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Nebulized Nitroglycerin for Coronavirus Disease 2019–Associated Acute Respiratory Distress Syndrome: A Case Report

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We present a case where nitroglycerin tablets dissolved in saline and intravenous nitroglycerin solution were nebulized as surrogates for inhaled nitric oxide (iNO) after our iNO supply was depleted during the coronavirus disease 2019 (COVID-19) surge in New York. We gave this treatment to a COVID-19 patient with severe acute respiratory distress syndrome (ARDS) and hypercarbia. In response, the patient had immediate and clinically meaningful improvement in multiple organ systems despite no other interventions or ventilator changes. (A&A Practice. 2021;15:e01376.)

GLOSSARY

ARDS = acute respiratory distress syndrome; **C-ARDS** = COVID-19–associated acute respiratory distress syndrome; **COVID-19** = coronavirus disease 2019; **ECMO** = extracorporeal membrane oxygenation; **FDA** = Food and Drug Administration; **Fio_2** = fraction of inspired oxygen; **iNO** = inhaled nitric oxide; **Spo_2** = pulse oximetry saturation; **V/Q** = ventilation/perfusion

Coronavirus disease 2019 (COVID-19) can result in profound lung pathology with potentially large fractions of dead space ventilation. Given this and the growing evidence for microvascular occlusions of the pulmonary vessels, inhaled pulmonary vasodilators are suggested as a potential therapy.[1] The surge of COVID-19 patients in New York in 2020 exhausted of our hospital's supply of nitric oxide (ie, the preferred pulmonary vasodilator), and epoprostenol (ie, a synthetic analog of prostacyclin that is also a pulmonary vasodilator) was not available. Previous studies in humans have demonstrated that nebulized intravenous nitroglycerin solution is an effective pulmonary vasodilator.[2,3] It is readily absorbed into the pulmonary vasculature and quickly converted into nitric oxide, resulting in improved ventilation/perfusion (V/Q) matching and reduced right heart afterload with minimal systemic side effects.

Given the scarcity of pulmonary vasodilators and the potential for benefit in a patient with acute pulmonary failure, we trialed a form of inhaled pulmonary vasodilator therapy that has not been reported previously. We dissolved nitroglycerin tablets in saline and nebulized the resulting solution as a surrogate for traditional pulmonary vasodilators. We administered this therapy to a patient with COVID-19 and multiorgan failure, that included COVID-19–associated acute respiratory distress syndrome (C-ARDS) with profound hypercarbia. Without any changes to the ventilator, there was an immediate and clinically meaningful improvement in the patient's hypercarbia as well as in several other organ functions.

This case report reflects the potential role for pulmonary vasodilators in C-ARDS, the feasibility of inhaled nitroglycerin as a pulmonary vasodilator, and the need for ingenuity and creativity in the face of resource scarcity during a pandemic.

Written Health Insurance Portability and Accountability Act authorization and consent for this case report was obtained from the patient's family. All personal health information identifiers have been removed.

CASE DESCRIPTION

A 58-year-old man with COVID-19 had been hospitalized for 22 days and intubated and mechanically ventilated for 18 days. For a majority of that time, he had severe C-ARDS and multiorgan failure. For more than 48 hours, the patient's $Paco_2$ was >91 mm Hg, with the highest value being 154 mm Hg. He also required 100% inspired oxygen to maintain a pulse oximetry saturation (Spo_2) of 90%. Despite heavy sedation, he demonstrated significant ventilator dyssynchrony and was pharmacologically paralyzed for approximately two-thirds of these 48 hours. He received scheduled acetaminophen (1000 mg every 6 hours intravenously) and cold packs to decrease his core temperature (bladder temperature consistently kept <38°C) and lessen CO_2 production. His ventilator settings were adjusted numerous times, eventually increasing to a ventilatory rate of 35 times/min with a tidal volume of 450 mL (resulting in an expired minute ventilation of approximately 16 L/min), but his $Paco_2$

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Accepted for publication November 18, 2020.

Funding: None.

The authors declare no conflicts of interest.

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DOI: 10.1213/XAA.0000000000001376

remained significantly elevated at 104 mm Hg with an arterial pH of 7.14 (Figure 1). As his CO_2 became more difficult to manage, he needed increasing doses of norepinephrine to maintain a mean arterial pressure of 65 mm Hg, eventually requiring the addition of epinephrine and vasopressin infusions. His heart rate was 100–110 beats/min. Coinciding with increasing vasopressor needs, the patient's urine output declined to <0.5 mL/kg/h for over 6 hours. Given his pathology, we thought a pulmonary vasodilator would benefit him, but the hospital's supply of inhaled nitric oxide (iNO) was exhausted due to the surge of COVID-19 patients and it was unknown when additional supplies would arrive. Inhaled epoprostenol was also not available. The patient was not an extracorporeal membrane oxygenation (ECMO) candidate given his prolonged mechanical ventilation with high pressures and fraction of inspired oxygen (Fio_2) and regional resource constraints on ECMO during the pandemic.

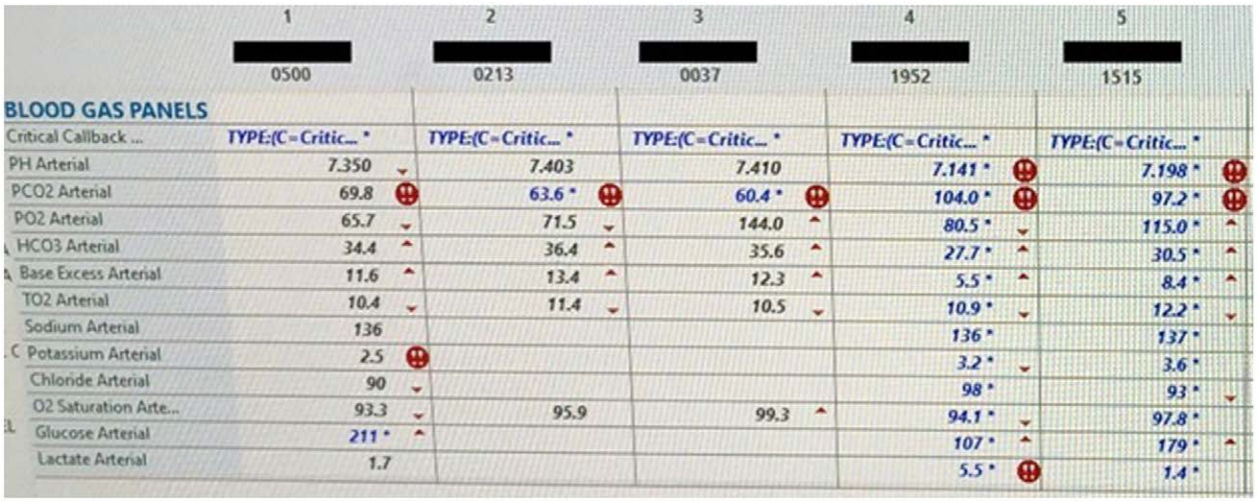
We decided to trial inhaled nitroglycerin. There was initial difficulty procuring intravenous nitroglycerin, so we dissolved three 0.3 mg nitroglycerine tablets (the form intended for sublingual use) with 3 mL of 0.9% normal saline. This mixture was placed into a vibrating mesh nebulizer and incorporated into the airway circuit (Figure 2). After approximately 10–15 minutes, the solution was exhausted, and an arterial blood gas showed that the $Paco_2$ had decreased from 104 to 60 mm Hg—a 44 mm Hg decrease—despite no changes to the ventilator (Figure 1). Concurrently, arterial pH increased from 7.14 to 7.41, and Pao_2 increased from 80 to 144 mm Hg on 100% Fio_2.

Given this success, we attempted to create another solution of a higher nitroglycerin concentration by placing 6 tablets in 3 mL of 0.9% saline, but the tablets did not appear to fully dissolve. Additionally, we had no way to regulate the rate of aerosolization, that is, whatever was placed into the aerosolization chamber was delivered at a constant rate. Because our mixture needed redosing every 10–15 minutes and each mixture required 3 tablets, we potentially needed over 430 tablets for one 24-hour period. There was also significant labor associated with constantly dissolving and replenishing the nitroglycerin tablet solution. Fortunately, we were able to procure a bottle of intravenous nitroglycerin solution (concentration 100 µg/mL) approximately 1 hour after trialing the nebulized nitroglycerin. Intravenous tubing and a 3-way stopcock were used to continuously transfer the solution into the nebulizer chamber (Figure 2), with the rate of transfer adjusted using a roller clamp. Because the aerosolization chamber was always full and the aerosolization rate was constant, we were not able to increase the delivered dose of nebulized nitroglycerin. Approximately 1 hour after starting the continuously nebulized intravenous nitroglycerin solution, $Paco_2$ remained stable at 63 mm Hg and arterial pH was 7.40 (Figure 1).

During the initial 4 hours of nebulized nitroglycerin, the epinephrine and vasopressin infusions that had been started 10 hours previously were successfully weaned off, with a resulting mean arterial pressure of 65 mm Hg. The urine output increased to over 1 mL/kg and lactate decreased from 5.5 to 1.7 mmol/L. Fio_2 was decreased from 100% to 80% while the Spo_2 remained approximately 90%. Despite these initial improvements, the patient's multiorgan failure and C-ARDS continued to worsen and he eventually died 5 days later from hypoxemic respiratory failure.

DISCUSSION

Pulmonary vasodilators are important therapeutic interventions in ARDS, a condition partially characterized by increased right ventricular afterload and disruption of normal V/Q matching. Inhaled administration of pulmonary vasodilators are favored over intravenous administration in ARDS because they selectively act on the pulmonary circulation to improve gas exchange while limiting systemic side effects.[4] By preferentially improving pulmonary blood flow in well-ventilated regions, inhaled vasodilators



	1 [redacted] 0500	2 [redacted] 0213	3 [redacted] 0037	4 [redacted] 1952	5 [redacted] 1515
BLOOD GAS PANELS					
Critical Callback ...	TYPE:(C=Critic... *	TYPE:(C=Critic... *	TYPE:(C=Critic... *	TYPE:(C=Critic... *	TYPE:(C=Critic... *
PH Arterial	7.350	7.403	7.410	7.141 *	7.198 *
PCO2 Arterial	69.8	63.6 *	60.4 *	104.0 *	97.2 *
PO2 Arterial	65.7	71.5	144.0	80.5 *	115.0 *
HCO3 Arterial	34.4	36.4	35.6	27.7 *	30.5 *
Base Excess Arterial	11.6	13.4	12.3	5.5 *	8.4 *
TO2 Arterial	10.4	11.4	10.5	10.9 *	12.2 *
Sodium Arterial	136			136 *	137 *
Potassium Arterial	2.5			3.2 *	3.6 *
Chloride Arterial	90			98 *	93 *
O2 Saturation Arte...	93.3	95.9	99.3	94.1 *	97.8 *
Glucose Arterial	211 *			107 *	179 *
Lactate Arterial	1.7			5.5 *	1.4 *

Figure 1. Serial arterial blood gases over the course of 14 h. Column 4 shows a hypercarbic and acidotic blood gas with lactate increased from 1.4 to 5.5 mmol/L approximately 4.5 h earlier. Column 3 shows a blood gas taken immediately after trialing nebulized nitroglycerin tablets diluted in 0.9% normal saline with a decreased $Paco_2$ and improved Pao_2. Column 2 shows a stable $Paco_2$ reduction after transitioning to a nebulized intravenous nitroglycerin solution. And column 1 shows a persistently reduced $Paco_2$ with lactate decreased from 5.5 to 1.7 mmol/L after starting nebulized nitroglycerin approximately 5 h earlier.

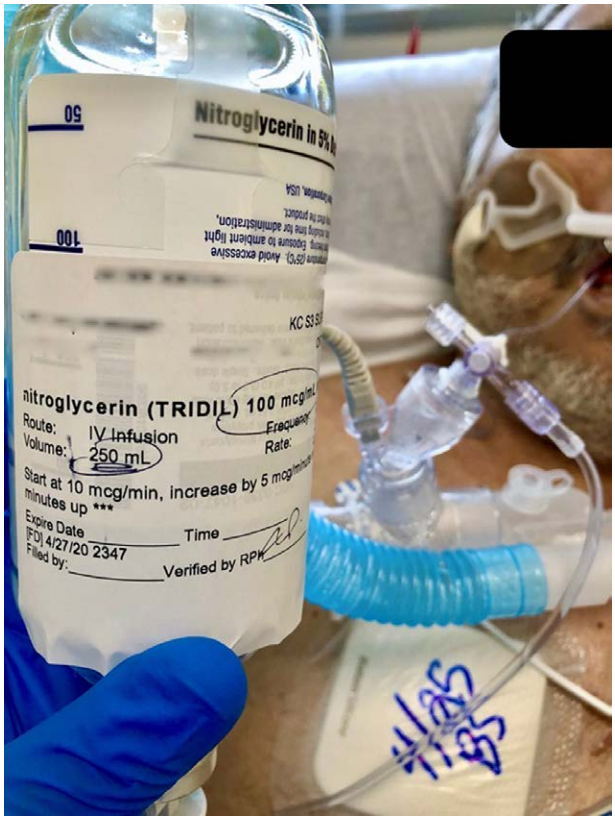


Figure 2. An intravenous nitroglycerin solution bottle is connected via intravenous tubing and a 3-way stopcock to a vibrating mesh nebulizer to facilitate delivery of inhaled nitroglycerin.

preserve or improve V/Q matching and reduce pulmonary vascular resistance, leading to improved cardiac output.[5] iNO is more effective at improving oxygenation than other inhaled vasodilators such as prostacyclin and milrinone.[6] Unfortunately, inhaled pulmonary vasodilators have failed to decrease mortality, as was true for our described patient.[7] Despite this lack of mortality benefit, inhaled pulmonary vasodilators remain useful tools when caring for patients with ARDS, refractory hypoxemia, and depressed right ventricular function.

Inhaled nitroglycerin is quickly metabolized to nitric oxide, making it an effective pulmonary vasodilator that decreases both mean pulmonary artery pressure and pulmonary vascular resistance while improving V/Q matching.[2,3,8] Reports of its use are mainly limited to cardiac surgery. Because nitroglycerin is readily available and does not require special equipment, it may be preferred in resource-limited environments. While inhaled pulmonary vasodilators demonstrate improved right heart function compared to intravenous forms, there are no trials comparing iNO to inhaled nitroglycerin.[9,10] Wang et al[11] compared inhaled nitroglycerin to inhaled milrinone and found similar decreases in pulmonary vascular resistance, although the effects of nitroglycerin were more transient.

Before the COVID-19 pandemic, the Food and Drug Administration (FDA) estimated that 56% of US community hospitals had drug shortages that changed or delayed patient care.[12] This has worsened with the COVID-19 pandemic. Since April 2020, the FDA has declared shortages of critical drugs such as dexmedetomidine, propofol, midazolam, cisatracurium, fentanyl, hydromorphone, furosemide, and continuous renal replacement therapy fluid.[13] Shortages of ventilators have prompted physicians, respiratory therapists, and ventilator production companies to collaborate on ways to safely ventilate multiple patients with a single device.[14] Our case demonstrates yet another example of ingenuity bred by resource constraints. We used existing supplies to make an improvised form of inhaled nitroglycerin as a surrogate for nitric oxide in a New York hospital during the height of the COVID-19 pandemic when conventional pulmonary vasodilators were unavailable. The result of our efforts proved safe, efficacious, and inspiring to many health care workers in our intensive care unit.

DISCLOSURES

Name: Benjamin T. Daxon, MD.
Contribution: This author coordinated all efforts and wrote the abstract and case description.
Name: Erin Lark, NP.
Contribution: This author helped retrieve patient information and family contact information for consent.
Name: Luke J. Matzek, MD.
Contribution: This author helped research pertinent literature and wrote part of the discussion.
Name: Amanda R. Fields, MD.
Contribution: This author helped research pertinent literature and wrote part of the discussion.
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Contribution: This author helped research pertinent literature and wrote part of the discussion.
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