Title: Heart-lung interaction to predict hemodynamic tolerance to Open Lung Approach

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Statistical Analysis Plan

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Introduction

This Statistical Analysis Plan (SAP) outlines the statistical methods and procedures to be used for analyzing data from the study evaluating the value of heart-lung interactions in predicting the hemodynamic response to the Open Lung Approach (OLA).

Study Objectives

Primary Objective

To evaluate capacity of baseline heart-lung interaction variables (Changes in Pulse pressure variation -PPV- with Tidal Volume Challenge -TVC-) in predicting the decrease in CI following the OLA approach (recruitment maneuver-RM- with individualized Positive End-Expiratory Pressure -PEEP-), by comparing baseline CI and CI 5 minutes post-MR. A clinically significant decrease in CI is defined as at least 10%

Secondary Objectives

- To evaluate the capacity of other heart-lung interaction variables (TVC, SVV, and PPV) in predicting a ≥10% decrease in CI at 1, 5, and 15 minutes after performing recruitment maneuver with individualized PEEP (OLA).

- To describe the correlation between changes in CI and MAP pre- and post-MR.

- To describe the effect of individualized PEEP on hemodynamic parameters obtained through minimally invasive monitoring using the PRAM method continuously during the first 15 minutes after MR with individualized PEEP, compared to baseline values of: indexed stroke volume (SVI), cardiac index (CI), pulse pressure variation (PPV), dynamic arterial elastance (EaDyn), and cardiovascular system impedance (Ztotal).

Study Design

Prospective observational cohort study

Study Population

Inclusion Criteria

Patients aged over 18 years undergoing scheduled non-cardiothoracic surgery; under controlled invasive mechanical ventilation with invasive arterial monitoring; in the supine position; with a positive air test or clinical indication for recruitment maneuver.

Exclusion criteria:

Chronic pulmonary disease (defined as chronic obstructive pulmonary disease grade 3 or higher, or any condition requiring long-term oxygen therapy); congenital cardiac malformations; severe valvulopathy; NYHA (New York Heart Association) grade III/IV heart failure; arrhythmias; history of decreased ventricular systolic function (Left Ventricular Ejection Fraction -LVEF- <40% or Tricuspid Annular Plane Systolic Excursion -TAPSE- <17 cm/s); history of pulmonary hypertension; Body Mass Index -BMI- >35 (due to altered pulmonary and thoracic compliance); heart rate to respiratory rate ratio <3.6; presence of inspiratory efforts; open chest; increased intra-abdominal pressure (due to pathology or pneumoperitoneum); altered pulmonary or thoracic compliance due to surgery (Trendelenburg or reverse Trendelenburg position); uncorrected arterial waveforms (resonant or dampened); and any contraindication to performing lung recruitment maneuvers. These contraindications include: pulmonary emphysema, pulmonary bullae, uncontrolled hemodynamic instability, right heart failure, elevated intracranial pressure (due to reduced jugular vein return flow) or absence of monitoring when necessary, bronchospasm, and undrained pneumothorax.

Endpoints

Primary

To evaluate the ability of changes in PPV with TVC to predict a ≥10% decrease in CI at 5 minutes post-OLA.

Secondary

- To evaluate the ability of TVC, PPV, and SVV to predict a ≥10% decrease in CI at different time points (1, 5, and 15 minutes).
- To assess the correlation between MAP and CI to monitor the hemodynamic impact of the OLA.
- To evaluate the hemodynamic impact of the OLA using various parameters obtained with the PRAM method continuously during the first 15 minutes

after RM with individualized PEEP, compared to baseline values of: indexed stroke volume (SVI), cardiac index (CI), pulse pressure variation (PPV), dynamic arterial elastance (EaDyn), and cardiovascular system impedance (Ztotal).

Randomization and Blinding

This study does not involve randomization as it is observational. Blinding is not applicable.

Sample Size and Power Calculations

Based on data from a pilot study with 6 patients, which reported an effect size (Cohen's d) of 0.7, a sample size of 66 patients was calculated to provide 80% power, ensuring the detection of a significant difference, if present, with a significance level (α) of 0.05. To account for an expected dropout rate of 10%, a recruitment target of 72 patients was set. This sample size also allows for the estimation of an area under the curve (AUC) of 0.75 for the ROC curve of the logistic regression model, demonstrating good discriminative ability with a precision of ±0.065.

Data Collection and Management

Patient data will be collected at baseline, after the tidal volume challenge, and during the 15 minutes following the recruitment maneuver. Demographic data will be extracted from the hospital electronic health records.

Statistical Methods

A statistical analysis of the results obtained from the data collection sheet will be conducted. This document includes the following hemodynamic and ventilatory variables:

- At baseline, after the tidal volume challenge, 1 minute after the recruitment maneuver, and 5 minutes after the recruitment maneuver: driving pressure, PEEP, mean airway pressure, respiratory rate, oxygen saturation by pulse oximetry, and the result of the tidal volume challenge.
- At baseline, after the tidal volume challenge, and every minute for 15 minutes after the recruitment maneuver: MAP, CI, SVI, heart rate, Ztotal, EaDyn, PPV, and SVV.

1. Ability of TVC, PPV, and SVV to predict a ≥10% decrease in CI following OLA (at 1, 5, and 15 minutes): Evaluation of the predictive value of heart-lung interaction variables for hemodynamic tolerance to MR, defined as a ≥10% decrease in CI. Logistic regression models will be developed using the following predictors: change in PPV with TVC, the categorical outcome of TVC, SVV with a V_T of 6 $mL \cdot kg^{-1}$ (SVV_6), SVV with a V_T of 8 $mL \cdot kg^{-1}$ (SVV_8), PPV with a V_T of 8 $mL \cdot kg^{-1}$ (PPV_8), and PPV with a V_T of 6 $mL \cdot kg^{-1}$ (PPV_6). The binary outcome will be a ≥10% decrease in CI. The model's performance will be evaluated using sensitivity, specificity, and predictive values. ROC curves and the AUC will be calculated to compare the predictive power of TVC, SVV_6, SVV_8 PPV_6 y PPV_8.
2. A Pearson correlation will be performed to evaluate the relationship between changes in CI and changes in MAP.
3. The hemodynamic consequences of MR with individualized PEEP will be described using repeated measures of CI, SVI, dP/dtMAX, EaDyn, and Ztotal.

All analyses will be conducted in R (version 4.4.1).