REVIEW

Potential mechanisms of cerebrovascular diseases in COVID-19 patients

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Abstract

Since the outbreak of coronavirus disease 2019 (COVID-19) in 2019, it is gaining worldwide attention at the moment. Apart from respiratory manifestations, neurological dysfunction in COVID-19 patients, especially the occurrence of cerebrovascular diseases (CVD), has been intensively investigated. In this review, the effects of COVID-19 infection on CVD were summarized as follows: (I) angiotensin-converting enzyme 2 (ACE2) may be involved in the attack on vascular endothelial cells by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), leading to endothelial damage and increased subintimal inflammation, which are followed by hemorrhage or thrombosis; (II) SARS-CoV-2 could alter the expression/activity of ACE2, consequently resulting in the disruption of renin-angiotensin system which is associated with the occurrence and progression of atherosclerosis; (III) upregulation of neutrophil extracellular traps has been detected in COVID-19 patients, which is closely associated with immunothrombosis; (IV) the inflammatory cascade induced by SARS-CoV-2 often leads to hypercoagulability and promotes the formation and progress of atherosclerosis; (V) antiphospholipid antibodies are also detected in plasma of some severe cases, which aggravate the thrombosis through the formation of immune complexes; (VI) hyperglycemia in COVID-19 patients may trigger CVD by increasing oxidative stress and blood viscosity; (VII) the COVID-19 outbreak is a global emergency and causes psychological stress, which could be a potential risk factor of CVD as coagulation, and fibrinolysis may be affected. In this review, we aimed to further our understanding of CVD-associated COVID-19 infection, which could improve the therapeutic outcomes of patients. Personalized treatments should be offered to COVID-19 patients at greater risk for stroke in future clinical practice.

Keywords COVID-19 · SARS-CoV-2 · Cerebrovascular disease · Stroke

Abbreviations

COVID-19	Coronavirus disease 2019
CVD	Cerebrovascular diseases
AIS	Acute ischemic stroke
CKD	Chronic kidney disease
N/A	Not applicable
MCA	Middle cerebral artery
ACA	Anterior cerebral artery
WBC	White blood cell
PT	Prothrombin time
D-D	D-dimer
aCL	Anticardiolipin
AF	Atrial fibrillation
CRP	C-reactive protein
aβ2GP1	Anti-β2-glycoprotein-1
ICU	Intense care unit
APTT	Activated partial thromboplastin time
PLT	Platelet
SAH	Subarachnoid hemorrhage
PICA	Posterior-inferior cerebellar artery

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Introduction

At the end of 2019, coronavirus disease 2019 (COVID-19) was discovered in Wuhan, China, followed by the global outbreak (Chan et al. 2020; Wang C et al. 2020); . COVID-19 infection is caused by a novel coronavirus, which was named as severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (Chan et al. 2020). On 11 March 2020, the World Health Organization (WHO) officially announced the COVID-19 outbreak a global pandemic. Until 21 December 2020, 75,479,471 cases have been confirmed worldwide including 1,686,267 deaths (https://covid19.who.int).

The COVID-19 infection is a type of viral pneumonia. However, apart from respiratory symptoms, some patients also exhibit neurological dysfunction (Huang et al. 2020). Furthermore, a previous study by Mao et al. has revealed the neurological manifestations in COVID-19 patients for the first time, which attracts physicians' particular attention to the neurological deficits caused by SARS-CoV-2 (Mao et al. 2020). Additionally, the patients with cerebrovascular diseases (CVD) have worse therapeutic outcomes and are more easily overlooked than other patients (Mao et al. 2020). During the pandemic of COVID-19, it is thus essential to further our understanding of the association between COVID-19 infection and neurological dysfunction, especially the effects on cerebrovascular system. Therefore, comprehensive treatments could be developed, and the therapeutic outcomes may be improved. In this review, the existing knowledge in SARS-CoV-2 was summarized, and the epidemiological characteristics and neurological manifestations in COVID-19 patients were analyzed. Moreover, the association between COVID-19 infection and the occurrence of CVD was elucidated. Our aim was to review the potential pathophysiological mechanisms and provide guidance for follow-up research and future clinical practice.

Background of SARS-CoV-2

Coronaviruses belong to the family of *Coronaviridae*, which is divided into four genera, α, β, γ, and δ (Fung and Liu 2019). Seven coronavirus strains are able to infect humans and cause respiratory diseases, including severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and the newly discovered SARS-CoV-2 (Fung and Liu 2019; Zhou et al. 2020). The abovementioned strains are pathogenic β-coronaviruses which could cause regional or even global outbreaks (Fung and Liu 2019; Lu et al. 2020; Oboho et al. 2015; Peiris et al. 2003; Wang C et al. 2020). Among them, Lu et al. and Chan et al. have

reported that SARS-CoV-2 shares a highly similar gene sequence (~79%) with SARS-CoV-1; thus, they are highly homologous.

Neurological manifestations in COVID-19 patients

Fever, dry cough, and fatigue are the most common symptoms at the onset of SARS-CoV-2 infection (Guan et al. 2020a, b; Wang et al. 2020). Although neurological symptoms are not often observed, small proportion of COVID-19 patients still exhibits neurological dysfunction. A previous study of the Union Hospital of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China), has revealed the characteristic neurologic manifestations in COVID-19 patients for the first time (Mao et al. 2020). A total of 214 cases were enrolled in this study, containing 78 patients (36.4%) with neurological symptoms and six cases with acute cerebrovascular disease (ACVD). Furthermore, two patients with ACVD did not exhibit the common symptoms such as fever and cough; however, the first symptom was sudden hemiplegia (Mao et al. 2020). These findings suggest that COVID-19 patients whose first symptom was ACVD alone could be missed or misdiagnosed. In this review, more COVID-19 cases with the occurrence of CVD were summarized (Table 1)(Al Saiegh et al. 2020; Avula et al. 2020; Beyrouti et al. 2020; Goldberg et al. 2020; Oxley et al. 2020; Tunç et al. 2020; Zhang Y et al. 2020). More importantly, according to the early published data, the fatality rate of COVID-19 patients with CVD is ~10.5% in China, which indicates that the occurrence of CVD in COVID-19 patients could lead to unfavorable outcomes (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020). Furthermore, patients with pre-existing chronic conditions, such as hypertension and diabetes, exhibit higher infection rate and poorer prognosis (Guan et al. 2020a, b). Aging, hypertension, and diabetes are the risk factors for the occurrence of cerebrovascular events (Boehme et al. 2017). As the outbreaks generally occur in winter, when the incidence of CVD is higher, more attention should be paid to the monitoring of elderly patients with severe COVID-19, especially those with cerebrovascular diseases or who have already developed CVD.

Potential mechanisms of COVID-19-induced cerebrovascular diseases

As previously reported, the risk of death in SARS patients was also increased by the occurrence of CVD (Wang et al. 2012). A previous study on five SARS cases with newly diagnosed large artery stroke suggested that

Table 1 Cerebrovascular diseases in COVID-19 patients

Articles/authors	COVID-19 patients with CVD	Types of CVD	Symptoms at COVID-19 onset	Medical history	Laboratory findings	Days from COVID-19 symptom onset to CVD onset, median (range)	Therapeutic outcomes
Mao L et al.	214 patients including 6 (2.8%) cases with acute CVD	AIS (5); Cerebral hemorrhage (1)	No typical symptoms of COVID-19 (2), sudden hemiplegia as the first symptom	Hypertension 51 (23.8%); Diabetes 30 (14.0%); Cardiocerebrovascular disease 15 (7.0%); Malignancy 13 (6.1%); CKD 6 (2.8%)	N/A	N/A	Patient with cerebral hemorrhage: died; patient with AIS: critical
Goldberg MF et al.	Case report (1 case)	AIS	Fever and myalgias	Hypertension; Aplastic anemia; Splenectomy	WBC↑; PT↑; Fibrinogen↑; D-D↑; Serum ferritin↑; aCL IgM↑	16	N/A
Beyrouti R et al.	Case series (6 cases)	AIS	Cough (5); Shortness of breath (5); Fever (4); Tachypnea (2); Myalgia (1); Malaise (1); Fatigue (1); Loss of appetite (1)	Hypertension (4); Diabetes (2); AF (2); Malignancy (2); Ischemic heart disease (2); Hypercholesterolemia (1)	WBC↑ (2); PT↑ (3); Fibrinogen↑ (4); D-D↑ (6); Ferritin↑ (5); CRP↑ (5); Lupus anticoagulant (+) (5); aCL IgM, aβ2GP1 IgG and IgM (+) (1)	12.5 (-2~24)	ICU (2)
Tunç A et al.	Case series (4 cases)	AIS	Fever (3); Cough (3); Shortness of breath (1)	Hypertension (3); Diabetes (1)	D-D↑ (3); CRP↑ (3); Ferritin↑ (1)	1.5 (1~4)	Bedridden (2); discharged (2)
Avula A et al.	Case series (4 cases)	AIS	Fever (2); Respiratory distress (1); Shortness of breath (1); Dry cough (1); No typical symptoms of COVID-19 (1), altered mental status and sudden hemiplegia as the first symptoms	Hypertension (4); Dyslipidemia (3); Diabetes (1); Carotid stenosis (1); CKD (1)	WBC↑ (2); PT↑ (4); CRP↑ (3); D-D↑ (2); Ferritin↑ (1)	Patients were hospitalized with CVD and simultaneously diagnosed with SARS-CoV-2 infection	Deteriorated (4)

Table 1 (continued)

Articles/authors	COVID-19 patients with CVD	Types of CVD	Symptoms at COVID-19 onset	Medical history	Laboratory findings	Days from COVID-19 symptom onset to CVD onset, median (range)	Therapeutic outcomes
Oxley TJ et al.	Case series (5 cases)	AIS	Cough (2) Lethargy (2) Headache (1) Chills (1) Fever (1)	Diabetes (2) Hypertension (1) Hyperlipidemia (1)	PLT↓ (1) Fibrinogen↑ (3) PT↑ (1) APTT↑ (2) D-D↑ (3) Ferritin↑ (3)	N/A	Discharged (3); ICU (1); transferred to stroke unit (1)
Al Saiegh F et al.	Case series (2 cases)	Patient 1: SAH	Fever, cough and arthralgia	None	N/A	7	Discharged
		Patient 2: AIS with hemorrhagic transformation	Hemiparesis and aphasia	N/A	N/A	0	N/A
Zhang Y et al.	Case series (3 cases)	Multiple cerebral infarctions	Fever (3) Dyspnea (3) Cough (2) Headache (2) Diarrhea (1) Fatigue (1)	Hypertension (3) Diabetes (2) Stroke (2) Coronary artery disease (1) Malignancy (1)	WBC↑ (3) PLT↓ (2) PT↑ (3) APTT↑ (3) Fibrinogen↑ (3) D-D↑ (3) CRP↑ (3) aCL IgA (+) (3) anti-β2-glycoprotein I IgA and IgG (+) (3)	18 (10～33)	Critical (3)

SARS-CoV-1 could trigger CVD and lead to worse outcomes (Umapathi et al. 2004). Furthermore, another study on 1291 SARS patients with confirmed CVD indicated that CVD is one of the most important risk factors in patients with SARS (Hu et al. 2004). Due to the current understanding of SARS-CoV-2-related CVD and the similarity of COVID-19 and SARS in terms of epidemiology, clinical manifestations, radiologic findings, and laboratory tests (Chan et al. 2020; Song et al. 2019), it is reasonable to use SARS-CoV-1 infection as a reference. In addition, Janardhan et al. has recently suggested that COVID-19 infection may be essentially a blood clotting disorder masquerading as a respiratory disease, as it involves the accumulation of angiotensin II (Ang II), oxidative stress, endothelial dysfunction, formation of antiphospholipid (APL) antibody complexes, platelet aggregation, coagulation cascade, and formation of cross-linked fibrin blood clots (Janardhan et al. 2020). This study also provides guidance to further explore the novel association between COVID-19 and CVD. After comprehensive analyses of the existing data, we hypothesized that COVID-19 may affect CVD through the following mechanisms (Fig. 1).

Attack against vascular endothelial cells by SARS-CoV-2

It is well established that SARS-CoV-2 and SARS-CoV-1 both enter the host cells through the recognition by angiotensin-converting enzyme 2 (ACE2), and the affinity of SARS-CoV-2 spike protein to ACE2 is much higher compared with SARS-CoV-1 (Li et al. 2003; Lu et al. 2020; Wan et al. 2020; Wrapp et al. 2020). The peptidase ACE2 is located on the surface of alveolar epithelial cells, small intestinal epithelial cells, vascular endothelial cells, arterial smooth muscle cells, immune cells, and neurons (Baig et al. 2020; Madjid et al. 2020). Therefore, SARS-CoV-2 may directly attack vascular endothelial cells via the ACE2 receptor, resulting in endothelial cell dysfunction and endothelial barrier damage (Janardhan et al. 2020). Furthermore, scholars have revealed the presence of SARS-CoV-2 in brain capillary endothelial cells in a COVID-19 patient (Paniz-Mondolfi et al. 2020).

Moreover, damage to the endothelium of cerebral capillaries may lead to endothelial ruptures accompanied by hemorrhage within cerebral tissues (Baig et al. 2020). Endothelial cells serve as a natural barrier by isolating
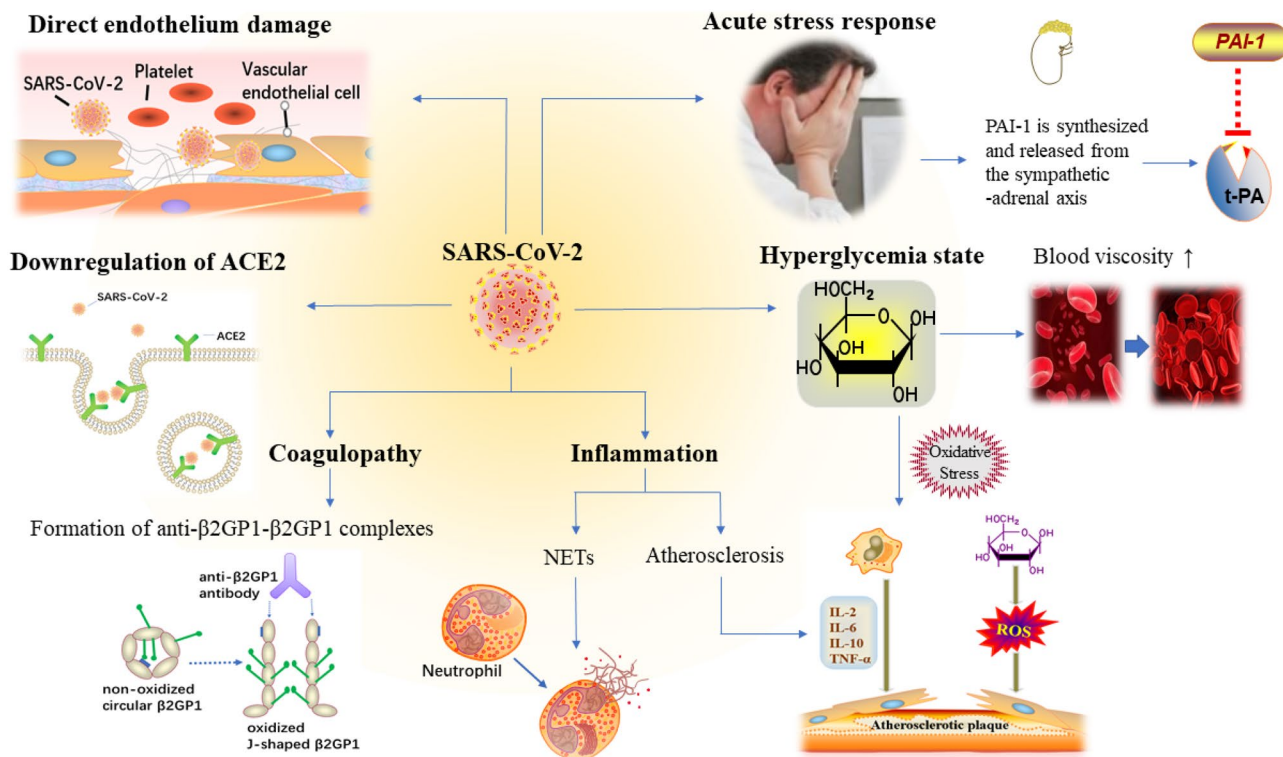

Fig. 1 Potential mechanisms of cerebrovascular diseases in COVID-19 patients. The potential mechanisms mainly include ACE2-mediated endothelium damage, downregulation of ACE2, acute infection-related inflammation and coagulopathy, formation of NETs and APL antibodies, hyperglycemia, and acute stress reaction. These are the risk factors of cardiocerebrovascular events in COVID-19 patients

platelets and coagulation factors from subintimal collagen, and they can produce heparin and vasodilating factors to regulate coagulation, fibrinolysis, and platelet activation (Prasad et al. 2016; van Hinsbergh 2012). If the endothelium is damaged, exposed subintimal collagen could induce platelet aggregation and adhesion, consequently leading to thrombosis and promoting the occurrence of ischemic events (Poredos and Jezovnik 2018). In addition, upon the damage of endothelium, numerous adhesion molecules are produced, and chemokines are released to recruit inflammatory cells. Furthermore, the disruption of cell permeability and intercellular barrier structure accelerates the penetration of inflammatory cells through the endodermis to the vascular wall and surrounding tissues, resulting in inflammatory infiltration (Chatzizis et al. 2007; Poredos and Jezovnik 2018; van Hinsbergh 2012). In addition, tissue interstitial edema was observed in various infected organs of some severe COVID-19 patients, as well as infiltration of mononuclear cells/lymphocytes, vascular endothelial inflammation/exfoliation, and intravascular transparent microthrombosis (Xu et al. 2020; Yao et al. 2020; Zhang et al. 2020). Moreover, similar pathologic features were detected in SARS patients with confirmed systemic vasculitis (Ding et al. 2003). Though the mechanisms of vasculitis are complex, it is suggested that the vessels at lesion site may form aneurysms due to reduced elasticity, which increases the risk of rupture and bleeding (Liberman et al. 2014). Moreover, inflammation may then cause stenosis or occlusion of the lumen and trigger ischemic events (Mourguet et al. 2019). Vasculitis is thus one of the promising causes of stroke (Schöberl et al. 2017).

Although the mechanisms of systemic vasculitis in patients with SARS-CoV-2 infection require further investigation using biopsies or autopsies, SARS-CoV-2 is able to induce endothelial dysfunction/exfoliation and endothelial/subendothelial inflammatory cell infiltration, which greatly increases the risk of thrombosis or hemorrhage in patients.

Downregulation of ACE2 leads to disruption of renin-angiotensin system

ACE2, a homolog of ACE1, serves essential roles in renin-angiotensin system (RAS: Fig. 2). Angiotensinogen is cleaved by Renin, which results in the formation of Ang I. Subsequently, Ang I is cleaved by ACE1, leading to the formation of Ang II which binds Ang II-type-1-receptor (AT1R), further inducing hypertension and atherosclerosis. In addition, ACE2 cleaves Ang II to form Ang 1-7 which promotes vasodilation and exerts anti-inflammatory/anti-atherosclerosis effects through Mas receptor (MasR) (Packer and McMurray 2017; Paz Ocaranza et al. 2020; Stegbauer et al. 2019; Wu et al. 2020). Overexpression of ACE2 in vascular endothelial cells can affect the expression of endothelial nitric oxide synthase and production of nitric oxide by altering the ratio of Ang 1-7 to Ang II. These effects could protect brain tissues against ischemic damage (Chen et al. 2014) and prevent aneurysms by suppressing activation of RAS thus reducing the risk of hemorrhage (Hao et al. 2018). Furthermore, pathophysiologic changes involving the activation of RAS and depletion of ACE2 have been reported in cardiocerebrovascular diseases, and activation of ACE2 may have beneficial effects in hypertension, myocardial infarction, stroke, and atherosclerosis (Velkoska et al. 2016). Taken all together, these findings indicate that ACE2 serves key roles in cardiocerebrovascular protection through opposite regulation of the ACE1/Ang II/AT1R axis.

Fig. 2 Schematic chart of the renin-angiotensin system. Angiotensinogen is cleaved by Renin, which results in the formation of Ang I. Subsequently, Ang I is cleaved ACE1, leading to the formation of Ang II which binds AT1R, further inducing hypertension and atherosclerosis. ACE2 cleaves Ang II, which results in the formation of Ang 1-7 which promote vasodilation and exert anti-inflammatory/anti-atherosclerosis effects through MasR. ACEI and ARB act on ACE1 and AT1R, respectively, subsequently inhibiting the ACE1/Ang II/AT1R axis
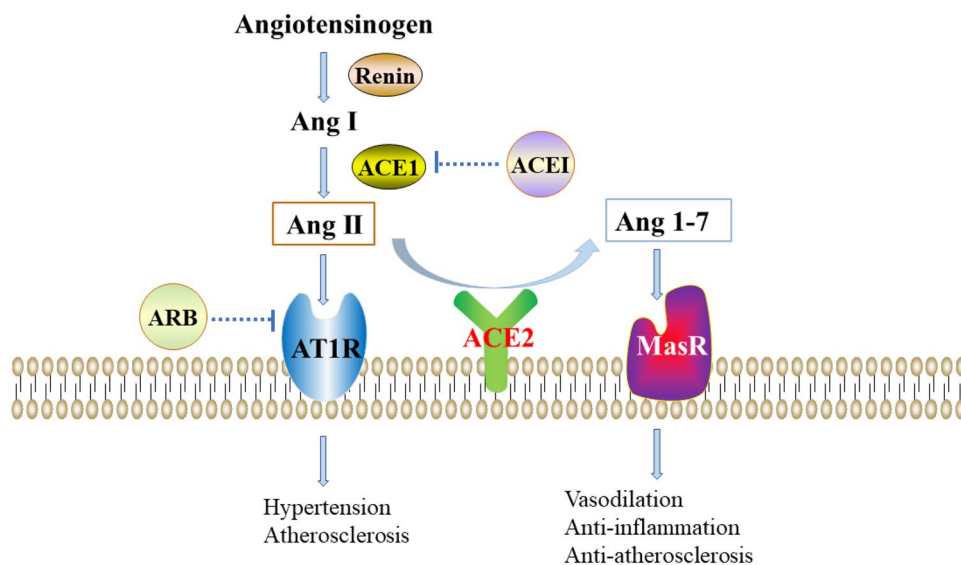
During the COVID-19 epidemic, Liu et al. have reported that plasma levels of Ang II are significantly increased in SARS-CoV-2-infected patients and are positively correlated with viral titer and disease severity (Liu et al. 2020). The accumulation of Ang II stimulates oxidative stress and further causes endothelial dysfunction (Janardhan et al. 2020). The dysregulation of RAS caused by SARS-CoV-2 infection may occur as spike protein interacts with the extracellular domain of ACE and triggers endocytosis to consume ACE2 on the surface of host cells, leading to the downregulation of ACE2 (Lan et al. 2020; Li et al. 2003; Turner et al. 2004). Interestingly, this interaction is significantly enhanced in patients with hypertension, coronary heart diseases, and diabetic conditions (Groß et al. 2020). In addition, reduced expression of ACE2 has been observed as the age increases, which is more common in men than in women (Xie et al. 2006). We hypothesized that endocytosis of ACE2 induced by virus together with age-related reduction of ACE2 contributes the dysregulation of RAS and then leads to increased risk of CVD in COVID-19 patients, especially in elderly male patients with pre-existing chronic conditions such as hypertension or diabetes.

Neutrophil extracellular traps (NETs) are the key factors of immunothrombosis

Activated leukocytes interact with platelets and plasma clotting factors to form microthrombus, which is called immunothrombosis (Engelmann and Massberg 2013). Due to the existence of transparent microthrombus in multiple organs such as the heart, lungs, and kidneys of SARS-CoV-2-infected patients (National Health Commission of the People's Republic of China 2020), Nicolai et al. suggested that neutrophils, immunogenic platelets, and dysregulated coagulation cascade could promote immunothrombosis, which is closely related to systemic hypercoagulability and acute respiratory distress syndrome in COVID-19 patients (Nicolai et al. 2020). These microthrombus are mainly composed of platelets, fibrin, and a large number of citrullinated histone H3 (citH3)-positive neutrophils (Middleton et al. 2020; Nicolai et al. 2020). citH3 is a biomarker of neutrophil extracellular traps (NETs) formation (Mauracher et al. 2018).

Previous studies have revealed the pathogenic roles of NETs on various thrombotic inflammatory states including sepsis (Chen et al. 2018; McDonald et al. 2017), thrombosis (Mauracher et al.), and respiratory failure (Ojima et al. 2020). The formation of NETs may also trigger immunothrombosis in SARS-CoV-2 infection. Furthermore, Zuo et al. (Zuo et al. 2020) and Middleton et al. (Middleton et al. 2020) have suggested that COVID-19 patients, especially those admitted to intensive care unit or receiving tracheal intubation or who died, exhibit

significantly increased NETs levels. Therefore, the levels of NETs could be associated with the severity of this disease.

Activated platelets are the major initiator which can induce the activation of neutrophils and formation of NETs (Gaertner et al. 2017). Pathogens including virus could cause serial functional reactions through the activation of platelet-activating factor receptors such as toll-like receptor, further inducing platelet-neutrophil interactions, leading to the production of NETs and promoting thrombosis (Clark et al. 2007; Hottz et al. 2018). Moreover, numerous chemokines including platelet factor 4 (PF4) could promote the recruitment of white blood cells (WBCs) toward vascular injury or inflammatory sites (Hottz et al. 2018). In addition, activated platelets express P-selectin and glycoprotein (GP)-Ib, which interact with the P-selectin glycoprotein ligand 1 and the integrin Mac-1 on neutrophil membrane, respectively, to gain the stable adhesion and trigger the release of NETs (Etulain et al. 2015; Gaertner et al. 2017). During this process, PF4 binds to NETs, which increase the density and resistance to DNase of platelet-neutrophil aggregates. Meanwhile, PF4/NET-positive feedback loop is activated, which could maintain a coagulative NETs cascade response (Malisch et al. 2018).

The pathogens activate platelets in the host to induce the formation of NETs, subsequently promoting the formation of immune-related microthrombus. Increased levels of PF4 and NETs are detected in patients with novel coronavirus pneumonia, which are associated with multiple organ failure and systemic hypercoagulability (Middleton et al. 2020), perhaps being one of the reasons of thrombotic events in COVID-19 patients.

Severe inflammation is one of the clinical features of COVID-19

"Sepsis-induced coagulopathy" (SIC), a precursor state of disseminated intravascular coagulation (DIC) with elevated D-dimer and fibrinogen levels, could be one of the emerging features of severe COVID-19. It could be associated with infection-induced systemic inflammatory response, endothelial dysfunction, and microthrombosis (Hess et al. 2020). Most COVID-19 patients, especially those with severe symptoms, exhibit remarkable inflammatory responses with prolonged prothrombin time, elevated levels of C-reactive protein (CRP), and upregulation of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and various interleukins (ILs) (Chen et al. 2020; Guan et al. 2020a, b; Huang et al. 2020; Mehta et al. 2020; Wang et al. 2020; Warren-Gash et al. 2018). Middleton et al. have revealed significant elevation of IL-6 and IL-8, two additional cytokines probably related to the enhanced platelet reactivity and induction of WBCs to form NETs. These findings can be supported by the results of an

in vitro assay, as the plasma from SARS-CoV-2-infected patients could induce the formation of NETs generated from neutrophils isolated from healthy people, while the plasma from healthy adults could not (Middleton et al. 2020). As mentioned above, the formation of NETs is closely associated with the prethrombotic state in COVID-19 patients.

In addition, pathogens can be recognized by the pattern recognition receptor on the surface of human immune cells, which triggers systemic inflammation (Wallet et al. 2018), and these effects could last for a long term even after the recovery from the disease (Yende et al. 2008). Atherosclerosis, a wide range of chronic inflammatory lesions of the arterial wall, could be induced by this long-term inflammatory stimulation (Stojanović et al. 2020). Apart from long-term stimulation, acute infection–induced inflammatory response can also aggravate local inflammation in atherosclerotic plaques, which in turn destroys the stability of plaques and leads to rupture (Madjid et al. 2007; Naghavi et al. 2003). The subsequent aggregation and activation of platelets on the surface of ruptured plaques followed by secondary thrombosis is one of the common pathophysiological mechanisms of acute ischemic stroke.

In summary, SARS-CoV-2 could induce inflammatory cascade, affect coagulation and fibrinolysis system, promote atherosclerosis, and influence plaque stability, consequently increasing the risk of CVD in COVID-19 patients. CRP, as an indicator of systemic inflammation, is also an independent predictor of all-cause death in patients with ischemic stroke (Huang et al. 2012). Therefore, the outcomes in patients with significantly elevated CRP, and D-dimer levels could be worse.

Antiphospholipid antibodies and their complexes are detected in COVID-19 patients

Antiphospholipid antibodies could target different phospholipid-binding protein antigens, including lupus anticoagulant, anticardiolipin, anti-β2 glycoprotein 1 (anti-β2GP1), and anti-prothrombin antibody, which are related to both arterial and venous thrombosis events (Mendoza-Pinto et al. 2018). APL antibodies have been detected in severely infectious patients (Asherson and Cervera 2003). Until now, upregulation of infection-related APL and thrombosis events have been documented in various infectious patients, especially in those infected with human immunodeficiency virus (Ramos-Casals et al. 2004) and hepatitis C virus (Rafai et al. 2006; Ramos-Casals et al. 2004).

There are two types of APL antibodies: "autoimmune" and "infectious" type. Apart from the presence in some healthy volunteers (de Groot and Urbanus 2012), anti-β2GP1 antibody can also be induced by certain microbial pathogens (Blank et al. 2002). The mechanisms underlying

the transformation of anti-β2GP1 antibody from normal to pathogenic state remain unclear, while infection might play a role (van Os et al. 2011). After binding with pathogenic phospholipids under the oxidative stress and systemic inflammatory state, the conformation of non-oxidized circular β2GP1 transforms into oxidized J-shaped β2GP1, the cryptic epitopes are exposed, which induce the formation of anti-β2GP1-β2GP1 complexes (Agar et al. 2010; Janardhan et al. 2020). These immune complexes activate platelet receptors, and then lead to platelet adhesion, secretion of granules, synthesis of thromboxane A2, and formation of blood clot finally (Ho et al. 2016; Li et al. 2010).

Although "infectious" APL antibodies are usually transient, antiphospholipid syndrome (APS) has been observed in COVID-19 patients who developed cerebral ischemia accompanied by coagulopathy, especially in the severe cases (Beyrouti et al. 2020; Goldberg et al. 2020; Zhang et al. 2020). Zhang et al. have reported three cases of COVID-19 patients with increased APL antibodies, and all of them develop multiple cerebral infarctions (Zhang et al. 2020). In addition, Beyrouti et al. (Beyrouti et al. 2020) and Goldberg et al. (Goldberg et al. 2020) have revealed similar findings. Nevertheless, the results of Borghi et al. (Borghi et al. 2020) and Devreese et al. (Devreese et al. 2020) indicated no obvious association between the increased APL antibodies and thrombosis in COVID-19 patients. Therefore, it is not clear whether the thrombotic events in COVID-19 patients are associated with the levels of APL antibodies and whether it is reasonable to routinely screen for these indicators. Further investigations are required to reveal the pathogenic relevance of APL antibodies to ischemic events.

Hyperglycemia promotes the occurrence and development of atherosclerosis

Chen et al. suggested that ~52% of COVID-19 patients exhibit hyperglycemia (Chen et al. 2020). This could be attributed to the stress response. Acute infection, as a potential source of stress, can induce self-protective defense in the human body. For instance, more hyperglycemic hormones could be secreted, consequently aggravating insulin resistance and resulting in a significant increase in blood glucose (Malisch et al. 2018). In addition, some patients may have pre-existing diseases such as diabetes (Guan et al. 2020a, b; Huang et al. 2020; Wang D et al. 2020); the treatment with glucocorticoids could accelerate glucose catabolism and lead to hyperglycemia (Guan et al. 2020a, b).

A previous study has revealed that the prevalence of abnormal glucose regulation is 68.7% among all stroke patients in China (Jia et al. 2012). Diabetes is an independent risk factor for stroke, which is closely related

to the mechanisms underlying hyperglycemia or glucose fluctuation, and it could promote the occurrence and development of atherosclerosis (Dahl-Jørgensen et al. 2005; Johnston et al. 2019; Poznyak et al. 2020). Hyperglycemia could induce the overexpression of reactive oxygen species (ROS) via the mitochondrial electron transport chain, resulting in increased oxidative stress (Marco et al. 2015; Yuan et al. 2019). ROS could further activate numerous events associated with the progression of atherosclerosis, including the formation of advanced glycation end-products (Watson et al. 2011), the protein kinase C pathway (Zuniga et al. 2017), and the polyol pathway (Ramasamy and Goldberg 2010). Additionally, excessive ROS increase the formation of oxidized low-density lipoprotein and promote insulin resistance, thus indirectly accelerating the inflammation in atherosclerosis (Yuan et al. 2019). Moreover, elevated blood glucose increases blood viscosity, promotes platelet adhesion and aggregation, and further alters blood flow state, consequently increasing the risk of thrombosis (Marini et al. 2017).

In a previous study of 185 deceased patients with SARS, all patients exhibited elevated levels of glucose at admission, with notably increased levels at the time of death (Li C and Pan 2003). During the Middle East Respiratory Syndrome pandemic, a middle-aged female patient was infected with MERS-CoV and developed a massive spontaneous intracranial hemorrhage with no other risk factors for hemorrhage such as hypertension, vascular malformation, coagulation disorders, or antiplatelet aggregation therapy. Furthermore, the glucose level in this patient reached 25 mmol/L on the day prior to hemorrhage (Al-Hameed 2017). Therefore, hyperglycemia may also induce vascular events in COVID-19 patients through the abovementioned mechanisms, leading to unfavorable therapeutic outcomes.

Acute psychological stress alters the state of coagulation and fibrinolysis

During the pandemic, the vast majority of people are more or less under psychological stress. COVID-19 patients not only experience physical discomfort and side effects of medication, but also suffer loneliness, anxiety and depression due to social isolation, uncertainty of the virus, and the overwhelming news (Xiang et al. 2020). These changes, as superimposed stressors, could cause stress responses in many patients. According to an online survey on a total of 714 COVID-19 patients, ~96.2% of patients exhibit post-traumatic stress symptoms (Bo et al. 2020).

It has also been reported that acute psychological stress events have great impact on CVD (Koton et al. 2004; Prasad et al. 2020), and a case-crossover study suggested that stress is an independent trigger for stroke (Prasad et al. 2020). However, the association between acute psychological stress and CVD remains unclear. Previous studies have revealed that the expression and release of plasminogen activator inhibitor type-1 (PAI-1) is increased under physiologic and pathologic stress (Jiang et al. 2011; Kozak et al. 2016). PAI-1, a serine protease inhibitor, is the only inhibitor that interacts with tissue plasminogen activator (t-PA). This interaction leads to rapid inactivation of t-PA, and PAI-1 could be an essential mediator in stress-related hypercoagulable state and thrombosis (Jiang et al. 2011). It is also reported that plasma PAI-1 is synthesized and released from the sympathetic-adrenal axis, and activation of this axis is considered as a characteristic of stress response (Issam et al. 2019). Therefore, there are some pathophysiologic connections within acute psychological stress, activation of the sympathetic-adrenal axis, altered fibrinolytic activity, and increased risk of thrombosis.

As a stressor that cannot be ignored, the COVID-19 outbreak could be associated with higher risk of CVD. Unfortunately, the levels of plasma PAI-1 are not routinely monitored in COVID-19 patients. Future studies with large sample size are required to further explore the relationship between CVD and acute stress and to elucidate the underlying pathophysiologic mechanisms.

Rapid vascular recanalization for COVID-19 patients with sudden ischemic stroke

Current guidelines recommend that intravenous recombinant tissue plasminogen activator (rt-PA) can be used in selected patients with acute ischemic stroke (AIS) within 3 h or in highly selected patients within 3–4.5 h of symptom onset or last known well (Powers et al. 2019). Leukocytosis and elevation of C-reactive protein/D-dimer are detected in patients with COVID-19 (Chen N et al. 2020; Guan et al. 2020a, b; Guan et al. 2020a, b; Huang et al. 2020; Mehta et al. 2020; Wang et al. 2020; Warren-Gash et al. 2018). Although these abnormalities are not absolute contraindications of intravenous thrombolysis (IVT), previous studies have revealed that leukocytosis and elevated CRP and D-dimer levels are more predictive for higher risk of hemorrhage transformation and higher mortality rate in AIS patients treated with rt-PA (Hsu et al. 2016; Sato et al. 2020; Tiainen et al. 2013). Data from 75 stroke centers in Italy have demonstrated that 1-month unfavorable outcomes in patients with stroke and COVID-19 who received IVT therapy are remarkably increased (Cappellari et al. 2020). However, a multicenter case study in the USA suggests that IVT may be safe and effective as it significantly improves the 24-h National Institutes of Health Stroke Scale (NIHSS) score without increasing systemic/symptomatic intracranial hemorrhage (Carneiro et al. 2020). The sample sizes are limited in both studies; thus, further investigation on larger

cohort is required to confirm the existing findings. At the moment, it is not a rare event to treat AIS with rt-PA in COVID-19 patients (Cappellari et al. 2020; Carneiro et al. 2020; Co et al. 2020; Escalard et al. 2020; Sangalli et al. 2020), but no sufficient evidence could confirm the efficacy of this treatment, and no clear regulation is available to prohibit the use of rt-PA just due to the abnormal laboratory indicators. Therefore, clinicians should be aware of the inherent risk of rt-PA treatment for patients with COVID-19 and stroke. Decision should be prudently made in clinical practice after the coagulation status in patients is carefully evaluated.

Additionally, for those who exceed the thrombolytic time window, endovascular thrombectomy (EVT) is also recommended to achieve vascular recanalization and protect potential salvageable tissues (Powers et al. 2019). In contrast, COVID-19 patients with large-vessel occlusions (LVOs) who treated with EVT exhibit higher discharge rate (47.1%) compared with those without treatment (32.4%) (de Havenon et al. 2020). However, compared with pre-epidemic cases with LVOs, COVID-19 with LVOs is more common in younger patients with higher NIHSS score, heavier thrombus load, more serial/multi-regional occlusions, lower first-pass effect, higher risk of clot rupture, distal migration, and vascular re-occlusions (Escalard et al. 2020; Pop et al. 2020; Wang et al. 2020), which may be associated with the hypercoagulability in COVID-19 patients. In addition, the use of stent device could be related to clot fragmentation, distal migration, and re-thrombosis, especially in COVID-19 patients with endothelial dysfunction (Wang et al. 2020). In contrast, suction device may cause lighter endothelial damage (Peschillo et al. 2018). Therefore, thrombectomy device for endovascular stroke therapy should be carefully chosen in the treatment of COVID-19 patients.

Implications and possible challenges in disease management

Upregulation/activation of ACE2 by ACEI/ARB

Based on the abovementioned analyses, SARS-CoV-2 affects the expression of ACE2, which in turn leads to the dysregulation of RAS, aggravates lung injuries, and promotes the development of atherosclerosis. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB), two commonly used antihypertensive drugs, could upregulate the expression and increase the activity of ACE2 (Ferrario et al. 2005; Ishiyama et al. 2004; Soro-Paavonen et al. 2012). Notably, a multi-center study indicated that in hospitalized COVID-19 patients with hypertension, treatment with ACEI/ARB was associated with lower risk of all-cause mortality (Zhang

et al. 2020). Therefore, whether these drugs could be used to prevent acute lung injuries and reduce the risk of stroke in COVID-19 patients should be further investigated, especially in those with severe symptoms.

Anti-inflammatory therapy is controversial

SARS-CoV-2 induces a series of inflammatory cascades which are closely related to hypercoagulable state and thrombosis (Zhang et al. 2020). However, after balancing the risks and benefits, whether to conduct anti-inflammatory therapy is controversial (Isidori et al. 2020). At present, glucocorticoids are commonly used as anti-inflammatory drugs in patients with COVID-19 (Guan et al. 2020a, b; Wang D et al. 2020). Although glucocorticoids prevent inflammation and lung damage, they could delay the clearance of virus and increase the risk of secondary infection, especially in immunodeficient patients (Zhang et al. 2020). Therefore, the WHO coronavirus management guidelines do not recommend the use of corticosteroids in COVID-19 patients (Isidori et al. 2020). Future studies are required to verify the use of corticosteroids and other anti-inflammatory drugs in COVID-19 patients.

Intervention of neonatal neutrophil extracellular trap inhibitor (nNIF)

SARS-CoV-2, as an invasive pathogen, can induce the formation of NETs by activating platelets in host. Nevertheless, NETs can also induce excessive thrombotic inflammatory responses, leading to thrombosis and ischemic events in patients. Increased levels of NETs have been detected in COVID-19 patients, which are also associated with disease severity (Middleton et al. 2020; Zuo et al. 2020). In previous study, neonatal NET-inhibitory factor (nNIF) is able to inhibit the formation of NETs, suggesting its therapeutic potential (Yost et al. 2016). Furthermore, in a cohort study conducted by Middleton et al., synthesized nNIF could significantly decrease the levels of NETs which are induced by COVID-19 plasma in vitro (Middleton et al. 2020). Therefore, nNIF inhibits the formation of NETs and may be used in the treatment of COVID-19 patients.

Close monitoring of the levels of blood glucose and D-dimer

Elevation of D-dimer and glucose could increase the risk of CVD; therefore, it is imperative that the levels of D-dimer and glucose should be closely monitored

and strictly controlled during the treatment of COVID-19 patients. For patients in hypercoagulable state or at higher risk of embolism, proper use of anticoagulants or antithrombotic therapy could be beneficial (Bikdeli et al. 2020; Spyropoulos et al. 2020). Neurological examinations should also be conducted on a daily basis, especially in patients with severe symptoms. Once the patients exhibit the signs of ACVD, neurologists should be immediately become involved in the treatment and follow-up management.

Prevention of acute stress response

As the global outbreak, a major acute stressor could cause significant posttraumatic stress responses among most patients, which can bring long-term effects on cardiocerebral vessels through various mechanisms (Xiang et al. 2020), appropriate psychological intervention for patients, such as education, consultation, long-term follow-up, and evaluation, are urgently required for COVID-19 patients.

Immediate treatments are necessary

According to recent statistics analyses, the number of admission rate for ischemic cerebrovascular events is significantly decreased in many countries or regions (Hoyer et al. 2020; McConachie et al. 2020; Schlachetzki et al. 2020). This may be a consequence of social distancing measures and patients' fear of being infected if going to hospital. Correspondingly, the volume of IVT is remarkably reduced during the COVID-19 pandemic (Plumereau et al. 2020), while intra-hospital delays are increased in patients transferred for EVT (Yang et al. 2020). Therefore, it is necessary to raise public understanding of ACVD and awareness of seeking for emergency treatments.

Conclusion

Based on our current knowledge of COVID-19, patients with SARS-COV-2 infection, especially those with severe symptoms, are at higher risk for CVD. Unfavorable therapeutic outcomes are observed in COVID-19 patients who developed acute cerebrovascular events. The potential mechanisms include ACE2-mediated endothelium damage, downregulation of ACE2, acute infection-related inflammation and coagulopathy, formation of NETs and APL antibodies, hyperglycemia, and acute stress reaction. These are the risk factors of cardiocerebrovascular events in COVID-19 patients. In future clinical practice, upregulation/activation of ACE2, inhibition of NETs, close monitoring

for inflammation/blood glucose/coagulation state, and reducing the psychological stress should be considered as novel therapeutic approaches for the treatment of COVID-19 with CVD.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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