# Associations of Intraoperative Hypocapnia with Patient Demographics, Ventilation Characteristics and Outcomes—statistical analysis plan for an individual patient data analysis of PROVHILO and PROBESE

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On behalf of the PROVHILO and PROBESE–investigators and the PROVE Network Investigators

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**Rationale**

Lung–protective intraoperative ventilation (LPV) has the potential to improve the outcome of surgery patients through a reduction in postoperative pulmonary complications [1, 2]. Use of intraoperative ventilation strategies that use a low tidal volume could result in intraoperative hypercapnia. However, hypocapnia remains surprisingly common during intraoperative ventilation [3, 4], possibly meaning that anesthesiologists continue to use high, if not too high respiratory rates or tidal volumes.

Previous studies suggested associations between intraoperative derangement of end–tidal carbon dioxide (et$CO_2$) and postoperative outcomes [5, 6]. Indeed, two studies in highly selected patient groups showed associations of intraoperative hypocapnia with prolonged length of hospital stay, in patients undergoing pancreaticoduodonectomy [7], and in patients undergoing hysterectomy [8].

To gain a better understanding of the epidemiology of intraoperative hypocapnia, in particular the associations of intraoperative hypocapnia with patient demographics, ventilator characteristics, and perioperative complications we will perform an Individual patient–level meta–analysis of two recent randomized clinical trials of intraoperative ventilation [3, 9].

**Hypothesis**

Intraoperative hypocapnia has an independent association with patient demographics, ventilation parameters, and perioperative complications.

**Objectives**

The current analysis will assess associations of intraoperative hypocapnia with patient demographics, ventilation characteristics, occurrence of intraoperative complications, postoperative pulmonary complications, and length of hospital stay in patients undergoing planned major surgery [3, 9].

**Study design**

For this analysis we will use the database of the two randomized clinical trials, named the 'High versus Low Positive End–expiratory Pressure During General Anesthesia for Open Abdominal Surgery (PROVHILO) [3], and the 'PRotective Ventilation with Higher versus Lower PEEP during General Anesthesia for Surgery in OBESE Patients'

(PROBESE) [9]. PROVHILO and PROBESE investigated the effects of an open lung approach during low tidal volume ventilation in patients undergoing major surgery.

**Study details**

The full list of inclusion and exclusion criteria of PROVHILO and PROBESE have been reported with the original publications [3, 9]. In short, patients were eligible for participation in the original studies if: (1) planned for major (abdominal) surgery; and (2) at risk for postoperative pulmonary complications. Major exclusion criteria in the original studies were planned thoracic surgery or neurosurgery.

For the purpose of this current analysis, we will additionally exclude patients that underwent unscheduled, i.e., urgent or emergent surgeries, because we consider it likely that these patients may have had metabolic abnormalities at the moment of surgery, i.e., metabolic acidosis, for which the anesthesiologist may have adjusted the intraoperative ventilator settings. This may have led to a 'compensatory' low $etCO_2$. We will also exclude patients for whom $etCO_2$ recordings are missing in the study databases.

**Patient categories**

We will use the intraoperatively collected $etCO_2$ levels to classify patients as either 'with hypocapnia' or 'without hypercapnia', using the cutoff of 35 mmHg. A patient is considered 'hypocapnic' if the $etCO_2$ was < 35 mm Hg at any point during surgery, from start of the study till end of the study, and classified as 'without hypocapnia' otherwise. In case of a missing value immediately before extubation, we will use the values as reported in the last hour of surgery [10].

**Study outcomes**

The primary outcome of this analysis is a composite of predefined and collected postoperative pulmonary complications within the first seven days after the surgery, as used in the parent studies. Postoperative pulmonary complications included mild, moderate, and severe respiratory failure; acute respiratory distress syndrome; bronchospasm; new pulmonary infiltrate; pulmonary infection; aspiration pneumonitis; pleural effusions; atelectasis; cardiopulmonary edema; and pneumothorax.

Secondary outcomes include intraoperative complications, a set of intraoperative ventilation parameters, intraoperative vital signs (heart rate, mean arterial pressure, and $SpO_2$) and any new arrhythmias needing intervention. Other endpoints are unexpected need for intensive care unit admission, ICU readmission, and length of stay in hospital up till day 90.

**Calculations**

Intraoperative ventilation variables collected in the parent studies included tidal volume ($V_T$), positive end–expiratory pressure (PEEP), plateau or maximum airway pressure (Pplat or Pmax) and respiratory rate (RR).

Ventilation parameters are calculated as follows:

For $V_T$, expressed in ml/kg predicted body weight:

$$50 \text{ kg} + 2.3 \text{ kg (height in inches -60) (in males)}$$

$$45.5 \text{ kg} + 2.3 \text{ Kg (height in inches -60) (in females)}$$

For driving pressure (ΔP):

$$\Delta P = Pplat - PEEP \text{ (with volume–controlled ventilation [VCV])}$$

$$\Delta P = Pmax - PEEP \text{ (with pressure–controlled ventilation [PCV]) [11]}$$

For mechanical power of ventilation (MP):

$$MP = 0.098 * V_T * RR* (Ppeak - 0.5 * \Delta P) \text{ (with VCV) [12]}$$

$$MP = 0.098 * V_T * RR * (Pmax - 0.5 * \Delta P) \text{ (with PCV) [13]}$$

For respiratory system compliance ($C_{RS}$):

$$C_{RS} = V_T/\Delta P$$

**Sample size**

The sample size will be based on the number of available patients.

**Statistical analysis plan**

Demographic, clinical and outcome variables are presented as medians with interquartile ranges (IQR), or number with percentage, where appropriate. Differences in baseline characteristics between patients with and patients without hypocapnia will be analyzed using the Pearson Chi–squared or Fisher exact tests for categorical variables and with a one–way ANOVA or Kruskal–Wallis test for continuous variables.

Data points for intraoperative variables (vital signs, ventilator settings and ventilation parameters) will include those collected in the first, second and third hour after start of the study, and before extubation.

Occurrence of postoperative pulmonary complications will be compared using a Fisher's exact test, time to event analyses will be performed using a Cox proportional hazard model or a competing risk model where appropriate. Next, we will perform a propensity matched cohort. Patients will be matched 1:1 with a maximum caliper of 0.02. The following covariates will be used for propensity matching: age, gender, BMI, type of surgery, compliance, history of COPD. We will calculate interaction term for the ARISCAT score as sensitivity analysis. We will perform time-weighted analysis for etCO2 levels in the primary end-points. Kaplan-Meier curve will be used to plot the relation between hypocapnia and the primary outcome.

A LOESS regression will be used to visualize the relationship of $etCO_2$ as a continuous variable with the primary outcome. The association between etCO2 and the primary outcome will be determined using a generalized mixed model in which age, gender, BMI, type of surgery, compliance and history of COPD will be used as covariates. Sankey plot will be used to demonstrate flow association between etCO2 and primary or secondary outcomes.

As a sensitivity analysis the main analyses will be repeated in obese patients and non–obese patients, using a cutoff of 30 $kg/m^2$ for BMI. Another sensitivity analysis will be performed to determine the effect of PEEP settings on outcome. For this analysis the interaction term for PEEP on the generalized mixed model will be calculated.

A P–value of $< 0.05$ will be considered statistically significant. All analyses will be performed with R statistics version 4.0.4.

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**Planned inserts**

Figure 1: CONSORT

Figure 2: Sankey plots

Figure 3: distribution plots of ventilation characteristics

Figure 4: LOESS regressions

Figure 5: Kaplan-Meier curve

Table 1: Patient characteristics

Table 2: Intraoperative characteristics, including ventilation and hemodynamic characteristics

Table 3: Comparison of outcomes between the patients with or without hypocapnia

eTable 1: Patient characteristics for studies

eTable 2: Ventilation characteristics

eTable 3: Sensitivity analyses