Cardiovascular Complications Associated with COVID-19 Infection

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Abstract — COVID-19 has spread worldwide and caused pneumonia-like illness similar to that caused by SARS-CoV and MERS-CoV. Apart from lung injury, coronaviruses cause severe cardiovascular disorders. Studies have confirmed that COVID-19 uses angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell similar to SARS-CoV. ACE2 receptors are found in various body organs including lungs, heart in kidneys. The most common complication observed are acute respiratory distress syndrome, acute cardiac injury and cardiovascular disorders including myocarditis, cardiac arrhythmias and myocardial infarction. It can also cause acute and chronic cardiovascular diseases. Almost 20% of patients progress to severe condition. Patients with underlying cardiovascular disorders have poor prognosis. It is believed that ACEI/ARBs can alleviate the cardiovascular problems in COVID-19 patients. Hence, the risk factors for cardiovascular disease and complications should be carefully considered.

Index Terms — SARS-CoV-2, 2019 Novel Coronavirus, COVID-19, SARS-CoV, MERS-CoV, Coronaviridae, Cardiovascular diseases, ACE1, ACE2, Diabetes, Hypertension, Hypotension, Bradycardia, Arrhythmias, Myocarditis, Acute cardiac injury, Shock, Sudden cardiac death, Myocardial infarction (MI), Epidemiology of COVID-19, Cardiovascular complications, Cardiovascular comorbidities, Myocardial injury, Heart failure, Renal failure, Liver failure.

I. ACE2 RECEPTORS AND THEIR CORRELATION TO ACE1 RECEPTORS

Angiotensin-converting enzyme 2 (ACE2) receptors are membrane associated aminopeptidases and have been identified in various organs in the body. The highest expression of ACE2 receptors is found in the epithelia of gastrointestinal tract followed by testis, kidney and lungs (Fig. 1) [1]. ACE2 has a role in immune system, heart function and in the development of diabetes mellitus and hypertension. Additionally, ACE2 receptors are also used by SARS-CoV-2 virus to gain entry in host cells.

ACE2 was discovered in 2000 as a homologue of ACE1, that converts angiotensin II to angiotensin 1-7. ACE2 protein is anchored at the apical surface of the cell. The extracellular domain of ACE2 is cleaved by ADAM17 and then released into the blood. The recombinant human ACE2 (rhACE2) generates angiotensin 1-7 from angiotensin II. It has the ability to prevent diastolic dysfunction, angiotensin-II induced myocardial hypertrophy, and myocardial fibrosis. This ACE2/angiotensin 1-7 axis is in contrast to the

effect of ACE1/angiotensin II axis within the renin-angiotensin system (RAS) [5].

Fig. 1: ACE2 mRNA expression levels in human organs. Adopted from [1].

Both ACE1 and ACE2 receptors are specific for angiotensin peptides and regulate the cellular signals in response to RAS. ACE1 and ACE2 receptors binds the hormone, angiotensin II, being produced by RAS. A protein, angiotensinogen is produced by the liver and processed by the proteases of RAS and generate hormonal peptides. Angiotensinogen is cleaved by renin and give angiotensin I. Angiotensin I is then further cleaved by ACE1 and is converted into octapeptide hormone, angiotensin II. This angiotensin II then binds to ACE1 and ACE2 receptors and functions to regulate blood pressure. Angiotensin I and angiotensin II are further cleaved into smaller peptides, namely angiotensin 1-9 and angiotensin 1-7, respectively by the action of ACE2 (Fig. 2).

Figure 2: Scheme of angiotensinogen cleavage into peptides [9].

The primary structure of ACE2 receptor is 34% homologous to the ACE1 receptor. Angiotensin II do not distinguish ACE2 receptors from ACE1 receptors and binds

with ACE2 receptors with nano molar range affinity. Both ACE1 and ACE2 receptors recognizes the same physiological ligands. The signaling of both ACE1 and ACE2 receptors can be mediated by G-proteins, however, the intra-signaling transduction process of ACE2 receptors is different from ACE1 and is unique among all G-protein coupled receptors. The level of ACE2 receptors is declined after birth and its low levels are expressed in the cardiovascular system of adults.

The pathophysiological roles of ACE1 and ACE2 receptors include regulation of cardiac growth response, vascular and fibrosis response in various tissues. Genetic polymorphism studies of ACE1 and ACE2 receptors have revealed the association of ACE1 receptors with higher aortic stiffness, hypertension and myocardial infarction (MI) while ACE2 receptors have been associated with ventricular structural changes, intellectual disability, and metabolic disorders [3].

II. ROLE OF ACE2 IN CARDIOVASCULAR DISEASES

As ACE2 receptors are found in the heart, it provides a connection between coronaviruses and cardiovascular complications. Human autopsy samples and murine models have demonstrated that SARS-CoV-2 mediates hypotension, bradycardia, arrhythmias, myocarditis, acute cardiac injury, shock or sudden cardiac death by down-regulating the ACE2 and myocardial pathways [13]. ACE2 is largely expressed in cardiac fibroblasts, cardiomyocytes, pericytes, smooth muscle cells, coronary endothelial cells, and previously unknown neuron-like cells. The highest expression of ACE2 is found in the pericytes of adult human heart. ACE2 has a role in heart function and in the development of diabetes mellitus and hypertension. This provides an intrinsic susceptibility of heart to COVID-19 infection [1]. Patients with heart failure have an increased activity of circulating ACE2 as compared to that in normal persons. This increased circulating ACE2 leads to poor prognosis of the patients. It is believed that this circulating ACE2 is derived from the shedding of membrane bound ACE2.

ACE2 can cause proinflammatory effects, strong vasoconstriction and profibrotic effects. The recombinant human ACE2 (rhACE2) generates angiotensin 1-7 from angiotensin II which has the ability to prevent diastolic dysfunction, angiotensin-II induced myocardial hypertrophy, and myocardial fibrosis. This is because angiotensin 1-7 has anti-apoptotic, anti-proliferative, mild vasodilating abilities and several cardiovascular protective effects. Studies have shown that the loss of ACE2 can lead to heart failure and accelerate underlying causes of heart failure [5].

Using renin angiotensin aldosterone system inhibitors can increase ACE2 levels and activity. It is found that olmesartan and losartan can increase ACE2 mRNA expression in the heart of rats after myocardial infarction. Losartan can increase both the mRNA expression and the protein activity of ACE2 in heart of normal Lewis rats. Also, enalapril can restore the expression of ACE2 levels in the left ventricle of rats with heart failure. It is believed that

Angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) are effective in the treatment of cardiovascular diseases and can improve health of patient [15].

III. ROLE OF ACE2 IN COVID-19

SARS-CoV-2 belong to the β -genus of the Coronaviridae family. It is a large family of single stranded positive-sense enveloped RNA viruses. Many symptoms of COVID-19 are similar to those of severe acute respiratory syndrome caused by SARS-CoV and MERS-CoV [4]. Studies on receptor recognition of SARS-CoV-2 have revealed that the transmission of SARS-CoV-2 is regulated by atomic level interactions between spike protein receptor-binding domain (RBD) of SARS-CoV-2 and the host ACE2 receptors. The RBD of SARS-CoV-2 contains a core structure and receptor binding motif (RBM) that binds to the ACE2 receptor (Fig. 3). This interaction is followed by fusion of the viral and host membranes that leads to the entry of virus in the cell. The affinity between the viral RBD and the host ACE2 receptors is responsible for host susceptibility [11]. The phylogenetic analysis of SARS-CoV-2 reveals that SARS-CoV-2 is 82% similar to SARS-CoV and more than 89% similar to two bat-SARS-CoVs, namely bat-SL-CoVZXC21 and bat-SL-CoVZC45. The overall spike sequence similarities between SARS-CoV-2 and SARS-CoV are $\approx 76\%$ - 78% at whole protein, $\approx 73\%$ - 76% at the RBD, and $\approx 50\%$ - 53% at the RBM level. These spike sequence similarities between SARS-CoV-2 and SARS-CoV provides evidence that SARS-CoV-2 also uses the same ACE2 receptors to gain entry in the cell [11]. The residues 441Leu, 472Phe, 479Gln, 480Ser, 487Asn, and 491Tyr of mature spike protein of SARS-CoV-2 are found to be necessary for binding the virus to the human ACE2 receptor. ACE2 is widely expressed in the pericytes of adult human heart suggesting that SARS-CoV-2 might attack heart pericytes leading to capillary endothelial cells dysfunction which results in micro-circulation disorder. It can be demonstrated by the elevated creatine kinase (CK) level among 13% of COVID-19 patients [1].

Fig. 3: Interaction between SARS-CoV and human ACE2 receptor (model). Adopted from [11].

Previous invitro studies of SARS-CoV infection showed that susceptibility to infection is correlated to ACE2 expression. However, the relation between the risk of COVID-19 infection to ACE2 expression is still unclear. It might be associated to the difference in the ACE2 expression among different age groups but there is little evidence on this possibility. Only one study has examined the age-related differences in the pulmonary host responses in acute respiratory distress syndrome and concluded that the activity of ACE2 in bronchoalveolar lavage fluids from neonates, children, adults, and older people has no difference [10]. It is also suggested that increased ACE2 level might be related to increased local viral load and cells with increased pseudo-type COVID-19 entry have relatively higher ACE2 expression [5].

ACE2 receptors are also widely distributed in lungs. Also, it has been reported that 3-20% patients of COVID-19 infection are combined with acute respiratory distress syndrome (ARDS). In these patients, acute cardiac injury was determined by increased levels of high-sensitivity troponin and secondary infections [8]. Studies have found that acute lung injury is related to the activation of RAS. Animal models demonstrated that reduced activity and loss of ACE2 can lead to elevated accumulation of neutrophils, increased vascular permeability and pulmonary edema which eventually results in acute respiratory distress syndrome. Previous studies on mice infected with SARS-CoV demonstrated downregulation of ACE2 expression in lung tissues, followed by increased vascular permeability and pulmonary edema. Studies have also found that the level of ACE2 expression can easily be decreased after injecting only the spike protein of SARS-CoV, leading to acute lung injury. As the spike protein of The RBD of SARS-CoV-2 contains a core structure and receptor binding motif (RBM) that binds to the ACE2 receptor and SARS-CoV are similar, it is believed that the pathological process leading to lung injury in COVID-19 patients can be attributed to the downregulation of ACE2 expression in lung tissue. The serum levels of angiotensin II are significantly higher in COVID-19 patients and it has a linear positive correlation with lung injury and viral load. RAS activation leads to widespread endothelial dysfunction and mild to severe injuries to multiple organs including heart, lungs and kidneys. Animal models have shown that the inflammatory response leading to acute respiratory distress syndrome can be attenuated by the supplement of exogenous ACE2. It also increases oxygenation in several animal models [5].

IV. EPIDEMIOLOGY OF COVID-19 AND CARDIOVASCULAR DISEASES

Since the past epidemics of various coronaviruses like SARS-CoV and MERS-CoV, it has been observed that the extra-pulmonary manifestations like cardiovascular involvement are also common among infected patients. Previous epidemics associated with coronaviruses have caused significant economic loss, mortality and have been associated with cardiovascular comorbidities and complications (Fig. 4). As of 16 March 2020, it has been reported to World Health Organization (WHO) that a total of 167,511 confirmed cases of COVID-19 infection are

found in 152 geographical territories. Out of these patients, 6,606 died due to infection [13]. Globally, the mortality rate of COVID-19 is about 3.4%. The most common comorbidities among COVID-19 infected patients include hypertension in 14.9%, diabetes in 7.4% and coronary heart disease in 2.5% patients. Studies from China showed that 4.2% of COVID-19 infected patients have cardiovascular diseases and composed of 22.7% of fatal cases, making the case fatality rate of 10.5%.

Figure 4. Primary and secondary cardiovascular complications associated with respiratory virus infection. Adopted from Xiong et al., 2020.

The first coronavirus in human was identified in embryonic tracheal cultures in the mid-1960s. Until now, seven different human coronavirus (HCoV) species have been identified. These include HCoV-NL63, HCoV-229E, HCoV-OC43, HCoV-HKU1, Middle East Respiratory Syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2. The four coronaviruses namely, HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1 are endemic in humans and are responsible for 15-30% of common colds. SARS-CoV and MERS-CoV have been associated with large outbreaks and resulted in cardiovascular complications [8]. The recent outbreak of COVID-19 is also associated with cardiovascular diseases in infected patients. In the early report of 41 confirmed COVID-19 infected patients, 5 patients (12%) had elevated levels of hypersensitive troponin-I (hs-cTn I) and were diagnosed with virus related cardiac injury. 4 of the 5 patients with cardiac injury were admitted to the intensive care unit (ICU) due to the severity of myocardial damage. The mean systolic blood pressure was significantly higher in patients admitted to the ICU versus those not admitted to the ICU [7]. In a study of 99 COVID-19 confirmed patients, the authors reported cardiac injury in most patients evident by abnormal cardiac zymogram. The blood biochemistry of 13% patients had elevated creatine kinase (CK) levels and 75% patients had elevated lactate dehydrogenase (LDH) levels [2]. Another report of 138 confirmed COVID-19 infected patients showed that 16.7% patients developed arrhythmias and 7.2% patients developed acute cardiac injury and among these patients 22.2% were admitted in the ICU. Elevated troponin I levels were observed in 7.2% patients [12]. A retrospective study of 1099 laboratory-confirmed COVID-19 infected patients showed that 90 of 675 (13.7%) patients had elevated levels of creatine kinase and 277 of 675

(37.2%) patients had elevated level of lactate dehydrogenase [4]. Furthermore, some patients presented with the early cardiovascular symptoms like chest tightness and heart palpitations rather than with pneumonia like symptoms, were later diagnosed with COVID-19 infection.

The myocardial abnormalities of SARS-CoV-2 infection might be due to reduced ACE2 activity in the heart similar to SARS-CoV infection, or it might be indirectly caused by cytokine storm triggered by the disturbed response of type 1 and type 2 helper T-cells [9], reduced oxygen supply and severe lung failure. SARS-CoV was also isolated from the autopsy of 7 out of 20 human hearts and the heart tissue damage was followed by reduced ACE2 protein expression. Markedly reduced ACE2 expression and the presence of SARS-CoV in heart of intranasal SARS-CoV infected mice was also reported. Recently, a moderate amount of transparent light-yellow fluid in the pericardial cavity and mild epicardial edema was reported in the autopsy of COVID-19 infected 85 year-old-man heart [5].

COVID-19 patients with underlying cardiovascular disorders are more likely at risk to develop severe illness and even death. The virus-induced increased metabolic demand and decreased cardiac reserve worsens the underlying cardiovascular disorder. Troponin elevation and electrocardiographic changes may indicate underlying myocarditis and echocardiography frequently signals sub-clinical left ventricular diastolic damage. The infection-induced systemic inflammation can trigger coronary plaque rupture in patients with heart failure and coronary artery disease. Hence, patients with preexisting cardiovascular disease are prone to develop severe symptoms when infected with SARS-CoV-2 [13]. In a study of 41 patients with COVID-19 infection, 32% of patients had underlying diseases, including hypertension (15%), cardiovascular disease (15%), and diabetes (20%) [6]. In the large cohort study of 1099 patients with confirmed COVID-19 infection, the most frequently observed underlying diseases include hypertension in 14.9%, diabetes in 7.4%, and coronary heart disease in 2.5% patients [4].

In a series of 138 patients with COVID-19 infection, 36 (26.1%) patients were admitted to the ICU due to the complications of arrhythmias, shock, and acute respiratory distress syndrome (ARDS). 64 (46.4%) patients had comorbidities including cardiovascular disease (14.5%), hypertension (31%), malignant neoplasms (7.2%), and diabetes (10%) [12]. In another study of 191 cases with COVID-19 infection, death was associated more frequently with comorbidities including coronary heart disease (24% vs 1%), hypertension (48% vs 23%), and diabetes (31% vs 14%) as compared to survivors, respectively. Non-survivors had increased rates of acute cardiac injury (59% vs 1%) and heart failure (52% vs 12%), also they had higher levels of high-sensitivity troponin-I, interleukin-6 (IL-6) and serum ferritin levels as compared to survivors [14]. In another series of 52-severely ill patients with COVID-19 infection, the mortality rate was 61.5% by 28 days. The overall rate of comorbidities was 40% (20% vs 53%), among the two groups of survivors (n=20) vs non-survivors (n=32), with chronic cardiac disease (10% vs 9%), cardiovascular disease (20% vs 53%) and cerebrovascular disease (0% vs 22%) consistently. Most severely-ill patients developed organ

function damage, including acute respiratory distress syndrome (67%), acute renal injury (29%), myocardial injury (23%), liver dysfunction (29%), and pneumothorax (2%) [16].

V. CONCLUSION

COVID-19 is thought to infect host cells via ACE2 receptors that are expressed in heart, lungs, kidneys and various organs, causing multiple organ damage. Underlying cardiovascular comorbidities may progress to adverse clinical outcomes and even death. Older patients with comorbidities are particularly at risk. Additionally, cardiovascular diseases are one of the frequently observed complications in critically ill patients that is often fatal. Careful clinical treatment of patients with comorbidities and complications of cardiovascular system is needed.

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