Effective Use of Angiotensin II in Coronavirus Disease 19–Associated Mixed Shock State: A Case Report

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The rapid spread of Coronavirus Disease 2019 (COVID-19) has sparked a search for effective therapies. The discovery that the virus binds the angiotensin-converting enzyme 2 (ACE2) receptor has led to investigation of the renin–angiotensin system for possible therapeutic targets. We present a case of an elderly woman with multiple comorbidities who developed severe acute respiratory distress syndrome (ARDS), a cardiomyopathy, and vasodilatory shock secondary to COVID-19 and was treated with exogenous angiotensin II. She rapidly demonstrated significant hemodynamic improvement without noted adverse effects. Thus, we propose further investigation into possible benefits of angiotensin II in shock secondary to COVID-19. (A&A Practice. 2020;14:e01221.)

GLOSSARY

ACE2 = angiotensin-converting enzyme 2; **ARDS** = adult respiratory distress syndrome; **ARDSnet** = ARDS Clinical Network; **ATHOS** = Angiotensin for the Treatment of Vasodilatory Shock; **CARE** = CAse REport; **COVID-19** = Coronavirus Disease 2019; **Fio_2** = fraction of inspired oxygen; **HFNC** = high-flow nasal cannula; **HIPAA** = Health Insurance Portability and Accountability Act; **ICU** = intensive care unit; **IL-6** = interleukin 6; **P:F ratio** = Pao_2:Fio_2 ratio; **Pao_2** = arterial partial pressure of oxygen; **PCR** = polymerase chain reaction; **RAAS** = renin–angiotensin–aldosterone system; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **VTE** = venous thromboembolism

In December 2019, there was an outbreak of a viral pneumonia caused by a novel coronavirus in Wuhan, China, now well known as Coronavirus Disease 2019 (COVID-19). In the subsequent months, the virus has been rapidly transmitted throughout the world, heavily affecting China, Europe, and now the United States.

Research has demonstrated that COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which enters the cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor.[1] This receptor is heavily concentrated in the heart, lungs, and upper respiratory mucosa, which possibly explains why these are the most commonly affected organs in COVID-19.[2,3] Normally, ACE2 has a key role in the renin–angiotensin–aldosterone system (RAAS) functioning to convert angiotensin II into angiotensin 1–7, which has anti-inflammatory effects.[4] Thus, there has been significant discussion over the impact of RAAS on the virulence of COVID-19. Although there has been a recently published article advocating for the use of angiotensin II in COVID-19 patients[5] and reported anecdotal success from Italian physicians, there has been no formal case description of its effectiveness.

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We present a case of an elderly woman with multiple comorbidities who developed acute respiratory distress syndrome (ARDS), multiorgan system failure, and septic shock from COVID-19 who improved with the use of angiotensin II and nitric oxide in addition to routine supportive care.

Signed Health Insurance Portability and Accountability Act (HIPAA) authorization has been obtained from the patient's health care proxy. This article adheres to the CAse REport (CARE) guideline.

CASE DESCRIPTION

An 80-year-old woman with a history of hypertension, hyperlipidemia, and remote breast and gastric cancers presented to the hospital with subjective fevers, diffuse myalgias, cough, and dyspnea on exertion. She denied recent travel or contact with recent travelers or sick individuals. On initial examination, the patient had a temperature of 100.9°F, a heart rate of 120 beats/min with new-onset atrial fibrillation, and hypoxia, requiring 2 L of oxygen via nasal cannula to maintain an oxygen saturation >90%. Her initial blood pressure was normal. Laboratory evaluation was notable for a normal white blood cell count of 6.2×10^9 cells/L and a normal complete metabolic panel but a mildly elevated lactate of 2.3 mmol/L. Chest radiography demonstrated moderate bilateral pulmonary infiltrates. Her respiratory panel by polymerase chain reaction (PCR) was negative, with a pending COVID-19 nasal PCR, and she was placed in isolation. She was treated empirically for community-acquired pneumonia with ceftriaxone and azithromycin and started on a continuous heparin infusion due to new atrial fibrillation.

Four hours after admission, the patient developed rapidly progressive hypoxic respiratory failure, requiring

temporary high-flow nasal cannula (HFNC) for stabilization during transfer to the intensive care unit (ICU). Repeat chest radiography demonstrated severe bilateral patchy opacities. She was intubated with a rapid sequence technique without the use of bag-valve-mask ventilation to limit aerosolization. Instead, she was maintained on HFNC for apneic ventilation during intubation, as the transmission rate with HFNC has been shown to be less than with bag-valve-mask ventilation.[6] She was initiated on ARDS Clinical Network (ARDSnet) protocols with lung protective strategies but had persistent hypoxia with a Pao_2:Fio_2 ratio (P:F ratio) <150 despite neuromuscular blockade. She was then ventilated in a prone position, which led to significant improvement in her P:F ratios. Her COVID-19 nasal PCR was positive 24 hours after admission, and her inflammatory markers were elevated, with an interleukin 6 (IL-6) level of 147.3 pg/mL, a ferritin of 3897 mg/dL, and a D-dimer of 1.98 µg/mL, consistent with poor prognosis. Forty-eight hours after admission, she developed renal and hepatic failure with severe hypotension requiring norepinephrine and vasopressin. Bedside echocardiography demonstrated a newly reduced ejection fraction of 30%–35% with apical ballooning, consistent with a stress-induced cardiomyopathy.

In the setting of multiorgan failure, she was not a candidate for remdesivir, which was not available at time of diagnosis. Given her progressive escalating vasopressor requirement and concern for catecholamine-resistant shock, angiotensin II was initiated. This therapy led to a rapid improvement in her blood pressure, and norepinephrine and vasopressin were weaned off within 24 hours. She was also started on inhaled nitric oxide due to its possible antiviral effects. Of note, she was started on hydroxychloroquine and azithromycin on hospital day 4 following recently published evidence for their effectiveness,[7] but she exhibited improvement before starting these 2 medications.

Despite remaining hemodynamically stable, her procalcitonin trended up over the next several days to 7 µg/L, prompting empiric treatment with vancomycin and meropenem with isavuconazole added due to reports of invasive aspergillosis in cases in China. Her procalcitonin and lactate dehydrogenase peaked after broadening of her antimicrobials and downtrended daily. Prone ventilation was stopped when her P:F ratio was maintained over 200 in the supine position. Angiotensin II was discontinued 8 days after its initiation without need for further vasopressors. The patient remains intubated after failing a trial of extubation on hospital day 15 due to respiratory weakness. She is otherwise clinically stable with normalized renal and hepatic function, and repeat chest X-ray after reintubation demonstrated resolution of her ARDS pattern. The benefits and risks of tracheostomy in the setting of the pandemic are currently being discussed with the family and the surgical services.

DISCUSSION

Since the outbreak of COVID-19 in December 2019, there has been extensive research on possible treatments. However, there is no proven effective therapy to date, and the death rate among the elderly with comorbidities is high.[8] We describe a case in which an elderly person with multiple comorbidities and multiorgan system failure survived with proper management of ARDS and several experimental therapies. While we cannot determine the individual impact of each therapy, we believe that the initiation of angiotensin II plays a significant role in hemodynamic stabilization and warrants further investigation in these patients.

The use of angiotensin II has multiple possible benefits in patients with COVID-19. First, the now well-described cytokine storm phase of COVID-19 can lead to a profound vasodilatory shock for which angiotensin II is well established as an effective treatment.[9] Second, acute renal failure is not uncommon in COVID-19, with up to 11.9% of patients requiring renal replacement therapy.[5] A post hoc analysis of the Angiotensin for the Treatment of Vasodilatory Shock (ATHOS)-III trial showed a significant benefit for the use of angiotensin II in patients with vasodilatory shock and renal failure, specifically showing a decrease in number of days on renal replacement therapy compared to other vasopressors.[10] This decreased need for renal replacement therapy could have a significant benefit in a resource-limited environment during a pandemic. Third, 1 recent article argues for a physiologic benefit of the use of exogenous angiotensin II to improve a possible angiotensin II deficiency and a possible downregulation of the ACE2 receptor.[5] However, the physiologic argument remains controversial. A Chinese study from February 2020 showed a correlation between elevated levels of endogenous angiotensin II and lung injury in patients with COVID-19,[11] which raises concerns about the use of exogenous angiotensin II in patients with COVID-19. However, elevated levels of angiotensin II were also noted in patients with vasodilatory shock in the ATHOS-III trial. This angiotensin II elevation was actually found to represent a relative deficiency when compared to markedly elevated angiotensin I levels. In fact, these patients showed significant hemodynamic improvement with angiotensin II infusion,[12] which could point toward a therapeutic use for angiotensin II in patients with COVID-19.

In patients with vasodilatory shock secondary to COVID-19, there are 2 other significant considerations with the use of angiotensin II. First, it is not frequently used in patients with cardiomyopathies, as the increased afterload can add additional stress to the left ventricle. However, angiotensin II is theoretically beneficial in stress cardiomyopathy, as recommendations have suggested catecholamine-sparing therapy for a stress-induced cardiomyopathy.[13] Second, angiotensin II has been linked with an increased risk of venous thromboembolism (VTE) compared to other vasopressors,[14] which is compounded by the higher risk of VTE found in the ARDS population.[15] No thromboembolism was identified in this case, but the patient was already maintained on a heparin infusion due to intermittent atrial fibrillation.

In this case, angiotensin II was safely used in a patient with cardiomyopathy and vasodilatory shock from COVID-19 with a rapid improvement in her hemodynamics and vasopressor requirement without adverse effect. Given the possible benefits above, we believe that further research is warranted into the safety and efficacy of the use of angiotensin II in patients with COVID-19.

DISCLOSURES

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