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Case Report

Initiation of Inhaled Nitric Oxide by an Air Transport Team in Adult Coronavirus Disease 2019 Respiratory Failure

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A B S T R A C T

The coronavirus disease 2019 (COVID-19) pandemic has caused a significant increase in the volume of critical care flight transports between outlying referral hospitals and tertiary care facilities. Because of the tropism of severe acute respiratory syndrome coronavirus 2, flight crews are often asked to transport mechanically ventilated patients in refractory hypoxemic respiratory failure. The authors present a case series of 5 patients with COVID-19 acute respiratory distress syndrome (ARDS) who were initiated on inhaled nitric oxide (iNO) by the transport team before rotor wing transport and survived the journey in stable or improved condition upon arrival. Previously, no case reports have described adults with COVID-19 ARDS transported after iNO initiation by the transport team. This case series shows the feasibility of iNO initiation by trained air medical transport teams and suggests a short-term stabilizing effect of iNO in patients with ARDS from COVID-19.

The coronavirus disease 2019 (COVID-19) pandemic has created a significant strain on the interfacility transport system because of the high volume of critically ill patients with respiratory failure.[1] Transport teams are being called on to transport patients from hospitals due to the lack of local advanced critical care capabilities or a lack of beds at the referral center's intensive care unit. Many of these patients are hypoxemic even with aggressive ventilatory settings and pose a significant risk of decompensation during air medical transport.

Nitric oxide is an endogenously produced compound that causes vascular smooth muscle cell relaxation and subsequent pulmonary vasodilation.[2] Clinically, the administration of exogenous gaseous nitric oxide has known therapeutic effects for select respiratory pathologies. However, because nitric oxide diffuses into the bloodstream, where it rapidly reacts and is rendered inactive, the half-life is seconds long; therefore, inhaled nitric oxide (iNO) must be administered continuously to elicit a lasting response.[3] Because iNO exerts its effect locally, it primarily dilates the pulmonary vasculature and can relieve pathologic pulmonary hypertension. In patients with acute respiratory distress syndrome (ARDS), iNO preferentially vasodilates pulmonary arterioles, which feed pulmonary capillaries that participate in gas exchange. Via this mechanism, iNO reduces right-to-left intrapulmonary shunting with subsequent improvement in ventilation-perfusion matching.[4,5]

Although not routinely used in ARDS, iNO is currently considered a potential bridge therapy in mechanically ventilated ARDS patients with refractory hypoxemia.[6-9] Although heavily researched in the era before COVID-19, the existing literature on the use of iNO in COVID-19 ARDS consists primarily of small studies and hypothesis-generating reviews.[10,11] Severe COVID-19 infection frequently presents with acute hypoxemic respiratory failure, often with ARDS. Additionally, it has been shown that COVID-19 accelerates endothelial cell dysfunction, leading to endogenous nitric oxide deficiency.[12] Because of this, there has been a resurgence of interest in the therapeutic use of iNO during the COVID-19 pandemic.

Management of acute decompensation in-flight poses challenges because of the natural limitations of the air medical environment. The use of iNO in COVID-19 patients with ARDS and refractory hypoxemia may allow for the safe transport of patients who would otherwise be too unstable to fly. There is scant literature describing the initiation or use of iNO in COVID-19 ARDS patients in this environment. In this study, we describe 5 cases from University of Wisconsin (UW) Health Med Flight in which iNO was used as therapy for safe

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transport in COVID-19 patients with refractory hypoxemia. In each of these cases, iNO therapy was initiated by a UW Health Med Flight rotor wing air medical transport team, which consisted of a flight physician, a flight nurse, and a flight respiratory therapist.

Case 1

A 55-year-old woman with a past medical history of obesity and metabolic syndrome was diagnosed with COVID-19 at a rural hospital approximately 150 miles from the accepting tertiary care hospital. Ten days before transport the patient required intubation for hypoxemic respiratory failure with ARDS. During this time, the patient was treated with remdesivir, dexamethasone, and convalescent plasma. Her hospital course was complicated by pneumomediastinum 5 days before intubation.

Upon arrival of the air transport team, she was being sedated with fentanyl, midazolam, and ketamine and was chemically paralyzed with cisatracurium. The ventilator mode was volume control (VC) with a tidal volume (Vt) of 420 mL, a respiratory rate (RR) of 20 breaths/min, positive end-expiratory pressure (PEEP) of 12 cm H_2O, and a fraction of inspired oxygen (F_{IO_2}) of 100%. The patient's ideal body weight (IBW) was 57 kg. The arterial blood gas (ABG) was a pH of 7.41, P_{aCO_2} was 59 mm Hg, and P_{aO_2} was 57 mm Hg with the patient in the prone position. The partial pressure arterial oxygen/fraction inspired oxygen (P:F) ratio was 57. Once supine, her vital signs were a heart rate (HR) of 81 beats/min, blood pressure (BP) of 164/76 mm Hg, RR of 20 breaths/min mechanical, and oxygen saturation (S_{pO_2}) of 91%.

On transfer to the air transport team ventilator, ventilator settings and medications were maintained. iNO was initiated at 20 ppm. Within minutes, S_{pO_2} improved to 93% to 99% which was maintained throughout transport. ABG on arrival at the tertiary care facility was a pH of 7.44, P_{aCO_2} of 60, and P_{aO_2} of 83. iNO was discontinued 6 days later when the patient was cannulated for venovenous (VV) extracorporeal membrane oxygenation (ECMO). After 41 days, she died after extubation due to the inability to wean from ECMO.

Case 2

A 48-year-old previously healthy man presented to a rural hospital in respiratory distress and was admitted after being diagnosed with COVID-19. He was initially started on bilevel positive airway pressure but subsequently required intubation due to hypoxemic respiratory failure. He then developed a right-sided pneumothorax requiring chest tube placement after a right internal jugular central venous catheter insertion attempt. He was put in the prone position the day before transport due to persistent hypoxemia. The air transport team was dispatched to retrieve the patient and transport him for ECMO evaluation at the accepting tertiary care hospital.

Upon arrival of the air transport team, the patient was in the prone position being sedated with midazolam and propofol infusions and was chemically paralyzed with cisatracurium. The referring facility ventilator settings were VC with a Vt of 420 mL, RR of 32 breaths/min, F_{IO_2} of 100%, and PEEP of 24 cm H_2O while in the prone position. Preflight ABG had a pH of 7.22, P_{aO_2} of 70 mm Hg, and P_{aCO_2} of 65 mm Hg. After supination, his vital signs were S_{pO_2} of 91% on $F_{IO}2$ of 100% and PEEP of 14 cm H_2O, BP of 117/72 mm Hg, and HR of 120 beats/min. His IBW was 73 kg. The patient was changed over to the transport ventilator, and iNO was initiated at 20 ppm in anticipation of a likely desaturation event upon supination. After approximately 10 minutes on iNO therapy, the patient was supinated, with an immediate desaturation to 69% that steadily recovered to 80%. The iNO dose was increased to 30 ppm, and PEEP was increased from 14 to 20 cm H_2O and then to 24 cm H_2O, with subsequent improvement of the patient's Spo2 to 90%.

During flight, sedation with propofol and midazolam was continued and supplemented with intermittent fentanyl boluses, and neuromuscular blockade was maintained. The ventilator mode was VC with a Vt of 420 mL, RR of 32 breaths/min, F_{IO_2} of 100%, and PEEP of 24 cm H_2O. During flight, his S_{pO_2} decreased to 88%. His BP also decreased to a systolic BP of 90 mm Hg, after which the propofol dose was decreased. On arrival at the destination facility, his initial ABG demonstrated a pH of 7.16, P_{aCO_2} of 81 mm Hg, and P_{aO_2} of 40 mm Hg. His vital signs were BP of 105/74 mm Hg, HR of 116 beats/-min, RR of 32 breaths/min mechanical, and S_{pO_2} of 76% after the initial transfer to the intensive care unit (ICU) ventilator (on PEEP of 20 cm H_2O). The patient was rapidly evaluated and initiated on VV ECMO. The patient developed severe lung injury and was not a candidate for lung transplant and eventually died after withdrawal of life support after over 1 month of critical care at the destination hospital.

Case 3

A 54-year-old man with a history of hypertension and epilepsy was admitted to a local community hospital with hypoxemia after contracting COVID-19. Because of progressive hypoxemia, he eventually required intubation after failing noninvasive ventilation. He had been treated with remdesivir, dexamethasone, and convalescent plasma. The hospital course was complicated by superimposed bacterial pneumonia treated with ceftriaxone and azithromycin. The patient underwent proning cycles on a 16-hour prone to 8-hour supine schedule, and while in the prone position, he tolerated an F_{IO_2} of 60%; however, when supine, he required an F_{IO_2} of 100% and a PEEP of 12 cm H_2O to maintain an S_{PO_2} of 92% to 93%. A request for transfer to a tertiary care hospital was made due to worsening oxygenation with the goal of consideration for the initiation of ECMO.

Upon the air transport team arrival, the patient was being sedated with dexmedetomidine, propofol, and fentanyl; was chemically paralyzed with atracurium; and required norepinephrine with concerns for septic shock. The ventilator mode was VC with a Vt of 450 mL, RR of 28 breaths/min, F_{IO_2} of 100%, and PEEP of 12 cm H_2O. His IBW was 71 kg. The last ABG before transport, taken with the patient in the prone position, was a pH of 7.17, P_{aO_2} in the 60s, no P_{aCO_2} available, and a P:F ratio in the 60s. His BP was 100/60, and S_{pO_2} was 92% with frequent desaturations into the mid-80s with any change in position.

Sedation, the neuromuscular blockade, and hemodynamic support were continued with the exception of discontinuing the fentanyl infusion and substituting it with intermittent fentanyl boluses. The ventilator settings were continued. iNO was initiated at 40 ppm, and S_{pO_2} improved to 93% to 96%. He was transported supine and transferred to the destination hospital with no desaturation events. The ABG on arrival showed a pH of 7.24, P_{aCO_2} of 51 mm Hg, and P_{aO_2} of 56 mm Hg. His vital signs were BP of 120s/50s to 70s measured by an arterial line, HR in the 80s, and S_{pO_2} of 93% to 96%. He was admitted to the ICU and was evaluated for and placed on VV ECMO. He was admitted for 27 days with his course complicated by septic shock from *Staphylococcus aureus* bacteremia and the need for significant hemodynamic support. Because of his poor prognosis, the patient's family withdrew life support, and the patient subsequently died.

Case 4

A 42-year-old woman with comorbid conditions of obesity, type 2 diabetes, rheumatoid arthritis, and asthma was admitted to a rural emergency department after 6 days of symptoms typical of COVID-19 infection. She was intubated 3 days later due to acute hypoxemic respiratory failure. She had been treated with convalescent plasma, remdesivir, tocilizumab, and antibiotics for possible superimposed bacterial infection.

The air transport team was dispatched 6 days later to transfer the patient for consideration for VV ECMO due to ARDS with limited improvement on current therapy. On arrival, the patient was being sedated with propofol and fentanyl. She had previously required neuromuscular blockade with cisatracurium and hemodynamic support

with norepinephrine; however, both of these had been discontinued by the time the air transport team arrived. The ventilator mode was VC with a Vt of 400 mL, RR of 30 breaths/min, PEEP of 13 cm H_2O, and F_{IO_2} of 80%. Her IBW was 62 kg. The most recent ABG had a pH of 7.30, P_{aCO_2} of 56 mm Hg, and P_{aO_2} of 70 mm Hg while in the prone position with an F_{IO_2} of 100%. The P:F ratio was 70.

Upon transfer to the transport gurney, she was supinated and placed on iNO, which was initiated at 20 ppm. Her sedation medications and ventilator settings were continued during flight, with adjustment to a Vt of 350 mL and RR of 32 breaths/min titrated to end-tidal carbon dioxide of 42. The initial ABG on arrival was a pH of 7.39, P_{aCO_2} of 49 mm Hg, and P_{aO_2} of 83 mm Hg. Her vital signs were BP of 116/72 mm Hg, HR of 70 beats/min, RR of 32 breaths/min, and S_{pO_2} of 95%. She was admitted to the ICU and cannulated for VV ECMO. Three days later she was cannulated for a tracheostomy. ECMO was discontinued 3 days later, and she was eventually discharged to a local long-term care facility neurocognitively intact with her tracheostomy taken down before discharge.

Case 5

A 52-year-old man with comorbidities of obesity, hypertension, and type 2 diabetes presented to a rural community hospital after 2 weeks of weakness, progressive dyspnea, and cough and was diagnosed with COVID-19. He was treated with convalescent plasma, remdesivir, and dexamethasone. He was also empirically treated for suspected superimposed bacterial pneumonia and was receiving meropenem and tigecycline on the day of transfer. Over the week before transport, he had progressively increasing oxygen demands and failed noninvasive ventilation and was intubated for hypoxemic respiratory failure.

On the day of transfer, he required an F_{IO_2} of 100% and did not tolerate proning due to hypoxemia. Upon arrival of the air transport team, the patient was being sedated with fentanyl and propofol and was chemically paralyzed with vecuronium. The ventilator mode was VC with a Vt of 420 mL, RR of 29 breaths/min, PEEP of 10 cm H_2O, and F_{IO_2} of 100%. His IBW was 78 kg. His vital signs before transport were BP of 172/91 mm Hg, HR of 91 beats/min, RR of 28 breaths/min, and S_{pO_2} of 88%. The ABG at that time demonstrated a pH of 7.26, P_{aCO_2} of 76 mm Hg, and P_{aO_2} of 73 mm Hg. The P:F ratio was 73. iNO was initiated at 20 ppm by the air transport team with subsequent improvement in S_{pO_2} to the low 90s.

Sedation and neuromuscular blocking medications as well as the ventilator settings were continued for the flight. iNO was continued for the duration of the flight, resulting in stable S_{pO_2} readings with a peak of 94% during the 25-minute flight. The ABG upon arrival at the destination hospital was a pH of 7.25, P_{aCO_2} of 77 mm Hg, and P_{aO_2} of 87 mm Hg. His vital signs were BP of 188/72 mm Hg, HR of 82 beats/min, RR of 29 breaths/min mechanical, and S_{pO_2} of 94%. He was admitted to the ICU and evaluated for ECMO but ultimately did not require cannulation. He was extubated 10 days later and discharged home after 15 days.

Discussion

These 5 cases highlight the potential for oxygenation improvement with iNO administration for adult patients with refractory hypoxemia due to severe COVID-19 ARDS. They also support the utility of iNO as a rescue therapy for air medical transport to a tertiary care facility. iNO has been used successfully in air and ground medical transport of neonatal patients since the 1990s. This practice fills the crucial role of connecting community hospitals, many of which do not have iNO capabilities, and tertiary care centers.[13-15] Before this case series, at least 2 interfacility transports have taken place in which iNO was continued for adult patients with COVID-19, although the mode of transport is not clear.[16] Notably, these transports occurred in the setting of a patient already on iNO therapy at the referring facility. In contrast, this case series describes the initiation of iNO therapy in patients by the flight team. iNO use in ARDS patients has been shown to cause a short-term increase in oxygenation, although large studies have failed to demonstrate a mortality benefit in the ARDS patient population.[17-19] However, a large portion of the available data on mortality with iNO use in ARDS does not include studies in which a lung-protective ventilation strategy was used.[20] Additionally, none of the studies focused on its use as a bridge in critically ill patients who may not otherwise survive transport to tertiary care facilities with advanced capabilities such as ECMO. In several of the cases included in this series, transport was initiated with the goal of evaluation for ECMO upon arrival.

Theoretical physiologic limitations of the use of iNO in the transport setting stem from its possible side effects, which include renal impairment and dose-dependent methemoglobinemia. Renal impairment was described in trials in which iNO was used in hospital and for longer durations than would occur in the air transport environment.[21,22] Methemoglobinemia is secondary to the metabolic breakdown of iNO; however, in our series, iNO was initiated at 20 or 40 ppm, and studies have shown that methemoglobinemia does not occur at these doses.[23]

Starting in the fall of 2020, advances in technology as well as clinical and operational capabilities have allowed UW Health Med Flight to expand its specialty flight profiles to include iNO. Our neonatal specialty team has used iNO on isolette transports on ground and rotor wing missions for approximately a decade. The recent transition to the Hamilton T-1 ventilator (Hamilton Medical, Bonaduz, Switzerland) and a larger airframe (Airbus EC145) introduced the option to expand iNO to adult and pediatric patients. Because of the potential technical complexity of these transports as well as the anticipated pathophysiology of the patients, we elected to include a transport respiratory therapist along with our typical nurse-physician medical crew configuration. After obtaining approval from our aviation vendor, we performed multiple in situ low-fidelity simulations to fine-tune the bedside, loading, unloading, and in-flight processes. We then provided in-person as well as asynchronous education to all of our team members as well as additional low-fidelity simulation and hands-on practice.

Given the heterogeneity of the patient population, the relative novelty of COVID-19 respiratory failure, and the lack of evidence-based guidance, there was no specific institutional protocol to determine which patients received iNO therapy during transport and at what dose to initiate iNO. Individualized treatment decisions were made for each of the patients in this case series based on their overall clinical status. Decisions regarding the initiation and dosing of iNO involved collaboration among the referring facility physician, the accepting facility intensivist, the flight physician, and the flight respiratory therapist.

Our critical care transport program uses the AeroNox (International Biomedical, Austin, TX) system for delivering iNO. The full system consists of the AeroNox and 2 D size nitric oxide cylinders. One cylinder is the primary cylinder for the AeroNox, and the other is a backup for emergency hand ventilation. The secondary cylinder always has a regulator and patient-appropriate bag valve mask connected during transport and can supply up to 20 ppm iNO. Our program has 2 nitric oxide systems mounted to isolettes for use for neonatal patients. A third system is kept at the ready and can be mounted into any of the program's EC145 helicopters or ground ambulances to deliver iNO during adult or pediatric transports outside of isolettes.

The system is mounted in the back of the helicopter and can be easily reached to make any adjustments needed throughout the transport (Fig. 1). iNO is delivered from the AeroNox to the ventilator, which is mounted toward the front of the patient care area via a delivery line that inserts into the ventilator circuit at the manifold on the inspiratory side of the circuit. The sample line is inserted

Figure 1. A photograph of the AeroNox mounted in an aircraft.

downstream on the inspiratory side of the circuit and back to the AeroNox. The lines are secured to the patient cot with carabiners to prevent them from becoming tangled or disconnected.

In this case series, the air medical transport team affiliated with the tertiary care center brought an advanced therapy to a referring facility, offering a bridge therapy unavailable locally and allowing for the safe transport of multiple critically ill COVID-19 patients in a generally unforgiving environment. Given the retrospective nature of this case series, a potential confounder regarding the potential benefit of iNO therapy is that in cases involving both ventilator setting adjustments and iNO initiation, it may be difficult to ascertain the relative contributions of each toward any improvement in the patient's oxygenation. Given the severity of the patients' illnesses, all possible avenues to improve their stability for transfer were pursued, including ventilator adjustments and adjustments to medication infusions (such as vasopressors, analgosedatives, and neuromuscular blocking agents). Nonetheless, each patient within this series might not have survived transport without iNO. With the proper expertise, skill set, and credentialing, iNO can be initiated by air transport teams for adult COVID-19 patients.

Conclusion

This case series illustrates how iNO initiation by an air transport team for adult COVID-19–associated hypoxemic respiratory failure with ARDS is feasible with proper staffing, training, and expertise. Each case presents a patient with significant respiratory compromise due to COVID-19 who had failed all available local therapy at distant rural hospitals. In each case, iNO may have contributed to improved oxygenation during helicopter transport to a tertiary care facility and, in some cases, served as a bridge to more advanced interventions. Further study is needed to validate the efficacy and safety of iNO administration in COVID-19 ARDS in the air medical transport environment.

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