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CHEST

Unexpected BP Sensitivity to Angiotensin II in a Patient With Coronavirus Disease 2019, ARDS, and Septic Shock

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We report the case of an 88-year-old man with coronavirus disease 2019 (COVID-19) who presented with ARDS and septic shock. The patient had exquisite BP sensitivity to low-dose angiotensin II (Ang-2), allowing for rapid liberation from high-dose vasopressors. We hypothesize that sensitivity to Ang-2 might be related to biological effect of severe acute respiratory syndrome coronavirus 2 infection. The case is suggestive of a potential role for synthetic Ang-2 for patients with COVID-19 and septic shock. Further studies are needed to confirm our observed clinical efficacy.

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KEY WORDS: angiotensin II; COVID-19; SARS-CoV-2; septic shock

As of March 26, 2020, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had 462,684 confirmed cases and 20,834 deaths globally.[1] An estimated 5.0% of patients with coronavirus disease 2019 (COVID-19) required ICU admission, 2.3% underwent mechanical ventilation, and 1.1% had septic shock.[2] Angiotensin II (Ang-2) is a synthetic vasopressor that received US Food and Drug Administration approval in 2017 for treatment of refractory vasodilatory shock. We report our experience with Ang-2 for septic shock in a critically ill patient with COVID-19.

Case Report

An 88-year-old man with a history of hypertension, coronary artery disease, and type 2 diabetes mellitus presented to clinic with a 3-day history of cough and shortness of breath. He denied any travel history outside of Minnesota.

The patient was febrile to 38.4°C, tachycardic, and tachypneic with oxygen saturation of 48% on room air. He was transferred to the ED and received intubation. Laboratory tests were notable for lymphopenia, leukocytosis, mildly increased creatinine, and markedly increased C-reactive protein and D-dimer (Table 1). CT chest angiogram showed diffuse perihilar ground-glass interstitial opacities with consolidation at lung bases. A nasopharyngeal swab was sent for SARS-CoV-2 polymerase chain reaction (Mayo Medical Laboratories, Rochester, MN). The patient promptly received 30 mL/kg of crystalloid resuscitation and guideline-concordant broad-spectrum antibiotics and was admitted to the

ABBREVIATIONS: ACE = angiotensin-converting enzyme; ACE2 = angiotensin-converting enzyme 2; Ang-2 = angiotensin II; ATHOS-3 = angiotensin II for the Treatment of High-Output Shock 3; COVID-19 = coronavirus disease 2019; SARS-CoV = severe acute respiratory syndrome-related coronavirus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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TABLE 1] Laboratory Results and Ventilator Settings by Days in ICU

Variable	Stay in ICU				
	Day 1	Day 2	Day 3	Day 4	Day 5
Laboratory results					
Leukocyte count, $\times 10^9$/L	15.9	15.5	15	14.4	13.2
Erythrocyte count, $\times 10^{12}$/L	4.63	3.71	3.95	3.82	3.64
Absolute neutrophil count, $\times 10^9$/L	14.78	13.18	14.18	13.51	12.38
Absolute lymphocyte count, $\times 10^9$/L	0.48	0.95	0.28	0.28	0.26
Platelet count, $\times 10^9$/L	258	210	201	233	244
Hemoglobin, g/dL	14.1	11.1	12	11.2	10.8
Hematocrit, %	42.7	34.8	35.4	33.9	33.1
Sodium, mmol/L	139	135	137	139	142
Potassium, mmol/L	4.7	4.4	4	3.6	3.9
Chloride, mmol/L	101	103	100	98	101
Calcium, mg/dL	9.1	8.4	8.6	8.5	8.4
Bicarbonate, mmol/L	20	18	24	29	28
Anion gap, mEq/L	18	14	13	12	10
Glucose, mg/dL	216	208	170	165	154
Serum urea nitrogen, mg/dL	37	34	28	32	34
Creatinine, mg/dL	1.18	1.24	1.06	0.74	0.76
Total protein, g/dL	7.3	6.4	…	…	…
Albumin, g/dL	3.5	2.9	…	…	…
Total bilirubin, mg/dL	0.4	0.3	…	…	…
Alanine aminotransferase, unit/L	24	21	…	…	…
Aspartate aminotransferase, unit/L	43	32	…	…	…
Alkaline phosphatase, unit/L	72	64	…	…	…
Prothrombin time, s	17.1	…	…	…	14.1
International normalized ratio	1.5	…	…	…	1.2
D-dimer, ng/mL FEU	…	5,404	…	…	…
Venous lactate, mmol/L	5.3	…	…	…	…
C-reactive protein, mg/L	219.5	…	…	…	…
Arterial blood gas pH	7.28	7.16	7.36	7.44	7.46
P_{CO_2}, mm Hg	51	65	50	50	50
P_{O_2}, mm Hg	65	74	100	100	77
F_{IO_2}	0.5	0.45	0.45	0.45	0.45
P_{AO_2}/F_{IO_2} ratio	130	164	222	222	171
Ventilator settings					
PEEP, cm H_2O	18	17	14	12	10
Tide volume, mL/kg	5.5	6	6	6	6

FEU = fibrinogen equivalent units; PEEP = positive end-expiratory pressure.

ICU. He became hypotensive and required norepinephrine and vasopressin. His ventilator treatment was started with high positive end-expiratory pressure and low F_{IO_2}, based on ARDSnet protocol.

On ICU day 2, the SARS-CoV-2 polymerase chain reaction result was positive. The infectious diseases team started hydroxychloroquine and azithromycin. The patient began neuromuscular blocker therapy for ventilator dyssynchrony and was placed in prone position to improve dorsal lung aeration. Throughout the day, his vasopressor requirements worsened severely. Transthoracic echocardiography showed an ejection fraction of 61%, normal right ventricular systolic function, and an estimated right ventricular systolic pressure of 57 mm Hg. Noninvasive cardiac output

monitor (FloTrac; Edwards Lifesciences Corp) showed severely reduced vascular resistance and high cardiac output. Although corticosteroids are not recommended for COVID-19, stress dose methylprednisolone was added for refractory septic shock. Ang-2 (10 ng/kg/min) was added as the third vasopressor. Soon after initiation of Ang-2 therapy, we observed considerable reduction in norepinephrine and vasopressin requirements (Fig 1).

On ICU day 3, he was weaned of all vasopressors. The patient's respiratory status improved, with a better P_{AO_2} to F_{IO_2} ratio and less positive end-expiratory pressure requirement. He had right upper extremity catheter-associated DVT and received therapeutic heparin. On ICU day 4, neuromuscular blocker and methylprednisolone were discontinued. On ICU day 7, the patient developed acute kidney injury with peak creatinine 2.7 mg/dL but did not require dialysis. He remained off vasopressor with stable ventilator requirement. On ICU day 9, family elected to transition to comfort measures and the patient died after compassionate extubation.

Discussion

Physiologically, angiotensin-converting enzyme (ACE) converts angiotensin I to Ang-2, which stimulates Ang-2 type 1 receptors in the systemic vasculature and causes potent vasoconstriction.[3] In the phase 3 approval study Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3), synthetic Ang-2 effectively increased BP for patients with vasodilatory shock unresponsive to high-dose vasopressor therapy.[4]

The patient with COVID-19 was critically ill with ARDS and septic shock. His acute sensitivity to low-dose Ang-2 treatment allowed for rapid liberation from high-dose vasopressors. Although he received hydroxychloroquine and corticosteroids before Ang-2, we would not expect these medications to have such marked hemodynamic effects.

Heterogeneous BP sensitivity to Ang-2 has been reported. In ATHOS-3, 48.5% of patients (79 of 163) in the treatment group were able to have Ang-2 downtitration to $\leq$ 5 ng/kg/min at 30 min.[5] This subgroup of patients had significantly lower endogenous serum Ang-2 levels, but unlike the present patient, they had lower baseline norepinephrine-equivalent requirements. The present patient had ARDS and was taking an ACE inhibitor (lisinopril). Severe ARDS has been shown to disrupt ACE function,[6] and an ACE inhibitor directly inhibits ACE activity.[7] These factors lead to endogenous Ang-2 insufficiency and were

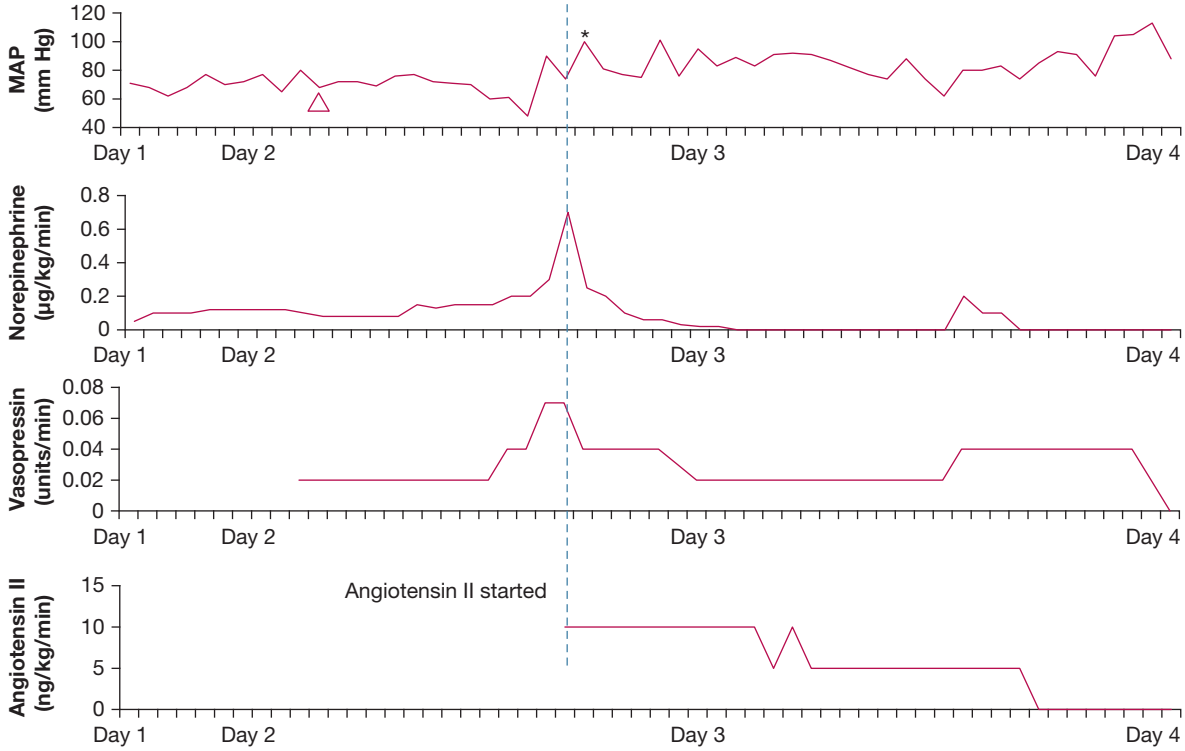

Figure 1 – *Hourly mean arterial pressure and vasopressor dose from ICU day 1 to ICU day 4. Triangle indicates the time when methylprednisolone was started, and asterisk indicates the time when neuromuscular blocker therapy was started. MAP = mean arterial pressure.*

suspected to be related to Ang-2 sensitivity in prior studies.[8,9] However, in ATHOS-3, no difference was observed in ARDS or exposure to ACE inhibitor between the different Ang-2 sensitivity subgroups.[5]

Treatment with Ang-2 in COVID-19 may have special biological consideration. SARS-CoV-2 recognizes angiotensin-converting enzyme 2 (ACE2) as a receptor for cell entry.[10] ACE2 converts Ang-2 to heptapeptide angiotensin (1-7), counteracting ACE effects.[3] In vitro, Ang-2 has been shown to downregulate ACE2 expression.[11,12] A recent paper promoted early use of Ang-2 for COVID-19-associated vasodilatory shock.[13] Chow et al[13] asked whether Ang-2 could cause downregulation of ACE2 in vivo and, subsequently, modulate cell entry and viral replication of SARS-CoV-2.

ACE2 is the same receptor used by severe acute respiratory syndrome-related coronavirus (SARS-CoV).[14] In animal models, SARS-CoV infection resulted in considerable reduction of ACE2 expression in the lung, with subsequent increase in Ang-2 level that promoted lung injury.[15] We expect SARS-CoV-2 infection to cause a similar biological process. However, exquisite sensitivity to Ang-2 in the present case raised the question of possible Ang-2 deficiency during SARS-CoV-2 infection. In the patient, we did not observe worsening ARDS with Ang-2 treatment.

Our case report has several limitations. First, Ang-2 hypersensitivity has been observed during septic shock without COVID-19 and is thought to be caused by relative Ang-2 insufficiency.[5] Although it is possible our observation may not have been directly related to SARS-CoV-2 infection, it is suggestive the patient had a dysregulated renin-angiotensin system. Second, although it is unlikely that the reduction in vasopressor requirements was secondary to receipt of corticosteroid, this cannot be entirely ruled out. Third, the biological effects of Ang-2 in patients with COVID-19 remain unknown, and are beyond the scope of our case report.

Conclusions

Our report highlights an interesting observation of Ang-2 treatment of COVID-19-related septic shock. Further studies are needed to confirm our observed clinical efficacy. Measurement of serum Ang-2, lung ACE2 activity, and SARS-CoV-2 viral load in patients with COVID-19 treated with Ang-2 may provide important insight. In Italy, compassionate use of Ang-2 for COVID-19-associated septic shock was approved.[16] We look forward to hearing about their experience.

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