Study Protocol

Title:

"The Effect of Asymmetrical vs. Symmetrical High Flow Nasal Cannula on the Work of Breathing: A randomised cross-over study."

NCT number: not yet assigned

Unique Protocol ID: 16171/09.04.2024

Date: 09.04.2024

INTRODUCTION - CURRENT KNOWLEDGE

Nasal High Flow (NHF) therapy has become increasingly popular as a non-invasive method of respiratory support, used alongside conventional oxygen therapy (COT) and noninvasive ventilation (NIV) in the management of acute respiratory failure. In 2020, the European Society of Intensive Care Medicine issued a strong recommendation for NHF over COT in patients with respiratory failure type I (RFI). Further, in 2022, the European Respiratory Society (ERS) recommended NHF over NIV for patients with RF-I. NHF also received a conditional recommendation for use in COPD patients with acute hypercapnic respiratory failure (RF-II) after a short trial of NIV, particularly for those who cannot tolerate NIV.

The traditional NHF interface design is symmetrical, intended to distribute airflow evenly between both nostrils. This design has been effective in providing respiratory support by generating dynamic Positive End-Expiratory Pressure (PEEP), decreasing the anatomical dead space, improving oxygenation by providing high and stable inspiratory oxygen fraction, enhancing secretion clearance through the provision of reliable humidification and reducing airway resistance. These benefits are well-documented in various studies, highlighting NHF's role in decreasing the work of breathing and improving overall respiratory mechanics. Work of breathing is a major contributor to respiratory distress in acute respiratory failure, and elevated work of breathing can lead to respiratory muscle fatigue, increased metabolic demand, and worsened oxygenation.

Recent developments have introduced a novel asymmetrical NHF interface, designed to optimize key mechanisms of NHF. Simulation studies of this new interface have shown promising results, indicating that the asymmetrical design increases PEEP and offers improved clearance of dead space compared to its symmetrical counterpart. These findings suggest that the asymmetrical interface may further enhance the efficiency of NHF therapy, potentially leading to greater reductions in the work of breathing and more effective respiratory support.

Pressure-Time Product (PTP) is widely regarded as one of the most accurate surrogates for quantifying the metabolic and mechanical work of breathing. Unlike traditional markers such as respiratory rate or tidal volume, which may not fully capture the respiratory load, PTP integrates pressure, volume, and timing, providing a comprehensive assessment of the total effort exerted by respiratory muscles. By using PTP in this study, we aim to capture subtle differences in the work of breathing between the two NHF interfaces.

Sassoon et al. have previously shown that the metabolic work and the oxygen consumption of the respiratory muscles can be estimated by the pressure-time product per minute, which is calculated as follows: $PTP = \int Pes + Vt / Ccw * dt * RR$, where PTP represents the pressure-time product, quantifying the total pressure generated by the respiratory muscles over time. Pes (esophageal pressure) reflects the pressure drop within the pleura from the respiratory muscles' contraction. Vt (tidal volume) is the amount of air moved in the lungs during a normal breath. Ccw (compliance of the chest wall) measures the elasticity of the chest wall, and in this context, is defined as 5% of the predicted vital capacity per cmH_2O. RR (respiratory rate) is the number of breaths per minute, and dt refers to the inspiratory time.

AIM

Despite the aforementioned encouraging simulation results, there is a lack of empirical data comparing the physiological effects of symmetrical versus asymmetrical NHF interfaces in real-world settings. This study using precise measurements of esophageal pressure, tidal volume, and respiratory flow to quantify the work of breathing, aims to fill this gap by directly assessing the impact of these two interface designs on the work of breathing in patients recovered from acute respiratory disease.

HYPOTHESIS

We hypothesize that the asymmetrical nasal cannula for high flow oxygen therapy will reduce the metabolic work of the respiratory muscles more effectively than the symmetrical interface in the individuals.

SUBJECTS

We will enroll 30 individuals who will be discharged from the Department of Respiratory Medicine of the General University Hospital of Larissa after hospitalization for acute respiratory disease, who meet the inclusion criteria outlined in the "Methods" section below. This sample size has been chosen arbitrarily due to the absence of prior studies that would support a formal sample size calculation.

METHODS

Study Design: Randomized, crossover design.

Inclusion and Exclusion Criteria:

Inclusion: age ≥18 years old and clinical stability (absence of symptoms and signs of respiratory failure, $SpO_2 \geq 95\%$ at FiO_2 0.21).

Exclusion: pregnancy, $SpO_2 < 94\%$ at FiO_2 0.21, neuromuscular disease and contraindications to esophageal pressure monitoring (e.g., uncontrolled coagulopathy, esophageal disease, nasal trauma, allergy to local lidocaine).

Interventions

Esophageal Balloon Catheter: A lubricated 10 French catheter will be inserted through the nostril, advanced to 40-45 cm into the esophagus, and inflated with 1 ml of air. Proper placement will be confirmed by performing an occlusion test. During a brief inspiratory hold, the patient will be instructed to perform an occlusion maneuver (i.e., a gentle effort against a closed airway). The esophageal and airway pressure signals should move in parallel during the occlusion. This confirms that the balloon is properly positioned and accurately reflects pleural pressure. Additionally, cardiac oscillations and negative deflections on the esophageal pressure waveform during inspiration will be observed for further confirmation.

NHF Oxygen: Administered at 50 L/min and 37°C. The fraction of inspired oxygen will be 21% for healthy individuals and adjusted for a target oxygen saturation of at least 92.

Interface Comparison: Participants will receive both the asymmetrical interface (Optiflow Duet) and the conventional symmetrical interface. Each interface will be applied for 15 minutes with a 3-minute washout period between sessions to prevent residual effects.

Data Collection

Pre-Randomization: Collect demographic data (age, sex) and baseline clinical information (body mass index, comorbidities, smoking status).

During Intervention:

Measurements: Esophageal pressure (Pes) with an esophageal balloon catheter, tidal volume (VT) with an impedance device (ExSpiron, Respiratory Motion Inc., Waltham,MA) device, and flow with a pneumotachograph. Collect five repeat measurements at baseline and throughout both interventions.

Parameters: Esophageal pressure, flow, tidal volume, inspiratory and expiratory time, respiratory rate, arterial blood gases, end-expiratory pCO_2.

Vital Signs: Monitor throughout both interventions.

Analysis

Flow-Time and Pressure-Time Graphs:

Flow-Time Graphs: Record air flow during inspiration and expiration using the pneumotachograph. Identify the onset and end of inspiration and measure the duration of inspiration.

Pressure-Time Graphs: Record esophageal pressure (Pes). Integrate the area under the pressure-time curve during inspiration to quantify the work done by respiratory muscles.

Static Recoil Pressure Calculation:

Compliance of the Chest Wall (Ccw): Estimated as 5% of the predicted vital capacity (VC). The elastance (Ecw) is the reciprocal of Ccw.

Static Recoil Pressure (Pcw): Calculated as: Pcw = Ecw × VT

Example Calculation: VC = 5000 mL, Ccw = 5% of VC = 250 mL/cmH2O, Ecw = 1 / Ccw = 0.004 cmH2O/mL, VT = 500 mL. Thus, Pcw = 0.005 cmH2O/mL × 500 mL = 2 cmH2O

Pressure-Time Product (PTP) Calculation: *Formula:* $PTP=(\int(Pes-PEEPi)\,dt) \times RR$

Procedure: Subtract static recoil pressure (Pcw) from Pes. Adjust for intrinsic PEEP (PEEPi) determined from end-expiration esophageal pressure recordings. Multiply the area under the pressure-time curve by the respiratory rate (RR).

Statistical Analysis: *Software:* GraphPad Prism, SPSS. *Descriptive Statistics:* Means, standard deviations, medians, interquartile ranges. *Comparisons:* Paired t-tests, Wilcoxon signed-rank tests, repeated-measures ANOVA. *Adjustments:* Bonferroni correction for multiple comparisons. *Significance:* $p < 0.05$.

Interobserver Reliability: *Graph Analysis:* Two independent investigators will use Image J to digitize and analyze flow-time and pressure-time graphs. Disagreements will be resolved by a third senior investigator.

EXPECTED RESULTS:

We expect that the asymmetrical high flow nasal cannula will result in a greater reduction in the PTP, indicating a lower work of breathing compared to the symmetrical interface. Additionally, we expect to observe a reduction in respiratory rate and hemodynamics parameters with the asymmetrical interface, alongside an increase in expiratory time.

IMPLICATIONS:

The findings from this study could influence clinical practice by providing evidence for the use of the asymmetrical NHF cannula as a more efficient option for reducing the work of breathing compared to the conventional symmetrical interface. If the asymmetrical interface demonstrates superiority, it could lead to its wider adoption in respiratory care. Clinically, this may result in improved patient comfort, reduced respiratory effort, and potentially shorter durations of NHF therapy, which could help minimize the need for escalation to more invasive respiratory support, such as mechanical ventilation. The implications extend beyond patient care, as improved NHF efficiency could also reduce healthcare costs by shortening hospital stays and decreasing the resources required for respiratory support. Moreover, this study could pave the way for future research exploring the benefits of asymmetrical interfaces in other patient populations or conditions. If proven successful, the asymmetrical design may set a new standard for NHF therapy, potentially influencing clinical guidelines and furthering technological innovation in respiratory support. Finally, should the asymmetrical interface prove effective, future studies could explore its potential benefits in patients with RF-II, where reducing the work of breathing and enhancing carbon dioxide clearance are critical therapeutic goals.

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