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Pathogenesis and preventive approach of hypercoagulopathy and microvascular thrombosis induced mortality from COVID-19

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Abstract

Background: COVID-19 is the current pandemic infection caused by severe acute respiratory syndrome coronavirus-2 (SARS Cov-2). Pulmonary collapse in severe critical COVID-19 patients may be due to development of multiple micro thrombi within pulmonary vasculature. As COVID-19 pandemic is accelerating, it is important to understand the molecular mechanism through which SARS-Cov2 induces hypercoagulopathy and intravascular thrombosis to be able to design more appropriate therapy. Focus of this review is to identify mechanisms through re-analysis of publicly available data by which SARS-Cov2 infection induce mortality by augmenting intravascular thrombosis and attempt to understand therapeutic approach to it. **Findings:** SARS Cov-2 accesses host cells via membrane bound angiotensin converting enzyme-2 (ACE2). This leads to imbalance of renin angiotensin system (RAS) increase ratio of Ag-II: Ag-1-7. Ag-II stimulates release of IP-10 from endothelium which upregulates local renin angiotensin system in endothelial cell by positive feedback process. Therefore it is suggested that angiotensin-II of renin angiotensin systemr in endothelial cells sustained proinflammatory signal and developed microvascular thrombosis. During inflammation both extrinsic and intrinsic coagulation pathways are activated. Fibrinolysis is suppressed by imbalance activity of two system: Ang-II-PAI-1 (plasminigen activator inhibitor-1) and Bradykinin-tPA (tissue plasminogen activator) system. Therapy with low molecular weight heparin (LMWH), which have anticoagulant and anti-inflammatory property, is associated with better prognostic in patients with severe COVID-19. ACE inhibitors decrease production of Ag-II and increases availability of bradykinin and consequence reduces coagulopathy **Conclusion**: Thus it is concluded that SARS-Cov2 infection induces microvascular thrombosis from hyperinflammation, misbalance between Ag-II and Ag-1-7 and imbalance activity of two system: Ang-II-PAI-1 and bradykinin-tPA system. ACE inhibitor and anticoagulant mainly LMWH and UFH may serve potential role in COVID-19 therapy particularly in patients with hypercoagulopathy and microvascular thrombosis.

Keywords: COVID19; angiotensin converting enzyme; renin angiotensin system; fibrinolysis; microvascular thrombosis; ACE inhibitor; heparin

1 Introduction

Corona virus disease 2019 (COVID-19) is the current pandemic infection caused by RNA virus named severe acute respiratory syndrome coronavirus-2 (SARS Cov-2). The disease was first observed in Wuhan, China in December 2019 and since then spread globally. On 11th March 2020[1] WHO declared corona outbreak as a pandemic. The COVID pandemic is still in progress. More than 200 countries of the world now suffer from COVID-19[2]. At present more than 8.0 million people are infected and more than 0.43 million people were died in COVID-19 worldwide mainly from viral pneumonia and multi-organ failure[3]. Primary symptoms include fever, cough and fatigue. There is no potential therapeutic treatment for COVID-19. The complete spectrum of complication from COVID19 is yet to be elucidated fully. The clinical manifestations vary from asymptomatic to severe illness and death. Immune responses in older people are less efficient hence they are more susceptible to COVID-19 infection[4].

Available literature suggest that COVIS-19 is not only a primary pulmonary disease but also associated with thrombosis of small pulmonary vessels[5]. Multiple occlusions and microthrombi in pulmonary vasculature[6] was noted, in biopsy or autopsy studies in COVID-19 patients. Thus mortality risk of COVID-19 patients is not only due to ARDS but also from thrombosis in pulmonary and other vessels. In non-survivors of COVID-19 Disseminated intravascular coagulation (DIC) was reported from studies in China[7].The development of DIC is supported by increase D-dimer, and fibrin degradation products in severe COVID-19 patients[7]. Multiple microthrombi within pulmonary vasculature may contribute deterioration in COVID-19 patients from pulmonary collapse and ARDS. With progressive hyper inflammation, and systemic micro-angiopathy may lead to multiple organ dysfunction, cardiomyopathy, acute kidney and liver failure, mesenteric ischemia and neurological insults[8]. In a recent clinical study on coagulation parameters it was suggested that anti-thrombin, prothrombin time and prothrombin time activity were lower in COVID-19 patients compared with healthy control[9]. Therefore effectively suppressing the hypercoagulopathy and microvascular thrombosis is an important way to prevent the deterioration of COVID-19 patients and save their lives. Use of ACE inhibitors may prevent the occurrence of VTE from RAS activation[10]. Studies have also suggested that anticoagulants like LMWH (Low Molecular Weight Heparin) is beneficial for patients with severe Covid-19 infection for its anticoagulant as well as anti-inflammatory properties.[11,12]. Administration of LMWH within 1 week of SARS-Cov2 infection is associated with significant reduction in 28 day mortality rate[13]. Chronic treatment with direct oral anticoagulants (DOA) those directly inhibit coagulation factors reduced mortality in COVID-19 patients[5]. However, the role of anticoagulants in COVID -19 patients require further study. Here we review the recent advances in hypercoagulopathy from SARS-Cov2 infection, including inflammation, and therapeutic approaches to inhibit microvascular thrombosis. By sharing knowledge and deepening our understanding of the COVID-19 mediated hypercoagulopathy and microvascular thrombosis we believe that the community can efficiently develop potential therapy to fight against corona pandemic.

2 Discussion

COVID-19 induced hypercoagulopathy, intravascular thrombosis and its preventive approach is explained next.

2.1 Disseminated intravascular coagulation

Coagulation dysfunction is one of the major cause for death in severe COVID-19[14]. Most of the COVID-19 patients who died have met the criteria of disseminated intravascular coagulation (DIC) proposed by the international Society on Thrombosis and Haemostasis[7,15]. Thus it is a pathological term that include both coagulation and fibrinolysis in circulating blood which leads to organ failure from disrupted microcirculation[16]. It is highly complex pathological process associated with unregulated thrombin explosion leading to release of free thrombin in the circulation that results in widespread microvascular thrombosis. It involves activation of procoagulant and modulation of fibrinolytic system to induce intravascular coagulation or hemorrhage or both depending on degree of involvement of these systems. Microvascular thrombosis is a type of DIC. COVID-19-induced hyper inflammation and RAS imbalance may contribute to development of intravascular coagulopathy and thrombosis.

Although COVID-19 patients are not typical DIC seen in septicemia in spite of coagulative abnormalities[17]. In DIC thrombocytopenia is a key finding along with elevated clotting time. But in COVID-19 confirmed patients platelet count did not change. Thus in COVID-19 patients there is local thrombosis rather than disseminated thrombin generation[17]. A recent study reported venous thromboembolism (VTE) in ICU patients with proven COVID-19 pneumonia[18].

2.2 COVID-19 and hyperinflammation

Innate immunity provides the first line of defense against viral infection. Hence, dysregulated and excessive immune response may cause immune damage[19]. SARS-Cov-2 enters into type-2 alveolar epithelial cells using membrane bound ACE2 as receptor. After entering into cell cytoplasm it replicate and releases new viral particles. Tissue macrophage (APC) represent the virus particle With MHC1 to cytotoxic T cells. The immune effector cells release cytokines (IL-1beta, IL-2, IL-6, TNF-alfa etc.) and chemokines (CC motif chemokine ligand: CCL-2, CCL-3, CCL-5)[20,21]. Chemokines attract phagocytic cells (monocyte and neutrophil) into infected area. The elevated level of serum cytokines and chemokines are observed in mild to moderate COVID-19 patients[22].

The pattern recognition receptors (PRRs) were expressed by innate immune cells. Such receptors are recognized by cytoplasmic PRR like TLR3 and TLR7[23]. SARS-COV inhibits production of IFN-1through inhibition of TLR3 and TLR7 signaling pathway. The antiviral interferon, INF-1 (IFN-alfa and IFN-beta), is the key molecule of natural immune response against viral infection. Delays release of IFN-1

in the early stage of SARS-Cov-2 infection sequesters body's antiviral response [12] and allowing rapid replication of virus and virus-induced direct pathogenic effects in early stage of the disease [24,25]. The subsequent delayed and persistent IFN-1 response along with cytokines, chemokines and DAMPs enhance monocyte and neutrophils infiltration into lung parenchyma [26]. Infiltered monocytes produce high levels of cytokines and chemokines which positively amplify recruitment of innate immune cells to induce hyperinflammation and cytokine storm. Cytokine storm is characteristic feature of severe cases of COVID-19 [27,28].

Death from COVID-19 is more in male than female [29]. TLR7 genes are located in X-chromosomes. In female there are two X chromosome. Thus one X-chromosome is escaped from viral-induced inactivation and causes more expression of TLR7 in females [30]. TLR7 agonist induces more IFN-1 release in females [31] beside this estradiol enhances IFN-1 release following TLR7 agonism [32].

Hence bi-allelic TLR7expression and estradiol signaling make females less prone to IFN-1 antagonism which lead to more IFN-1 release in early stage of the infection. Thus virus-induce cytokines storm may be due to IFN-1 antagonism (Figure 1).

SARS-Cov infection is associated with T-cell (both CD4+ and CD8+) lymphopenia [33] from direct cytopathic effect of virus and/or T-cell apoptosis from dysregulated cytokine release [34]. Decrease in T cell numbers are strongly correlated with severity of acute respiratory syndrome [35]. Normally CD4+ T-cell modulate immune response and suppress hyper inflammation through down regulation inflammatory process [36,37]. Beside this CD4+ lymphopenia impairs adaptive antiviral response through inadequate help to CD8+ T cells and B-cells [38].
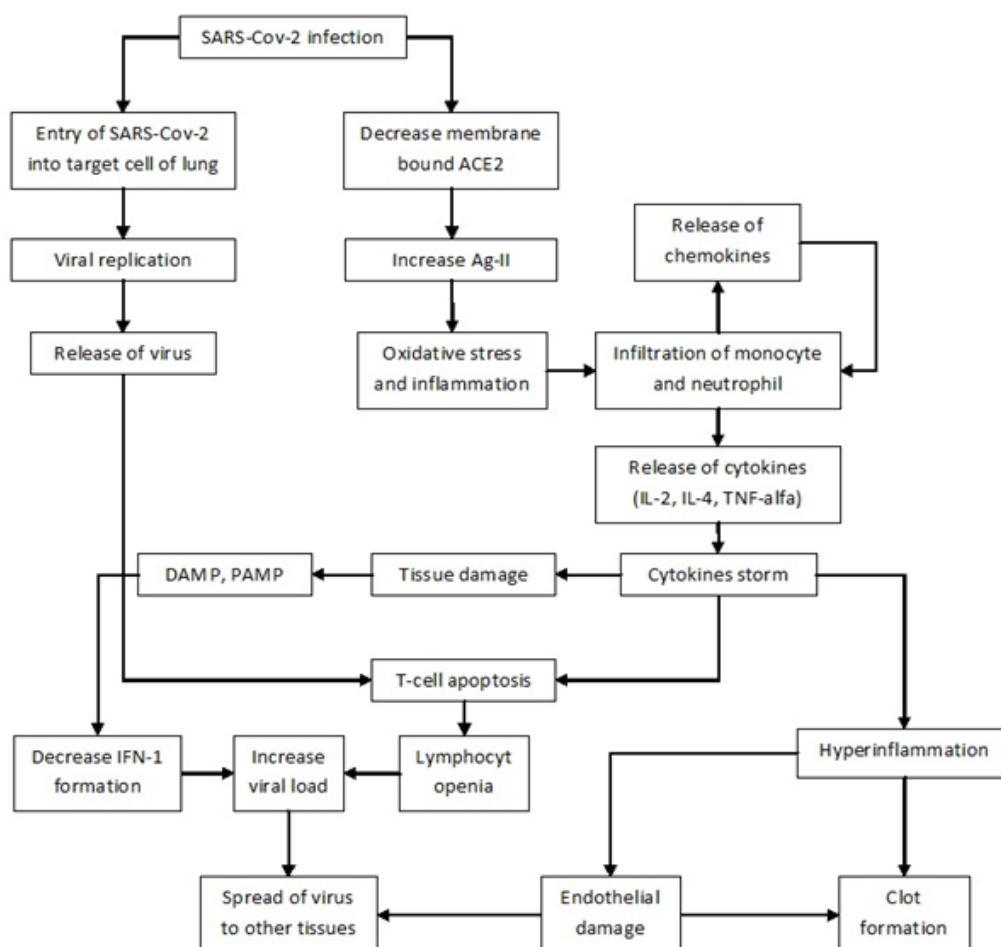

Fig 1. Mechanism of COVID-19-induced hyperinflammation andits consequences in COVID-19 victim (Abbreviations Ang-II: angiotensin-II; ACE2:angiotensin converting enzyme-2; IL: interleukin, TNF-alfa: tumor necrosisfactor-alfa; IFN: interferon; DAMP: damage associated molecular pattern; PAMP:pathogen associated molecular pattern)

2.3 COVID-19 and renin angiotensin system

SARS-Cov2 interact with membrane bound angiotensin converting enzyme-2 (ACE2) of target cells by their spike glycoproteins [39] and then enter into target cell by endocytosis [40]. Binding of spike protein with ACE2 can not be altered by the addition of a specific ACE2 inhibitor suggesting the inability of such receptor to block SARS infection [41]. Deficiency of ACE2 is associated with increased vascular permeability,

fluid accumulation in extra alveolar spaces and increased oxidative [42].

Renin angiotensin system (RAS) is a cascade of vasoactive peptides involve in the maintenance of cardiovascular homeostasis. This system consists of two principal enzymes: Angiotensin Converting Enzyme (ACE) and Angiotensin Converting enzyme-2 (ACE2). ACE cleaves angiotensin-I to angiotensin-II. ACE 2 is captopril insensitive carboxypeptidase [43], which cleaves carboxyl terminal peptide bond of angiotensin-I and angiotensin-II and produces Ag-(1-9) and Ag-(1-7) respectively. Catalytic efficiency of ACE2 against Ag-II is remarkably higher than Ag-I [44]. Thus, ACE2 is the main enzyme for Ag-(1-7) generation in many tissues. The elevated ACE activity is associated with reduced ACE2, increase Ag-II formation and increase Ag-(1-7) catabolism, while in reverse condition there is vasodilation from increase ACE2, decrease ACE, decrease Ag-II and increase Ag-(1-7). Ag-II induces lung inflammation, ROS formation, vasoconstriction, proliferation and thrombosis via angiotensin type1 receptor. Ag-(1-7) via mas receptor prevents lung inflammation, induces vasodilation and activates antioxidant system (Figure 2).
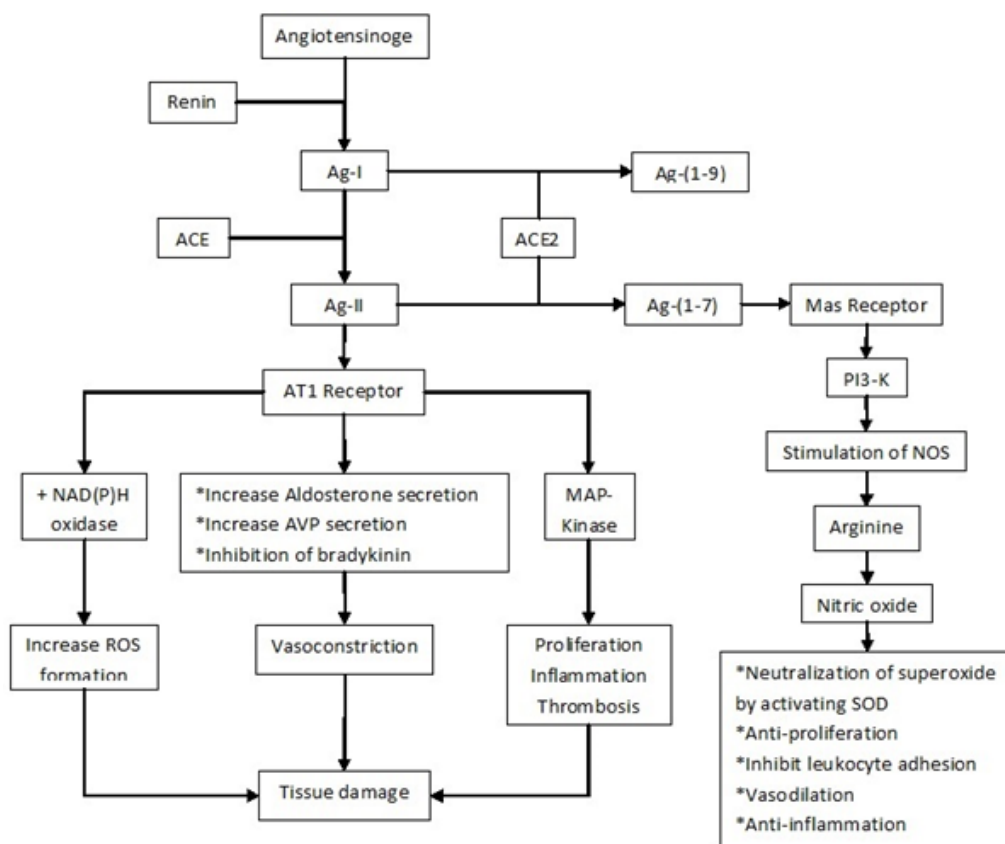

Fig 2. Principal components of renin angiotensin system andtheir roles (Abbreviations Ag-I: angiotensin-I; Ag-II: angiotensin-II; ACE:angiotensin converting enzyme; ACE2: angiotensin converting enzyme-2; PI3-K:Phosphotidyl inositol 3 kinase; NOS: Nitric oxide synthase; SOD: superoxidedismutase; AVP: arginine vaso pressin; AT1: angiotensin type-1)

Number of membrane bound ACE2 decreases as SARS-Cov-2 induces internalization of ACE2. At the same time proinflammatory cytokine, TNF-alfa activates ADAM-17. ADAM17, a membrane bound metallopeptidase, remains in close associated with RAS. ACE2 can be shed from the cell surface through proteolytic cleavage of its external domain by ADAM17 [45].

Neutrophil infiltration into lungs in response to bacterial endotoxin is enhanced from ACE2 deficiency [46]. Liu et al. suggested that plasma Ag-II level was elevated in COVID-19 patients in correlation with viral load [47]. COVID-19-induced lung injury is minimized by Restoration of ACE2 through the administration of recombinant ACE2 [48,49]. Children are less susceptible to COVID-19 than adults due to high ACE2 expression [50].

2.4 Microvascular thrombosis

Microvascular thrombosis is due to enhance intravascular coagulation, suppression of fibrinolysis and inactivation of intravascular anticoagulant. macrophages, neutrophils, the complement system, platelets and coagulation factors to form a clots to prevent spread of pathogens [51,52]. This type of coagulation is called immunothrombosis or thromboinflammation. Uncontrolled and widespread thromboinflammation increases severity of COVID-19. The persistant inflammatory status in severe and critical COID-19 patient's act as

an important trigger for the coagulation cascade [53]. Proinflammatory cytokines like IL-1beta, IL-6 and TNF-alfa upregulate pro-coagulants in patients with COVID-19 [54]. A cross talk between coagulative haemeostasis and inflammation as well as the activation of coagulation cascade during viral infections are well established [55]. During inflammation both extrinsic and intrinsic coagulation pathways are activated. Inflammated endothelial cells and macrophages release tissue factor to initiate activation of extrinsic coagulation system [52]. PMNs release neutrophil extracellular traps (NETs) which activate coagulation factor XII to initiate activation of intrinsic coagulation reaction and inactivates endogenous anticoagulant [56]. Platelets activation is associated with release of P-selectin from stored granules which facilitates the interaction between platelet and neutrophil. Such interaction promotes release of NETs from recruited neutrophil. This intern activates platelet and promotes coagulation by positive feedback system [57]. IL-1 and IL-6 damages vascular endothelium and enhances thrombosis along with tissue factor [58]. Colafrancesco et al (2020) suggested a bidirectional relationship between IL-1 mediated inflammation and coagulation [59]. IL-1beta upregulates the expression of tissue factor which leads to generation of intravascular thrombi [60]. Vascular endothelium releases selectin and endothelin in response to thrombin. The released selectin induces more cytokine release from granulocytes and macrophages [61].

The endothelin induces vasoconstriction and vasospasm to augment thrombosis [62]. Endothelin-1 which is linked to Ag-II via AT1 receptor [63], can also activate coagulation cascade and induced microvascular thrombosis [64] (Figure 3).
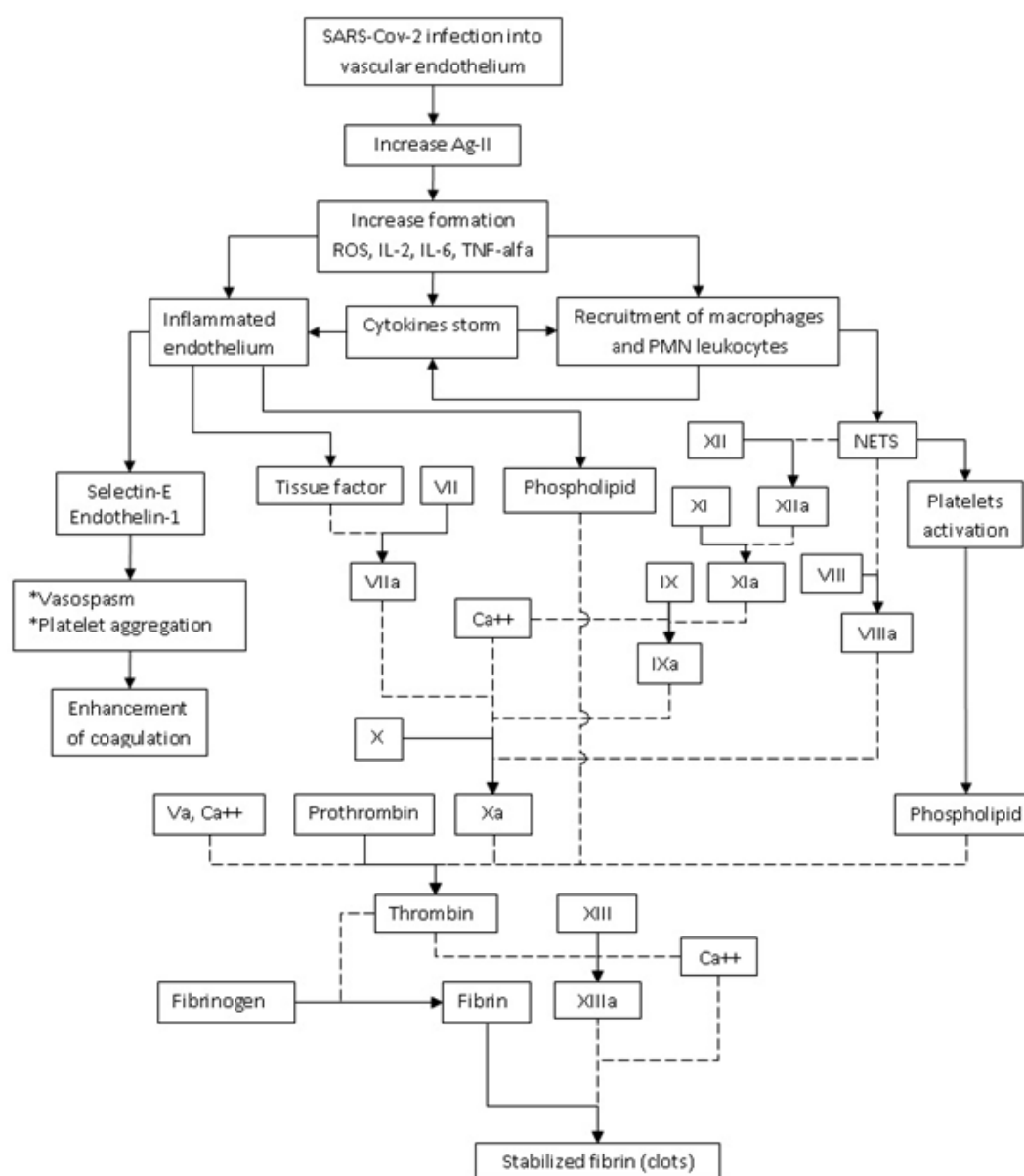

Fig 3. Role of SARS-Cov2 infection on augmentation of intravascular coagulation. (Numerical figures indicates number ofcoagulation factors, 'a' represent active factor, NETs indicates neutrophilextracellular traps)

In DIC complement is activated by TNF[65,66]. Complement induced platelets lysis provides more procoagulant to augment the coagulation process. C3a and C5a exert proinflammatory effect[67] and enhance coagulation process by increasing expression of tissue factor and von Willi brand factor[68].

The RAS is intrinsically linked to the coagulation cascade and may exacerbate microvascular thrombosis by suppressing fibrinolysis. Ang-II-PAI-1 and Bradykinin-tPA system maintain the rate of fibrinolysis. Ag-II induces PAI-1 expression by endothelial cells via AT1 receptor and develops PAI-1/tPA imbalance (increase ratio of PAI-1/tPA) to hampers fibrinolysis[69]. This leads to fibrin deposition in the alveoli in COVID-19 victims[70]. Ag-II also enhances release of PAI-1 from adipocytes[71]. This is an account for increased severity in obese corona victims.

Bradykinin acts on endothelial cells to increase release of plasminogen activator (tPA)[72]. Elevated Ag-II increase production of aldosterone which enhances activity of ACE. There are two different catalytic domains of ACE, one cleaving Ag-I to Ag-II and other converts bradykinin to inactive peptide. Thus COVID-19-induce increase Ag-II-aldosterone blunts bradykinin mediated increase of tPA. Therefore in COVID-19 patients there is decreased tPA to PAI-1 ratio and promotes hypofibrinolysis. Hyper aldosteronism in COVID-19 is supported by hypokalemia in COVID-19 victims[73]. It has been shown that aldosterone directly increases PAI-1 expression[74]. Aldosterone levels have been shown to correlate with PAI-1 levels[75]. ACE inhibitors have been shown to reduces PAI-1 levels and increase release of tPA via elevated bradykinin[76,77]. Spironolactone, an aldosterone receptor blocker has been shown to decrease PAI-1 levels[78] (Figure 4).
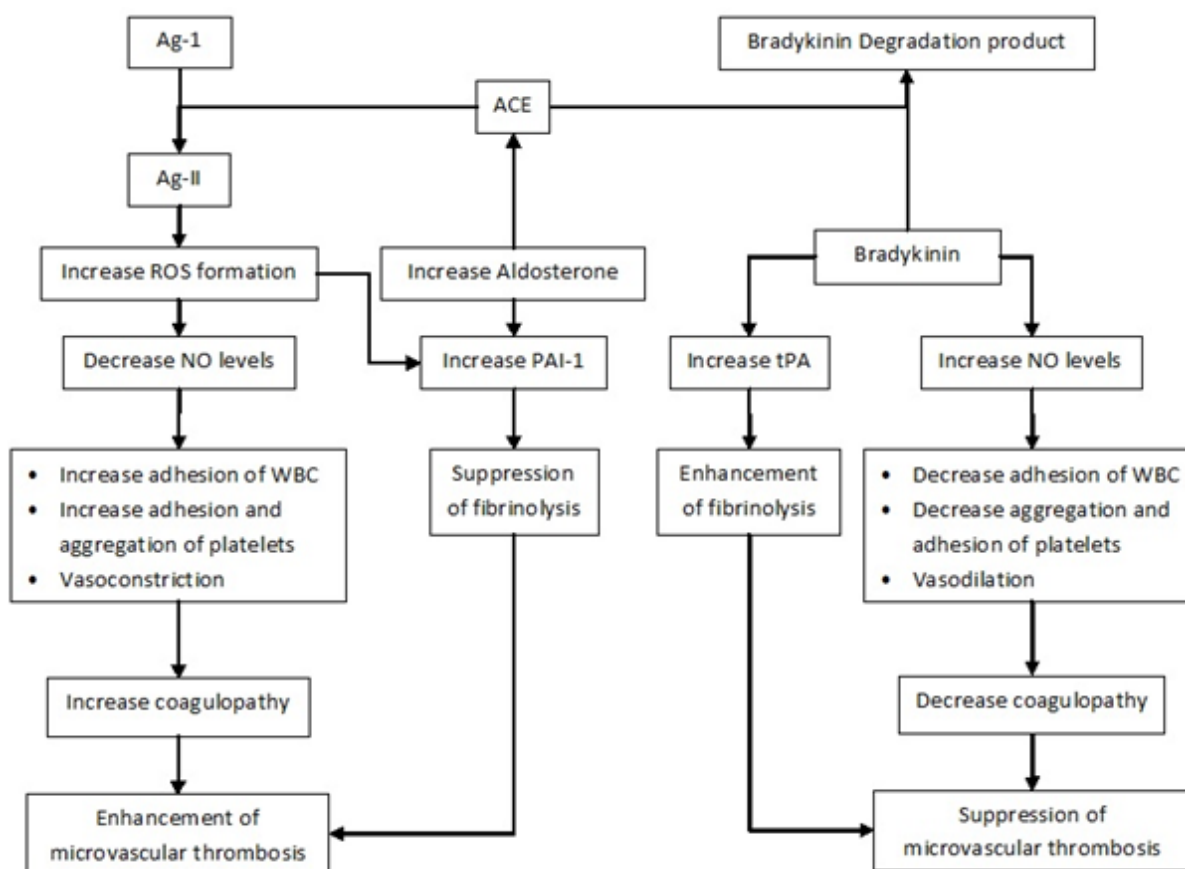

Fig 4. ACE-Ag-II and ACE-bradykinin system for the maintenance of endothelial homeostasis (AbbreviationsAng-I: angiotensin-I; Ang-II: angiotensin-II; ACE: angiotensin convertingenzyme;; NO: Nitric oxide; tPA: tissue plasminogen activator; PAI-1: plasminogenactivator inhibitor-1)

Renin- angiotensin system and bradykinin-nitric oxide system have major role in endothelial homeostasis.Bradykinin via bradykinin receptor-2 (B2R) induces the release of nitric oxide, prostacyclin and endothelium-derived- hyperpolarizing-factor (EDHF) and tissue plasminogen activator from endothelium. Thus it induces vasodilation with increasing formation of NO and prostacyclin and hyperpolarization of membrane via EDHF[79,80]. In endothelial cell bradykinin via bradykinin receptor-2 (B2R) induces the release of nitric oxide, prostacyclin and endothelium-derived- hyperpolarizing-factor (EDHF) and tissue plasminogen activator. Bradykinin induces vasodilation with increasing formation of NO and prostacyclin and hyperpolarization of membrane via EDHF[79,80]. NO from endothelium diffuses to surrounding tissues and perform various cardioprotective effects include smooth muscle relaxation, prevention of leukocytes and platelet adhesion into vascular wall[81].

Ag-II -induces ROS which is responsible for NO breakdown and reduced eNOS derived NO [82]. It induces oxidative stress to increases expression of PTI-1 and thereby favoring thrombosis [83]. Ag-II also increase release of cytokines to increase adhesiveness of endothelium to inflammatory cells and consequently induces inflammation and thrombosis [84].
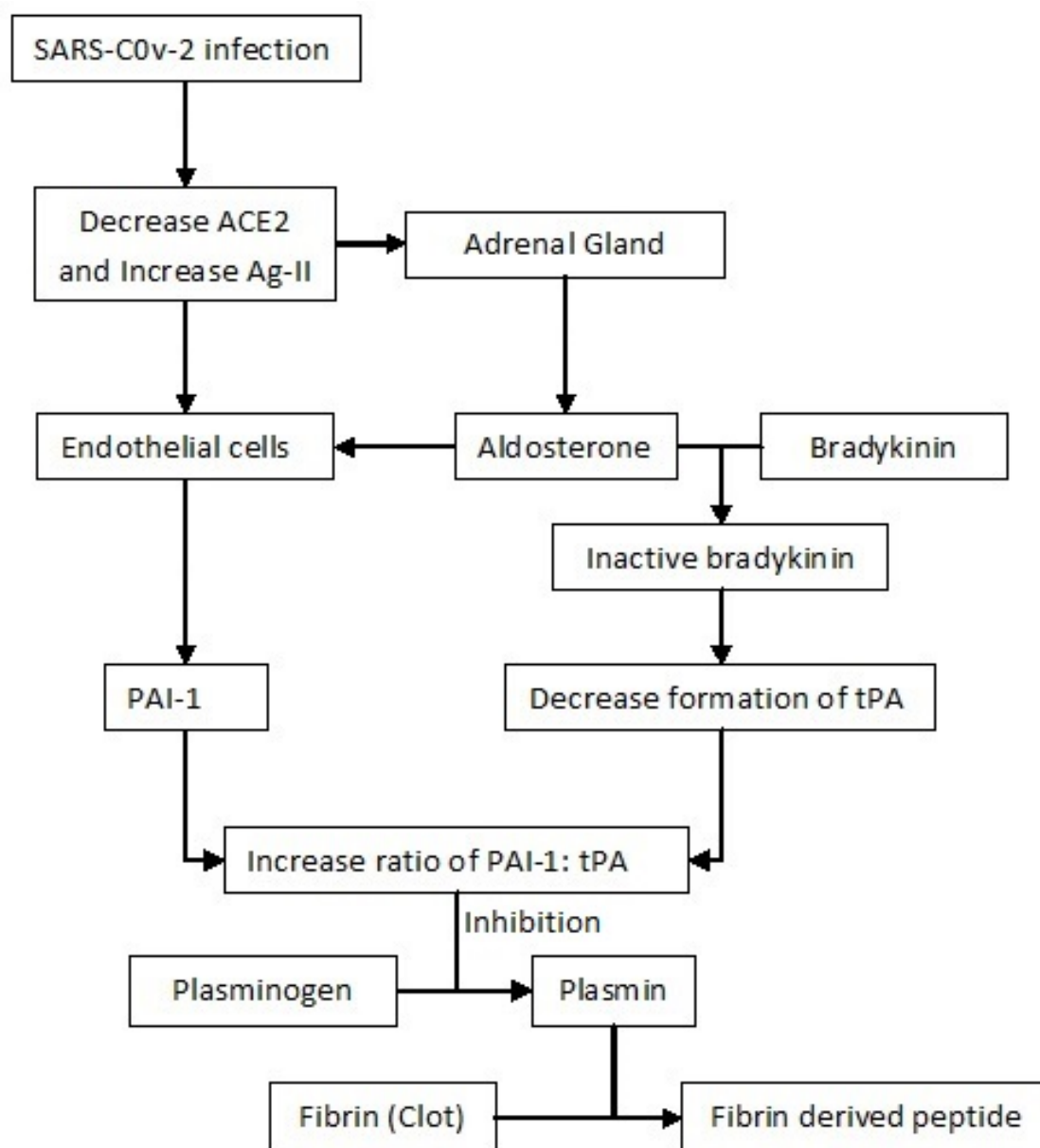

Fig 5. Molecular mechanism of suppression of fibrinolysis in COVID-19victims (Abbreviations Ag-II: angiotensin-II; ACE2:angiotensin converting enzyme2; tPA: tissue plasminogen activator; PAI-1:plasminogen activator inhibitor-1)

Ag-II activates nuclear factor kB (NF-kB) in monocytes, macrophages and endothelial cells which induces production of chemokines like monocyte chemoattractant protein-1 (MCP-1), IL-6, and IL-8 [85,86]. Release chemokines recruit monocytes and neutrophils at the infective tissue to induce cytokines storm.

Ag-II stimulates release of CXC chemokines, IP-10 from endothelium [87] and augments apoptosis and cell senescence of endothelial cell [88]. Neutralization of IP-10 inhibits Ag-II-induced apoptosis. It is now established that IP-10 upregulates local renin angiotensin system in endothelial cell by positive feedback process. Therefore it is suggested that angiotensin-II renin angiotensin system circuit in endothelial cells sustained proinflammatory signal and microvascular thrombosis (Figure 6).
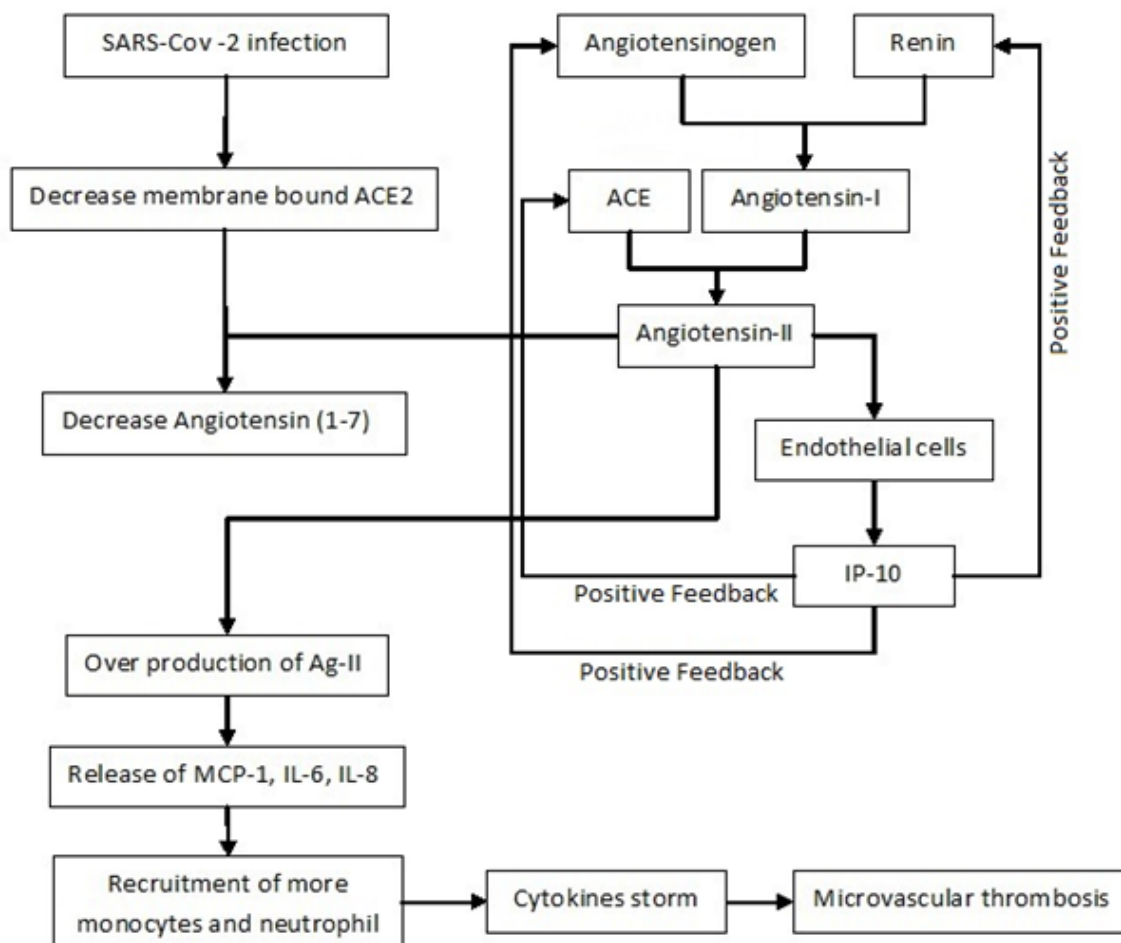
Fig 6. Endothelial positive feedback on renin-angiotensinsystem for over formation of Ag-II and augmentation of microvascular thrombosisin COVID-19 victim (Abbreviations ACE: angiotensin converting enzyme;ACE2: angiotensin converting enzyme 2; IL: Interleukin; MCP: monocyte chemoattractant protein)

2.5 Theoretical treatment strategy

Vascular health depends on functional integrity of endothelium. SARS-Cov2 infection is associated with Ag-II-induced oxidative stress. Such stressful environment develops pro-inflammatory and thrombotic state. NO, endothelial derived factor, maintain endothelial function. Thus endothelial dysfunction is associated with decreased bioavailability of NO[89] either from reduced production or increased breakdown[90]. From endothelium NO diffuses to surrounding tissues and perform cardio-protective action include relaxation of smooth muscle cells, prevention of leukocyte adhesion to vascular wall, prevention of platelet adhesion and aggregation and proliferation of smooth muscle cell[81,90].

Endothelial cell activation is a unique mechanism of COVID-19 mediated microvascular injury, thrombosis and multi organ failure[91] which is aggravated by hypoxia[92]. Pulmonary embolism with occlusion and micro thrombosis in pulmonary small vessels is observed in critical COVID-19 patients[93]. Beside pulmonary embolism, COVD-19 can cause a sepsis associated DIC[94]. Thus there is an increasing interest in the treatment of COVID-19 using agents that ameliorate endothelial dysfunctions and hypo-fibrinolysis and prevent intravascular coagulation.

Ag-II is the main culprit in COVID-induced endothelial dysfunction[95]. Elevated Ag-II Stimulates ROS generation which causes breakdown of NO[73]. Besides this ROS also inhibits eNOS by inducing uncoupling to decease NO production[82].Oxidative stress increases expression of Plasminogen activator Inhibitor-1 (PAI-1) to enhance thrombosis[83]. The adhesiveness of endothelial cell surface to inflammatory cells is enhanced by ROS. Thus oxidative stress condition promotes inflammation and thrombosis[96,97].

Ag-II-induced endothelial dysfunction is augmented in absence of counter-actor, bradykinin. Bradykinin via bradykinin receptor-2 (abundantly expressed in endothelium) causes release of NO and prostacyclin to induce vasodilation[98]. Bradykinin has antithrombotic property by increasing tissue type plasminogen activator[99]. In COVD-19 victims there is degradation of bradykinin via Ag-II mediated hyperaldosteronism. The increase level of Ag-II and aldosterone in COVID-19 infection may be associated with hypofibrinolysis leading to

a decrease tPA to PAI-1 ratio. This leads to poor resolution of alveolar lesions and fibrosis in COVID-19 patients[100]. High level of Ag-II may exacerbate endothelial dysfunction and enhance lung injury. ACE inhibitors have been shown to improve endothelial function[8]. It also increase NO production by two ways: inhibiting production of Ag-II (which decrease NO production by inhibiting eNOS and enhances NO breakdown) and inhibiting the breakdown of bradykinin (which stimulate local release of NO). Beside this ACE inhibitor increases availability of bradykinin to enhance fibrinolysis and consequence reduces coagulopathy of endothelium. There are two different catalytic domains of ACE, one cleaves Ag-I and other degrades bradykinin. ACE inhibitor have a greater affinity for the bradykinin than for Ag-I. Thus such inhibitor decreases bradykinin degradation[101]. Thus ACE inhibitor can be considered as pharmacological therapeutic agent to prevent COVID-19 associated microvascular thrombosis. The combined effects of ACE inhibitor on both the pulmonary system and haemostasis may be a tentative target in COVID-19.

A previous study indicated that anticoagulation treatment using LMWH reduced mortality in severe COVID-19 patients with coagulopathy[11]. Anticoagulation treatment was recommended in patients in the viremia and acute clinical phases of COVID-19 induced pathogenesis[102]. SARS-Cov-induced inflammation may lead to excessive activation of coagulation in these phases[103]. Anticoagulation therapy with unfractionated heparin (UFH) caused successfully recovered from moderate to severe COVID-19 cases in Japan[104]. In addition to anticoagulant property heparin has anti-inflammatory and direct antiviral[105]. Heparin inhibits neutrophil activation to minimize formation of cytokines and reduces activation of endothelium after binding with cytokines[106]. It was reported that heparin directly occupies spike protein to prevent SARS-Cov-ACE2 interaction, and thereby blocks entry of virus into host cell[107]. It also down regulates IL-6[108], which is elevated in COVID-19 patients[109]. Heparin binds and forms a complex with plasma antithrombin III, activating it. This produces a conformational change in antithrombin which accelerates its binding to clotting factors Xa, IIa, IXa, XIIa and XIIIa resulting in inhibition of the factors. In this way Heparin works as an anticoagulant which can be used to treat Covid-19 patients. Prophylactic LMWH is recommended by WHO against venous thromboembolism in critically ill COVID-19 patients[110]

3 Summary and Conclusion

The hall mark of SARS-COV2 infection is hyperinflammation which promotes thrombosis through activation of endothelium, platelets, and coagulation factors, and inhibition of fibrinolysis. COVID-19 associated coagulopathy is accompanied by high mortality rate from thrombotic complications. Ag-II is the main culprit in COVID-induced endothelial dysfunction. SARS-Cov2 infection is associated with misbalance between Ag-II and Ag-1-7 (increase ratio of Ag-II: Ag-1-7) which leads to hyperinflammation. Imbalance activity of two system: Ang-II-PAI-1 and bradykinin-tPA system (with increased activity of Ag-II-PAI-1) suppress fibrinolysis. ACE inhibitor which decreases the formation of Ag-II as well as prevents degradation of bradykinin may serve potential role against microvascular thrombosis from COVID-19. On the other hand LMWH may be considered as potent therapeutic agent not only due to its antithrombotic property but also from anti-inflammatory and anti-viral activity.

Acknowledgement

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