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# Brief Report: Rapid Clinical Recovery From Critical Coronavirus Disease 2019 With Respiratory Failure in a Pregnant Patient Treated With IV Vasoactive Intestinal Peptide

**BACKGROUND:** Aviptadil, a synthetic form of human vasoactive intestinal peptide, has entered clinical trials to treat critical coronavirus disease 2019 pneumonia with respiratory failure. Vasoactive intestinal peptide protects the lung against a broad array of injuries by binding to the vasoactive intestinal peptide receptor 1 receptor of alveolar type II cells, the cells that severe acute respiratory syndrome coronavirus 2 binds to. As the role of Aviptadil in treating pregnant patients with critical coronavirus disease 2019 pneumonia is unknown, the authors report successful treatment in such a patient who is ineligible for phase 3 trials of Aviptadil.

**CASE SUMMARY:** Under an open-label Food and Drug Administration-approved Expanded Access Protocol NCT04453839, a 32-year-old female patient Gravida 6 Para 4 at 27-week gestation, body mass index 42.5 kg/m<sup>2</sup>, admitted to the ICU of a quaternary care hospital with critical coronavirus disease 2019 was treated in January 2021 and followed for 4 months post-ICU admission. Standard of care included remdesivir, methylprednisolone, enoxaparin, and inhaled epoprostenol. In addition, the patient received three successive 12-hour IV infusions of Aviptadil at 50/100/150 pmol/kg/hr escalating doses, per randomized clinical trial NCT04311697. Human subjects' protection was overseen by the Institutional Review Board of the Houston Methodist Hospital. The patient was enrolled in the treatment and was given informed consent approved by the Food and Drug Administration and the Institutional Review Board. Data on the patient was incorporated based on her consent for de-identified data to be used in research given at the time of hospital admission in a manner approved by the Institutional Review Board (PRO00025607). Baseline inflammatory markers, arterial blood gases, radiologic imaging, oxygen requirements, PaO<sub>2</sub>/FiO<sub>2</sub>, continuous fetal monitoring at baseline, throughout the patient's treatment with the investigational drug, and throughout the patient's hospital course.

**CONCLUSION:** The rapid clinical improvement seen in this patient treated with IV vasoactive intestinal peptide is consistent with the theory that vasoactive intestinal peptide protects the alveolar type II cell, ameliorates cytokine storm, and improves oxygenation in acute lung injury. This specific role of vasoactive intestinal peptide in the lung may be vital to combating the lethal effects of severe acute respiratory syndrome coronavirus 2 infection. In addition, the role of vasoactive intestinal peptide in the human maternal-fetal interface suggests that vasoactive intestinal peptide is a safe treatment of severe coronavirus disease 2019 respiratory failure during pregnancy.

**KEY WORDS:** acute respiratory distress syndrome; alveolar type II; coronavirus disease 2019; severe acute respiratory syndrome coronavirus 2; surfactant; vasoactive intestinal peptide









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**A**viptadil, a synthetic form of human vasoactive intestinal peptide (VIP), has been awarded Food and Drug Administration Fast Track Designation for the treatment of severe coronavirus

disease 2019 (COVID-19) respiratory failure and has entered clinical trials in the United States and internationally. VIP has previously demonstrated effectiveness in the treatment of acute respiratory distress syndrome

	Day of Admission	Day of ICU Transfer/Aviptadil	Day 1	Day 2
Portable Chest X-Ray				
LDH U/L	275	334	365	433
CRP mg/dL	11.18	18.95	12.85	7.93
Troponin	<0.0006			
BNP	<3			
Il-6 pg/mL	65	17.2	47.8	5.7
D-dimer ug/mL	1.76	0.62	1.69	3.38
Ventilation	Nasal Canula 3L/min	BiPAP 12/6 High Flow Nasal Canula (HFNC) 60L FiO2 100%	HFNC 45L/70%	HFNC 40/65%
P/F Ratio	223	123		151
	Day 3	Day 4	Day 5	Day 6
Portable Chest X-Ray				
LDH U/L	384	385	342	284
CRP mg/dL	8.67	4.33	1.64	<0.3
Troponin				
BNP				
Il-6 pg/mL	5.9	<2.5	<2.5	<2.5
D-dimer ug/mL	6.62	5.72	3.6	3.3
Ventilation	HFNC 40L/40%	HFNC 15L/45%	Nasal Canula 2L/min	Room Air
P/F Ratio	228	208	348	

**Figure 1.** Radiographic appearance and blood oxygen saturation before and after treatment. BiPaP = bilevel positive airway pressure, BNP = brain natriuretic peptide, CRP = c-reactive protein, HFNC = high-flow nasal cannula, IL-6 = interleukin, LDH = lactate dehydrogenase, P/F ratio = ratio of Pao<sub>2</sub>/FiO<sub>2</sub>.

(ARDS) related to sepsis, sarcoid, and pulmonary hypertension (1–4).

## CLINICAL REPORT

A 32-year-old female patient, Gravida 6 Para 4 at 27-week gestation, body mass index 42.5 kg/m<sup>2</sup>, presented to the emergency department with 4 days of loss of appetite, nausea, vomiting along with shortness of breath, cough, high-grade fever, and hypoxemia of 88%. The patient contracted severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), confirmed by positive reverse transcriptase-quantitative polymerase chain reaction from a nasopharyngeal swab, with refractory acute hypoxemic respiratory failure. Chest CT showed multilobar patchy consolidation and ground-glass opacities with no pulmonary embolism. The patient was admitted to the high-risk obstetrics ward, where she received remdesivir, methylprednisolone, and enoxaparin. The patient was not a candidate for monoclonal antibodies or convalescent plasma. Therefore, no other experimental therapies were administered.

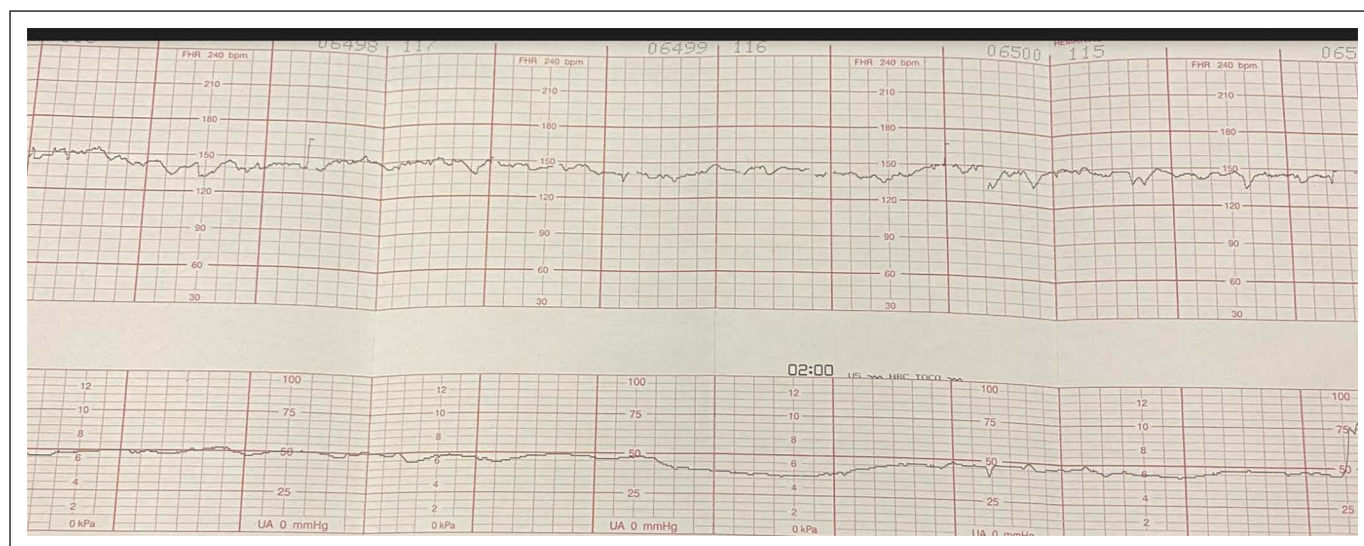
Despite therapy 3 days later, the patient developed worsening hypoxemic respiratory failure and was transferred to the ICU on high-flow nasal cannula (oxygen 60 L/min with FiO<sub>2</sub> 100%) alternating with bilevel positive airway pressure (BiPAP) in anticipation of needing intubation to avoid patient self-inflicted lung injury seen in COVID-19. Inflammatory markers (reflecting cytokine storm) were elevated on the day of

admission and day of ICU transfer, despite systemic steroids and remdesivir. The echocardiogram was normal.

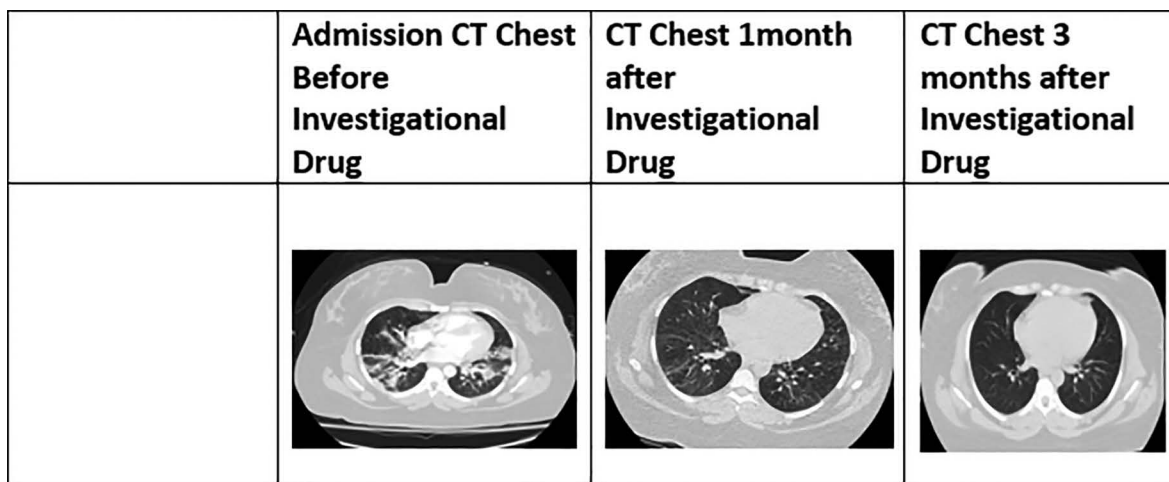
The patient received three successive 12-hour IV infusions of Aviptadil at 50/100/150 pmol/kg/hr. This treatment was associated with dramatically improved oxygenation, inflammatory markers, and radiologic pneumonitis (**Fig. 1**). These improvements allowed for the weaning of BIPAP to nasal cannula after administration of the second dose of Aviptadil. Continuous fetal monitoring throughout her hospital stay showed no adverse outcomes (**Fig. 2**). The patient was discharged from the ICU 24 hours following the third infusion. Neither the patient nor the clinical staff reported any treatment-associated adverse effects; the patient was discharged home on room air 6 days following the first infusion. Phone call visit revealed patient continued to do quite well on room air and gave full-term birth through vaginal delivery to a healthy 8 lb., 1 ounce, and 18 inches newborn. At 4, 6, and 9 months follow-up visits, both patient and baby continued to be in excellent medical condition (**Fig. 3**).

## DISCUSSION

To our knowledge, this is the first reported case of VIP being used to treat a critical COVID-19 respiratory failure in a morbidly obese pregnant patient who is at increased risk of severe pregnancy complications, including preterm birth, low birth weight, and higher mortality (5), with rapid clinical and radiographic



**Figure 2.** Fetal monitoring. bpm = beats per minute, FHR = fetal heart rate, UA = uterine activity.



**PFTS 4 months after COVID- 19ARDS**

		Ref	LLN	Pre
Level date				05/24/21
Level time				10:37AM
FEV1	L	2.42	1.87	2.51
FVC	L	2.85	2.20	2.67
FEV1/FVC	%	85	74	94
FEF25-75%	L/s	2.89	1.64	4.22
PEF	L/s	6.32	4.50	6.32
VC	L	2.85	2.20	2.03
ERV	L	1.17	1.17	0.20
FRCpl	L	2.50	1.68	1.58
IC	L	1.98	1.98	1.83
RV	L	1.33	0.76	1.38
RV%TLC	%	30	21	41
TLC	L	4.44	3.45	3.41
Raw	cmH2O*s/L	3.06	3.06	4.14
R0.5IN	cmH2O*s/L	3.06	3.06	2.52
sR05IN	cmH2O*s			4.55
sGaw	1/(cmH2O*s)	0.10	0.10	0.13
DLCO_SB	ml/(min*mmHg)	23.39	16.89	17.86
DLCOcSB	ml/(min*mmHg)	23.39	16.89	17.86
DL/VA	ml/(min*mmHg*L)	5.01	3.69	4.78
KCOc_SB	ml/(min*mmHg*L)	5.01	3.69	4.78
VA_SB	L	4.57	3.47	3.74
Hb	g(Hb)/dL			13.40

**Figure 3.** Follow-up at 1, 3, and 4 mo. ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, DL/VA = ratio of DLCO to alveolar volume, DLCO\_SB= diffusing capacity for carbon monoxide single breath, DLCOcSB = diffusing capacity for carbon monoxide corrected for hemoglobin single breath, ERV = expiratory reserve volume, FEF = forced expiratory flow, FEV<sub>1</sub> = forced expiratory volume in 1 s, FRCpl = functional residual capacity by plethysmography, FVC = force vital capacity, Hb = hemoglobin, IC = inspiratory capacity, KCOc\_SB = carbon monoxide transfer coefficient corrected for hemoglobin single breath, LLN = lower limit of normal, PEF = peak expiratory flow, PFTS = pulmonary function test(s), Raw = airway resistance, R0.5IN = raw at a flow rate of 0.5 L/s, RV = residual volume, sGaw = specific airway conductance, sR0.5IN = specific R0.5IN, TLC = total lung capacity, VA\_SB = alveolar volume single breath, VC = vital capacity.

improvement. In a 21-patient report of those affected with COVID-19 respiratory failure and those with checkpoint inhibitor pneumonitis, patients who were given VIP were treated successfully and saw a dramatic improvement in their outcomes (6, 7).

Early COVID-19 lung injury is characterized by a remarkable degree of hypoxemia in the absence of overwhelming pneumonia, suggesting primary pulmonary gas exchange mechanism damage. The SARS-CoV-2 virus specifically attacks alveolar type II (ATII) cells by binding to angiotensin converting enzyme 2 receptors (8–12). Since its discovery in 1970 by Said and Mutt (13), VIP is shown to prevent ATII cells apoptosis in models of lung injury (14). Unlike synthetic anti-cytokines, such as anti-interleukin-6 drugs, VIP has been demonstrated to play a specific role in preserving surfactant production in the lung and in protecting type 2 alveolar cells (14–19). Accordingly, VIP and longer-acting VIP modifications have been proposed as respiratory therapeutics (20). Loss of ATII cells reduces the lung's oxygenation capacity, mainly because the ATII cell is responsible for the production and recycling of surfactants and its other roles in supporting the pulmonary epithelium (15). Furthermore, VIP is a pleiotropic neuropeptide synthesized and released at the maternal-fetal interface. Animal models revealed that the treatment of pregnant mice with VIP at the first week of gestation resulted in more viable implantations. In pregnant humans, cytotrophoblast and syncytiotrophoblast cells of first- and third-trimester placenta and trophoblast cell lines also express VIP (21). Deficiencies in VIP production have been associated with recurrent pregnancy loss (22). The preservation of ATII cells increased pulmonary surfactant and anti-cytokine properties likely played a significant role in the dramatic recovery of this 27 weeks pregnant patient with COVID-19 ARDS, leading to full-term pregnancy and delivery of a healthy newborn. A recently published randomized clinical trial suggests that treatment with Aviptadil improves the likelihood of recovery from respiratory failure and survival at 60 days post-treatment in critically ill patients with respiratory failure caused by COVID-19 (23).

## CONCLUSIONS

The rapid clinical improvement seen in this patient treated with Aviptadil is consistent with the theory that

VIP protects the ATII cell, ameliorates cytokine storm, and improves oxygenation in acute lung injury. This highly specific role of VIP in the lung may be vital in combating the lethal effects of SARS-CoV-2 infection. In addition, the role of VIP in the human maternal-fetal interface suggests that VIP is a safe treatment of severe COVID-19 respiratory failure during pregnancy.

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Clinical trials of RLF-100 in patients with coronavirus disease 2019.

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