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Featured Article

The Use of Nitric Oxide as a Rescue Modality for Severe Adult Acute Respiratory Distress Syndrome Patients, Including COVID-19, in Critical Care Rotor Transport: A Retrospective Community Outcome Study

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ABSTRACT

Objective: Severe acute respiratory distress syndrome (ARDS) mortality increases in smaller outlying facilities, and patients (especially those diagnosed with coronavirus disease 2019 [COVID-19]) are often "stuck" at these facilities. These patients are on maximal ventilator settings and are often in the prone position. Our purpose was to show that with the use of inhaled nitric oxide (iNO), a "community-based" rotor wing critical care transport (CCT) team can safely, consistently, and effectively transport these extremely precarious patients to the tertiary care that is needed.

Methods: This was a retrospective database review of 50 patients (39 patients with COVID-19) transported between 2017 and 2021 in whom iNO was brought to the bedside and initiated by the rotor wing critical care transport team. The review included patient demographics, vital signs, and ventilator settings from the sending hospital, in-flight, and the receiving hospital. We reviewed the transition from transport to venovenous extracorporeal membrane oxygenation (if applicable), hospital disposition, and length of stay from the receiving hospital side. Concerning the actual transport, we reviewed the mode of transport, the sending facility size, and the distances covered.

Results: Upon arrival at the sending facilities, we found severely ill patients with almost half (46%) in the prone position or recently transitioned from a prone position within the last 2 hours. Eighty-six percent were pharmaceutically paralyzed, and 44% were in shock. There was a younger and heavier predominance with an average age of 44 years and an average weight of 103 kg. Thirty-nine patients were diagnosed with COVID-19. The other 11 had a mix of non–COVID-19 ARDS, pulmonary embolism, and pulmonary edema. The patients presented from 27 different community hospitals. Forty-four percent were from small referring hospitals that had less than 200 beds. Twenty-eight patients were transported by a Bell 407 helicopter, 18 with an Airbus H135 helicopter, and 4 by ground ambulance. Forty-one percent of patients were transported within 25 miles, and 4 patients were transferred from > 100 miles away. All 50 patients were safely transported without significant deterioration or significant pulmonary pressure increases. Thirty-seven patients were placed on venovenous extracorporeal membrane oxygenation (34 of those patients cannulated within 2 hours of arrival). The overall mortality rate was 27%, and the COVID-19 mortality rate was 24%.

Conclusion: iNO retrieval for severe ARDS can be safely and effectively completed within the COVID-19 population and the nonacademic community setting using helicopters prevalent in the global air medical industry (Bell 407 and Airbus H135).

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Acute respiratory distress syndrome (ARDS) is a severe inflammatory response in the lungs due to multiple inciting injuries. These "injuries" can vary from different types of pneumonia (bacterial, viral, or aspiration), to trauma, to a severe sepsis reaction. The mortality of ARDS before coronavirus disease 2019 (COVID-19) ranged from approximately 30% to 50%.[1-4] In the COVID-19 mechanically ventilated patient, the mortality varies across studies but can range from 25% to 45%, as was demonstrated by a large European cohort study.[5] According to the Centers for Disease Control and Prevention data, mortality is up to 65% for COVID-19 mechanically ventilated patients.[6]

More importantly to note for the transport community, the ARDS mortality rate increases in centers that have lower hospital volume,[7] have a lower ARDS case volume,[1] and are in nonmetropolitan centers.[8] Therefore, an effective method to stabilize and transport severe ARDS patients from smaller/rural facilities to tertiary care centers is vital. Additionally, the higher incidence of barotrauma in COVID-19 has made us even more aware of the deliberate ventilation strategies/pressures that must be used during transport.[9]

Inhaled nitric oxide (iNO) is a selective pulmonary artery vasodilating agent. Initially described in the neonatal literature and still commonly used, it has progressed over the last decade to adult use. Originally used in adults with right ventricular failure by helping decrease the afterload to the failing right ventricle, it is now also recognized as rescue therapy for refractory hypoxia in adult ARDS patients. The mechanism is thought to decrease the intrapulmonary shunt by overcoming hypoxic pulmonary vasoconstriction. Prolonged use of nitric oxide in the intensive care unit (ICU) has not been shown to improve mortality[10-12]; yet, a temporary increase in oxygenation has been measured by the fraction of inspired oxygen, Pao_2, and positive end-expiratory pressure (PEEP) improvement.[13,14] For this reason, iNO has been used as a temporary bridge to allow other therapies to be instated or given time to work. This is often a bridge to venovenous extracorporeal membrane oxygenation (VV-ECMO), but iNO can also be used to temporize the patient until proning, aggressive diuresis, or even antibiotics have time to work.

The "iNO bridge" concept is of most interest in the transport community. Specifically, patients are often considered too unstable to transport on regular or even extreme ventilator settings. The instability of these patients regrettably results in the inability to transport them to tertiary (or quaternary) care, leaving the patient "stuck" at a facility that cannot offer additional treatments. In contrast, a tertiary care facility with an iNO-equipped critical care transport (CCT) team has the opportunity to provide temporary stabilization for effective and safe transportation. The iNO often allows the CCT team to proactively manage the ventilator pressures lower and out of barotrauma range during transport.

Unfortunately, a large portion of sending facilities (especially those outside of the academic realm) do not have iNO capabilities, and, if they do, they do not have a way to convert that to a transport mechanism. However, if iNO can be brought to the bedside by a CCT team, appropriately initiated, and titrated along with adjusting ventilator settings, the patient may be transported with less risk.

Within the air medical transport community, the transportation of iNO in adults has been done, but this usually is in the setting where iNO has already been initiated by the sending facility. Within this study, we show and discuss the use of "rescue" iNO retrieval in which the transport team brings the nitric oxide and advanced ventilator care capabilities to the sending facility. The CCT team initiates the iNO, adjusts the ventilator, and transports the patient safely.

Although this "rescue" and initiation of iNO are not often described in adult transport literature, they have been performed safely. One such study was done in Norway with flying anesthesiologists to decrease the ECMO transport load.[15] They described using the iNO in conjunction with "adjusted intensive care treatment." The airframe for the Norwegian study was not mentioned. In another study, the University of Michigan's Survival Flight published their iNO transport results in 2015 using a large EC-155 airframe. They showed promising results on "responding" patients. Again, iNO is used as "an additional tool in the management of severe hypoxia," and their stepwise protocol was very well-defined.[16]

In conjunction with Medical City HealthCare, a 16-hospital system across the Dallas–Fort Worth metroplex, PHI Air Medical, a world-leading air ambulance provider, began using iNO in 2017 to safely transport severe ARDS patients otherwise too unstable to travel within the North Texas area. A small number of transports were completed before 2020, but with the COVID-19 pandemic beginning in the spring of 2020, our experience of using iNO as a rescue therapy for bringing in severe ARDS patients has dramatically increased.

We describe our experience using iNO as a rescue therapy within the community nonacademic setting. This experience includes the initiation of iNO by the CCT flight team, adjusting the ventilator, and transporting patients in Bell 407 and H-135 helicopters. We hope to demonstrate that, especially during a severe respiratory viral pandemic, iNO, along with advanced critical care support, can be used to transport patients to end-goal therapy safely.

Methods

Data Collection

We created a protected transport database for our iNO and ECMO transport patients. This database was shared between entities (Medical City Healthcare and PHI Air Medical) and filled in prospectively on both the transport and the hospital respiratory therapy sides. This database included all items listed in Table 1. This database was retrospectively reviewed, analyzed, and prepared for study.

The appropriate institutional review board approved all portions of the database, patient data, and study. Because this was a retrospective data review with no direct patient changes, the institutional review board consent was waived.

Transport Process

Patients with severe ARDS at outlying community hospitals are called into the local transfer center for possible acceptance into tertiary care centers (Medical City Healthcare) for a higher level of care and ECMO consideration. Acceptance is dependent on the receiving intensivist's evaluation of the case along with VV-ECMO criteria guidelines.[17] This includes patients with severe ARDS with a Pao_2/fraction of inspired oxygen ratio < 100 as defined by the Berlin definition.[18] Once the patient is accepted by the receiving intensivist and a need for possible iNO retrieval is indicated, the CCT medical director is notified. Based on the case presentation, a decision is made whether to use the H-135 or Bell 407 helicopter airframe for transport. The airframe decision depends on the weather, distance, size of the patient, and CCT MD accompaniment. Then, the appropriate airframe from PHI Air Medicalis launched to retrieve specialty equipment and staffing as applicable and subsequently the patient.

Table 1
Metrics Within the Transport Database

- Patient sex, age, weight, and payer
- Sending and receiving facility (includes size and distance)
- Aircraft, crew, and MD (if flying)
- Vitals of patient prior, during, and after transport
- Ventilator settings prior, during, and after inhaled nitric oxide and transport
- Extracorporeal membrane oxygenation cannulation time (if applicable)
- Patient disposition and outcome

Upon arrival at the bedside, the CCT team initiates iNO (INOmax and INOmaxDS$_{IR}$ Delivery System; Mallinckrodt Pharmaceuticals, Dublin, Ireland) at 20 ppm through the transport ventilator (ReVel Ventilator [model 19260-001]; Vyaire, Mettawa, IL), and adjustments are made to optimize the settings per protocols and training. These adjustments include optimizing driving pressure, PEEP, rate, and mode change if necessary. These optimizations often include assisting in "supining" the patient if prone while on iNO. The CCT team can titrate iNO from 20 ppm up to 40 ppm if needed. Once the patient is stabilized on iNO, the updated patient status and estimated arrival time are provided to the receiving facility and team to anticipate acceptance of care. The CCT team medical director is engaged as needed for consultation. If the patient cannot be stabilized on iNO for transport and meets ECMO criteria, the receiving facility is informed, and an ECMO cannulation team is launched.

Crew Composition/Training

The PHI Air Medical critical care transport team is composed of specialty-certified clinicians, including a flight paramedic and a flight registered nurse. All crew members undergo rigorous initial and ongoing training that meets and exceeds Commission on Accreditation of Medical Transport Systems accreditation standards. Specialized training includes advanced critical care techniques, high-fidelity simulation experiences, and a quarterly complex/high-acuity didactic curriculum. Objectives of the curriculum are based on evidence-based practice and continuous quality improvement review, including postcall case study reviews.

In addition to the previously mentioned quarterly training, there is also additional biannual training explicitly focused on iNO and mechanical cardiac assist devices, such as left-ventricular assist devices, intra-aortic balloon pumps, and ECMO. Specifically, regarding iNO, hands-on training with lead respiratory therapists is conducted in partnership with Medical City Plano and the CCT medical director. Notably, the clinicians must demonstrate multiple competency levels, including understanding the INOmax system components and functions, preuse checkout, setup, calibration, and troubleshooting. The training also includes placing the components in-line with the ventilator circuit, setting the nitric dosage and alarms, and when to use the INOblender. An intense focus is placed on the logistics/strategy of moving patients with multiple mechanical cardiac assist devices, including iNO, from bedside to bedside.

Results

Patient Baseline Data

Between 2017 and October 2021, we responded to 50 patients, initiated iNO, and transported them into our tertiary care system. Thirty-nine patients (78%) were diagnosed with COVID-19 viral pneumonia. The other 11 patients were non-COVID causes for ARDS/acute respiratory failure (Fig. 1). Most of our flights included in this study were in 2020 and 2021 (45 patients).

Of note, within this period, 60 iNO transports were flown. However, 10 were excluded due to being flown out of our system instead of into the health system. Outcome data were not available for the 10 excluded flights. Notably, no complications or adverse events were reported with these 10 patients. In addition, only 1 patient could not be successfully transported even after iNO stabilization, and the ECMO team was flown in to cannulate on-site. This patient was not included in the 50 patients represented in the study.

Table 2 shows the baseline data of our patients, with a predominance of male patients, a younger age (as is biased by COVID diagnosis), and a higher body mass index. On average, the patient had been in the sending facility for 7.6 days and was intubated for 3.3 days. We found no significant difference in the baseline data and the severity of illness of our COVID patients when it came to the timeline of the pandemic (ie, between whether they were transported in early 2020 vs. late 2021).

The patients' conditions were severe and not unlike what is being seen with ICU COVID-19 cohorts. Almost all patients were pharmaceutically paralyzed (86%), and nearly half (46%) were actually in the prone position either on our arrival or placed in the supine position within 2 hours before our arrival. Higher PEEP and peak inspiratory pressures (PIPs) were common (Table 3).

Patient Transport Data

All patients (50) included in this study were started on iNO at 20 ppm. The iNO was titrated after making appropriate ventilator settings if applicable. The ventilator settings adjusted included ensuring appropriate PEEP, driving pressure,[19] fraction of inspired oxygen, and adjusting inspiratory:expiratory ratios. In addition, appropriate sedation and paralytics were used. By the end of the transport, the average iNO ppm was 29 ppm.

Our ventilator training and standardization across the system emphasize pressure control modes of ventilation, especially in the

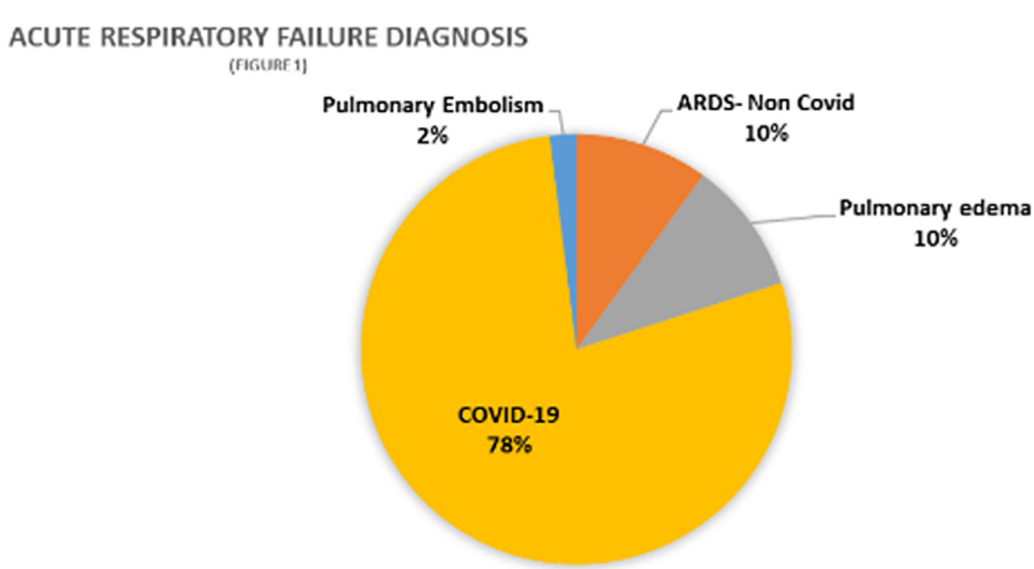

Figure 1. Acute Respiratory Failure Diagnosis.

Table 2
Patient Baseline Data

Male	28 patients
Female	22 patients
Mean age	44.9
Mean weight	103.9kg
Mean body mass index	44.5
Mean days intubated before transport	3.3 days
Mean days at sending facility before transport	7.6 days

Table 3
Patient Condition on Arrival at Sending Facility

Paralyzed	86% (43 patients)
Prone positioning	46% (23 patients)
Chest tubes present	10% (5 patients)
Shock	44% (22 patients)
Mean positive end-expiratory pressure	14 cm H_2O
Mean peak inspiratory pressure	33 cm H_2O
Mean delivered fraction of inspired oxygen	91%

hypoxic COVID-19 patient. Upon arrival at the bedside, 27 patients (54%) were on a volume control mode, and 9 patients (18%) were on pressure-regulated volume control (72% total not on assist control pressure control). With iNO, we were able to transport 80% of patients in the assist control pressure control mode. There were no reported significant desaturations or deterioration of status during transport that could not be corrected with an appropriate ventilator, vasoactive pressor, or iNO adjustment.

Aircraft Transport Data

Forty-six patients were transported by helicopter (39% by Airbus H135 and 61% by Bell 407). Four patients were transported by ground because of weather limitations or the patient's size being incompatible with helicopter transport. All Airbus H135 transports (18) included a critical care physician during patient transport. As the program matured and the crews' acumen increased, the physician flew less. Notably, 100% of iNO flights in 2017 to 2019 included a physician, whereas the physician accompanied iNO transports 47% and 27% of the time in 2020 and 2021, respectively.

During the study period, 27 different facilities referred to us in which we used rotor wing air ambulances to access and complete transport. Forty-four percent of the referring hospitals have less than 200 beds (Fig. 2). Eleven (41%) of these facilities were within 25 nautical miles (nm) spread across the Dallas–Fort Worth metroplex. Twelve (44%) were between 25 and 100 nm away, and 4 (15%) were > 100 nm away. The longest distance transported was 182 miles 1 way. (Six flights were > 150 nm.)

Outcomes/Disposition

All 50 patients were transported successfully without significant desaturations or deterioration. On average, fraction of inspired oxygen increased by 9.1% (from 90.4% to 95.8%), PEEP was decreased from 13.4 cm H_2O to 12.8 cm H_2O, and iNO ppm increased an average of 9 ppm during transport. Notably, the total PIP did not need to be increased in transport, and it remained on average the same for the duration of the flight (33.35-33.06 cm H_2O).

Of the 50 patients transported into the system, 37 patients were subsequently placed on VV-ECMO. The average time from arrival to cannulation was 6 hours 22 minutes. This number is deviated to the side by 3 outlying (before 2021) patients who were cannulated > 16 hours. An analysis of the patients demonstrated an average time to cannulation of 1 hour 53 minutes (excluding the 3 outliers mentioned earlier). Remarkably, in 2021 (23 patients), the time to cannulation was lower at 1 hour 31 minutes.

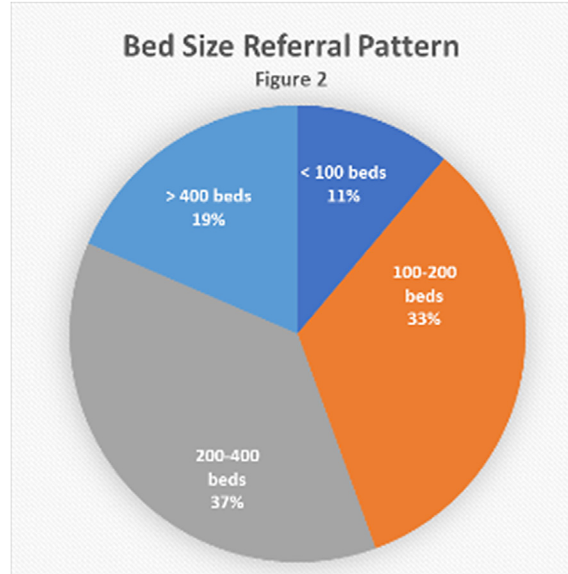

Figure 2. Bed Size Referral Pattern.

At the time of this publication, two patients remain hospitalized. One remains as an inpatient; the second was discharged to another facility and lost to follow-up. Both of these excluded patients had COVID. Of the remaining 48 patients, the study group survival rate was 73%, with 29% ultimately discharged home. Among those cannulated and placed on VV-ECMO, the survival rate was 77%, and 29% were discharged home. Patients remained on VV-ECMO for an average of 21.1 days. The patients who did not go on ECMO had a survival rate of 62% with 31% being discharged to home (Table 4). Overall, the total ICU length of stay was 26.8 days, and the total hospital length of stay was 28.6 days.

Concerning our COVID cohort, excluding the remaining inpatient and one lost to follow-up, for 37 patients the survival rate was 76%, and the discharge to home rate was 27% (Table 4). Thirty-three of the 37 included COVID patients had been placed on VV-ECMO. Our COVID patients did remain in the ICU and hospital longer (30.4 days and 32.1 days, respectively).

Discussion

The mortality rate for severe ARDS (non-COVID) without ECMO is 30% to 50%.[1-4] In addition, per the Centers for Disease Control and Prevention, the mortality rate for COVID-19 intubated patients over this pandemic has ranged from 40% to 60%.[5,6] This ARDS mortality rate increases in centers that have lower hospital volume,[7] have lower ARDS case volume,[1] and are in nonmetropolitan areas.[8] The transport of these severe ARDS patients has never been as vital, especially with the younger ages seen in the COVID population. Unfortunately, many cannot be transported safely and effectively due to being unstable or attempted transport, and the patient deteriorates en route to the tertiary care facility.

We describe the transport of 50 severe ARDS patients using iNO as a stabilization modality to retrieve the patient from a referring facility to receive a higher level of care. The patients described in the study were very ill with explicitly higher PEEPs and PIPs, and almost half had been recently/actively proned. Forty-four percent of patients were transported from smaller-sized hospitals (< 200 beds). All patients were transported safely to the tertiary care they needed, with no significant changes in their pulmonary pressures. On average, the outcomes and dispositions of patients transported by the iNO-equipped CCT team were better than standard ARDS and COVID ARDS outcome rates.

Table 4
Dispositions

	LTAC/REHAB (%)	Home (%)	Died (%)
Patients placed on VV-ECMO (35 patients, including 33 with COVID-19)	48.6	28.6	22.8
Patients placed on iNO only (13 patients, including 4 with COVID-19)	30.7	30.7	38.5
All COVID-19 patients (37 patients) (37 patients total: 33 placed on ECMO, 4 only iNO)	48.6	27.0	24.3
All included patients (48 total) (2 patients excluded: 1 remains inpatient and 1 lost to follow-up	43.7	29.2	27.1

COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; iNO = inhaled nitric oxide; LTAC = long-term acute care; REHAB = rehabilitation; VV-ECMO = venovenous extracorporeal membrane oxygenation.

Although a couple of previous studies have used iNO as a retrieval agent,[15,16] several points make this study and cohort notable. The first is that this cohort included a significant portion (78%) of COVID-19 patients. ARDS COVID-19 patients tend to be younger, have higher mortality, and have higher rates of barotrauma.[9] Although this by itself is a unique challenge for a CCT team, the use of personal protective equipment and viral precautions add another layer regardless of the life support mechanism.[20] This study is the largest reported cohort of COVID-19 patients transported via a CCT team while undergoing iNO treatment.

Second, our iNO CCT team is operated outside a single unifying system (ie, university/academic setting). The CCT team is a collaboration between PHI Air Medical (flight clinicians, helicopters, and flight operations), Medical City Healthcare (iNO, respiratory therapy training and support, and tertiary care destination), and Envision Physician Services (critical care MD support). Furthermore, this necessitated communication and coordination between multiple stakeholders of the three organizations, including clarifying the iNO retrieval process, the activation of the “CCT nitric retrieval team,” communication flow diagrams through the Medical City Healthcare -supported transfer center, and the iNO equipment. For example, the unique iNO retrieval bag, which was initially developed by one of our PHI Air Medical sister programs in Michigan, was modified with input by Medical City Plano respiratory therapists, the local PHI Air medical flight crew, and critical care physicians. The retrieval bag has evolved through multiple generations, and now numerous bags allow for faster CCT team deployment.

In addition to being outside of a single unifying system, having 27 distinct community hospitals as referral centers, with almost half being small hospitals, is unusual and remarks on the community outreach and success of the program.

Finally, the airframes make this type of transport notable. Of the 50 patients transported by rotor wing aircraft, 39% were in an AIRBUS H135 helicopter and 61% in a Bell 407 helicopter. This study represents the largest cohort of iNO transported patients in these “smaller” airframes found in the literature. This often includes a third medical crewmember (the CCT medical director). Although large airframes, such as the AIRBUS H135, allow for more space and more equipment, they are often not practical from a financial and logistic viewpoint. The COVID-19 pandemic created an urgent need to deliver the highest level of cardiopulmonary care possible in the existing airframes, such as the Bell 407, which are commonly available for air medical operations.

Concerning the study’s limitations, the retrospective nature of this study is the most significant one. A fully randomized prospective trial would be ideal but likely not feasible considering the severity of the patients’ illness and the precarious nature of the condition. Yet, as a next step, we continue to collect data on all of our ARDS transported patients to build a cohort match study with our iNO transported patients.

In addition, as another limitation of this study, we realize the outcomes of the patients have a significant portion to do with the care at the receiving facility, including ECMO. Yet, considering the severity of the patients (including the percentage of prone patients), they may have never been able to be transported without advanced ventilation management and rescue therapies such as iNO or ECMO cannulation. Although ECMO cannulation has been done at the sending facility and transport is often successful,[21] the logistics (both equipment and financial) can be challenging to set up and work through, especially outside the nonuniversity setting. Overall, cannulation at the tertiary facility is preferred where supporting resources are readily available to the cannulating surgeon.

In conclusion, in understanding the limitations of a retrospective study, iNO can be initiated and used as an additional “rescue agent” by the critical care flight team to stabilize and safely transport severe ARDS patients via rotor wing aircraft, especially those suffering from COVID-19−induced ARDS. We have also shown that it is feasible in the community (nonuniversity) setting and commonly used light airframes.

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