# GO$^2$ PEEP Study: The Use of a Bidirectional Oxygenation Valve in the Management of Pulmonary Complications of COVID-19

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**Protocol Short Title: $GO^2$ PEEP COVID-19 Study**


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## Study Objective

The objective of this study is to determine the safety, feasibility and efficacy of a bidirectional oxygenation PEEP mouthpiece in COVID-19 patients requiring supplemental oxygen.

## Hypothesis:

We hypothesize that the bidirectional oxygenation PEEP mouthpiece is a safe and effective respiratory therapy and will improve oxygenation, reduce the need for intubation, and improve survival in patients with COVID-19 and pulmonary compromise.

## Background and Significance

The COVID-19 virus is a rapidly spreading threat which is already placing a strain on healthcare systems across the world. Both public and private entities at all levels are attempting to develop diagnostic and therapeutic tools to diagnosis, treat, and limit its global impact. The basis of treatment is supportive care. These supportive measures, especially in patients with advanced pulmonary complications, are limited. Furthermore, treatments with non-invasive ventilation such as BIPAP and CPAP are contraindicated due to aerosolization of the virus.

Severe cases of COVID-19 often mimic the typical course of Adult Respiratory Distress Syndrome (ARDS) and its predictable sequelae. These patients often require intubation and ventilator support in order to sustain adequate oxygenation. Once a COVID-19 patient is intubated, Positive End Expiratory Pressure (PEEP) is a mainstay of treatment and is used in order to improve lung function, treat underlying atelectasis, improve oxygenation, and improve survival. In fact, early clinical data as well as reports from front line physicians treating COVID-19 suggest that PEEP has been the MOST EFFECTIVE treatment modality. In many cases, PEEP has resulted in improved oxygenation and improved survival.

PEEP decreases the propensity for the alveoli to collapse by increasing the air pressure in the lungs. This residual pressure in the lungs at the end of exhalation decreases shunting and allows for more complete gas exchange and improved oxygenation. In patients, PEEP is one of the safest ways to increase PaO2 and is used on almost all modern ventilator settings.

We have developed a simple, comfortable, and straightforward mouthpiece with a bidirectional valve that effectively delivers PEEP with every breath (GO2 PEEP MOUTHPIECE, image 1). The GO2 device is a 60% TPS (thermoplastic styrene-internal component)/30% PP (polypropylene-rigid external component)/10% silicone (external valve component) mouthpiece.

**Image 1. GO2 PEEP MOUTHPIECE**

1a – PEEP Mouthpiece valve closed during expiration.

1b – PEEP Mouthpiece valve open during inhalation.

Initial testing using the bidirectional oxygenation mouthpiece on healthy subjects has been encouraging. Crouse et al. studied nine subjects during exercise and reported that the "Wearable Positive End-Expiratory Pressure Valve Increases Aerobic Capacity and Performance." [1] Subjects were assigned at random to the novel bidirectional oxygenation mouthpiece, a standard oxygenation mouthpiece, or nothing at all. Subjects wearing the bidirectional oxygenation mouthpiece showed an improvement in VO2 max of 6.1% compared to the standard mouthpiece and 4.0% compared to no mouthpiece. The endurance test showed an improvement of 6.5% compared to the standard mouthpiece and 6.0% compared to no mouthpiece. All results had p-values < 0.05. No adverse events were reported during the testing. Furthermore, the consumer version of this device, which is being used by athletes during vigorous exercise, has sold over 10,000 units to date with no reported adverse events.

Prior to the current pandemic, we planned to compare the GO2 PEEP MOUTHPIECE to incentive spirometry in cardiac surgical patients. We submitted our protocol for a randomized pilot study in postoperative heart surgery patients to the Emory IRB several months ago and it was recently approved. We were gearing up to start our clinical trial at Emory when the pandemic hit. Our study enrollment, like most clinical trials at Emory, is currently temporarily suspended.

We believe that early application of the GO2 PEEP MOUTHPIECE in non-intubated COVID-19 patients may improve outcomes and save lives. Furthermore, this device may allow for less strain on limited resources, especially ventilators. This PEEP mouthpiece could be employed in conjunction with oxygen therapy to improve oxygenation and avoid intubation.

## Requirements

We are seeking a rapid evaluation of the safety, efficacy, and feasibility of the device in patients with COVID-19 and pulmonary compromise. In order to test the performance of the device, we would identify a cohort of patients with a diagnosis of COVID-19. This cohort would be

characterized as those who require supportive care with supplemental oxygen but for whom ventilator support is not yet indicated or available. Once the patient is identified, consents to the study, and progresses to meet inclusion criteria based on oxygen requirements (>6L NC), then baseline measurements of oxygen saturation, respiratory rate, heart rate, blood pressure and blood gas results (when available) would be recorded. Furthermore, perceived effort of respiration would be measured including stridor, grunting, nasal flaring, or accessory muscle use. Patients would then be given the GO2 PEEP MOUTHPIECE for use in conjunction with oxygen therapy. Metrics would be recorded prior to initiation of therapy, 5, 10 and 15 minutes after GO2 PEEP therapy and 15 minutes after cessation of therapy.

## Safety

This design allows for rapid analysis in a safe manner. The brief and limited application of the GO2 PEEP MOUTHPIECE will limit patient exposure if the device is determined to be non-efficacious. The level of pressure generated by our device is 10 cm H20. This is safe when compared to the safe levels of PEEP generated by the ventilator, typically in the range of 5-10 cm/H2O. Furthermore, we are well below maximal PEEP levels of up to 30 cm/H2O, which is often required in severe cases or when positive pressure ventilation mode is required.

## Deliverables and Timing

This would serve as a limited safety and feasibility study to determine if further investigation is necessary. We estimate evaluation in 5 patients could be reached within one week. Thereafter, a more formal analysis could be performed as necessary.

## Research Design and Methods

*Design*
This study will utilize a single center, single arm, pilot study design.

*Target Study Population*
COVID-19 positive patients with pulmonary compromise requiring supplemental oxygen.

*Inclusion Criteria*

1) COVID-19 positive
2) Oxygen saturation $\leq$92%
3) Able to provide informed consent
4) Receiving oxygen $\geq$ 6L nasal cannula
5) Not currently requiring intubation

*Exclusion Criteria*

1) Unable or unwilling to provide informed consent

2) Cognitive impairment
3) Rapidly decompensating status requiring urgent or emergent higher level of care

**Study Endpoints**

*Primary Endpoint*

Improved oxygen saturation by pulse oximetry after treatment with the GO2 PEEP MOUTHPIECE.

The secondary endpoints include:

1. Respiratory rate
2. Heart rate
3. Blood pressure
4. Subjective work of breathing
5. Arterial blood gases (if available)

Both primary and secondary endpoints will be used to evaluate the safety as well as the efficacy of the GO2 PEEP MOUTHPIECE.

**Study Procedures**

After an eligible COVID-19 patient on supplemental oxygen has been identified, the research coordinator will contact patient via HIPPA compliant communication technology. The study will be verbally explained in detail with the patient. At time of verbal consent, instruction on use of the device will be performed by research team. If the patient progresses to meet the inclusion criteria and is enrolled in the trial, baseline metrics as above will be recorded. Patients will be provided a GO2 mouthpiece to be used in conjunction with and oxygen delivery face mask set to deliver an equivalent FIO2 to their previous therapy. **All patients will be instructed to breathe slowly and deeply through the mouthpiece for 15 minutes total.** Metrics for primary and secondary endpoints will be recorded before and after use of the mouthpiece (immediately prior to use and then at 5, 10 and 15 minutes of use and then 15 minutes after cessation of use).

Any decline in patient condition will result in immediate removal of the GO2 PEEP MOUTHPIECE and further appropriate care by the critical care team.

**Schedule of Assessments**

| Study Procedures | Prior to treatment with the mouthpiece | 5 mins after PEEP therapy | 10 mins after PEEP therapy | 15 mins after PEEP therapy | 15 minutes of after cessation of PEEP therapy |
|---|---|---|---|---|---|
| Consent | X | | | | |
| Oxygen saturation | X | X | X | X | X |
| Respiratory rate | X | X | X | X | X |
| Heart rate | X | X | X | X | X |
| Blood pressure | X | X | X | X | X |
| Work of breathing[1] | X | X | X | X | X |
| Arterial blood gases (if available) | X | | | X | |
| Adverse events | X | X | X | X | X |

1 presence of any of the following: stridor, grunting, nasal flaring, or accessory muscle use

**Statistical Analysis Plan**

As an emergent COVID-19 study, our goal is to examine the safety, feasibility and efficacy of adding the GO2 PEEP MOUTHPIECE to COVID-19 patients already on oxygen therapy.

We will assess safety, feasibility and efficacy by observation of changes in the primary and secondary endpoints. At the conclusion of the study, we will assess metrics before and after application of the GO2 PEEP MOUTHPIECE, but given the few number of patients and low power of this initial study, statistical significance is not the focus of the analysis. However, we plan to provide statistical summaries that would be useful in a possible subsequent study, such as overall efficacy of the device and patterns and trends in primary and secondary endpoints.

Summary statistics on oxygen saturation (primary endpoint) and respiratory rate, heart rate, blood pressure, subjective work of breathing, and arterial blood gases as available (secondary endpoints) will be reported at each measurement occasion for each patient.

**Sample Size and Accrual**

The sample size for this emergent study will be 5 patients admitted with laboratory proven COVID-19 and pulmonary compromise. This number will be sufficient to demonstrate the safety, feasibility and possible efficacy of the GO2 PEEP MOUTHPIECE in improving oxygenation.

## General Design Limitations

Possible pitfalls may include the variable course of COVID-19 infection that may affect the results of the analysis and the unknown nature and progression of this disease.

## Protection of Human Subjects

*Institutional Review Board (IRB) Review and Informed Consent*
Screening and enrollment will not begin until the Emory University IRB has approved the study protocol and informed consent form.

A physician investigator or study team designee(s) will obtain the informed consent via HIPPA compliant communication technology. A physician-investigator or study team member designee(s) will begin the verbal informed consent process with the subject with a diagnosis of COVID-19 infection. The nature of this infection precludes the research team from obtaining written consent before admission or in-person once the patient is admitted due to possible COVID-19 exposure and the handling of contaminated documents/pens. According to Emory critical care physicians, research staff are not permitted to enter COVID + rooms.

All COVID-19 positive patients will be screened for potential participation in the study. For the patients located in a telemetry unit or medical floor, a member of the research team will contact the patient remotely via phone (landline or via HIPAA compliant telehealth) to obtain verbal consent and give instruction on use of the device. Should the patient already be located in the ICU, and is unable to use the phone, the investigator will obtain consent via eICU. The patient must verbalize understanding of the consent before he/she consents. The subject's verbal consent will be obtained before any research related procedures are performed.

Once the patient meets inclusion criteria and is enrolled in the study, the investigator is responsible for getting the mouthpiece to the patient via healthcare staff. During the actual 15 minutes that the patient is using the GO2 PEEP MOUTHPIECE, the investigator will be able to monitor and communicate with the patient via eICU. The patient will also be able to communicate/view the investigator as well. The investigator will be able to collect all data remotely during this period.

*Subject Confidentiality*
Subject confidentiality will be guaranteed by storing all data collected in a password-protected database with no associated PHI or patient identifier information included. Patients in this database will only be identified via a unique study ID number. This study ID number will link the electronic data set of each patient to their PHI that will be stored separately in the research study binder.

*Subject Safety*

Subject safety is of utmost importance throughout this study. If at any time there is a worsening of the patient's condition, the GO-2 PEEP MOUTHPIECE will be immediately removed and standard therapy will be directed by the critical care medicine team.

*Adverse Events*
Patients will be assessed for the following adverse events:

- Decreased oxygen saturation
- Increased respiratory rate
- Increased heart rate
- Low blood pressure
- Increased work of breathing
- Worsening arterial blood gases (if available)
- Patient unable to tolerate the mouthpiece

All serious adverse events will be assessed and reported per the Emory IRB Policies and Procedures.

## Data Collection

Study data will be collected from the patient's electronic medical records. All information will be entered in a de-identified fashion into a password protected Microsoft Excel spreadsheet created for the study. All study data will be coded using indirect identifiers consisting of a unique numeric study ID code linked to each study participant's name to enable verification of study data against source data, as needed.

Study data, including Protected Health Information (PHI), will be obtained with the patient's direct authorization through the consent form in accordance with HIPAA policy. PHI will be obtained via patient medical records as noted above. Permission for use or evaluation of PHI will be limited to the principal investigator, and research study staff. The PHI will be a part of the clinic record and patient study binder. The binders will be kept in a secure location when not being used by the research staff. The PHI collected will be used by the PI and research staff for study tracking purposes, to link and confirm study data with the information located in the patient's clinical record, and if patient safety necessitates, to communicate relevant findings with the patient's healthcare providers. The PHI will be destroyed using the institution's official recycling system once the study is completed. The PI and staff will maintain the records of the study including all correspondence, the study protocol with any/all amendments, all correspondence with and approval from the Emory IRB, and signed informed consent forms in the Regulatory Binder. All these materials, along with individual patient files, data collection forms and source data will be stored and maintained, along with a record of the location of storage, for up to 6 years after the completion of the study. Records will be destroyed using the official institutional recycling system.

## Data Management

Upon study completion the final data set will be provided to Sponsor and stored within the secure server in the Houston Plastic Craniofacial and Sinus Surgery office (9230 Katy Freeway, Houston, TX 77055). All non-identifiable patient data collected will be stored on a password encrypted Microsoft Excel document on the same server. No information will be transmitted electronically outside of the server nor will any data be stored off of the server on any portable type media storage device. All study participant PHI and personal contact information will be securely stored on an encrypted, password-protected drive or device or in a study binder at Emory Saint Joseph's research office.

### Data Safety Monitoring Plan

With this very small, single-center, open label trial, there will not be a DSMB. However, the Principal Investigator will personally monitor each patient's use of the device. Therefore, there will be one-on-one physician monitoring, assessment and documentation for adverse effects and intolerance of device usage. If the subject experiences an adverse event as a result of the device, and the investigator staff believe it is in the best interest to discontinue study participation, the patient will be withdrawn. Any unanticipated or unforeseen complications will be reported by the investigator (or authorized designee) to the IRB.

## Facilities

The study will take place at Emory University Hospital, The Emory Clinic and Emory Saint Joseph's Hospital.

## Funding Source

There will not be funding for this study. GO-2 PEEP MOUTHPIECEs will be provided at no cost by PEEP Medical, LLC.

**Appendix A**

**Instructions for Patients**

Thank you for participating in the GO-2 PEEP MOUTHPIECE research study.

1. To use mouth piece, place the device inside the mouth. Allow your lips to surround the lip flange.

2. Breathe in slowly and deeply in a steady manner. Exhale through the device as completely and forcibly as possible.

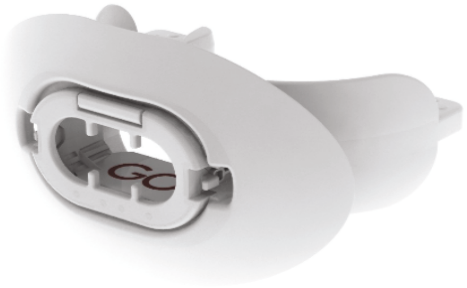
3. B**reathe slowly and deeply through the mouthpiece for 15 minutes total as tolerated.**

4. The device can then be removed.

If there are any issues or problems contact Dr. Jeffery Miller or the research coordinator at 678-843-6092 as soon as possible.

**GO2 PEEP MOUTHPIECE**


1a – PEEP Mouthpiece valve closed during expiration.




1b – PEEP Mouthpiece valve open during inhalation.

**References.**

1. Crouse SF, Lytle JR, Martin SE, Green JS, Moreno M, McCulloch P, Boutros S, Benton W, Lambert BS. Wearable positive end-expiratory pressure valve increases aerobic capacity and performance. Poster presentation. Applied Exercise Science Lab. 2018.