revealed more frequent elevations in LDH (mean level: 244 U/L (without MI) vs. 655 U/L (with MI)

and creatinine (71 μmol/L (without MI) vs. 155 μmol/L (with MI) in the MI group during their hospitalization [67]. In addition to acute MI, differential diagnoses for increased serum cardiac biomarkers include stress-induced cardiomyopathy as well as myocarditis [68][69][70].

Evidence is accumulating that cardiac injury combined with COVID-19 infection, whether the myocardial injury is pre-existing or occurs during the infection, is associated with poorer outcomes [71][72][73]. A prospective, multicenter cohort study in Spain found that in patients with acute MI, COVID-19 is an independent risk factor for in-hospital mortality [74]. A small study of 77 COVID-19 patients who died in Wuhan, China, in early 2020 found that heart disease was present in 32%, and heart disease patients were more likely to be in the short-term survival group and to die within 14 days of COVID-19 onset [66].

Subclinical atherosclerosis can impact the course of COVID-19. Coronary artery calcification (CAC), a specific imaging marker of coronary atherosclerosis that correlates with the plaque burden, can reveal previously undiagnosed CVD in COVID-19 patients [75]. In a cross-sectional study of 209 consecutively admitted COVID-19 patients without known CVD, assessed for CAC, CAC was detected in 106 (**Table 1**) (50.7%). Half of those positive patients required mechanical ventilation, extracorporeal membrane oxygenation, or died, whereas only 17.5% of patients negative for CAC had such poor outcomes [76]. A separate study by Nai Fovino et al. from Italy also found that high CAC as a surrogate for subclinical atherosclerosis was a marker for worse outcomes [77]. In this study, 75% of patients with high CAC either died or were admitted to the ICU, in contrast with only 20% of the group with lower CAC scores. Patients with a high score were also more likely to experience an MI.

4. Summary and Conclusions

There is frequent involvement of the cardiovascular system in COVID-19 and this presents a particular danger in the elderly who are likely to have multiple heart-related comorbidities such as diabetes, hypertension and hyperlipidemia [1][2]. The cardiovascular manifestations most commonly associated with COVID-19 infection are thromboembolic events, sepsis-related coagulopathy, cardiac arrhythmias, myocardial infarction, heart failure and sudden death. A meta-analysis of 38 studies covering 19 countries found that, early in the pandemic, in-hospital mortality of ST-segment elevation myocardial infarction (STEMI) patients with COVID-19 was significantly higher than that of non-COVID-19 STEMI patients [3]. Excessive inflammation and oxidative stress from COVID-19 sepsis may cause hypoxia, tissue injury and heart damage[4]. COVID-19 incites endothelial dysfunction upon entry into endothelial cells which occurs via the high level of ACE2 receptors on the surface of this cell type. Endothelial damage from invading viral particles likely plays a role in the procoagulant state [5]. COVID-19 can also enter cardiomyocytes [6][7]. All of these mechanisms likely play a role in the pathophysiology of the cardiac manifestations which are part of the Post-acute Covid-19 syndrome as well [8]. In addition to treatment of the underlying CVD and related conditions (diabetes, hypertension), anti-coagulation may be introduced and statins are being studied as a way to reduce inflammation and improve endothelial dysfunction [9][10][11] The role of viral load is also being explored and a small study from Detroit Medical Center USA found that there was no relationship between viral load measured via PCR from a nasopharyngeal swab and incidence of myocardial injury (defined by high

sensitivity cardiac troponin I above 100 ng/L) . However, high viral load accompanying myocardial injury was associated with decreased survival versus myocardial injury alone or high viral load alone [12].

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