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Enhancing Lung Injury Treatment Modalities with Nitric Oxide

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14. ABSTRACT
Inhaled Nitric Oxide (INO) is a selective pulmonary vasodilator delivered from compressed gas cylinders filled to 2200 pounds per square inch gauge (psig) with 800 parts per million (ppm) of Nitric Oxide (NO) in a balance of nitrogen. NO is currently FDA approved for use in term or near-term infants with hypoxemia and signs of pulmonary hypertension in the absence of cardiac disease. NO has also been shown to improve oxygenation in adults with refractory hypoxemia. Current doctrine precludes the use of NO during military aeromedical transport owing to the requirement for large, compressed gas cylinders. We performed a bench evaluation of two delivery systems that create NO from room air without the need for pressurized cylinders.

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1.0. SUMMARY/DISCLAIMER

We performed a bench evaluation of two delivery systems that create NO from room air without the need for pressurized cylinder. We evaluated two portable NO generation systems (LungFit PH, Beyond Air Inc, Garden City, NJ and a prototype NO generator, Odic Inc, Littleton, MA) at ground level, 8,000 and 14,000 feet simulated altitude in an altitude chamber. The final report will include information covering the methods, results for each research activity.

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2.0. BACKGROUND

Inhaled Nitric Oxide (INO) is a selective pulmonary vasodilator traditionally delivered from compressed gas cylinders filled to 2000 pounds per square inch gauge (psig) with 800 parts per million (ppm) of Nitric Oxide (NO) in a balance of nitrogen. INO is currently Food and Drug Administration (FDA) approved for use in term or near-term infants with hypoxemia and signs of pulmonary hypertension in the absence of cardiac disease.[1] Additionally, INO has been shown to improve oxygenation in adults with refractory hypoxemia[2-8] and was evaluated as a rescue therapy to treat hypoxemia in patients with severe Coronavirus disease COVID-19.[9-12]

Current doctrine precludes the use of INO during military aeromedical transport owing to the requirement for large, compressed gas cylinders. Currently there are two INO gas and delivery systems utilizing pressurized cylinders approved for use in the U.S. (INOmax DS_{IR}, Mallinckrodt Pharmaceuticals, Dublin, Ireland and Noxivent, Linde, Danbury, CT). These systems are primarily utilized in the hospital setting. Although the systems can be used for transport in

civilian healthcare settings, the practice is limited to the transport of extremely ill patients due to the logistical issues of managing the cylinders in which the gas is stored and the delivery device. More recently, devices have been developed that create NO from ambient air without the need for pressurized storage cylinders. We performed a bench evaluation of two such INO delivery systems.

3.0. METHODS

3.1 Experiment setup

The LungFit PH System (Beyond Air, Garden City, NJ) and High Altitude NO Generator (Odic Inc, Littleton, MA) (Figure 1) were evaluated using the ventilator and lung conditions in Table 1 using two portable ventilators (731, Zoll Medical, Chelmsford, MA, and T1, Hamilton Medical, Reno, NV).

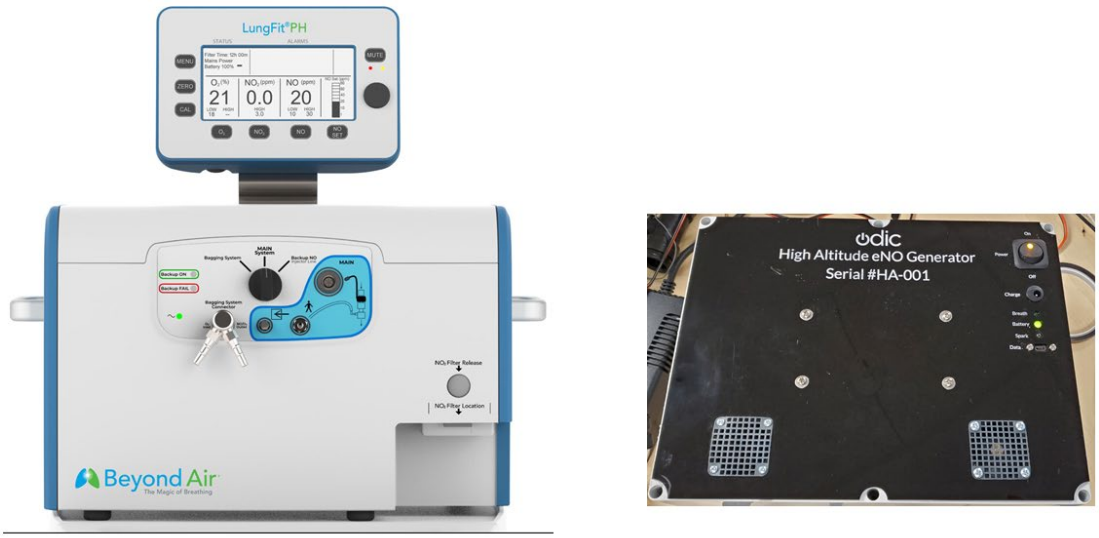

Figure 1 NO generator devices used for the experiment. Lungfit image provided by Beyond Air, Inc.

Table 1 Ventilator Settings and Lung Conditions Used For The Experiment

Resp Rate (breaths/min and Tidal Volumes (mL)	FiO_2	NO delivery setting (ppm)	Breath Type	Lung compliance (cm H_20)/ Airway resistance (cm H_2O/L/s)	Measured Values
30/250 20/450 20/650	0.21 0.60	20	Pressure & volume	80/5 & 20/5	NO, NO_2, FiO_2

Centimeter (cm) / water (H_20)

The output of each INO generating device was injected into the ventilator circuit at the ventilator outlet. NO and nitrogen dioxide (NO_2) reference measurements were accomplished using the electrochemical gas sensor from INO_{MAX} DS_{IR} commercially available INO delivery system. This device is rated to operate up to 15,000 feet altitude (427 millimeters of mercury (mmHg))[13]. Inspired oxygen fraction (FiO_2) reference measurement was accomplished with a fast response oxygen (O_2) analyzer (O_2CAP, Oxigraf Inc, Sunnyvale, CA) via gas sampled from the ventilator circuit inspiratory limb near the patient connector. The ventilator circuit was attached to a single chamber test lung (Training & Test Lung, Michigan Instruments, Grand Rapids, MI). Testing was accomplished at ground level and 8,000 and 14,000 feet simulated altitude in a custom altitude chamber (Abbess Instruments and Systems Inc, Holliston, MA). Each test was done in duplicate and continuous data was recorded for analysis. Target INO for all tests was 20 ppm. The duty cycle used to attain INO concentrations of approximately 20 ppm with the Odic device at ground level was used at both altitudes in order to compare differences in INO at altitude as compared to ground level.

3.2 Device descriptions

The Lungfit device generates INO by drawing ambient air into the system and passing it through a reaction chamber, ionizing the nitrogen and oxygen molecules. The molecules recombine as NO and NO_2 (figure 2)[14].

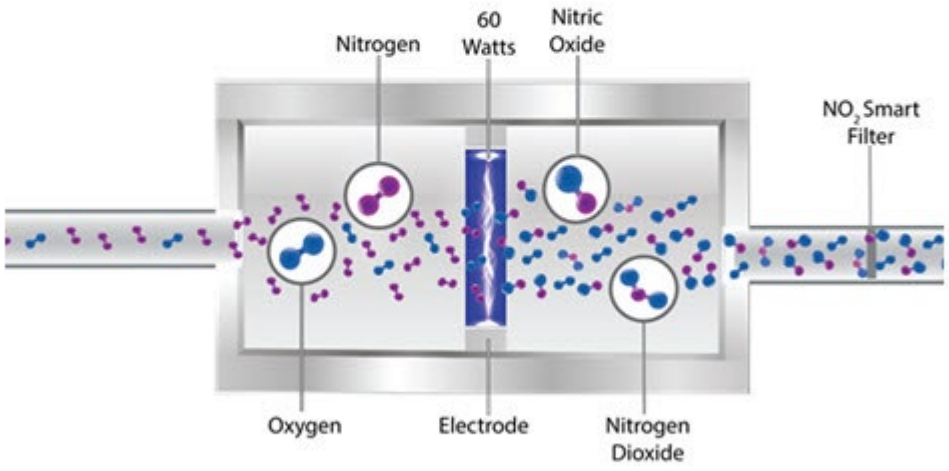

Figure 2 LungFit Mechanism of Producing NO

The device provides continuous monitoring of NO, NO_2, and FiO_2 and has integrated alarms. The device also provides a backup battery and NO system that delivers approximately 40 ppm NO, depending on the gas flow in the ventilator circuit, in the event of main system failure. The range of delivered NO concentration is 0.1-80 ppm. LungFit contains a disposable calcium hydroxide ($Ca(OH)_2$) filter that captures NO_2 before it exits the device. The Lungfit dimensions are 50cm x 38cm x 48cm length x height x width (LxWxH) and weight is 20 kilogram (kg)[15]. The Odic device is a prototype that uses a high voltage spark from an automotive-type iridium spark plug in a pressurized chamber to produce NO from ambient air. The device requires attachment to a computer and open source software (PuTTY, www.putty.com) to manipulate

INO output. The device does not have INO settings as such but relies on a number of variables within the software to set INO. The main variable that controls NO output is duty cycle which is the percent of time that the spark is being initiated. The range of delivered INO concentration is not documented. The device utilizes an in-line $Ca(OH)_2$ filter to capture NO_2 at the device outlet[16]. The absence of settings and monitoring capabilities necessitates using external monitors for NO, NO_2, and FiO_2. The Odic dimensions are (LxWxH) 30cm x 22cm x 11cm and weight is 3.7kg.

3.3 Statistical plan

The primary outcomes were delivered FiO_2, NO, NO_2. Measures were compared as mean difference. For each NO delivery device and ventilator, the following measurements were taken:

- Delivered NO and NO_2 concentration as measured by the reference device and LungFit
- Difference between reference and LungFit NO measurements.
- Delivered FiO_2 measured by the reference device and Lungfit
- Difference between reference and LungFit FiO_2 measurement
- Delivered NO, NO_2, and FiO_2 concentration as measured by the reference devices using the Odic device

All statistical comparisons used nonparametric tests: Wilcoxon's two-tailed rank sum test, signed rank test, Kruskal-Wallis, or Fisher's exact as appropriate. INO differences greater than ±5 ppm of set/baseline, FiO_2 differences more than ±10 percent (%) of set FiO_2, and NO_2 values >2ppm were considered clinically important.

4.0. RESULTS

4.1 Lungfit

Mean combined INO with both ventilators was 19.9 ± 1.6 ppm (range 16.5-25.4, interquartile range (IQR) 19.0-20.5) at ground level, 16.1 ± 1.9 ppm (range 12.5-19.5, IQR 14.8-17.0) at

8,000 feet and 11.6 ± 1.7 ppm (range 8.0-15.0, IQR 10.5-13.0). Differences in set versus delivered mean NO were statistically significant at 8,000 and 14,000 feet ($p<0.001$) but were clinically important only at 14,000 feet. Delivered mean INO comparisons within each altitude between the 731 and T1 ventilators showed statistically significant differences at ground level, 8,000 and 14,000 feet ($p=0.01$, $p=0.002$, and $p=0.04$ respectively) but were not clinically important (INO differences in the mean <5 ppm) (figure 3).

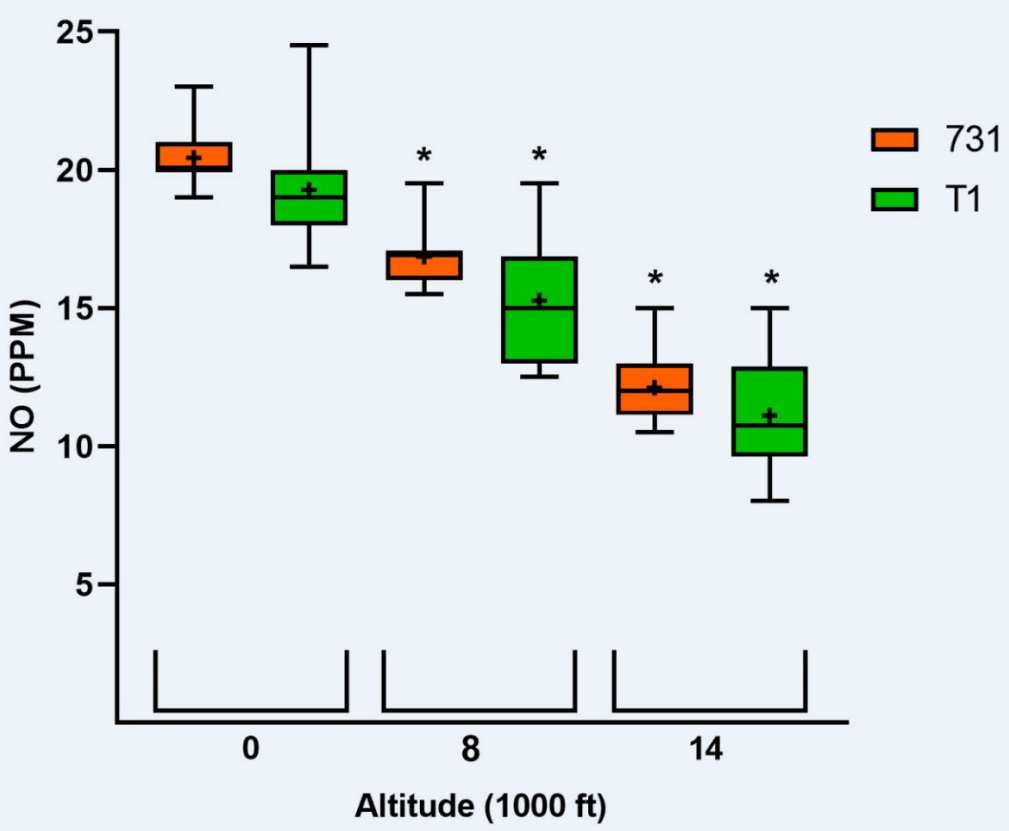

Figure 3 Measured NO concentrations across all ventilator and lung condition settings with each ventilator at ground level and at altitude. Box and whisker plots show minimum, maximum, IQR, mean (+), and median NO. *Statistically significant differences from set NO of 20 ppm

Differences in mean INO measured by the reference device versus Lungfit were statistically significant at ground level and 14,000 feet ($p=0.02$ and $p<0.001$ respectively) but not at 8,000 feet ($p=0.3$) (figure 4).

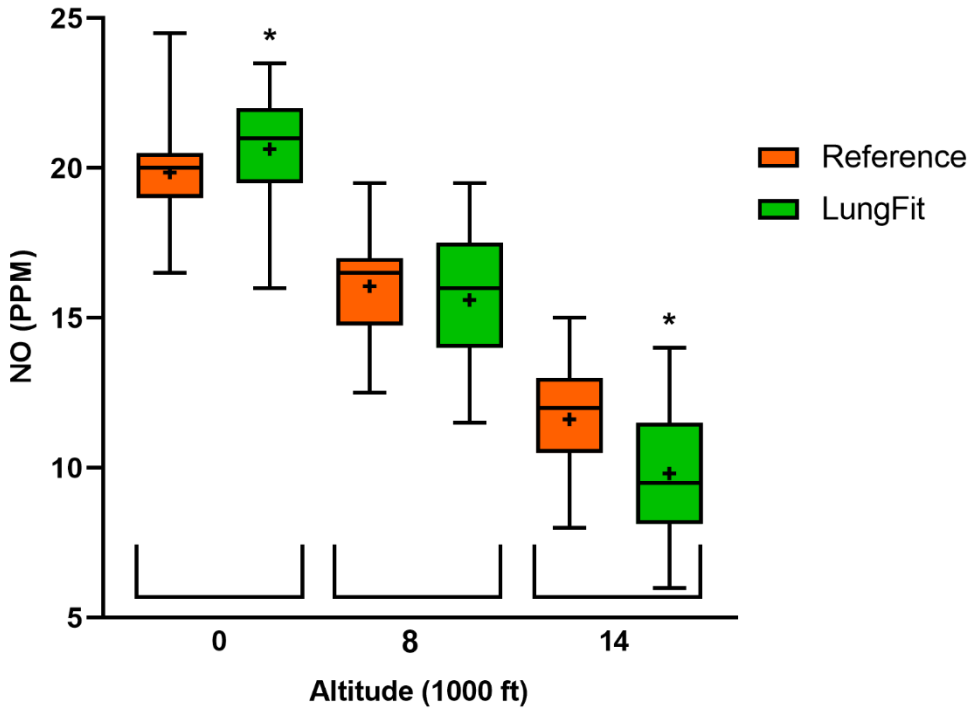

Figure 4 NO concentrations across all ventilator settings, lung conditions, and both ventilators as measured by the reference device and Lungfit at ground level and at altitude. Box and whisker plots show minimum, maximum, IQR, mean (+), and median NO. *Statistically significant differences in NO measurement as compared to reference device

FiO_2 measurement by the reference device and set FiO_2 (0.21 and 0.6) were not significantly different at ground and both altitudes ($p>0.05$). At set FiO_2 of 0.6, the reference device measured mean FiO_2 was 0.59 ± 0.01 at ground level, 0.58 ± 0.02 at 8,000 feet, and 0.58 ± 0.01 at 14,000 feet. Set FiO_2 compared to ground level was significantly different ($p=0.008$) but was not clinically important (data not shown). Measured FiO_2 remained at 0.21 with all testing conditions at set FiO_2 of 0.21.

Mean FiO_2 measurements with Lungfit at the 0.21 and 0.6 FiO_2 settings respectively were 0.15 ± 0.002 and 0.42 ± 0.01 at 8,000 feet and 0.12 ± 0.001 and 0.33 ± 0.01 at 14,000 feet. These differences were all statistically significant ($p<0.001$) and clinically important as compared to the reference device. Measured NO_2 was <1ppm at all test conditions.

4.2 Odic

The Odic device did not have NO and FiO_2 measurement capabilities, so all measurements were made with the reference devices. Comparisons were made to the reference measured ground level values since there was no INO setting. Mean combined INO utilizing both ventilators were 20.6 ± 1.4 ppm (range 18.5-24.5, IQR 19.6-21.5) at ground level, 21.3 ± 5.5 ppm (range 11.0-36.5, IQR 19.0-23.0) at 8,000 feet and 20.4 ± 9.1 ppm (range 5.0-41.0, IQR 14.0-23.9) at 14,000 feet (figure 5).

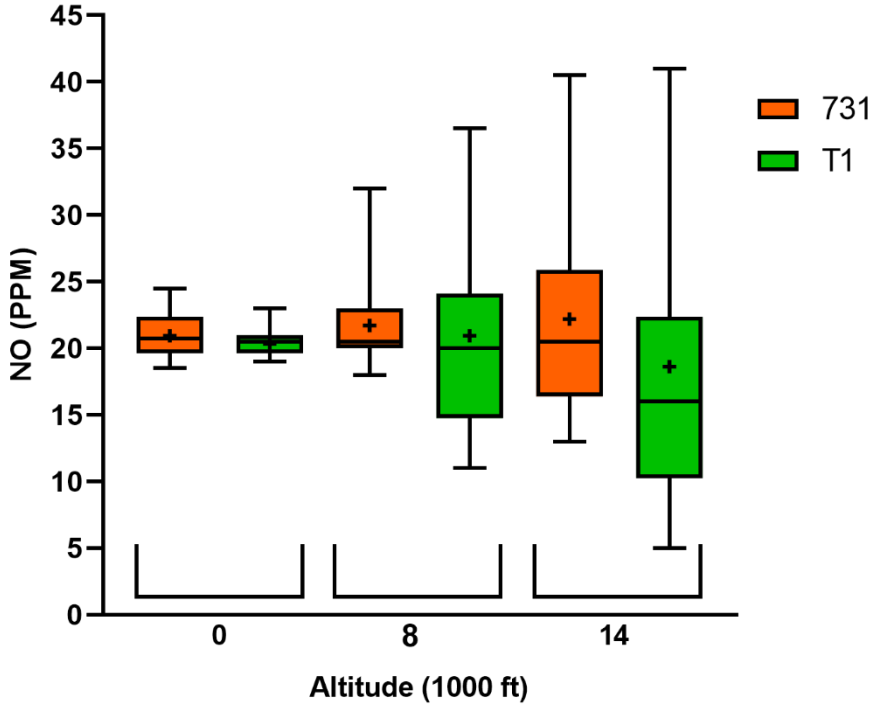

Figure 5 Measured NO concentrations across all ventilator and lung condition settings with each ventilator at ground level and at altitude with the Odic device. Box and whisker plots show minimum, maximum, IQR, mean (+), and median NO

Differences in mean delivered INO were not significant when comparing 8,000 feet (p=0.41) and 14,000 feet (p=0.86) to ground level, although variability increased with increasing altitude as

indicated by the wider range and IQR at altitude. Differences in mean NO comparing ventilators were not statistically significant at ground level (p=0.14), 8,000 feet (p=0.63), or 14,000 feet (p=0.18).

At set FiO_2 of 0.6, the reference device measured mean FiO_2 was 0.55 ± 0.02 at ground level, 0.55 ± 0.02 at 8,000 feet, and 0.54 ± 0.02 at 14,000 feet. Set FiO_2 compared to ground level was significantly different (p<0.001) but was not clinically important (data not shown). Compared to ground level the FiO_2 at 8,000 feet and 14,000 feet were not significantly different (p=0.37 and p=0.13 respectively) and were not clinically important. Measured FiO_2 remained at 0.21 with all testing conditions at set FiO_2 of 0.21. Measured NO_2 was <1ppm at all test conditions.

5.0. DISCUSSION

This study showed that INO can effectively be produced from ambient air without the use of storage cylinders, but the delivery devices and NO concentrations were affected by lower barometric pressure as a result of altitude exposure. To our knowledge, this is the first study to expose NO delivery devices to altitude. The traditional method for delivering INO involved large, pressurized cylinders containing NO gas and a delivery system. Currently there are three such systems cleared by the FDA for use in the U.S ($INOM_{ax}$ DS_{IR}, Mallinckrodt Pharmaceuticals, Madison, WI; NOxBOXi, Linde plc, Danbury, CT; AeroNOx 2.0, International Biomedical, Austin, TX). More recently a chemical-based INO delivery system (Genosyl DS, Vero Biotech, Atlanta, GA) gained FDA clearance. Unlike the cylinder-based INO systems, Genosyl is a smaller, portable delivery device that uses cartridges containing chemicals that are converted to NO[17].

Patients receiving INO therapy often require intra-hospital transport for diagnostics[18] or inter-hospital transport for escalation of care.[6, 19-24] The logistics and personnel requirements for

transporting these patients with cylinder-based INO delivery systems can be technically challenging but transporting safely without INO is often not optional or requires placing patients on extracorporeal membrane oxygenation, depending on disease severity. Many of these transports involved aeromedical transport via fixed-wing or rotor-wing aircraft.

To our knowledge, performance and accuracy of INO delivery devices at altitude have not been assessed. In our current study we assessed two novel INO technologies that create NO from ambient air at ground level and at altitudes that may be encountered during aeromedical transport. Due to different operating characteristics, ability to set INO, and monitoring capabilities, direct comparisons between the Lungfit and Odic devices could not be made. Lungfit had the ability to set INO directly and monitor delivered INO, NO_2, and FiO_2 whereas the Odic device did not. In order to set INO on the Odic device an external measuring device was required therefore comparison of set to target INO at ground level could not be made. Altitude affected INO concentration delivery and INO and FiO_2 measurement with Lungfit. Although mean differences at each altitude between ventilators were similar, the low INO range was lower with the T1 likely due to ventilator bias flow diluting the NO concentration whereas the upper range was similar (figure 3). T1 bias flow is utilized to facilitate triggering and is variable based on the ventilator settings. Differences in mean INO measured by Lungfit as compared to the reference measurement was statistically significant at ground level and 14,000 feet but were not clinically important (figure 4).

Altitude similarly affected INO concentrations with the Odic device. Despite no statistically different or clinically important mean INO values, the range was much wider than with the Odic device as compared to Lungfit and was largest at 14,000 feet. The large variations in INO at altitude was likely due to the lower barometric pressure effecting the internal pressure and flow

sensors which control the rate of NO delivery. The larger variations with the Odic device using the T1 as compared to the 731 was likely compounded due to the ventilator bias flow and increased delivered tidal volumes at altitude. Previous work from our group showed that for a set tidal volume there was a progressive increase in delivered tidal volume with increasing altitude with the T1[25]. Delivered tidal volume with the 731 was not affected by altitude.

FiO_2 was not significantly affected under any of the testing conditions, likely due to the lower NO setting used in the study and the use of room air as the NO carrying gas as opposed to cylinder-based NO which utilizes nitrogen as the carrying gas.

5.1 Limitations

This project was a bench study under controlled conditions. We cannot be certain that we would obtain the same results if used in a patient population under similar conditions. We used two ventilators, three respiratory rate/tidal volume combinations, two positive end expiratory pressure, FiO_2, lung compliance settings, and one INO concentration setting. Although we attempted to use a range of settings and conditions, these INO delivery devices may not perform similarly at different ventilator settings, lung compliance, INO settings or altitudes. Although not affected in this study, FiO_2 may be diminished at higher INO settings due to dilution of set FiO_2.

6.0. CONCLUSION

This is the first evaluation of technologies that create of an unlimited supply of INO from ambient air using ionization or high voltage spark name the method as long as there is available power supply, without the use of cylinders. This simplifies the current logistics and technical issues of providing INO during transport. The devices in this study were affected by lower barometric pressure at altitude, therefore constant monitoring of INO, NO2, and FiO_2 delivery is paramount to ensure accurate INO delivery and for patient safety.

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

%	percent
<	less than
=	equal to
>	greater than
±	plus/minus
$Ca(OH)_2$	calcium hydroxide
Cm	centimeter
COVID-19	coronavirus disease
FiO_2	inspired oxygen fraction
FDA	food and drug administration
H	height
INO	inhaled nitric oxide
IQR	interquartile range
Kg	kilogram
L	length
mmHg	millimeters of mercury
NO	nitric oxide
NO_2	nitrogen dioxide
O_2	oxygen
P	p value
ppm	parts per million
psig	pounds per square inch gauge
W	width