Documents: Study protocol and statical analysis plan

Document date: September 17, 2018

Official title:

Effect of Mechanical power on dead space assessed with volumetric capnography: Preliminary studies and pilot testing in ARDS patients.

Objectives

1- The objective of this study will be to evaluate the behavior of the dead space monitored by volumetric capnography after using mechanical ventilation strategies aimed at reducing mechanical power, maintaining constant positive end-expiratory pressure (PEEP) levels in ARDS patients.

2- Describe each ventilatory strategy used and evaluate their association with dead space and alveolar ventilation monitored by volumetric capnography.

Materials and methods:

Design: An observational, prospective, and single-center study. Preliminary studies and pilot testing in ARDS patients.

Sample size: 10 participants.

Place of study: Clínica las Condes, Santiago, Chile.

Variable records in the study: Variables will be measured and recorded at baseline, and every time the mechanical ventilator setting is modified. Each phase will last 30 minutes. The estimated time of recording will be 150 min.

Inclusive Criteria

- Patients with pulmonary and extra-pulmonary ARDS.
- The partial pressure of arterial oxygen over fraction of inspired oxygen (PaO2/FiO2) under 200 mmHg.

Exclusion criteria

- Pregnancy.
- Under 18 years old.
- Heart failure stage IV.
- COPD with home oxygen.
- Bronchopulmonary fistula.
- Hypovolemic Shock with active hemorrhage.
- Gastrointestinal bleeding.
- Oesophageal Varices.
- Nasopharynx surgery, recent oesophageal or gastric surgery
- Massive Pulmonary Thromboembolism.
- Patients with catastrophic respiratory failure that require urgent extracorporeal life support.
- Respiratory acidosis. Basal pH less than 7.20 and basal PaCO2 greater than 60 mmHg.

Study time: 12 months.

Study protocol

Tests and sequential proceedings during the study: After 30 minutes of monitoring in each phase, ventilatory mechanics, VD/Vt Bohr fraction, and arterial gasometry will be performed.

Baseline: Variables in basal conditions will be registered to allow comparison among the several phases of the study.
The tidal volume (VT) at baseline will be set at 7 ml/kg/Predicted body weight (PBW) with PEEP set at the value that allows a transpulmonary pressure at end-expiratory equal to 0 - +5 cmH20 and a respiratory rate between 22 and 30 per minute. Patients whose baseline arterial pH is less than or equal to 7.20 and or PaCO2 greater than or equal to 60 mmHg will be excluded from the study.
In each phase will be documented: peak pressure (Ppeak), end inspiring plateau pressure (Pplateau), mean airway pressure, PEEP, respiratory rate (RR), flow, Raw, End- inspiratory pause prolongation, inspiratory-expiratory relation (I:E), driving pressure of respiratory system, Compliance (Csr), Elastance (Esr), end-inspiratory transpulmonary pressure (PL at the end-inspiratory), end-expiratory trans-pulmonary pressure (PL at end-expiratory), and transpulmonary driving pressure (PL driving pressure) PL driving pressure. Will be used to measure oesophageal pressure, a FluxMed GrT– FluxView MBMed device.

Mechanical Power: Mechanical power will be calculated with the following equation:

PowerRS = 0,0098 . RR . { Vt2 . [1/2 . EL rs + RR . (1+ I:E)/ (60. I:E) . Raw] + Vt . PEEP }

Power: Mechanical power, 0,098: constant, RR: respiratory rate, V: Tidal volume, ELrs: Respiratory System Elastance, I:E: inspiratory time relation with expiratory time, Raw: airway resistance, PEEP: positive end-expiratory pressure.

This equation is included in an Excel calculating sheet with data of each variable, and the mechanical power value will be registered automatically in Joules/min.

Volumetric capnography: Volumetric capnography will be recorded with a carbon dioxide (CO2) analyzer (mainstream) connected to between the orotracheal tube and the proximal flow sensor. The signals will be analyzed by the FluxMed monitor and the FluxView software. The device has software programmed in MatLab ® (Mathworks, Natick, MA, USA) that allows analyzing respiration to volumetric capnograms, using a mathematical algorithm (Levenberg-Marquardt) that allows adjusting the volume to the expired CO2. In this way, it will be possible to obtain all the variables under study that allow obtaining the results of dead space and alveolar ventilation.
Protocol design The protocol will start recording the data during baseline protective ventilation. After 30 minutes of data recording, we studied four levels of setting in mechanical ventilation. Each level will last 30 minutes.
Variables that will be obtained from the Volumetric capnography monitoring: Bohr's dead space to tidal volume ratio (VDBohr/VT), Enghoff's index of gas exchange (VDEnhoff/VT), physiological dead space (VDphys), airway dead space (VDaw), alveolar dead space (VDalv), VTalv alveolar expiratory tidal volume, VDaw/VTe airway dead space to tidal volume ratio, alveolar dead space to expiratory tidal volume ratio (VDalv/VT), alveolar dead space to alveolar tidal volume ratio (VDalv/VTalv), tidal elimination of carbon dioxide VTCO2br, normalized slope of phase III (SnIII), end-tidal CO2 (ETCO2), mean alveolar partial pressure of CO2 (PACO2), and mixed-expired partial pressure of CO2 (PECO2)
We will analyze the last 20 breaths of each step of the protocol and calculate the average value to obtain the result of dead space and all its variables by volumetric capnography. Respiratory, hemodynamic, and arterial blood gas analysis will also be recorded.

Cardiac output: Continuous measurement of cardiac output and the cardiac index will be conducted using Volume View or Flow Track Vigileo devices. These are minimally invasive devices that are connected to an arterial line.

Esophageal Temperature: Continuous measurement of central Temperature will be registered in all patients. It must be constant with a variability of +/- 0,3°C to avoid generating variations in the volumetric capnography results.

Phase 1: Reduction of tidal volume
The tidal volume will be decreased from baseline Vt of 7 ml/kg/PBW to 6 ml/kg/PBW.

Phase 2: Reduction of tidal volume:
The tidal volume will be decreased from baseline Vt of 6 ml/kg/PBW to 5 ml/kg/PBW.
Phase 3: End-inspiratory pause prolongation
The end-inspiratory pause will be increased until it results in an I: E ratio equal to 1.
Phase 4: Respiratory rate reduction.
Reduce respiratory rate to 20% of the baseline condition. The study will be suspended in patients who at the beginning of phase 3 present Ph less than 7.20 or PaCO2 more significant than 60.

Study suspension

The recording of physiological variables will be suspended in the following clinical situations, which are conditioned by the severity of each patient:
- Vasopressor refractory hypotension.
- Ventricular arrhythmias,
- Symptomatic bradycardia,
- Cardiopulmonary arrest.
- Catastrophic respiratory failure.

Sampling size

Due to the specific characteristics of the study subjects and the lack of scientific evidence available, this project intends to study 10 patients.

Statistical analysis plan

We will perform the Shapiro Wilks's statistic test to confirm normal distribution. Data will be expressed as mean ± standard deviation, median, and interquartile range (IQR), as appropriate. Within each ventilatory strategy, a paired t-test or Wilcoxon signed-rank test (WST) will be used as appropriate. Continuous variables among ventilatory strategies will be compared using repeated measure ANOVA with Bonferroni post hoc analysis or Friedman test and Kruskal Wallis test for multiple comparisons. Pearson or Spearman correlation test will be used to compare data and correlations between phases and variables. Percentages will be analyzed using two- proportion z-test. Categorical variables will be compared with the X2 test. The SPSS software (version 22.0, IBM SPSS Inc., Chicago, IL, USA) A probability value (p-value) of less than 0.05 will be considered statistically significant.

Ethical principles
Document date: January 9, 2019

The present research project has been revised and approved by the ethics and research committee of Clínica Las Condes. It will carry out the process of execution authorization of the study. The internal number of the project is S022018.