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Case Study

Review of SARS-COV-2 Systemic Impact: Building the Case for Sepsis *via* Virus in the Circulatory System

Gina Sizemore[1], Brandon Lucke-Wold[2]* and Coulter Small[2]

[1]West Virginia University School of Medicine Morgantown, WV

[2]Department of Neurosurgery, University of Florida, Gainesville, FL

Abstract

SARS-COV-2 can contribute to long term consequences associated with sepsis and circulatory dysfunction. In this insightful paper, we highlight the emerging pathophysiology utilizing two case examples. Both systemic and organ specific features are discussed. In addition, a novel laboratory assay is presented that identified SARS-COV-2 in the circulation using conserved SARS ion channels rather than the spike protein. The presentation is linked to the pathophysiology with the emphasis for early recognition and continued research. This paper will serve as a catalyst for continued discovery.

Keywords: SARS-COV-2; Systemic Impact; Organ Dysfunction; Long-Term Consequences

Introduction

The two SARS-COV-2 cases shared here demonstrate the multiple organ involvement that can occur with this disease. Growing evidence points to the role of viral sepsis as a key component in severe SARS-COV-2 and even newer research reveals an assay that can identify the virus in the bloodstream. This new evidence creates the opportunity to improve patient outcomes by better understanding of its replication and transport in its human host. This paper will summarize two cases with multi-organ involvement and discuss the impact on those organ systems. In addition, it will summarize research of a new assay which identified live SARS-COV2 virus in the bloodstream of patients. The goal of this paper is to put forth thoughtful evaluation of the disease and promote development of new tools that will assist in identifying virus in the circulation as well as quantifying risk for disease severity to improve patient outcomes.

SARS-COV-2 Characterization Review

Structure

COVID-19 is spread primarily when a person infected with SARS-CoV-2 exhales and another individual inhales the virus. Indoors, droplets from people speaking can linger in the air for approximately 8 to 14 minutes and this is likely a factor for increased transmission of COVID-19 in enclosed spaces [1]. When an uninfected person inhales the virus, it enters the respiratory tract where it attaches to epithelial cells using the virus's spike proteins (S proteins that resemble a crown) that cover a large portion of the exterior of the COVID-19 virus [2,3]. These spike proteins recognize Angiotensin-2 (ACE2) receptors, which are abundant on most human cells (including the heart, kidneys, and lungs) and provide critical roles including vasodilation and protecting the cell from injury under normal physiologic conditions [3,4]. There are 2 subunits (S1 and S2) on the SARS-CoV-2 spike protein, but it is the S1 subunit that facilitates effective docking of the SARS-CoV-2 virus to the host cell at the ACE2 receptor [3]. The spike protein of the SARS-CoV-2 virus is also longer than that of other coronaviruses which likely facilitates docking of the SARS-CoV-2 virus to the host cell further increasing its effectiveness [5].

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***Corresponding author:** Brandon Lucke-Wold, Department of Neurosurgery, University of Florida, Gainesville, FL, E-mail: bwold@mix.wvu.edu

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Research features and circulation risk

Identifying SARS-COV-2 in the circulation: Ion channels in SARS-COV-2 are conserved from SARS and allow rapid replication of the virus [6]. Variants add to the complexity of the fight against the disease. Researchers evaluate variants from clinical, therapeutic, epidemiologic, and pathophysiologic points. This most recent Omicron variant has 50 mutations with 32 of them in the spike protein sequence [7]. Variation in this spike region can impact diagnostic, vaccination, and therapeutic tools. A new novel assay uses the viruses' ion channels rather than the spike protein to identify it creating the ability to locate the virus in the bloodstream irrespective of variant [6]. New evidence from publications support the proposal of viral sepsis as a contributor to the complexity creating multi-organ illness. The two presented cases to follow, as well as many others across the globe, reflect this multi-organ impact. These details combined with the evidence from this new research assay, identifying active virus in the circulation, means it is a path we must consider.

Pulmonary risk for viral contamination to the circulation: Once the alveolus is exposed to the SARS-COV2 virus, the spike protein binds to the ACE2 receptor on the alveolar type II epithelial cell and begins the process of making the cell a host for replication of SARS-COV2 virus [8]. The lung inflammatory

process is still not fully understood; however, it is recognized that in the lung, neutrophil recruitment accompanies inflammation and injury of the airway and alveolar epithelium, leading to protein transudation [9]. The alveolar cell becomes a factory for SARS-COV2 virus reducing its production of surfactant which begins the gas exchange problems [10]. Once it is identified that the alveolar type II epithelial cell is compromised, and destruction of the cell begins the virus has been replicated and released. Macrophages begin the process of cell debris clean-up and adds the release of immune factors such as IL-6 to recruit help [11]. Neutrophils in the circulation respond to the chemical signaling and cross over to assist adding signaling of their own which increases IL-6 release and other inflammatory signals causing alveolar inflammation [12]. This inflammation further exacerbates the gas exchange as the virus is allowed to pass into the circulation while a failing alveolus struggles to repair itself and recover gas exchange [13].

Case Studies

Case study I

79year-old female with ascending aortic aneurysm, mild coronary artery disease, and hypertension. Patient was a neurologically intact female with sharp wit and excellent self-management of her health care who developed severe delusional symptoms during her SARS-COV-2 hospital stay and was declared incompetent to manage her affairs. Following recovery, she requested full psychiatric evaluation to re-evaluate her incompetency and was declared competent. This raises concerns regarding active SARS-COV-2 virus circulating and crossing the BBB.

Disease diagnosis/treatment course case study I: 79 year-old female diagnosed at local hospital with SARS-COV-2. She was hospitalized early 2021 and treated for SARS-COV-2 pneumonia, hypoxia, and altered mental status. She did not require intubation. Her altered mental status persisted through her hospital stay and her medical power of attorney oversaw her care when she was discharged from the local hospital with improving pneumonia on early 2021. She was home for one day before shortness of breath and worsening mental status resulted in her transfer to a larger facility for care early 2021. There she recovered fully and requested psychiatric evaluation to reinstate her competence and care for herself. Patient returned home and has effectively managed her care since that time with a return to her physical and mental baseline.

Case study II

57 year-old male with mild sensory neuropathy secondary to disk space narrowing lumbosacral spine with surgical back history, Sick Sinus Syndrome, mild cardiomyopathy with pacemaker in 2011 followed by Automatic Implantable Cardioverter Defibrillator in 2015 after a seven-minute run of Ventricular Fibrillation. Cardiology check-up fall 2020 was unchanged from baseline with review of 2019 ECHO at 57% EF, MUGA 59% EF and Lexiscan with no ischemia or infarction.

Disease diagnosis/treatment course case study II: Fall 2020 patient was diagnosed at local urgent care with SARS-COV-2 by rapid antigen. By winter 2020 patient declined and was transferred by ambulance to a local hospital for shortness of breath. There, his SARS-COV-2 was confirmed, and he was diagnosed with hypoxia and acute respiratory alkalosis. By 6pm patient was intubated, and chest x-ray revealed bilateral infiltrates interstitial and alveolar. The patient was diagnosed with acute respiratory failure with hypoxia and flown to larger hospital to facilitate his more aggressive treatment needs. During flight his saturations were 85-91% on 20 of positive end expiratory pressure 55% O2. The following day the patient given continuous propanol for sedation due to the requirement of intubated ventilation and pronation. Patient treatment regimen required ventilation and pronation for 20 days when he was extubated. Neurology consult revealed severe chronic sensory motor polyneuropathy due to (CIDP) Chronic Inflammatory Demyelinating Polyneuropathy.

Patient remained in hospital for another month before being transferred to rehab facility due to inability to walk and overall weakness with final diagnoses at discharge of Acute Hypoxic/Hypercapnic Respiratory Failure due to SARS-COV-2 Pneumonia, ARDS due to SARS-COV-2, Severe Sensory Motor Polyneuropathy due to CIDP, and Acute Metabolic Encephalopathy. Patient remained in therapy facility for 2 months when he was discharged home and monitored by home health. Following discharge patient developed shortness of breath and was seen at the local hospital where CTA revealed nine of ten segments of right lung with embolus and 1 embolus left lung. Patient was again transferred to a larger facility for management. It was five months from his diagnosis before he was walking again and eight months before he regained 90% of his baseline.

Clinical Features

Case study I & II cardiology impact - Cardiac impact of SARS-CoV-2

The cardiac impact of Covid has been significant. Patients with heart disease often had more severe disease, worse progression, and poorer outcomes [14]. In addition, the secondary risks for heart disease even in patients without original heart disease has been demonstrated [15]. Research by Luo et all indicates that the major comorbidity of COVID-19 is cardiovascular disease [16]. Various mechanisms of COVID illness create acute and chronic injury in the heart which can be evaluated with cardiac biomarkers [17]. However, by this time injury can be irreversible. Multiple systems contribute to cardiac failure in COVID patients; it is a complex interaction between the renin-angiotensin system, cardiac injury, and inflammatory signaling that triggers systemic response [18].

High expression of the ACEII receptor in myocardium represents a high risk for viral impact on cardiac tissue which can counter even the most aggressive efforts of ventilation [19]. A 2022 publication to update the clinical community regarding COVID 19 states the evidence supports significant impact to the cardiovascular system [20]. These 2022 updates confirming systemic impact combined with the data from the novel blood

assay indicating virus prevalence in the circulation raises the stakes and reflects a need for improved tools to detect, and determine risk for illness severity. Testing that can determine if the virus is prevalent in the blood may be a tool to help identify patients at higher risk for severe illness. The assay developed in the Yu lab uses a methodology of fluorescence [6]. This method detects not only positive from negative disease, but also offers the future possibility of using the fluorescence to quantify virus amount in the circulation which may correlate with severity of disease and warrants further investigation.

Case study I - neurologic impact: Although many of the traditional manifestations of SARS-CoV-2 were recognized early in the pandemic that began in 2019-such as cough, fever, diarrhea, and fatigue-neurological manifestations of the disease were quickly determined to be a frequent and severe complication [21]. It was also seen that neurological symptoms may be the primary manifestation of SARS-CoV-2, with some patients presenting only with delirium without cough or dyspnea [22]. Although not all patients are at high-risk for SARS-CoV-2 encephalopathy, encephalopathy was determined to be more common in older patients, those with severe illness, and those with medical comorbidities, including diabetes, hypertension, tobacco use, dyslipidemia, cancer, and chronic kidney disease [21,23-25]. However, many patients who develop severe illness from SARS-CoV-2 have the above listed risk factors. A multicenter cohort study of patients admitted to the Intensive Care Unit (ICU), for SARS-CoV-2, found a prevalence of delirium of approximately 55% [25]. The presentation of delirium in patients with SARS-CoV-2 may be a hyperactive or hypoactive delirium and may have concomitant manifestations of rigidity, alogia, myoclonus, and abulia [26,27].

The exact mechanism by which SARS-CoV-2 causes encephalopathy is uncertain; it is likely multifactorial and discussed in further depth below. However, there is evidence that it is mediated by endothelial cell dysfunction and subsequent blood brain barrier disruption, a dysregulated immune response from excessive proinflammatory cytokines, molecular mimicry, and direct invasion of neural tissues [26-30]. Currently, the management of SARS-CoV-2 encephalopathy is similar to treatment of other causes of delirium and focuses on the treatment of the underlying disease and behavioral modifications [26]. However, pharmacological therapy may be required when these measures fail, or agitation or perceptual disturbances are present [26]. For pharmacotherapy, a proposed algorithm recommends sequential tiers starting with melatonin and subsequent escalation to alpha-2 agonists, antipsychotic agents, valproic acid or trazadone, and finally dopamine agonists [26].

Overall, encephalopathy is associated with worse outcomes [24], and the neurological dysfunction may persist after the acute phase of the illness, with prolonged neuropsychiatric symptoms and cognitive impairment being increasingly recognized [31-33]. Further work is needed to determine the extent of long-term neurologic consequences.

Case study II - neurologic impact: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is an acquired inflammatory disorder of the peripheral nervous system that commonly presents as a predominantly symmetric motor weakness affecting both the proximal and distal muscles lasting longer than eight weeks [34]. Sensory symptoms may also be present but are less pronounced than the motor symptoms [34]. CIDP is mediated by aberrant host cellular immunity and humoral immunity [34-36]. Evidence for cellular immunity in the pathogenesis of CIDP includes disruption of the blood brain barrier, proinflammatory cytokine expression, increased MHC class I, and loss of autoimmune regulatory mechanisms [35,36]. There is also evidence for immunoglobulin and complement deposition on Schwann cells, supporting an element of humoral immunity in the pathogenesis of CIDP [35,37].

There have been proposed associations with viral and bacterial infections as well as well as autoimmune disorders, including rheumatoid arthritis, myasthenia gravis, and multiple sclerosis [38]. Severe inflammatory conditions, like those experienced in a subset of SARS-CoV-2 infections, may induce CIDP in genetically susceptible individuals, and SARS-CoV-2 has been implicated in the onset and exacerbation of CIDP [38-40]. Initial management of CIDP includes therapy targeting its autoimmune genesis: corticosteroids, intravenous immunoglobulins, and plasma exchange [41]. Corticosteroids offer rapid relief, but due to the long-term sequela of corticosteroid therapy, patients may also benefit from maintenance therapy with immunosuppressive agents, like azathioprine or cyclosporine [41].

Discussion

The nature of SARS-CoV-2 provides valuable insight into its neurological manifestations, and through examination of the pathophysiology of SARS-CoV-2, its neurological sequalae will be explored. Severe SARS-CoV-2 infection may induce cytokine storming, which is a dysfunctional immune response caused by excessive proinflammatory cytokines release [42,43]. This inflammatory cascade may result in a toxic-metabolic encephalopathy, which is supported by the increased prevalence of encephalopathy in patients with severe illness from SARS-CoV-2 [26,42]. This inflammatory state may also be a trigger for inflammatory demyelinating processes through the overactivation of the host immune system [38,40]. Additionally, these proinflammatory cytokines may mediate vascular remodeling resulting in the loss of vascular wall integrity, which may result in intraparenchymal hemorrhage [44]. Finally, cytokine storming is a known risk for coagulopathy, which may precipitate stroke [45].

However, the presence of encephalopathy in patients with severe illness may indicate additional mechanisms. Anosmia is a known feature of SARS-CoV-2 infection, and it has been proposed that SARS-CoV-2 may enter the Central Nervous System (CNS) through retrograde transport through the olfactory bulb [26,29]. Once the virus has reached the CNS, it may interact with Angiotensin-Converting Enzyme 2 (ACE2) receptors on endothelial cells [29]. This subsequent depletion of the ACE2 receptor results in the overactivation of the renin-angiotensin system and dysfunctional vasoregulation [46,47]. Dysfunction of cerebral vasoregulation may result in stroke and may act

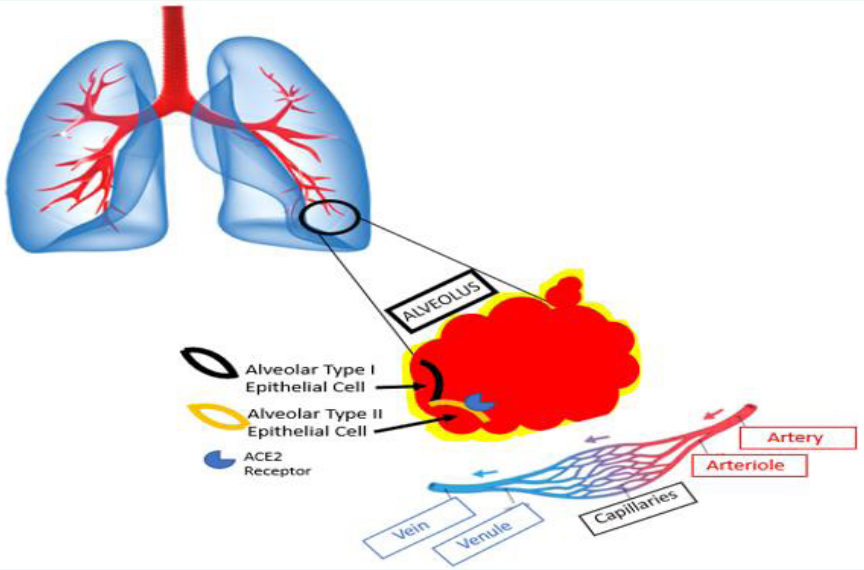

Figure 1 The Alveolus is the lungs connection to the circulation for gas exchange. The Alveolus has both type I and type II alveolar epithelial cells. The alveolar type II epithelial cells provide surfactant to enhance gas exchange. This type II epithelial cell also has an ACE2 receptor which allows binding of the SARS-COV2 spike protein.

synergistically with the inflammatory response discussed above [46]. The effect of the ACE2 receptor may explain the increased risk of stroke in patients with SARS-CoV-2 compared to those with influenza [48].

Additionally, the viral infection of endothelial cells then results in disruption of the blood brain barrier that triggers acute inflammation, resulting in neuron damage, disruption of neurogenesis, and encephalopathy [29]. Furthermore, the neuroinvasive potential of SARS-CoV-2 in animal models has been demonstrated [28]. Following the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), another highly pathogenic coronavirus named SARS-CoV-2 (previously known as 2019-nCoV) emerged in December 2019 in Wuhan, China, and rapidly spreads around the world. This virus shares highly homological sequence with SARS-CoV, and causes acute, highly lethal pneumonia coronavirus disease 2019 (COVID-19) with clinical symptoms similar to those reported for SARS-CoV and MERS-CoV. The most characteristic symptom of patients with COVID-19 is respiratory distress, and most of the patients admitted to the intensive care could not breathe spontaneously. Additionally, some patients with COVID-19 also showed neurologic signs, such as headache, nausea, and vomiting. Increasing evidence shows that coronaviruses are not always confined to the respiratory tract and that they may also invade the central nervous system inducing neurological diseases. The infection of SARS-CoV has been reported in the brains from both patients and experimental animals, where the brainstem was heavily infected. Furthermore, some coronaviruses have been demonstrated able to spread *via* a synapse-connected route to the medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways. Considering the high similarity between SARS-CoV and SARS-CoV2, it remains to make clear whether the potential invasion of SARS-CoV2 is partially responsible for the acute respiratory failure of patients with COVID-19. Awareness of this may have a guiding significance for the prevention and treatment of the SARS-CoV-2-induced respiratory failure [28]. This direct invasion may result in neurological symptoms, and case reports of SARS-CoV-2 encephalitis and meningitis have emerged [49].

Neurological manifestations may also present after the acute phase of SARS-CoV-2 infection. There is evidence that SARS-CoV-2 may cause subsequent autoimmune encephalitis *via* molecular mimicry of NMDA receptors [26,30,50]. This may account for some of the manifestations of the "Long COVID syndrome," which are prolonged symptoms after SARS-CoV-2 infection and is manifest by its neuropsychiatric effects [31-33]. Likewise, the cascade of injury in the pulmonary and cardiovascular system creates significant vascular dysfunction and supports discussion for further evaluation of septic disease *via* virus in the vascular system. Research as early as 2020 was showing the impact of both SARS-CoV-2 inflammatory response and the virus itself not only on organs but also on the vascular system [51]. This research demonstrated impact on the endothelial tissue specific to the circulatory system. This level of impact would require the virus to be in the vasculature not just the organs. Research in 2021 describes the vasculature as a pathway of convergence for the inflammatory, thrombotic, and renin-angiotensin-aldosterone forces [52]. Now, in 2022, with the results of assays demonstrating detectable virus in the blood [6] we are pushing the envelope to include the virus itself as one of those contributing forces within the vasculature.

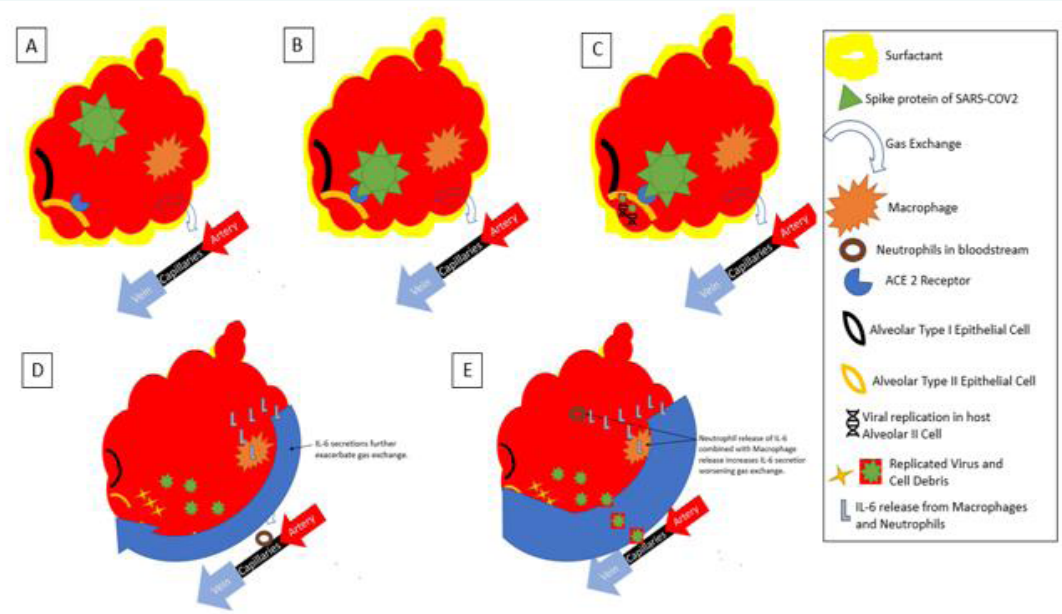

Figure 2 A - Alveolus with exposure to the SARS-COV2 virus. B -The spike protein binds to the ACE2 receptor on the alveolar type II epithelial cell and begins the process of making the cell a host for replication of SARS-COV2 virus. C -The alveolar cell becomes a factory for SARS-COV2 virus reducing its production of surfactant which begins the gas exchange problems. D - Once it is identified that the alveolar type II epithelial cell is compromised, and destruction of the cell begins the virus has been replicated and released. Macrophages begin the process of cell debris clean-up and adds the release of immune factors such as IL-6 to recruit help. E - Neutrophils in the circulation respond to the chemical signaling and cross over to assist adding signaling of their own which increases IL-6 release and other inflammatory signals causing alveolar inflammation. This inflammation further exacerbates the gas exchange as the virus is allowed to pass into the circulation while a failing alveolus struggles to repair itself and recover gas exchange.

Conclusions

Evidence for severity of symptoms correlates well with sepsis and the presence of virus in the bloodstream. More data is required to evaluate if virus in the circulation correlates with more severe illness. As we are beginning to have data that lets research begin to establish prospective studies based on the path behind us, this evaluation of systemic injury *via* virus in the circulation is one that has potential to create new knowledge for better patient outcomes. Recognition of the complexity of damage that occurs within the vasculature as well as the organs it serves is a primary next step in our understanding. Tools such as the ion channel assay to evaluate for SARS-CoV2 in the blood may prove a novel way to evaluate for risk of severity and assist with prognosis and treatment in a global pandemic experiencing variation and diversity of disease. It's mechanism of evaluation is on ion channels that are conserved within the different variants rather than on the spike protein which often has mutation. As vaccination numbers increase and treatments emerge it is easy to forget the significant impact this illness can have on the human multi-organ system and the vasculature system that serves it. However, longer data periods status post COVID-19 are demonstrating that we have not seen all the damage yet. These case studies are a reminder of that severity and the need to press forward with tools to identify risk for severe disease early. Testing that can determine if the virus is prevalent in the blood may be a tool to help identify patients at higher risk for severe illness. The assay developed in the Yu lab uses a methodology of fluorescence.[6] This method detects not only positive from negative disease, but also offers the possibility for using the fluorescence to quantify virus amount in the circulation which may correlate with severity of disease. The possibility generates thoughtful consideration for future research.

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