Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

Research Protocol

Effect of different types of respiratory support [helmet continuous positive airway pressure (helmet CPAP) vs. high-flow nasal cannula oxygen (HFNC) vs. helmet CPAP plus HFNC] on the work of breathing in critically ill patients with acute respiratory failure: a physiological, interventional, randomized, crossover study

Research proposed by the Anesthesia and Intensive Care Unit 1 of Santa Chiara Hospital, Trento.

Principal investigators:
Dr Sergio Lassola
Dr Sara Miori
Dr Andrea Sanna
Dr Silvia De Rosa
Prof. Giacomo Bellani

Statistical contacts
Dr Sara Miori
Dr Riccardo Pertile

26 April 2023

Title

Effect of different types of non-invasive respiratory support [helmet continuous positive airway pressure (helmet CPAP) vs. high-flow nasal cannula oxygen (HFNC) vs. helmet CPAP plus HFNC] on the work of breathing in critically ill patients with acute respiratory failure: a physiological, interventional, randomized, crossover study.

Study setting

Patients diagnosed with acute hypoxemic respiratory failure, admitted to the Intensive Care Unit (Anesthesia and Intensive Care 1) and with a clinical indication for non-invasive respiratory support.

Background

Acute hypoxemic respiratory failure is defined by PaO_2 values < 60 mmHg on room air. The initial management of acute hypoxemic respiratory failure (AHRF) is controversial (1). Non-invasive ventilation may help avoid endotracheal intubation; however, maintaining spontaneous breathing may cause lung injury due to the patient's high inspiratory effort (patient self-inflicted lung injury - P-SILI), and endotracheal intubation may be delayed in patients who fail a trial of non-invasive ventilation (1, 2).

Recent research has focused on identifying indices that can recognize inspiratory effort harmful to the patient, in order to reduce the risk of P-SILI during a trial of non-invasive ventilation and limit trial failure (3). This would allow early identification of the need for endotracheal intubation. High-flow nasal cannula oxygen (HFNC) is an emerging technique designed to deliver oxygen at high flow rates, with a known and constant fraction of inspired oxygen and optimal temperature and humidification. It is well tolerated and easy to use in all clinical settings. Physiologically, HFNC reduces anatomical dead space and the work of breathing and generates modest positive end-expiratory pressure. Clinically, HFNC effectively reduces dyspnea and improves oxygenation (4) [Figure 1].

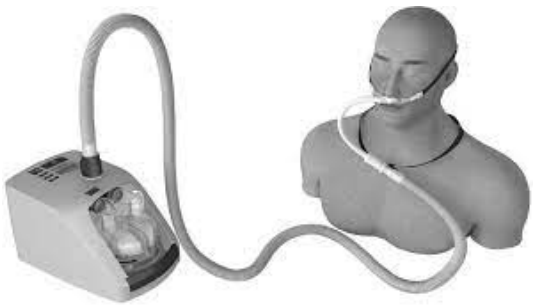

Figure 1. HFNC

CPAP (continuous positive airway pressure) consists of delivering positive pressure continuously and non-invasively throughout the respiratory cycle. CPAP can be delivered through a mask (face or nasal) or a helmet [Figure 2]. CPAP increases end-expiratory volume, optimizing ventilation/perfusion mismatch and therefore oxygenation; it reduces the work of breathing and ensures delivery of a constant O_2 fraction (5).

Figure 2. Helmet CPAP

Recently, the effectiveness of combining a helmet with high-flow nasal cannula oxygen (HFNC) has been evaluated in healthy volunteers and patients as a further possible strategy for non-invasive respiratory support (6, 7).

Research hypothesis:

Different modes of non-invasive respiratory support (HFNC, helmet CPAP, helmet CPAP plus HFNC) may have different effects on the work of breathing.

Study objective:

Primary objective: to evaluate the effect of different types of non-invasive respiratory support (HFNC, helmet CPAP, helmet CPAP plus HFNC) on inspiratory effort estimated using parameters derived from esophageal pressure.

Secondary objectives:
1) to evaluate the impact on gas exchange in terms of the PaO_2/FiO_2 ratio and $PaCO_2$;
2) to evaluate diaphragmatic function and intercostal and expiratory muscle function by ultrasound;

3) to evaluate the effect of different types of non-invasive respiratory support on fluid and electrolyte balance and cardiovascular function.

Study design

Physiological, single-center, prospective, interventional, crossover, non-profit clinical study (Anesthesia and Intensive Care Unit 1, Santa Chiara Hospital, Trento).

Population and inclusion criteria

The study population will include patients aged over 18 years admitted to Anesthesia and Intensive Care Unit 1 of Santa Chiara Hospital, Trento, with a diagnosis of acute hypoxemic respiratory failure and an indication for non-invasive respiratory support.

The inclusion criteria are therefore:

- Need for supplemental oxygen therapy to achieve PaO_2 > 60 mmHg or SpO_2 > 90%;
- Respiratory rate > 25 breaths/min;
- Presence of infiltrates on chest X-ray;
- Acute onset: within 7 days of hospital admission;
- Patients aged 18 years or older;
- Prior informed consent from the patient or legal representative;
- Presence of a Nutrivent nasogastric tube for esophageal pressure monitoring in accordance with clinical practice.

Exclusion criteria

- Pregnancy and/or breastfeeding
- COPD
- Acute cardiogenic pulmonary edema
- Massive pulmonary embolism
- Neuromuscular disease
- Refusal to provide informed consent

Protocol

Eligible patients enrolled in the study will be ventilated in randomized crossover order using the three different modes of non-invasive support (HFNC, helmet CPAP, helmet CPAP plus HFNC). Each phase will last 30 minutes with no washout interval. There are six possible sequences. Randomization will be computerized using the RAND function in Microsoft Excel.

In all critically ill patients with acute hypoxemic respiratory failure, the following monitoring will be applied in accordance with clinical practice: electrodes for continuous electrocardiographic monitoring (heart rate and ECG); pulse oximetry (SpO_2); arterial catheter for invasive monitoring of systemic arterial blood pressure; urinary catheter for urine-output monitoring; and central venous catheter (CVC) for drug infusions and central venous pressure monitoring.

The main demographic and clinical characteristics will be collected for each patient.

At baseline and 30 minutes after application of each respiratory support allocated by randomization in crossover order, the following parameters will be collected:

- PaO_2, $PaCO_2$, pH, PvO_2, $PvCO_2$, $ScvO_2$, venous admixture, lactate and electrolytes by arterial and venous blood-gas analysis performed when changing non-invasive ventilatory support, in accordance with clinical practice;
- Hemodynamic and respiratory parameters (SBP-DBP, heart rate, CVP, SpO_2, respiratory rate).
- Tidal volume and minute ventilation
- Borg scale

Work-of-breathing parameters collected by esophageal pressure measurement: ΔPes, Pdi, PTPes, PTPdi, Gilbert index, end-expiratory and end-inspiratory transpulmonary pressure, transpulmonary driving pressure, and ΔPaw during helmet CPAP.

- Diaphragm ultrasound (inspiratory and expiratory diaphragm thickness, diaphragmatic excursion) and intercostal ultrasound (any activation of the intercostal muscles).

At baseline and 30 minutes after application of non-invasive respiratory support, urine will also be collected, after clamping the urinary catheter, to evaluate the effect of the various techniques on fluid and electrolyte balance (fluid balance, % fluid overload) and urine output.

HFNC
High-flow nasal cannula oxygen will be delivered using AIRVO 2 (Fisher & Paykel) at a flow rate of 40 L/min and at the minimum FiO_2 required to achieve oxygen saturation > 90%.

Helmet CPAP
CPAP (continuous positive airway pressure) will be delivered through a helmet with an oxygen flow of 80 L/min and an independent-flow PEEP valve set at 7.5 cmH_2O.

HFNC combined with helmet CPAP
High-flow nasal cannula oxygen will be delivered using AIRVO 2 (Fisher & Paykel) at a flow rate of 40 L/min and at the minimum FiO_2 required to achieve oxygen saturation > 90%. A CPAP helmet will then be fitted

(continuous positive airway pressure), with an oxygen flow of 80 L/min and an independent-flow PEEP valve set at 7.5 cmH_2O.

For sedation, to improve tolerance of the devices, administration of remifentanil by continuous infusion at 0.02 µg/kg/min and dexmedetomidine by continuous infusion at 0.7 µg/kg/min will be considered.

Descriptive variables

In addition to the values described above, other descriptive characteristics of the study population will be recorded: age, sex, BMI, medical history, diagnosis, SOFA score and SAPS score. Data on the course and duration of ICU and hospital stay will also be collected, as will data on any orotracheal intubation and mechanical ventilation. Personal data will be processed in accordance with the rules established by the Italian Data Protection Authority.

Consent

Patients will be informed upon admission to the intensive care unit using a dedicated paper form; the physician will also conduct a detailed interview with the patient, explaining all the characteristics and specific features of the study. If the patient states that they do not wish to participate in the study, they will not be enrolled.

Conflicts of interest and sponsorship

No sponsorship is planned for this study, and there are no conflicts of interest.

Timeframe

The study aims to enroll 20 patients over 12 months, from June 2023 to June 2024. The results are expected to be summarized and published by December 2024.

Sample size

As this is a physiological study, no formal sample-size calculation was performed. Based on previous similar studies (6), we decided to enroll 20 patients, a number that appears sufficient to analyze the predefined objectives.

Statistical analysis

Quantitative variables will be expressed as mean and standard deviation or median and interquartile range, depending on their distribution. Absolute and relative frequency distributions will be calculated for qualitative variables.

Variables at the different stages will be analyzed using one-way repeated-measures analysis of variance, with appropriate post hoc tests, or the Friedman test, depending on the type of data.

Proportions will be compared using the chi-square test or Fisher’s exact test.

Correlation analysis will be performed by calculating Pearson’s correlation coefficient or Spearman’s rho, depending on the data distribution.

A two-sided P value below 0.05 will be considered statistically significant.

The analysis will be performed using R: R Core Team (2022). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.

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