

Original Contribution

Associations of intraoperative end-tidal CO₂ levels with postoperative outcome—secondary analysis of a worldwide observational study

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Abbreviations: **etCO₂**, End-tidal Carbon Dioxide; **PPCs**, Postoperative Pulmonary Complications; **LAS VEGAS**, Local ASsessment of VEntilatory Management during General Anesthesia for Surgery; **V_T**, Tidal Volume; **RR**, Respiratory Rate; **ARISCAT**, Assess Respiratory Risk in Surgical Patients in Catalonia; **MP**, Mechanical Power; **P_{max}**, Maximum Peak Inspiratory Airway Pressure; **PEEP**, Positive End-expiratory Pressure; **PaCO₂**, Partial pressure of Carbon Dioxide; **Pplat**, Plateau Pressure; **ΔP**, Driving pressure; **PBW**, Predicted Body Weight; **FiO₂**, Fraction of Inspired Oxygen; **IQR**, Interquartile Range; **COPD**, Chronic Obstructive Pulmonary Disease; **RR**, Relative Risk.

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¹ LAS VEGAS, Local ASsessment of VEntilatory management during General Anaesthesia for Surgery

² PROVE Network, 'PROtective VEntilation Network'

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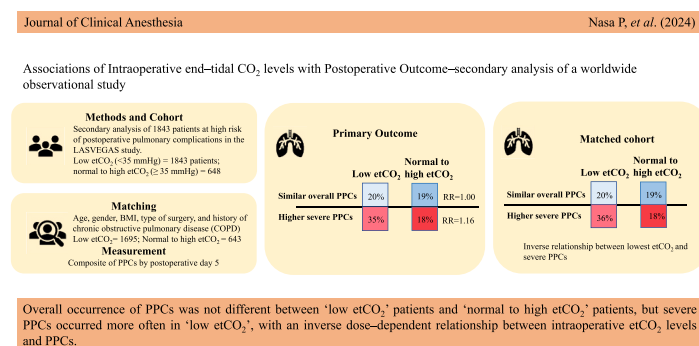
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HIGHLIGHTS

- This secondary analysis of the LAS VEGAS study, aimed to examine the association between etCO_2 levels and the occurrence of PPCs.
- No significant difference was found in overall PPCs between 'low etCO_2 (below 35 mmHg)' and 'normal to high etCO_2 (≥ 35 mmHg)' patients (20 % vs. 19 %).
- Severe PPCs were more common in the 'low etCO_2 ' group (35 % vs. 18 %).
- Propensity score matching did not alter the results, showing a robust association.
- Potential mechanisms include hypoventilation causing ventilator-induced lung injury, ventilation-perfusion mismatching, or an underlying pulmonary pathology.
- Future prospective studies should explore the causality between low etCO_2 and severe PPCs.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Patients receiving intraoperative ventilation during general anesthesia often have low end-tidal CO_2 (etCO_2). We examined the association of intraoperative etCO_2 levels with the occurrence of postoperative pulmonary complications (PPCs) in a conveniently-sized international, prospective study named 'Local ASsessment of Ventilatory management during General Anesthesia for Surgery' (LAS VEGAS).

Methods: Patients at high risk of PPCs were categorized as 'low etCO_2 ' or 'normal to high etCO_2 ' patients, using a cut-off of 35 mmHg. The primary endpoint was a composite of previously defined PPCs; the individual PPCs served as secondary endpoints. The need for unplanned oxygen was defined as mild PPCs and severe PPCs included pneumonia, respiratory failure, acute respiratory distress syndrome, barotrauma, and new invasive ventilation. We performed propensity score matching and LOESS regression to evaluate the relationship between the lowest etCO_2 and PPCs.

Results: The analysis included 1843 (74 %) 'low etCO_2 ' patients and 648 (26 %) 'normal to high etCO_2 ' patients. There was no difference in the occurrence of PPCs between 'low etCO_2 ' and 'normal to high etCO_2 ' patients (20 % vs. 19 %; RR 1.00 [95 %-confidence interval 0.94 to 1.06]; $P = 0.84$). The proportion of severe PPCs among total occurring PPCs, were higher in 'low etCO_2 ' patients compared to 'normal to high etCO_2 ' patients (35 % vs. 18 %; RR 1.16 [1.08 to 1.25]; $P < 0.001$). Propensity score matching did not change these findings. LOESS plot showed an inverse relationship of intraoperative etCO_2 levels with the occurrence of PPCs.

Conclusions: In this cohort of patients at high risk of PPCs, the overall occurrence of PPCs was not different between 'low etCO_2 ' patients and 'normal to high etCO_2 ' patients, but severe PPCs occurred more often in 'low etCO_2 ', with an inverse dose-dependent relationship between intraoperative etCO_2 levels and PPCs.

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Registration: LAS VEGAS was registered at [Clinicaltrials.gov](https://clinicaltrials.gov) (NCT01601223), first posted on May 17, 2012.

1. Background

Patients receiving intraoperative ventilation during general anesthesia for surgery often have a low end-tidal CO_2 (etCO_2) level [1–7]. This could at least suggest that anesthesiologists frequently apply intraoperative ventilation with either too high tidal volumes (V_T) or too high respiratory rates (RR) [1–3]. It could also indicate that these patients have a larger dead space fraction, possibly indicative of underlying lung pathology or low cardiac output state [8–10]. Of note, previously intraoperative low etCO_2 levels have been linked to higher mortality rates [5], and longer hospital length of stay [5–7].

The exact relation between intraoperative low etCO_2 levels and patient factors, type of surgery and ventilation characteristics on the one hand, and its link with outcomes on the other hand have not yet been thoroughly studied in sufficiently-sized patient cohorts. For instance, it remains uncertain how often low etCO_2 levels depend on how the

ventilator is set, but more important it is questionable whether the occurrence of a low etCO_2 is truly associated with the occurrence of postoperative pulmonary complications (PPCs).

Therefore, we conducted a secondary analysis of a database of the worldwide, observational 'Local ASsessment of Ventilatory management during General Anaesthesia for Surgery study' (LAS VEGAS) [1]. We hypothesized that the occurrence of a low etCO_2 is associated with the development and severity of PPCs. We performed propensity score matching to correct for factors with a known association with PPCs, and to determine the relation between intraoperative etCO_2 level and the occurrence of PPCs.

2. Methods

2.1. Aim, study design and setting

This is a secondary analysis of LAS VEGAS, conducted in compliance with the current guidelines and the recommendations of STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (available at: www.strobe-statement.org) (**Supplement Table S1**). The statistical analysis plan was defined and finalized a priori to data extraction. LAS VEGAS was a worldwide, multicenter (in 146 hospitals across 29 countries), 1 – week (between January 14 and March 4, 2013), observational study to determine the incidence of patients with increased risk of PPCs, and to evaluate the impact of intraoperative ventilation practices on postoperative outcomes [1].

2.2. Ethics

The study protocol (W12_190#12.17.0227) of LAS VEGAS was first approved on August 22, 2012 by the ethics committee (Chairperson Prof. M.P.M. Burger) of the Amsterdam University Medical Center, location ‘AMC’, Amsterdam, the Netherlands and thereafter by the institutional review boards of each participating center.

Consent to participate: If required, written informed consent from the patient or their legal representative was obtained from the investigators of the original trial.

2.3. Inclusion and exclusion criteria

LAS VEGAS recruited consecutive patients receiving invasive ventilation, via endotracheal tube or supraglottic device, during general anesthesia for elective or non-elective surgery. Patients aged below 18 years, patients undergoing pregnancy-related surgery, patients undergoing surgery outside the operating room or procedures requiring cardiopulmonary bypass were excluded from LAS VEGAS.

Patients were eligible for this current analysis if they had an increased risk of PPCs, defined as an Assess Respiratory Risk in Surgical Patients in Catalonia for Postoperative Pulmonary Complications' (ARISCAT) risk score of 26 or more [11]. We excluded patients that had received mechanical ventilation in the 30 days prior to surgery, patients that underwent thoracic surgery, surgery that required one-lung ventilation, patients with missing etCO₂ recordings, and patients that were lost to follow up with regard to the endpoints of this study. We also excluded patients that underwent urgent or emergency surgery, because we considered it likely that these patients may have had metabolic abnormalities at the time of surgery for which anesthesiologists may have adjusted intraoperative ventilator management—specifically, the presence of a metabolic acidosis may have triggered the use of a higher alveolar minute ventilation, resulting in a lower etCO₂.

2.4. Data collected in LAS VEGAS

From the LAS VEGAS database the following patient demographics, and patients and surgery characteristics were used, i.e., age; gender; body weight and height; American Society of Anesthesiologists classification; ARISCAT score; coexisting conditions such as heart failure, chronic obstructive pulmonary disease, metastatic cancer; surgical technique. In LAS VEGAS, detailed ventilation data were collected after induction of anesthesia and start of invasive ventilation and every hour thereafter until tracheal extubation, including V_T, positive end-expiratory pressure (PEEP), plateau pressure (P_{plat}), maximum peak inspiratory airway pressure (P_{max}), fraction of inspired oxygen (FiO₂), respiratory rate (RR).

2.5. Patient classification

Using the lowest intraoperatively recorded etCO₂, an etCO₂ cut-off

of 35 mmHg was used to categorize patients as ‘low etCO₂’ (<35 mmHg) or ‘normal to high etCO₂’ (≥35 mmHg), as done in previous studies [3,6,7]. Herein, all of the included patients had a minimum ventilation time of one hour, and we did not use etCO₂ collected directly after anesthesia induction, as this first measurement may not be representative, due to hyperventilation during bag-mask ventilation before placement of the airway device.

2.6. Endpoints

The primary endpoint was a composite of PPCs by postoperative day 5, as was collected in LAS VEGAS. PPCs included unplanned supplemental oxygen, barotrauma, pneumonia, respiratory failure, invasive ventilation, acute respiratory distress syndrome (ARDS), as described before and detailed in **Supplement Table S2**. Secondary endpoints comprised of the individual PPCs, categorized based on their severity, wherein unplanned supplemental oxygen was classified as ‘mild’ and the PPCs as ‘severe’.

2.7. Calculations

V_T was expressed in ml per kg predicted body weight (PBW), in males using the eq. $50 + (0.91 \times (\text{height [cm]} - 152.4))$ and for females: $45.5 + (0.91 \times (\text{height [cm]} - 152.4))$. Driving pressure (ΔP) was calculated using the equations: $\Delta P = P_{\text{plat}} - \text{PEEP}$ (for volume-controlled ventilation) or $\Delta P = P_{\text{max}} - \text{PEEP}$ (for pressure-controlled ventilation) [12]. Respiratory system compliance ($\text{ml cmH}_2\text{O}^{-1}$) was calculated using the equation $V_T / \text{dynamic } \Delta P$. Mechanical power (MP) of ventilation (J/min) was calculated using the equation; $\text{MP} = 0.098 \times V_T \times \text{RR} \times (P_{\text{max}} - 0.5 \times \Delta P)$ [13].

2.8. Statistical analysis

No formal sample size calculation was performed, the number of eligible patients available in the LAS VEGAS database served as the sample size. Missing data (**Supplement Table S3**) was imputed using multiple imputations (MICE package in R statistics) if: (1) data was considered missing at random and (2) not exceeding 5 % of all observations. Demographic, baseline characteristics and outcome variables are presented as mean, medians (interquartile ranges [IQR]), or number with percentage, where appropriate. Differences in baseline characteristics between ‘low etCO₂’ and ‘normal to high etCO₂’ patients were analyzed using the Pearson Chi-squared or Fisher exact tests for categorical variables and one-way ANOVA or Kruskal–Wallis test for continuous variables.

The incidence of PPCs in ‘low etCO₂’ and ‘normal to high etCO₂’ patients was compared using Fisher's exact test. Likewise, the incidence of mild and severe PPCs was compared between the two groups. In addition, a time-weighted average of etCO₂ was used to categorize patients as low etCO₂ (<35 mmHg) or normal to high etCO₂ (≥35 mmHg) and evaluate impact on overall, mild and severe PPCs [14].

As one sensitivity analysis, we performed propensity score matching using a generalized mixed logit model to control for clustering in the study sites, in which age, gender, BMI, type of surgery, and history of chronic obstructive pulmonary disease (COPD) were used as covariates. A maximum caliper of 0.02 was used. The method of nearest neighbor matching without replacement was applied in a 1:3 ratio. The balance of covariates between the two groups was assessed using the standardized mean difference (SMD) and LOVE plots.

As a second sensitivity analysis locally estimated scatterplot smoothing (LOESS) regression was used to visualize the relationship between lowest etCO₂ and relative minute ventilation as a continuous variable and PPCs. The values were generated by the LOESS smoothing procedure, which in this case reflects the smoothed estimate of the probability of PPCs.

Statistical significance was set at $P < 0.05$. As all secondary analyses

should be considered exploratory, no correction for multiple testing was performed. All analyses were performed using the R statistics version 4.0.4 (Core Team, Vienna, Austria, 2021).

3. Results

3.1. Patients

Out of the 10,520 patients enrolled in LAS VEGAS, 2491 subjects were included in the present analysis (Supplementary Fig. S1). Main reason for exclusion was ARISCAT <26 (low risk for PPCs). Among the included patients, 1843 (74 %) were categorized as ‘low etCO₂’ patients, and 648 (26 %) were classified as ‘normal to high etCO₂’ patients. Compared to ‘normal to high etCO₂’ patients, ‘low etCO₂’ patients were older, shorter, and had a lower body mass index (Table 1). Patients in ‘normal to high etCO₂’ were more likely to undergo minimally invasive surgery compared to low etCO₂’ patients.

3.2. Ventilation characteristics

‘Low etCO₂’ patients were ventilated with higher V_T and a higher relative minute ventilation compared to ‘normal to high etCO₂’ patients

Table 1
Patient characteristics in the unmatched and matched cohort.

| Characteristics | Unmatched cohort | | Matched cohort | | SMD |
|---|-----------------------------------|---|-----------------------------------|---|-------|
| | Low etCO ₂ N = 1843 | Normal to high etCO ₂ N = 648 | Low etCO ₂ N = 1695 | Normal to high etCO ₂ N = 643 | |
| Age, Years | 63 [51 to 72] | 61 [48 to 69] | 61 [51 to 72] | 62 [48 to 69] | 0.10 |
| Female sex, n (%) | 960 (52 %) | 318 (49.1 %) | 854 (50 %) | 315 (49 %) | 0.02 |
| Height, cm | 168 [161 to 174] | 170 [163 to 177] | 168 [162 to 175] | 170 [163 to 177] | 0.12 |
| Weight, kg | 75 [65 to 86] | 81 [69 to 94] | 77 [65 to 88] | 81 [69 to 93] | −0.07 |
| PBW, kg | 61 [54 to 69] | 64 [55 to 71] | 62 [54 to 70] | 64 [55 to 71] | 0.07 |
| BMI, kg/m ² | 27 [24 to 30] | 28 [24 to 32] | 27 [24 to 30] | 27 [24 to 32] | −0.14 |
| ARISCAT score | 34 [31 to 41] | 34 [29 to 41] | 34 [31 to 41] | 34 [29 to 41] | 0.11 |
| ASA physical status classification, n (%) | 243 (13 %) | | 238 (14 %) | | |
| ASA I | 843 (46 %) | 83 (13 %) | 771 (46 %) | 81 (13 %) | 0.0 |
| ASA II | | 344 (53 %) | | 343 (53 %) | |
| ASA III | 674 (35 %) | 198 (31 %) | 614 (36 %) | 196 (31 %) | |
| ASA IV | | 23 (4 %) | | 23 (4 %) | |
| Comorbid disease, n (%) | 83 (5 %) | | 72 (4 %) | | |
| Cancer | 20 (1 %) | 50 (8 %) | 170 (10 %) | 50 (8 %) | 0.03 |
| Heart failure | 172 (9 %) | 64 (10 %) | 159 (9 %) | 64 (10 %) | −0.01 |
| COPD | 183 (10 %) | 58 (9 %) | 161 (10 %) | 58 (9 %) | 0.01 |
| Type of surgery, n (%) | 1447 (79 %) | | 1078 (64 %) | | 0.0 |
| Open | | 406 (63 %) | | 425 (66 %) | |
| Minimally invasive | 396 (22 %) | 242 (37 %) | 617 (36 %) | 218 (34 %) | |

Abbreviations: APACHE, Acute physiology and chronic health evaluation; BMI, Body mass index; PBW, Predicted body weight; SAPS, Simplified acute physiology score; SOFA, Sequential organ failure assessment, ARISCAT: Assess respiratory risk in surgical patients in Catalonia, COPD: Chronic obstructive pulmonary disease, ASA, American Society of Anesthesiologists, SMD, Standardized mean difference.

Table 2
Ventilation characteristics in the unmatched cohort.

| Characteristics | Unmatched cohort | | P value |
|--|-----------------------------------|---|---------|
| | Low etCO ₂ N = 1843 | Normal to high etCO ₂ N = 648 | |
| Tidal volume, ml | 500 [460 to 564] | 500 [460 to 550] | 0.008 |
| <300 | 4 (0 %) | 8 (1 %) | 0.004 |
| 300–400 | 94 (5 %) | 41 (6 %) | |
| 400–500 | 631 (34 %) | 222 (35 %) | |
| >500 | 1108 (60 %) | 372 (58 %) | |
| Tidal volume, ml/kg PBW | 8.3 [7.5 to 9.2] | 7.9 [7.0 to 9.0] | <0.001 |
| <6 | 42 (3 %) | 22 (4 %) | <0.001 |
| 6–8 | 605 (38 %) | 251 (47 %) | |
| >8 | 965 (60 %) | 260 (49 %) | |
| Respiratory rate, breaths/min | 12 [12 to 13] | 12 [12 to 14] | <0.001 |
| <10 | 42 (3 %) | 15 (3 %) | <0.001 |
| 10–15 | 1441 (89 %) | 439 (81 %) | |
| >15 | 143 (9 %) | 85 (16 %) | |
| Minute Ventilation, l/min | 6.1 [5.5 to 7.0] | 6.2 [5.5 to 7.1] | 0.37 |
| <4 | 28 (2 %) | 14 (2 %) | 0.11 |
| 4–6 | 702 (38 %) | 229 (36 %) | |
| 6–8 | 950 (52 %) | 326 (51 %) | |
| >8 | 111 (6 %) | 80 (14 %) | |
| Relative minute ventilation, ml/kg PBW/min | 81 [72 to 94] | 78 [66 to 92] | <0.001 |
| <60 | 111 (6.4 %) | 80 (13.6 %) | <0.001 |
| 60–80 | 662 (38.3 %) | 230 (39.2 %) | |
| 80–100 | 666 (38.5 %) | 190 (32.4 %) | |
| >100 | 289 (16.7 %) | 87 (14.8 %) | |
| FiO ₂ , % | 50 [45 to 60] | 50 [45 to 64] | 0.04 |
| etCO ₂ , mmHg | 32 [30 to 34] | 37 [36 to 39] | <0.001 |
| Compliance, ml/cmH ₂ O | 34 [27 to 41] | 32 [26 to 41] | 0.14 |
| PEEP, cmH ₂ O | 5 [2 to 5] | 5 [2 to 5] | 0.007 |
| <5 | 900 (49.1 %) | 317 (48.9 %) | 0.87 |
| 5–10 | 933 (50.9 %) | 331 (51.1 %) | |
| >10 | 0 | 0 | |
| Pplat, cm H ₂ O | 17 [14 to 20] | 17 [15 to 20] | 0.02 |
| Ppeak, cm H ₂ O | 19 [16 to 22] | 19 [16 to 23] | 0.008 |
| Driving pressure, cm H ₂ O | 13 [10 to 16] | 13 [10 to 17] | 0.45 |
| <14 | 674 (58.6 %) | 210 (54.8 %) | 0.19 |
| ≥ 14 | 476 (41.4 %) | 173 (45.2 %) | |
| MP, J/min | 7 [6 to 10] | 8 [6 to 10] | 0.11 |
| <17 | 664 (58.1 %) | 208 (55 %) | 0.29 |
| ≥ 17 | 478 (41.9 %) | 170 (45 %) | |
| MP normalized to PBW | 0.13 [0.1 to 0.18] | 0.13 [0.1 to 0.21] | 0.18 |

Abbreviations: PBW, Predicted body weight, calculated as: 50 + (0.91 × (height [cm] – 152.4)) for males and 45.5 + (0.91 × (height [cm] – 152.4)) for females; FiO₂, Fraction of inspired oxygen score; etCO₂, End-tidal carbon dioxide; Respiratory system compliance was calculated as tidal volume/dynamic ΔP; PEEP, Positive end-expiratory pressure; Pplat, Plateau pressure; Pmax, Peak pressure; Pmax: Maximum airway pressure. Driving pressure was calculated using the equations: ΔP = Pplat – PEEP (for volume-controlled ventilation [VCV]) or ΔP = Pmax – PEEP (for pressure-controlled ventilation [PCV]); Mechanical power (MP) of ventilation was calculated using the equations: MP = 0.098 * V_T * RR * (Pmax – 0.5 * ΔP) (for VCV)^{9,10}.

(Table 2, Supplementary Table S4). Other ventilation characteristics were not different.

3.3. Occurrence of PPCs

There was no difference in incidence of PPCs between ‘low etCO₂’ and ‘normal to high etCO₂’ patients (20 % vs. 19 %, RR 1.00 [95 %–confidence interval 0.94 to 1.06]; P = 0.84) (Table 3 and Figs. 1 and 2). Severe PPCs, however, occurred more often in ‘low etCO₂’ patients compared to ‘normal to high etCO₂’ patients (35 % vs. 18 %, RR 1.16 [1.08 to 1.25]; P < 0.001) (Table 3, Fig. 3). Similar results were seen with categorization of patients using time-weighted average of etCO₂

Table 3
Outcomes in the unmatched cohort.

| Outcome | Unmatched cohort | | |
|--|-----------------------------------|--|---------|
| | Low etCO ₂ N = 1843 | Normal to high etCO ₂ N = 648 | P value |
| Postoperative pulmonary complications, n (%) | 365/1843 (20 %) | 126/648 (19 %) | 0.84 |
| Mild PPCs | | | |
| Unplanned oxygen, n (%) | 283/365 (79 %) | 112/126 (89 %) | <0.001 |
| Severe PPCs | 127/365 (35 %) | 23/126 (18 %) | <0.001 |
| Pneumonia, n (%) | 23/365 (6 %) | 4/126 (3 %) | 0.18 |
| Respiratory failure, n (%) | 72/365 (20 %) | 13/126 (10 %) | 0.02 |
| ARDS, n (%) | 6/365 (2 %) | 2/126 (2 %) | 0.97 |
| Barotrauma, n (%) | 4/365 (1 %) | 0 | 0.23 |
| New invasive ventilation, n (%) | 52/365 (14 %) | 8/126 (6 %) | 0.02 |
| Intraoperative complications, n (%) | 868/1843 (47 %) | 313/648 (48 %) | 0.65 |
| Desaturation | 95/868 (11 %) | 47/313 (15 %) | 0.06 |
| Unplanned recruitment | 108/868 (12 %) | 34/313 (11 %) | 0.46 |
| Pressure reduction | 72/868 (8 %) | 44/313 (14 %) | 0.17 |
| Flow limitation | 15/868 (2 %) | 6/313 (2 %) | 0.83 |
| Hypotension | 670/868 (77 %) | 224/313 (72 %) | 0.05 |
| Vasopressor | 630/868 (73 %) | 228/313 (73 %) | 0.93 |
| Arrhythmia | 22/868 (3 %) | 9/313 (3 %) | 0.75 |

Abbreviations: PPC: Postoperative pulmonary complications; ARDS: Acute respiratory distress syndrome; etCO₂, End-tidal carbon dioxide.

(Table 4).

3.4. Sensitivity analyses

Propensity score matching resulted in two well-balanced cohorts (Tables 1 and Supplementary Table S4 and Fig. S2). The matched analysis did not change the findings of the unmatched analysis (Supplementary Table S5 and Fig. S3). There was an inverse relationship between lowest etCO₂ and severe PPCs on the LOESS plot (Supplementary Fig. S4). There was a linear increase in mild PPCs with the relative minute ventilation (Supplementary Fig. S5).

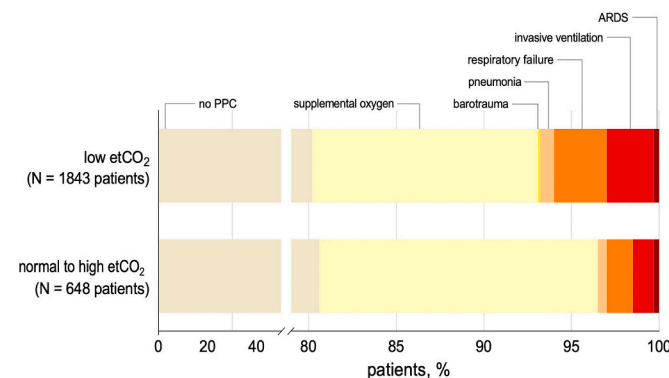


Fig. 1. Distribution plot for postoperative pulmonary complications between 'low etCO₂' patients and 'normal to high' etCO₂ patients.

Plot left: unmatched cohort.

Plot right: propensity-matched cohort.

etCO₂: end-tidal carbon dioxide; PPCs: postoperative pulmonary complications; ARDS: acute respiratory distress syndrome

4. Discussion

The findings of this secondary analysis of LAS VEGAS can be summarized as follows: (1) there was no difference in overall PPCs between 'low etCO₂' and 'normal to high etCO₂' patients; (2) compared to 'normal to high etCO₂' patients, 'low etCO₂' patients developed more often severe PPCs; (3) propensity score matching did not change these findings; and (4) an inverse relationship was observed between lowest etCO₂ levels and occurrence of severe PPCs.

Our findings are in line with findings in previous studies. Intraoperative hypocapnia occurs often [2,5,15], and high V_T are frequently used [1,2]. Indeed, nearly three-quarter of the patients in our study had a low etCO₂, which was associated with the use of a higher V_T and a higher relative minute ventilation. In the 'low etCO₂' patients a respiratory rate below 10 breaths per minute was infrequent, possibly due to

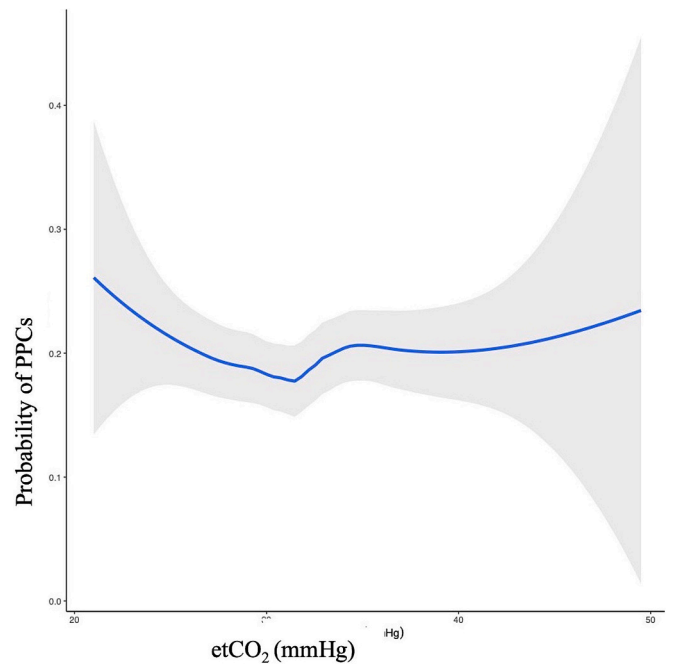
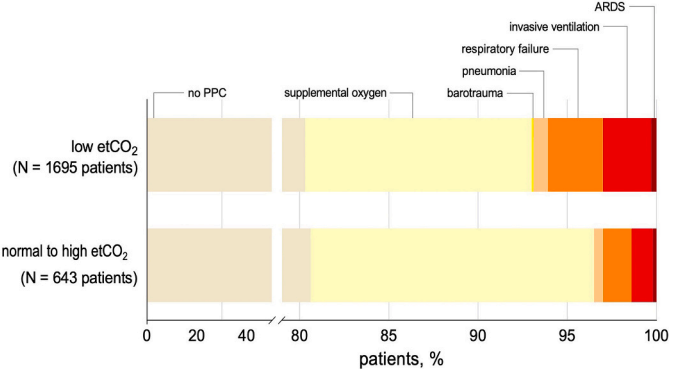


Fig. 2. Relationship between probability of overall PPCs (n/N) and lowest end-tidal carbon dioxide (mm Hg) in unmatched cohort.

PPCs: postoperative pulmonary complications; etCO₂: end-tidal carbon dioxide. The lowest end-tidal carbon dioxide refers to lowest etCO₂ captured intra-operatively for each patient.



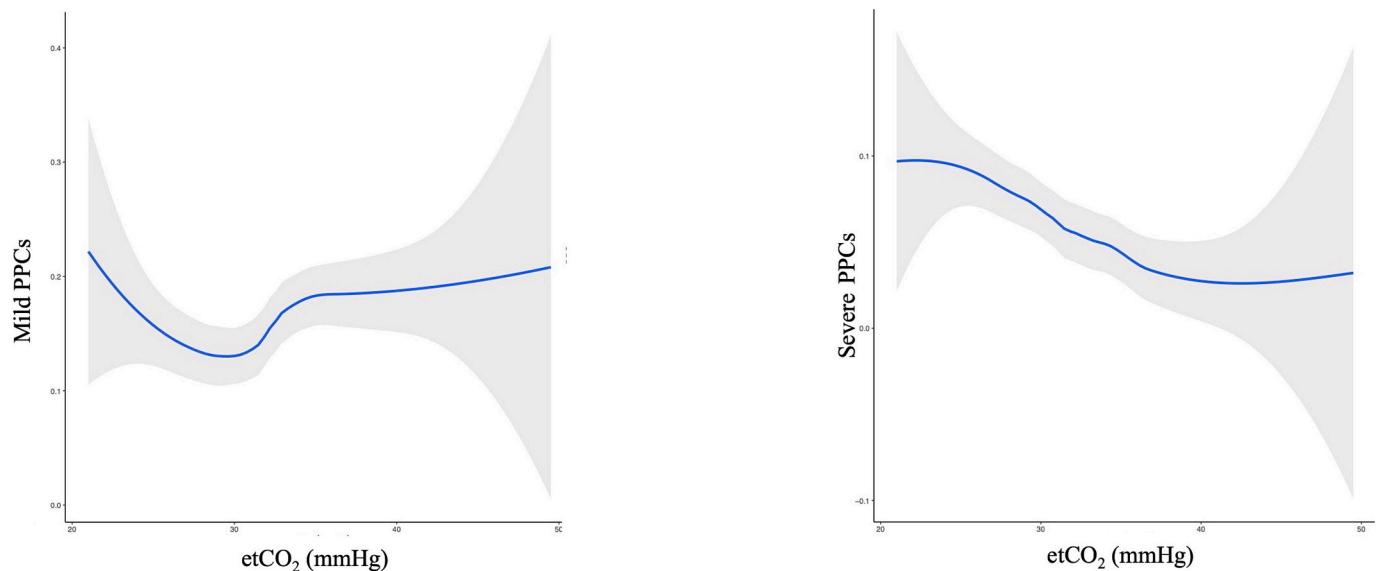


Fig. 3. Relationship between primary outcome divided into probability of mild (left) or severe (right) PPCs (n/N) and lowest end–tidal carbon dioxide (mm Hg) in unmatched cohort.
PPCs: postoperative pulmonary complications; etCO₂: end-tidal carbon dioxide.

Table 4
Outcomes using time–weighted average of end-tidal carbon dioxide.

| Outcome | Unmatched cohort | | |
|--|-----------------------------------|--|------------|
| | Low etCO ₂ N = 1590 | Normal to high etCO ₂ N = 903 | P value |
| Postoperative pulmonary complications, n (%) | 301/1590 (19 %) | 188/903 (21 %) | 0.25 |
| Mild PPCs | 233/1590 (15 %) | 162/903 (18 %) | 0.03 |
| Severe PPCs | 108/1590 (7 %) | 40/903 (4 %) | 0.02 |

Abbreviations: PPC: Postoperative pulmonary complications; etCO₂, End-tidal carbon dioxide.

a hesitancy to reduce the respiratory rate below this frequency.

Our analysis expands our current knowledge by showing an association between etCO₂ and outcome, when we restrict our composite endpoint to severe PPCs, by ignoring ‘unplanned supplementary oxygen’. This supports previous findings linking intraoperative low etCO₂ levels with adverse outcomes such as increased postoperative mortality rates and longer length of hospital stay [5–7]. Although severe PPCs include more relevant patient–centered outcomes, need for supplement oxygen (mild PPCs) postoperatively could be a sign of atelectasis with hypoventilation and may delay the discharge from hospital.

Several potential factors may contribute to our finding that ‘low etCO₂’ patients more often developed severe PPCs compared to ‘normal to high etCO₂’ patients. Inadvertent hyperventilation with relatively higher V_T may cause more intense ventilation, rendering the lung parenchyma susceptible to ventilator–induced lung injury. Hypocapnia in itself, can compromise ventilation/perfusion matching, through various mechanisms such as attenuation of hypoxic pulmonary vasoconstriction, bronchospasm, and intrapulmonary shunting [8,16,17]. In an isolated rat lung model for example, severe hypocapnia was associated with an increased risk of pulmonary oedema due to impaired alveolar fluid resorption [18].

A low etCO₂ could also reflect an increased dead space fraction. Patients with higher risk of PPCs may exhibit a higher partial pressure of carbon dioxide (PaCO₂)–etCO₂ gap due to pre-existing pulmonary pathology, low cardiac output states or hypovolemia, pulmonary

embolism, and pulmonary hypertension [8–10,19–21]. While it is plausible that intraoperative low etCO₂ in some patients may not reflect true hypocapnia but rather indicate underlying lung disease and/or decrease in cardiac output due to anesthesia, vasodilation, and/or blood loss. However, the propensity score matching in which we matched for COPD, did not change the findings; the observed linear association between etCO₂ and severe PPCs across the entire cohort also suggests otherwise. The pneumoperitoneum and Trendelenburg positioning during laparoscopic surgeries could contribute to PPCs and may even interfere with etCO₂ measurement [22]. However, matching the group for the type of surgery did not alter the results.

As LAS VEGAS did not capture arterial blood gas analysis results, we cannot be sure whether a low etCO₂ reflects true hypocapnia in all patients. Hypotension [19–21], and a not well–fitted supraglottic device [23], could also result in low etCO₂ readings. In LAS VEGAS, however, ventilation data including etCO₂ measurements were to be collected only when a patient was deemed hemodynamically stable. Also, supraglottic devices were seldom used in this cohort of patients, and it was equally used in the two groups.

The LOESS plot shows an inverse relationship of intraoperative etCO₂ levels and severe PPCs in the higher range of etCO₂ values (Fig. 3). The protective effect of mild hypercapnia has been previously reported both intraoperatively [24,25], and in critically ill patients [24]. Hypercapnia with acidemia, though, is associated with increased mortality in patients with sepsis especially with prolonged exposure of hypercapnia [26].

Theoretically, a U–shaped curve would be expected, showing higher incidences of PPCs at both extremes of CO₂ levels. However, this expected U–shaped relationship was not seen in the LOESS plot. This discrepancy might be due to the lower number of data points at extreme CO₂ values in our analysis. Future prospective research should investigate whether lung-protective ventilation with higher CO₂ levels is beneficial, particularly in various patient subgroups or specific surgical procedures.

4.1. Strengths and limitations

Our study has several strengths. First, we used the database of a conveniently–sized worldwide prospective observational study examining ventilation practice and outcomes in patients under general

anesthesia for surgery [1]. LAS VEGAS was a robust study, with a near to complete follow-up including both academic and non-academic hospitals, and teaching and non-teaching centers, increasing the generalizability of the findings. Second, the study included a wide variety of surgical patients, and the risk for PPCs, an inclusion criterion for this current analysis, which was predefined and therefore useful for patient selection. Finally, an analysis plan for this study was in place, which was strictly followed, and we used a sophisticated statistical approach to make the findings more robust, including propensity score matching and LOESS plot.

This analysis has some limitations. First, the parent LAS VEGAS dataset is a large and observational dataset which was not specifically designed for our research question. Even though we corrected for observed differences with a known association for PPCs, by performing propensity score matching, we cannot rule out the presence of non-observed differences, that could explain the findings. Second, in the absence of PaCO₂, etCO₂ was a surrogate used for hypocapnia. Expiratory CO₂ is not a precise representation of the milieu interior, as PaCO₂ is approximately 2–5 mmHg higher than etCO₂. It is plausible that hypocapnia was overestimated in this cohort due to the impact of general anesthesia and blood loss on cardiac output. However, cardiac output was not collected in the LAS VEGAS study. Nevertheless, a good correlation exists between etCO₂ and PaCO₂ in mechanically ventilated patients, especially in healthy lungs [19,27]. Last, the relationship between hypocapnia and severe PPCs can only be interpreted as an association and not as a causal relationship. It is hypothesis-generating at best and should be confirmed in future studies.

5. Conclusion

In patients receiving intraoperative invasive ventilation during general anesthesia for surgery at high risk of PPCs, PPCs occurred as often in 'low etCO₂' as in 'normal to high etCO₂' patients. Compared to 'normal to high etCO₂' patients, 'low etCO₂' patients developed more often severe PPCs.

Human ethics and consent to participate

The study protocol (W12_190#12.17.0227) of LAS VEGAS was first approved on August 22, 2022 by the ethics committee (Chairperson Prof. M.P.M. Burger) of the Amsterdam University Medical Center, location 'AMC', Amsterdam, the Netherlands and thereafter by the institutional review boards of each participating center. If required, written informed consent from the patient or their legal representative was obtained from the investigators of the original trial.

Consent for publication

Not applicable.

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CRedit authorship contribution statement

Prashant Nasa: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **David M.P. van Meenen:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Frederique Paulus:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Marcelo Gama de Abreu:** Writing – review & editing, Supervision, Methodology.

Sebastiaan M. Bossers: Writing – review & editing, Supervision, Methodology. **Patrick Schober:** Writing – review & editing, Validation, Supervision. **Marcus J. Schultz:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Ary Serpa Neto:** Writing – review & editing, Validation, Methodology. **Sabrina N.T. Hemmes:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Patrice Forget:** Writing – review & editing, Validation, Supervision. **Marcel Gama de Abreu:** Writing – review & editing, Supervision, Methodology. **Sabrina Hemmes:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Marcus Schultz:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The dataset used and analyzed during this study are available from the corresponding author upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinane.2024.111728>.

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