Cerebral Vasomotor Reactivity in COVID-19

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the respiratory system but can also lead to neurological complications. Among COVID-19 patients, the endothelium is considered the Achilles heel. A variety of endothelial dysfunctions may result from SARS-CoV-2 infection and subsequent endotheliitis, such as altered vascular tone, oxidative stress, and cytokine storms. The cerebral hemodynamic impairment that is caused is associated with a higher probability of severe disease and poor outcomes in patients with COVID-19.

SARS-CoV-2 post-COVID complications vasomotor reactivity Transcranial doppler

1. Introduction

COVID-19 has become one of the leading causes of death worldwide, making it one of the most devastating health issues of the past few decades [1]. Despite the primary target of COVID-19 being the respiratory system, mounting evidence indicates that it may also negatively impact the cerebrovascular system [2][3]. In addition to respiratory symptoms, reports of neurological manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are emerging. These neurological manifestations include headache, ageusia (loss of taste), anosmia (loss of smell), as well as severe complications including seizures, ischemic stroke, cerebral hemorrhage, encephalitis, and meningitis [4][5][6]. Patients who suffer from severe clinical manifestations of SARS-CoV-2 infection are more likely to experience neurological symptoms compared to those who suffer from mild symptoms [7]. This virus is distinguished by the presence of the spike (S) glycoprotein, which provides the virus with access to neural, glial, and endothelial cells containing angiotensin-converting enzyme 2 (ACE2) [8]. There is still much to be discovered about the pathophysiology of this virus and how it affects the nervous system. However, it is believed that the neurological manifestations of acute COVID-19 can be attributed to multiple overlapping pathogenetic mechanisms [9]. These include viral neuroinvasion, endotheliopathy associated with blood–brain barrier dysfunction, coagulopathies that precipitate hypoxic-ischemic neuronal damage, metabolic imbalances, oxidative stress cascades, and cellular apoptosis [10].

In COVID-19 patients, the endothelial cells are regarded as the Achilles heel since injury to the endothelium will initiate and propagate SARS-CoV-2 infection [11]. The endothelium produces substances that cause blood vessels to contract or relax, which corresponds to cerebral hemodynamic vasomotor reactivity (VMR) [12]. With vasodilator stimulation, such as CO_2 inhalation, breath-holding test (BHT), or acetazolamide administration, VMR can be assessed using rates of blood flow in cerebral arteries and changes in blood flow caused by hypercarbia [13]. The impairment of vasoreactivity and reduced reserve capacity in brain arteries predispose patients to cerebrovascular disease. Recently, researchers have found that impaired VMR is associated with a higher probability of severe

illness and poor outcomes in patients with COVID-19 [14]. It is worth mentioning that structural changes in vasculature occur more slowly than functional changes. Hence, functional assessment of the vasculature, such as the VMR assessment, is more sensitive than structural analysis when acute exposure to the disease process is present [15]. Researchers have shown that viruses other than SARS-CoV-2, such as the Human Herpesvirus 8 and Hantavirus, can negatively impact cerebral hemodynamics [16]. In treating patients with viral infections such as COVID-19, physicians should consider VMR because of its potential to implement an appropriate, speedy, and aggressive treatment to improve neurological sequelae. Additionally, VMR has been observed to change over time in patients with different clinical neurologic manifestations, suggesting it could be a biomarker for the disease's progression [14]. It may be possible to prescribe targeted interventions to patients who might benefit from them, resulting in improved patient outcomes. Furthermore, it would reduce the burden associated with cerebrovascular disorders by utilizing valuable information obtained from a VMR evaluation.

2. COVID-19 Infection and Cerebral Vascular Health

There are a variety of neurological manifestations associated with COVID-19, ranging from minor symptoms like dizziness, headache, and loss or disruption of the sense of smell (anosmia/dysosmia) and taste (ageusia/dysgeusia), as well as severe conditions like stroke, Guillain-Barré syndrome (GBS), acute hemorrhagic necrotizing encephalopathy, and cerebral venous thrombosis [10]. ACE2 receptors enable SARS-CoV-2 to enter host cells via its spike protein [6]. It is reported that these receptors are highly expressed in various tissues, such as the heart, lungs, respiratory tract epithelium, endothelial cells, and brain [17]. The fusion of viral and cellular membranes is initiated by the spike protein, which is activated by the serine protease TMPRSS2. This fusion process leads to virus and receptor internalization, representing the initial step of cellular infection [18]. The spike protein in SARS-CoV-2 exhibits a higher binding affinity to ACE2 than SARS-CoV. Consequently, this increased affinity enhances the potential of SARS-CoV-2 to infect brain cells expressing ACE2 [19].

Evidence suggests that coronavirus can penetrate the brain, infecting neurons and glial cells [20][21]. The presence of central nervous system (CNS) coronavirus infection has been detected in the neural cells and cerebrospinal fluid (CSF) of individuals affected by COVID-19 [22]. ACE2 is expressed in distinct neuronal groups within the brain and brainstem [23]. Given that neurons possess a unique chemical signature, any alteration in this signature may lead to functional abnormalities at various levels, possibly explaining some of the clinical manifestations of COVID-19. The mechanism by which SARS-CoV-2 invades the CNS is not fully understood. Still, there are several theories, including retrograde transmission from the peripheral nervous system (PNS), hematologic spread, and transmission across the blood–brain barrier (BBB) [24].

The infection caused by SARS-CoV-2 specifically targets endothelial cells [25]. It has not yet been fully characterized how SARS-CoV-2 affects endothelial cells and its implications for apoptosis and function. However, viral bodies within the cells indicate that the virus is involved. The presence of viral components inside endothelial cells has been demonstrated [26] along with the accumulation in inflammatory cells, as well as evidence of both endothelial and inflammatory cell death. Viruses can use different mechanisms to harm the endothelium. Aside from causing apoptosis in endothelial cells, viruses also significantly increase cytokine levels, resulting in

alterations to the cell junctions, increasing vascular permeability, and altering endothelial function [27]. As a result of COVID-19, endothelial cells are likely to detach rapidly, and cell regeneration may not occur as effectively as expected [28]. The endothelium becomes activated due to the cytokine storm, resulting in endothelial dysfunction, endothelial cell death, increased vascular permeability, and impaired endothelial barrier functionality, ultimately leading to cell detachment [27]. As a result, parts of the inner surface devoid of endothelial cells appear, and the detached endothelial cells enter the bloodstream. In recent studies [29], researchers have demonstrated that both adherent and detached endothelial cells become procoagulant. Coagulability is due to increased phosphatidylserine expression and an absence of anticoagulant components such as thrombomodulin and tissue factor (TF) pathway inhibitors. In the presence of TF, an extrinsic coagulation cascade is initiated, leading to disseminated, uncontrolled, and widespread intravascular coagulation [29].

The cerebral vasculature can maintain a consistent blood flow despite alterations in cerebral perfusion pressure known as cerebral autoregulation [13]. Usually, cerebral blood flow is regulated by the diameter of arterioles, which influences cerebral blood flow (CBF) resistance. It remains unclear exactly how autoregulation is mediated at the molecular level [30]. Vasomotor responses are modulated by several processes including myogenic, neuro-genic, endothelial, and metabolic responses. The vascular endothelium is a crucial neurovascular unit (NVU), and it plays a fundamental role in regulating the blood–brain barrier and cerebrovascular reserve [31]. The endothelium also encompasses a substantial surface area responsible for regulating hemodynamic functions through the secretion of relaxing and contracting factors [25]. Vascular dysfunction manifests as an imbalance between the production of relaxing and contracting factors. Cerebrovascular reactivity (CVR) is a quantitative measure of NVU function. The CVR reflects NVU-mediated changes in cerebral blood flow in response to vasoactive stimuli.

This impairment of vascular function is likely a result of inflammation, the senescence of vascular cells, an increase in oxidative stress, reduced production or release of nitric oxide (NO) and other relaxing factors, as well as an increase in the production of vessel-contracting factors [32][33][34]. By losing endothelial cells on the luminal surface, normal reactivity mechanisms mediated by the endothelium, such as NO production, are disrupted [35]. Besides preventing abnormal contractions, NO inhibits platelet aggregation [36], suppresses the expression of adhesion molecules on endothelial cell surfaces, and therefore restricts white blood cell adhesion and penetration [28]. Decreasing NO production eliminates these protective effects of coagulation and inflammation [37]. Furthermore, disruption to the endothelial barrier allows aggregating platelets to approach vascular smooth muscle cells, triggering their contraction, which initiates the vascular phase of hemostasis. The breath-holding examination serves as a physiological test to assess ventilatory and metabolic responses during voluntary breath retention. This evaluation involves the deliberate cessation of respiration for a predetermined duration while closely monitoring various physiological reactions [38]. A primary objective of this test is to determine the body's ability to regulate ventilation and metabolism. By assessing VMR through the breath-holding test (BHT), valuable insights are obtained into the intricate control mechanisms governing respiration and metabolism. The BHT for VMR assessment can assist in evaluating the autonomic nervous system's response.

By analyzing the function of the endothelial cells, helpful information on the severity of the disease can be obtained since this disease rapidly affects the endothelial cells through various mechanisms. VMR serves as a critical

marker of cerebral vascular function, particularly endothelial function, determining the ability of cerebral arteries to constrict or dilate in response to changes in carbon dioxide levels and resistance to blood flow within the brain. Assessing VMR can provide valuable insights into chronic endothelial dysfunction in populations at risk of experiencing long-term effects of COVID-19. Additionally, it can aid in closely monitoring COVID-19 patients to reduce the impact of the disease on high-risk patients.

3. Flow Assessment in the Brain following Infection with COVID-19

CVR is a term used to describe the ability of brain blood vessels to dilate or constrict when metabolic demands or the microenvironment change [13]. Throughout the brain, oxygen and nutrients are delivered to brain tissue by this mechanism, which ensures continuous cerebral perfusion. Cerebral circulation is sensitive to arterial pCO_2 as it is a powerful vasomotor stimulus. Increased pCO_2 and decreased pH raise cerebral blood flow (CBF), whereas increased pO2 has the opposite effect [12].

CO_2 reactivity, acetazolamide, and the BHT can be used in clinical practice to assess CVR [12]. An easy, noninvasive, reproducible, and reliable method can be obtained using carbon dioxide reactivity tests if the mixture of CO_2 (3–7%) is inhaled for approximately 90 s [39]. The BHT induces hypercapnia via 30 s of apnea in order to calculate the breath-holding index (BHI) [40]. A breath BHI is calculated as a percentage increase in velocity from resting baseline values divided by the duration of breath holding (PSVmax—PSVrest/seconds) [41]. While BHT is noninvasive, easily performed, well-tolerated, and widely accepted, it has limited pCO_2 changes (roughly 3–4 mm Hg), requires patient collaboration, and is less reproducible.

As a final procedure, the Acetazolamide test involves the intravenous infusion of 500–2000 mg of carbonic anhydrase inhibitor, acetazolamide, which causes a transient marked amount of cerebral acidosis and vasodilation. Although this test is widely used due to its simplicity and absence of patient collaboration, it is less accurate and reproducible than the former, and it has undesirable side effects such as arterial hypertension, headaches, nausea, and perioral dysesthesia.

The response of cerebral vessels to vasoactive stimuli can be measured using various nuclear medicine and imaging techniques. PET is considered the gold standard for investigating CVR because it measures CBF directly. It is also possible to use near-infrared spectroscopy (NIRS), single photon emission computed tomography (SPECT), fMRI, CT with xenon enhancement, and transcranial Doppler sonography (TCD) [41][42][43]. TCD is a relatively reliable, inexpensive, widely available, and noninvasive method of measuring hemodynamic parameters in the main intracranial arteries, including peak systolic, diastolic, and mean velocity (MV) [44]. There are some limitations to TCD with transient vasodilator stimulations. Still, it is widely used in clinical practice to assess CVR and MV reduction indicating decreased global or regional CBF, pulsatility index (PI), and particularly, VMR [45]. CVR can be estimated by measuring changes in flow velocities in response to vasodilator stimuli in the main cerebral arteries as an indirect indication of changes in CBF.

Recently, researchers have found that impaired VMR is associated with a higher probability of severe disease and poor outcomes in patients with COVID-19. A functional dynamic assessment of the vascular function is more sensitive than a structural or morphological assessment after acute exposure to the disease process or factors affecting the vascular conduits are present. The structural changes in vasculature occur more slowly than the functional changes [15]. Therefore, cerebrovascular function can be assessed to provide valuable information regarding the progression of the disease and to assist in selecting an appropriate treatment plan. Additionally, CVR has been observed to change over time in patients with different clinical neurologic manifestations, suggesting that it could serve as a biomarker for the progression of the disease [12].

A study by Marcic et al. [46] evaluated cerebral hemodynamics and BHI in 25 patients with mild COVID-19 experiencing non-specific neurological symptoms 40 days after receiving a negative result for SARS-CoV-2, compared to 25 healthy individuals recruited as controls. The study did not identify any significant risk factors for cerebrovascular disease, and the BHI was significantly lower in the infectious patients than in the control group, suggesting an impaired VMR. A similar finding has been reported in other studies that have demonstrated impaired VMR following infection with COVID-19 [14][47]. In another study, Abdo-Cuza et al. [48] compared cerebral hemodynamic reserve between two groups. The first group consisted of 25 recovered COVID-19 patients who suffered from varying degrees of disease severity and were free of neurological symptoms or diseases at the time of inclusion. Taking into account the severity of the disease and its impact on VMR, patients were further categorized into two groups: asymptomatic, mildly ill, and severely ill. The second group consisted of 26 individuals who had never been diagnosed with COVID-19 and had tested negative at enrollment. Their findings showed a lower CVR and BHI in those with COVID-19 compared with control participants (19.9% vs. 36.8%, and 0.7 vs. 1.2). It is noteworthy that these variables were similar among patients with asymptomatic (1.9%) or mild disease (19.8%) and those with severe and critical (0.7%) disease. An increase in endothelial dysfunction among patients who are asymptomatic or mildly infected with COVID-19 may impact a large percentage of the infected patients; however, their study population is relatively small, and further studies are necessary to test this hypothesis. In contrast, Nandadeva et al. [49] reported no significant differences in cerebral VMR between 16 young adults diagnosed with COVID-19 at least four weeks prior and 12 controls not diagnosed.

A global healthcare crisis and strain on healthcare resources have resulted from the COVID-19 pandemic. As the population of patients recovering from COVID-19 grows, it is paramount to understand the healthcare issues surrounding them [50][51]. COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestations. Similar to post-acute viral syndromes described in survivors of other virulent coronavirus epidemics, there are increasing reports of persistent and prolonged effects after acute COVID-19. Many patients still experience physical, psychological, or cognitive symptoms after recovering from acute COVID-19 [52]. Long-COVID refers to the prolonged symptoms of SARS-CoV-2, which can involve a wide range of extrapulmonary organ dysfunction, including structural neurologic defects [53]. More patients require ‘long-COVID’ care, making it challenging for neurologists to keep up with the demands [54]. Most studies investigating post-acute COVID-19 clinical neurodegenerative disorders have been conducted on patients admitted during the acute phase of COVID-19, and very few studies have examined the long-term effects after the acute phase [54]. To integrate multispecialty care in the outpatient setting, COVID-19 clinics will need a comprehensive understanding of patient care needs

beyond the acute phase. It is vital to construct post-acute COVID-19 care strategies and guide healthcare system capacity planning. To assess long-term consequences after COVID-19 infection, Marcic et al. [55] conducted a cross-sectional study of 49 individuals diagnosed with COVID-19 who were experiencing mild neurological symptoms 300 days following the onset of the disease, along with 50 controls of similar age and gender. The study found a statistically significant reduction in BHI among subjects who acquired COVID-19 infection compared to the control group, indicating chronic endothelial dysfunction. Assessing VMR through TCD may provide helpful information about chronic endothelial dysfunction in a population prone to long-COVID. It could be used to closely monitor COVID-19 patients with cerebrovascular diseases, as methods like MRI may not be accessible or repeatable.

4. The Impact of Infection Severity and Neurologic Symptoms on VMR

According to the early reports from Wuhan, China, 36% of infected patients suffer from neurological manifestations [56]. Since this information was released, there have been several multicenter cohort studies, comprehensive reviews, and meta-analyses investigating the neurological effects of COVID-19 [57][58]. Survivors of COVID-19 with neurologic involvement seem to be uniformly associated with poorer outcomes, including hospital admissions, mortality, and disability. Recent studies note that neurologic syndromes are not exclusively associated with the critically ill [59][60]. There are several significant cerebrovascular diseases, including acute cerebrovascular events (ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage), acute encephalopathy, encephalitis or meningitis, polyneuropathy, demyelinating spectrum of illness, and seizures, that can affect VMR and alter cerebral hemodynamics [61].

Callen et al. [62] was a unique study, as they included patients who experienced critical illness during their infection (acute ischemic stroke requiring hospitalization). The study examined CVR and vessel wall imaging in fifteen patients with COVID-19 and ten control participants. Of the infected, twelve were mildly ill (no acute neurovascular events, hospitalizations, or other critical illnesses) and three were critically ill. Furthermore, seven reported persistent neurologic symptoms for at least one month following the illness, including headache, memory impairment, insomnia, depression, disequilibrium, dysgeusia, and tinnitus. Prior infection was associated with a decrease in whole-brain CVR after excluding the three critically ill participants and adjusting for age and sex (p = 0.001). The CVR was lower in those with post-COVID neurologic conditions than those without, but the difference was not statistically significant (p = 0.22).

In a few studies investigating VMR disturbances in patients with COVID-19, most recruited patients without neurologic disease and excluded patients with significant risk factors for cerebrovascular disease [46][55]. Two studies included COVID-19 patients with non-specific neurological symptoms such as smell and taste dysfunction, vertigo, headache, dizziness, or fatigue, and excluded cerebrovascular disease. The authors did not recruit healthy control patients and did not examine the relationship between mild neurologic symptoms and VMR impairment. Those with persistent post-COVID neurologic conditions may have experienced heterogeneous symptoms, and SARS-CoV-2 infection has not been proven to cause these symptoms. More research is required to delineate the

relationship between chronic CVR impairment and the chronic neuropsychologic sequelae of SARS-CoV-2 infection.

Only two studies examined the impact of infection severity on the VMR. The study conducted by Abdo-Cuza et al. [48] recruited two groups of patients. The first group consisted of twenty-five patients who recovered from COVID-19. The recovered patients were divided into two categories: those who suffered from mild or asymptomatic disease and those who suffered from severe or critical illness. The second group consisted of twenty-six patients who tested negative for COVID-19. All participants were asymptomatic at the time of enrollment into the study. The cerebral hemodynamic reserve and breath-holding index of patients who recovered from SARS-CoV-2 infection were decreased, regardless of the severity of the disease or the presence of neurological symptoms. This finding is likely consistent with the damage to cerebral microvasculature that occurs in various conditions, including COVID-19. Additional research is required to understand neurological signs and symptoms during the disease's initial clinical presentation or recovery and how COVID-19's clinical severity affects the VMR.

Another study recruited patients admitted to the ICU; however, they evaluated intracranial compliance (ICC) without assessing VMR [14]. The clinical outcomes of mechanically ventilated COVID-19 patients were examined in the context of cerebrovascular hemodynamics (CVH) and intracranial compliance (ICC). To assess CVH, the mean flow velocities in the middle cerebral arteries (mCBFV), pulsatility index (PI), and estimated cerebral perfusion pressure (eCPP) were used. To evaluate ICC, the ratio of P1/P2 of the non-invasive intracranial pressure curve (ICP) was utilized. Fifty critically ill COVID-19 patients were studied with TCD and noninvasive monitoring of ICC. CVH and ICC were assessed twice: once during the first three days following intubation and again within 72 h following extubation or tracheostomy without the administration of sedatives. The first evaluation was used only for patients who died while intubated. Most COVID-19 patients who were on a ventilator had abnormal brain hemodynamics. They used a combination of ICC and CVH measurements to investigate if there was a link between those values and patient outcomes. There was a significant difference between CVH/ICC scores for patients with a favorable outcome (p = 0.001) and those with an unfavorable outcome (UO). A UO was defined as failure to wean from respiratory support or death on day seven following weaning.

5. MRI for Cerebral Blood Flow Assessment following COVID-19 Infection

Functional magnetic resonance imaging (fMRI) is a noninvasive neuroimaging technique that measures the hemodynamic response to neural activity in the brain. A critical component of the method is that changes in blood flow, mainly oxygenated blood, correlate with neural activity. In addition to providing valuable insights into neural mechanisms underlying vascular dysfunction in neurological diseases, fMRI has several advantages over traditional methods, such as TCD and positron emission tomography (PET). The technique is noninvasive, requires no ionizing radiation, and has a high spatial resolution, enabling detailed mapping of brain regions involved in vasomotor control. While this method has some advantages, it has certain limitations. One of these limitations is that it is a relatively slow technology, with a time resolution on the order of seconds, making it challenging to capture rapid changes in neural activity. A second limitation of fMRI scanners is that their magnetic field may be

uncomfortable or even distressing for some individuals, particularly those who experience claustrophobia or anxiety. Furthermore, fMRI is an expensive technology requiring specialized equipment and expertise, which may limit its availability and accessibility to some researchers and patients. In a study by Callen and colleagues [62], the authors examined the CVR and vessel wall imaging of patients with prior COVID-19 (including seven individuals with post-COVID neurologic conditions) and ten control participants who had never had SARS-CoV-2 infection. The study utilized MRI that included arterial spin labeling perfusion imaging with acetazolamide stimulus. After adjusting for age and sex, a linear model was used to assess associations between CVR and prior infection. The difference in CVR between the two groups remained statistically significant even after excluding the three participants with previous illnesses who experienced an acute ischemic stroke and hospitalization after infection ($p < 0.001$). Although the difference was insignificant, the authors found that CVR was lower in individuals with post-COVID neurologic conditions than those without (16.9 vs. 21.0 mL/100 g/min; $p = 0.22$).

The authors concluded that SARS-CoV-2 infection is associated with chronic impairment of CVR, but the mechanistic basis of this chronic neurovascular endothelial dysfunction remains unknown.

6. Cerebral Blood Flow Evaluation following Other Virus Infections

Recent research has demonstrated that viruses such as Human Herpesvirus 8 and the Hantavirus predominantly affect endothelial cells and, therefore, affect cerebral hemodynamics [63][64][65]. A study by Grahame-Clarke et al. [16] demonstrated that people with human cytomegalovirus seropositivity have impaired endothelial function and impaired NO responses. Moreover, the effect of human immunodeficiency virus (HIV) on endothelial cells has been extensively studied [66]. VMR of the brain and hemodynamic changes following viral infections are not fully understood. However, some authors have suggested that these alterations may be due to direct viral invasion of the brain or indirect effects, such as inflammation and cytokines. The immune response to viral infection may also contribute to the alterations.

The assessment of the endothelium by VMR could aid in improving patient care during the acute or chronic phase of other viral infections. Further research is required to comprehend the mechanisms fully. Furthermore, efforts should be made to standardize the method used to measure cerebral blood flow velocity and cerebral autoregulation to allow for better comparison between studies.

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