AirFLO2 Treatment for Hypoxia and/or Tachypnea in Patients with COVID-19

Research Protocol

Version 3 – 21SEP2020

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Study Summary

Title	**AirFIO2 Treatment for Hypoxia and/or Tachypnea in Patients with COVID-19**
Short Title	AirFLO2 with COVID-19
IRB Protocol number	Pro00105246
Study Center	Duke
Study Aims	Primary: Determine if use of the AirFLO2 device will reduce hypoxia in patients admitted to the hospital with COVID-19 infection. The aim of our study is to determine whether the use of the AirFLO2 device can improve hypoxia as measured by change between baseline P:F ratio and repeat P:F ratio between 1 to 6 hours after using the device. Secondary: Determine if use of the AirFLO2 device will a) Improve subjective symptoms related to dyspnea and comfort b) reduce risk of progression to high flow nasal cannula (HFNC), non-invasive ventilation (NIV), or invasive ventilation c) reduce intensive care unit (ICU) transfer risk d) reduce intubation risk e) reduce days of hospitalization f) increase survival to discharge
Number of Subjects	A targeted sample size of 46 subjects will be required, with an expected dropout rate of 10%, a total sample size of 50 subjects will be necessary to complete the study.
Inclusion Criteria	• Adults ≥18 years of age with confirmed COVID-19 infection • Patient must be able to complete consent and hold mask • Baseline room air oxygen saturation </=94% or patient with new supplemental oxygen requirement at presentation or patient on supplemental oxygen at baseline and requiring up-titration of oxygen setting Patient must have access to an internet-connected device
Exclusion Criteria	• Tracheostomy • History of pneumothorax or known bullous lung disease • Recent cataract surgery • Patient receiving NIV (Noninvasive Ventilation) or HFNC (High Flow Nasal Cannula) • Patient receiving mechanical ventilation • Active TB • Seizures

	• Delirium
Study Schedule	Following prescreening for eligibility, participants will provide consent. It is expected the primary consent will be performed at the in-patient bedside with a study coordinator to facilitate and answer questions. After consent, baseline clinical data will be recorded and study related parameters post consent will be collected

Parameter	1 hr pre	baseline	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	Every 24 hr	disch arge	withd raw	death
Sp02	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**
ABG	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**
P/F	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**
NC L/m	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**
HFNC			**Yes /No**	**Yes /No**	**Yes /No**		**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**
NIV			**Yes /No**	**Yes /No**	**Yes /No**		**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**
Ventilator free			**Yes /No**	**Yes /No**	**Yes /No**		**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**	**Yes /No**
Roth scale		**X**								**X**		
CV		**X**	**(betw**	**een**	**1 &**	**6hrs)**				**X**		
LCQ		**X**	**(betw**	**een**	**1 &**	**6hrs)**				**X**		
SOFA score		**X**										
Platelet		**X**										
Creatinine		**X**										
MAP		**X**										
Vasopressor tx		**X**										
Vasopressor dose		**X**										
Bilirubin		**X**										
Glasgow coma scale		**X**										
COVID-19 inflamm		**X**										

atory markers												
D-Dimer		**X**										
Ferritin		**X**										
CRP		**X**										
Creatine kinase		**X**										

Primary objective:
Determine if use of the AirFLO2 device will reduce hypoxia in patients admitted to the hospital with COVID-19 infection. The aim of our study is to determine whether the use of the AirFLO2 device can improve hypoxia as measured by change between baseline PaO2:FiO2 ratio and repeat PaO2:FiO2 ratio between 1 to 6 hours after using the device.

Secondary Objectives:
Determine if use of the AirFLO2 device will

g) Improve subjective symptoms related to dyspnea and comfort
h) reduce risk of progression to high flow nasal cannula (HFNC), non-invasive ventilation (NIV), or invasive ventilation
i) reduce intensive care unit (ICU) transfer risk
j) reduce intubation risk
k) reduce days of hospitalization
l) increase survival to discharge

Background and Significance:
The coronavirus disease 2019 (COVID-19) outbreak that started in Wuhan, China in December 2019 has now extended across the globe with > 1 million cases world-wide and 52,863 deaths as of April 1, 2020 (Johns Hopkins data). In North Carolina, 2016 cases have thus far been identified with 24 deaths and 184 admitted to hospitals in the state. These numbers are rapidly rising. In patients admitted with acute viral infection due to COVID-19, traditional methods to treat respiratory failure with non-invasive positive pressure ventilation are often being bypassed for fear of aerosolization of virus resulting in presumptive intubation for COVID-19 and a shortage of ventilators (PMID: 32212516). There is an urgent need to identify interventions which can retard or block progression to ARDS and reduce the need for invasive ventilation.

In adults with COVID-19 at risk for respiratory failure, the addition of conventional oxygen is recommended for O2 saturations </=94%. If hypoxemia progresses, the Surviving Sepsis Campaign recommends using high flow nasal cannula over conventional oxygen therapy and a high PEEP strategy in the management of ARDS (PMID:32222812).

Methods:
We propose an innovative device that can provide a low-cost, non-invasive, portable method to provide positive end expiratory pressure to improve oxygenation by decreasing respiratory muscle work of breathing, decreasing atelectasis, and increasing functional residual capacity (PMID: 23115688). Our novel device (**Figure 1**) features a mask, an adjustable pressure (5-20cm H_2O) outflow valve to meet individual patients' needs and an inflow valve to allow for free-flowing inhalation. If short of breath, the patient will apply the AirFlO2^{TM} mask over their nose and mouth, forming an air-tight seal. The patient can breathe through the outflow valve; the valve will create positive pressure within the mask according to the

adjustable pressure setting. The pressure provided by the mask helps to reduce atelectasis and recruit alveoli to reduce ventilation-perfusion mismatch. By leveraging well established technologies, we have created an accessible device with a low barrier for training and adoption. In addition, it can easily be decontaminated by removing the valve, wiping down and performing a simple at-home washing protocol with soap and water.

Design & Procedures:

We propose an unblinded, randomized, controlled trial for use of the AirFIO2 device for patients admitted to Duke Hospital with COVID-19 and tachypnea (RR >20 breaths/min) and/or hypoxia (Oxygen saturation </=94% on room air or requiring supplemental oxygen at baseline).

Inclusion criteria:

- Adults ≥18 years of age with confirmed COVID-19 infection
- Patient must be able to complete consent and hold mask
- Room air oxygen saturation </=94%, patient with new supplemental oxygen requirement, or patient on supplemental oxygen at baseline and requiring up-titration of oxygen setting
- Patient must have access to an internet-connected device

Exclusion criteria:

- Tracheostomy (current)
- History of pneumothorax or known bullous lung disease
- Recent cataract surgery
- Patient receiving NIV (Noninvasive Ventilation) or HFNC (High Flow Nasal Cannula)
- Patient receiving mechanical ventilation
- Active TB
- Seizures
- Delirium preventing patient from providing informed consent or self-applying mask

Study groups:

We will enroll n=50 patients with hypoxia (O2 saturation 90% or less on RA) and use clinical data including:

- Room air oxygen saturation
- PaO2/FiO2 ratio 1 hour prior to and then 1, 2, 4, 8, 12 and every 24hours after using AirFLO2.
    - If arterial blood gas result is not available for any time point then the P:F ratio will be imputed using the SpO2.
    - If the patient is on nasal cannula, the estimated FiO2 delivery will be calculated based on the oxygen flow rate in liters per minute (LPM).
- Transition to HFNC or NIV
- ICU transfer
- Ventilator free days
- Survival to discharge
- Cardiovascular (CV) Questionnaire, Cough questionnaire, and Roth score will be completed at baseline, and before discharge by all consented participants and the two questionniares repeated 1-6 hours after using the device for subjects randomized to receive the AirFLO2.

Additional clinical data pertaining to overall disease severity as measured by the Sequential Organ Function Assessment (SOFA) score and inflammatory markers related to COVID-19 infection will be collected:

- SOFA score
    - Platelet count

    - Creatinine
    - Mean arterial pressure
    - Vasopressor treatment and dose
    - Bilirubin
    - Glasgow Coma Score (extracted from clinical documentation)
- COVID-19 inflammatory markers
    - D-dimer
    - Ferritin
    - C reactive protein (CRP)
    - Creatine kinase
    - Lymphocyte percentage

These clinical data will be obtained via chart review. For each lab value, the collection time point nearest to study enrollment will be recorded.

Subject Recruitment and Compensation
Study participants will be recruited from the COVID-19 positive in-patient population at Duke Hospital. Subjects will not be compensated for their participation in the trial.
Patients will receive the AirFLO2 which will be collected and destroyed upon discharge from the hospital.

Consent Process
Consent will be obtained by a COVID Core CRC with the participant. No additional consent is required for analysis of clinical data.

Randomization
After consent, subjects will be randomized to the intervention or the control group via randomization software.

Intervention
Intervention subjects will receive the AirFLO2 device and training via video with reinforcement from the coordinator how to use and to self-apply it. Bedside nurses will also be given instructions, access to the study video and verbal training as well, so that they can answer simple questions for the patients.
Initially the CRC will hand device to the patient. Oxygen saturation at baseline will be recorded. The patient will set the PEEP at 5 on the mask, then hold the mask firmly against the face, take a full slow deep breath in, then exhale steadily out until out of breath. Record oxygen saturation. Wait 3-5 minutes then repeat maneuver with PEEP at 10. Record oxygen saturation. Repeat again with PEEP at a setting of 15, then again at 20. The highest O2 saturation achieved with the lowest PEEP is the PEEP setting to use. If oxygen saturation does not change or decreases, leave at PEEP of 5.

All other elements of patient care will be managed by the treating physician(s).

Control
Control subjects will receive usual care, managed by the treating physician(s).

Data Analysis & Statistical Considerations

Sample size calculation was performed, assuming a hypothesized increase in P:F ratio of +25 in the intervention group, no change in P:F ratio in the control group, and standard deviation of 30 in both groups. With these assumptions, for statistical power of 80%, a sample size of 46 subjects will be required. With an expected dropout rate of 10%, a sample size of 50 subjects will be necessary to complete the study.

Groups will be analyzed by intention to treat. Per-protocol analyses will also be performed.

Descriptive statistics will be reported for the overall subject population, and for the two groups.

The primary outcome of intra-subject change in P:F ratio before and after using the device will be analyzed with a paired student's t-test. The absolute change and percent change in P:F ratio will be compared between the control and intervention groups with student's t-tests. A multivariate analysis will be performed comparing the change in P:F ratio using linear regression, controlling for baseline P:F ratio, baseline overall disease severity (SOFA), and baseline COVID-19 related disease activity markers.

Secondary outcomes of risk for high flow nasal cannula, noninvasive ventilation, invasive ventilation will be compared between the intervention and control groups with the χ-squared test. Survival to discharge will be compared with the χ-squared test. Logistic regression analysis will be performed for each of these outcomes, controlling for baseline P:F ratio, baseline overall disease severity (SOFA), and baseline COVID-19 related disease activity markers.

Ventilator-free days will be compared using the student's t-test for bivariate analysis, and linear regression for multivariate analysis, controlling for baseline P:F ratio, baseline overall disease severity (SOFA), and baseline COVID-19 related disease activity markers.

Secondary outcomes of questionnaires related to subject symptoms before and after using the device will be analyzed for intra-subject change in questionnaire scores using paired student's t-tests. A multivariate analysis will be performed comparing the change in questionnaire scores using linear regression, controlling for baseline questionnaire score, baseline P:F ratio, baseline overall disease severity (SOFA), and baseline COVID-19 related disease activity markers.

Privacy, Data Storage & Confidentiality
Storage of clinical data is outlined in Pro00105246; subjects will be de-identified per Pro00105246.

Figure 1