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Title: A Novel Inhalation Mask System to Deliver High Concentrations of Nitric Oxide Gas in Spontaneously Breathing Subjects

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Author Questionnaire

1. **Microscopy**: Does your protocol require the use of a dissecting or stereomicroscope for performing a complex dissection, microinjection technique, or similar? **N**

2. **Software:** Does the part of your protocol being filmed demonstrate software usage? **N**

3. **Interview statements:** Considering the Covid-19-imposed mask-wearing and social distancing recommendations, which interview statement filming option is the most appropriate for your group? **Please select one**.

   ☒ Interviewees wear masks until the videographer steps away (≥6 ft/2 m) and begins filming. The interviewee then removes the mask for line delivery only. When the shot is acquired, the interviewee puts the mask back on. Statements can be filmed outside if weather permits.

4. **Filming location:** Will the filming need to take place in multiple locations (greater than walking distance)? **N**

Protocol Length
Number of Shots: **23**

Introduction

1. Introductory Interview Statements

REQUIRED:

1.1. **Raffaele Di Fenza**: Inhaled nitric oxide can improve oxygenation in patient with severe hypoxia. At high concentrations, NO displays broad antimicrobial effects. Several trials are testing the efficacy of NO against COVID-19 **[1]**

1.1.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

REQUIRED:

1.2. **Lisa Traeger**: To date, no device is available to administer inhaled NO at concentrations higher than 80 parts per million without the need for dedicated, heavy, and costly equipment **[1]**.

1.2.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

OPTIONAL:

1.3. **Lisa Traeger**: This device will allow high dose NO gas delivery outside of the hospital. Patients with lung colonization from multiresistant bacteria, like patients with cystic fibrosis, might benefit from this treatment from home **[1]**.

1.3.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

Introduction of Demonstrator on Camera

1.4. **Raffaele Di Fenza**: Demonstrating the procedure with Lisa Traeger will be Caio C. A. Morais, a PhD researcher from my laboratory **[1][2]**.

1.4.1. INTERVIEW: Author saying the above

1.4.2. The named demonstrator(s) looks up from workbench or desk or microscope and acknowledges the camera

Ethics Title Card

1.5. Procedures involving human subjects have been approved by the Institutional Review Board (IRB) at Massachusetts General Hospital.

Protocol

2. Patient Interface and Y-Piece Preparation

2.1. To set up the patient interface, connect the built-in elbow port of a snug-fitting, standard, non-invasive ventilation face mask of the appropriate size for the Subject to a high-efficiency particulate air filter through the 22-millimeter outer diameter-15-millimeter inner diameter connector **[1-TXT]**.

2.1.1. WIDE: Talent connecting port to filter **TEXT: e.g., highly hydrophobic bacterial/viral filter, HEPA class 13**

2.2. To facilitate the Subject's movement and reduce the risk of disconnection, add a flexible 5- to 6.5-centimeter 15-millimeter outer diameter by 22-millimeter outer diameter-15-milimeter inner diameter patient connector for an endotracheal or tracheostomy tube between the mask interface and the HEPA filter **[1]**.

2.2.1. Talent adding tube between mask interface and filter

2.3. To build a Y-piece, use two, opposite-sense, low-resistance, 22-millimeter male-female, one-way valves to create expiratory and inspiratory limbs on the two distal ends of a 22-millimeter to 22-millimeter and 15-French Y-piece connector with 7.6-millimeter ports **[1]**.

2.3.1. Talent adding valve(s) to limb(s)

2.4. Position the one-way valve connector of the expiratory limb with the arrow pointing downward to allow a proximal-to-distal flow only **[1]** and position the connector for the inspiratory limb with the arrow pointing upward to allow a distal-to-proximal flow only **[2]**.

2.4.1. Connector being positioned with arrow pointing down *Videographer: Difficult step*

2.4.2. Connector being positioned with arrow pointing up *Videographer: Difficult step*

2.5. Then connect the proximal end of the Y-piece to the HEPA filter **[1]** and use standard, kink-resistant, vinyl gas tubing with universal adaptors at both ends to connect the oxygen source to the inspiratory limb **[2-TXT]**.

2.5.1. Talent connecting Y-piece of filter *Videographer: Difficult step*

2.5.2. Talent connecting tubing to oxygen source *Videographer: Difficult step* **TEXT:**

Select tubing based on distance between subject and gas source

3. Scavenging Chamber Preparation

3.1. To prepare the scavenging chamber, connect a 22- x 22-millimeter, flexible, silicon rubber connector adapter to the proximal end of a scavenger chamber containing 100 grams of calcium hydroxide **[1-TXT]**.

3.1.1. WIDE: Talent connecting adapter to chamber **TEXT: chamber internal diameter: 60 mm; internal length: 53 mm; volume: 150 mL**

3.2. Attach a flexible, 5- to 6.5-centimeter 15-millimeter outer diameter by 22-millimeter outer diameter-15-millimeter inner diameter corrugated tube to the silicon rubber adapter **[1]** and connect another 22- x 22-millimeter flexible, silicon rubber connector adapter to the distal end of the scavenger **[2]**.

3.2.1. Talent connecting tube to adapter
3.2.2. Talent connecting tube to scavenger

3.3. Then use a 15-22-millimeter two-step adapter to attach the scavenging chamber and tubing assembly to the inspiratory limb of the Y-piece **[1]**.

3.3.1. Talent connecting chamber and Y-piece

4. Nitric Oxide (NO) Reservoir and Medical Air Supply System Preparation

4.1. To prepare the nitric oxide reservoir system, connect a 3-liter, latex-free breathing reservoir bag and a 90-degree ventilator elbow connector without ports **[1]** and connect the other end of the elbow to the central opening of the aerosol T-piece **[2]**.

4.1.1. WIDE: Talent connecting bag and connector
4.1.2. Talent connecting elbow to T-piece

4.2. Advance the T-piece into the distal end of the scavenging chamber until it tightly fits the silicon rubber connector **[1]** and attach two, consecutive 15-millimeter outer diameter by 22-millimeter outer diameter-15-millimeter inner diameter connectors with 7.6-millimeter sampling ports and flip-top caps **[2]**.

4.2.1. Piece being advanced
4.2.2. Talent attaching connector(s)

4.3. Attach another one-way inspiratory valve with the arrow pointing up at the distal end of the nitric oxide-air supply system **[1]** and connect a 15-22-millimeter two-step

adapter to the proximal end of the system **[2]**.

4.3.1. Talent attaching valve
4.3.2. Talent connecting adapter

4.4. At the proximal end of the nitric oxide-air supply system, connect a 15-22-millimeter two-step adapter **[1]** and connect the proximal two-step adapter to the remaining free inlet of the green T-piece from the nitric oxide reservoir system **[2]**.

4.4.1. Talent connecting adapter
4.4.2. Talent connect adapter

4.5. To attach the air and nitric oxide gas flow lines, use standard, kink-resistant, star-lumen vinyl oxygen gas tubing to connect the medical air flow to the most distal gas inlet port **[1]** and connect the nitric oxide gas flow from an 800-parts per million medical-grade nitric oxide tank to the next port downstream **[2]**.

4.5.1. Talent connecting air to inlet port
4.5.2. Talent connecting tank to downstream port

5. NO Delivery in Spontaneously Breathing Subjects

5.1. To administer nitric oxide to a spontaneously breathing Subject, set the air, oxygen, and nitric oxide gas flow according to the Table **[1]** and position the tight-fitting mask onto the Subject's face, similar to a non-invasive ventilation interface setup **[2]**.

5.1.1. LAB MEDIA: Table 1
5.1.2. WIDE: Talent positioning mask onto Subject's face *Videographer: Difficult step*

5.2. Then start the inhalation session for the desired duration **[1]**. The nitric oxygen and nitrogen dioxide concentrations can be traced to assess the stability of the gas delivery during the treatment **[2]**.

5.2.1. Talent starting inhalation session
5.2.2. LAB MEDIA: Figure 2

Protocol Script Questions

A. Which steps from the protocol are the most important for viewers to see? Please list 4 to 6 individual steps.
n/a

B. What is the single most difficult aspect of this procedure and what do you do to ensure success? Please list 1 or 2 individual steps from the script above.
2.5./4.5. (connecting the tubing systems in the correct order)
5.1. (communicate the possible discomfort related to the interface to the patient)

Results

6. Results: Representative NO and NO_2 Concentration Tracings During a 160 ppm NO Inhalation in a Healthy Healthcare Worker

6.1. A 33-year-old respiratory therapist working at the ICU at Mass General Hospital during the surge of ICU admission for COVID-19 volunteered to receive nitric oxide as part of the trial involving healthcare workers **[1]**.

6.1.1. LAB MEDIA: Figure 2

6.2. The resulting nitric oxide concentration was 160 parts per million at a total gas flow rate of 19.5 liters/minute as measured by three standard 15 liter/minute flowmeters **[1]** and remained stable throughout the entire period of inhalation **[2]**.

6.2.1. LAB MEDIA: Figure 2 *Video Editor: please emphasize red data line*
6.2.2. LAB MEDIA: Figure 2

6.3. Nitrogen dioxide peaked at 0.77 parts per million and was therefore safely below the recommended toxicity threshold **[1]**.

6.3.1. LAB MEDIA: Figure 2 *Video Editor: please emphasize black data line*

Conclusion

7. Conclusion Interview Statements

7.1. **Lisa Traeger**: The possibility of safely delivering high concentration, inhaled nitric oxide opens the field for the application of this therapy to other diseases in which NO can be an effective treatment **[1]**.

7.1.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera