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Case Report

COVID-19 Halts CRRT: Pathogenesis of Hypercoagulability

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Abstract

The novel Coronavirus Disease 19 (COVID-19) first emerging in China has quickly spread worldwide with a current 6% mortality rate. As we study the means of this virus, complications and trends have been noted. We present another with a middle age man admitted with acute hypoxic respiratory failure secondary to COVID-19 pneumonia complicated by acute renal failure requiring Continuous Renal Replacement Therapy (CRRT). However, due to hypercoagulability the patient was unable to complete therapy, halting life saving measures, even in the setting of systemic heparin. To our knowledge, there have yet to be any published reports acknowledging the complications accompanying COVID-19 patients on CRRT. We utilize this case report to explore the mechanism by which COVID-19 may be initiating its hypercoagulable environment through its effect on Angiotensin-Converting Enzyme 2 (ACE-2) and Reactive Oxygen Species (ROS). We believe that this may provide insight to future therapies pertaining to combating COVID-19 induced hypercoagulability including its effect on CRRT.

Keywords: Acute Renal Injury; Continuous Renal Replacement Therapy; COVID-19; Hypercoagulability; Renal Failure

Background

A potentially fatal virus, COVID-19, first emerged November 2019 in Wuhan, China [1]. It has quickly become a pandemic with a multitude of complications. Of those complications, arguably one of the most intriguing has been its hyper viscosity effects. This has presented itself as cerebral vascular accidents, pulmonary embolism and deep venous thrombosis [2]. Another, yet to be published, manifestation of this hypercoagulability has presented itself by clotting of the CRRT circuit. We present a case of COVID-19 pneumonia complicated by hyper viscosity presenting as immediate clotting of CRRT, in the setting of systemic anticoagulation. As previously studied, CRRT has had significant benefits pre COVID-19 [3-7]. Echoing those findings has been reported in retrospective studies analyzing the effect of CRRT in COVID-19, which was associated with a decreased mortality- reirrigating its already known importance [8]. To continue to provide this lifesaving intervention, without hinderance, one needs to focus on patency of the CRRT circuit.

There are several factors that can be altered to increase patency in CRRT including: catheter size, flow rate, ultrafiltration rate and anticoagulants [9]. In our patient these alterations did not prove to be beneficial, including systemic anticoagulation. This has led us to analyze the pathway by which COVID-19 initiates its hypercoagulability effects. We hypothesize that this may involve COVID-19 inhibition of ACE-2. Normally, ACE-2 converts Angiotension-2 (AT-2) into Angiotensin 1,7 (AT-1,7) [10]. The function of AT-2 includes stimulation of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase resulting in oxidative stress, while AT-1,7 attenuates the function of NADPH oxidase [10-13]. It can be eluded from this information that COVID-19's effect of decreasing AT-1,7 by inhibiting ACE-2 leads to a proinflammatory state and ROS. The effect of ROS is damaging, particularly to the endothelium leading to release of von Will brand Factor (vWF) and factor VIII [14-16]. This leads to initiation of hypercoagulability and ultimately thrombosis. As we continue to combat COVID-19 and its hypercoagulable complications, including those encountered during CRRT this pathway may be of interest.

Case Report

A 45-year-old-man with a history of diabetes and hyperlipidemia presented with dyspnea and fevers was found have COVID-19. On admission he was tachycardic, febrile, and in respiratory distress. He was treated with plaquenil and azithromycin for a five-day course. However, his respiratory status continued to worsen, becoming dire and leading to intubation along with tocilizumab. His labs were impressive for D-Dimer of >20 mcg/mL, ferritin of >3,000 ng/mL, C-reactive protein of >270 mg/dL, Creatinine kinase of >4,000 units/L, Lactate dehydrogenase of >2,900 units/L, triglyceride level of 908 mg/dL, and interleukin-6 level of >3,000 pg/mL (normal reference range < or =1.8 pg/mL). His kidney function worsened with a creatine of 7.2 mg/dL from a baseline of 1.0mg/dL requiring CRRT. This was started through a right intrajugular 14 French trialysis catheter with the following settings: blood flow rate of 250 cubmic centimeter per minute, a fluid rate of 2.5 liters per hour and a net ultrafiltration of 0-200 cubic centimeter per hour. However, this was complicated by clotting of the hemofilter within minutes, although the patient was started on systemic heparin at CRRT initiation. His heparin Partial Prothrombin Time (PTT) goal was 45 seconds, which was achieved. The patient's overall clinical status continued to worsen with hypoxia, hypotension, and cardiac arrythmia resistant to all medical measures and he expired.

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Discussion

The pandemic of COVID-19 has affected millions worldwide [1]. While there is a spectrum of disease severity, the patients that suffer the worst consequences of this virus usually experience concomitant rhabdomyolysis, renal failure, cytokine storm, and hypercoagulability. The pathogenesis of COVID-19, has been largely unknown, although the proposed mechanism entails ACE-2. In our case report we present a patient with COVID-19 pneumonia complicated by acute renal failure requiring CRRT. However, due to a hypercoagulable state the patient was unable to complete therapy, even in the setting of systemic heparin administration. We explore the reasons this patient may have failed systemic anticoagulation through exploring COVID-19's pathogenesis, focusing on its ACE-2 effect.

The function of ACE-2 includes conversion of AT-2 into AT-1,7. The function of these enzymes have been studied prior and were shown to have opposite effects on oxidative stress. AT-2 functions to increase NADPH oxidase while AT-1,7 functions to attenuate it [10-13]. By decreasing AT-1,7 and increasing levels of AT-2, COVID-19 produces a proinflammatory environment leading to ROS. Endothelium damage is almost inevitable in a high ROS environment leading to release of vWF and factor VIII, initiating a prothrombotic state [13-16]. To combat this complication, anticoagulant medications are of importance. In our patient, we administered, systemic heparin dosed at 30 units per kilogram bolus followed by a rate of 5 to 10 units per kilogram per hour, with a PTT goal of 45 seconds [17]. This unfortunately did not prevent clotting of the CRRT membrane and hindered our ability to correct the patient's fluid status and electrolyte abnormalities leading to worsening respiratory distress and cardiac arrhythmias. We question if antioxidants or other means of ROS blockade may prove to be of importance, similar to what has been shown with anticoagulation therapy [18-23].

Means of decreasing ROS could be focused on blockage of AT-2 or increasing antioxidants with therapies such as glutathione and N-Acetylcysteine. This may play a vital role as it has been well documented that COVID-19 infected patients, such as ours, at times fail to respond to anticoagulation alone. While we note that our intervention with systemic heparin did not prove to be successful for this patient, there are factors that could be altered in future patients. This includes a higher PTT goal, earlier initiation of anticoagulation and administration of other anticoagulants and possibly the addition of antiplatelets. So we ask should we be administrating medications such as N-Acetylcysteine to our COVID-19 patients? Would measuring levels of vWF prove to be of prognostic value in these patients based on the above hypothesis? Could this possibly explain why certain ethnicities have a higher propensity for this disease? We leave many questions unanswered.

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