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Original Contribution

Associations of intraoperative end–tidal CO_2 levels with postoperative outcome–secondary analysis of a worldwide observational study

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Abbreviations: **$etCO_2$**, 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; **Pmax**, Maximum Peak Inspiratory Airway Pressure; **PEEP**, Positive End–expiratory Pressure; **$PaCO_2$**, Partial pressure of Carbon Dioxide; **Pplat**, Plateau Pressure; **ΔP**, Driving pressure; **PBW**, Predicted Body Weight; **FiO_2**, 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'
[3] ESAIC CTN, 'Clinical Trial Network of the European Society of Anaesthesiology and Intensive Care'

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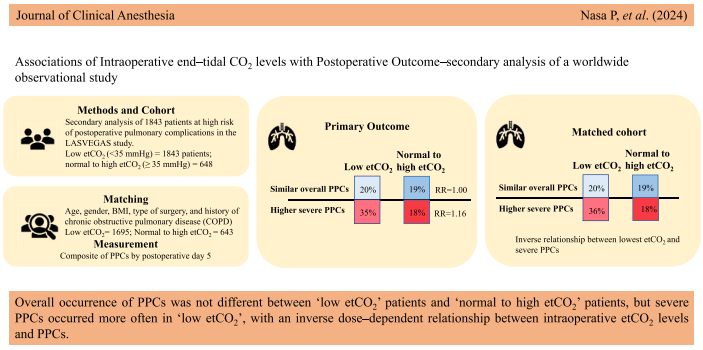
HIGHLIGHTS

- 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 $etCO_2$ ($\geq$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 hyperventilation 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.

Funding: This analysis was performed without additional funding. LAS VEGAS was partially funded and endorsed by the European Society of Anesthesiology and Intensive Care (ESAIC) and the Amsterdam University Medical Centers, location 'AMC'.

Registration: LAS VEGAS was registered at 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-statemenent.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 $etCO_2$ 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 $etCO_2$.

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 (Pplat), maximum peak inspiratory airway pressure (Pmax), fraction of inspired oxygen (FiO_2), respiratory rate (RR).

2.5. Patient classification

Using the lowest intraoperatively recorded $etCO_2$, an $etCO_2$ cut–off of 35 mmHg was used to categorize patients as 'low $etCO_2$' (<35 mmHg) or 'normal to high $etCO_2$' (≥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 $etCO_2$ 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: $\Delta P = Pplat - PEEP$ (for volume–controlled ventilation) or $\Delta P = Pmax - PEEP$ (for pressure–controlled ventilation) [12]. Respiratory system compliance (ml cmH_2O^{-1}) was calculated using the equation V_T/dynamic ΔP. Mechanical power (MP) of ventilation (J/min) was calculated using the equation; $MP = 0.098 * V_T * RR * (Pmax - 0.5 * \Delta P)$ [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 $etCO_2$' and 'normal to high $etCO_2$' 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 $etCO_2$' and 'normal to high $etCO_2$' 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 $etCO_2$ was used to categorize patients as low $etCO_2$ (<35 mmHg) or normal to high $etCO_2$ (≥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 $etCO_2$ 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 $etCO_2$' patients, and 648 (26 %) were classified as 'normal to high $etCO_2$' patients. Compared to 'normal to high $etCO_2$' patients, 'low $etCO_2$' patients were older, shorter, and had a lower body mass index (Table 1). Patients in 'normal to high $etCO_2$' were more likely to undergo minimally invasive surgery compared to low $etCO_2$' patients.

3.2. Ventilation characteristics

'Low $etCO_2$' patients were ventilated with higher V_T and a higher relative minute ventilation compared to 'normal to high $etCO_2$' patients (Table 2, **Supplementary Table S4**). Other ventilation characteristics were not different.

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 (%)					
ASA I	243 (13 %)	83 (13 %)	238 (14 %)	81 (13 %)	0.0
ASA II	843 (46 %)	344 (53 %)	771 (46 %)	343 (53 %)	
ASA III	674 (35 %)	198 (31 %)	614 (36 %)	196 (31 %)	
ASA IV	83 (5 %)	23 (4 %)	72 (4 %)	23 (4 %)	
Comorbid disease, n (%)					
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 (%)					0.0
Open	1447 (79 %)	406 (63 %)	1078 (64 %)	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		
	Low $etCO_2$ $N = 1843$	Normal to high $etCO_2$ $N = 648$	*P value*
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 %)	
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_2O^-	34 [27 to 41]	32 [26 to 41]	0.14
PEEP, cmH_2O	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_2O	17 [14 to 20]	17 [15 to 20]	0·02
Ppeak, cm H_2O	19 [16 to 22]	19 [16 to 23]	0·008
Driving pressure, cm H_2O	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; FiO_2, Fraction of inspired oxygen score; $etCO_2$, 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].

3.3. Occurrence of PPCs

There was no difference in incidence 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]; $P = 0.84$) (Table 3 and Figs. 1 and 2). Severe PPCs, however, occurred more often in 'low $etCO_2$' patients compared to 'normal to high $etCO_2$' patients (35 % vs. 18 %, RR 1.16 [1.08 to 1.25]; $P < 0.001$) (Table 3, Fig. 3). Similar results were seen with categorization of patients using time–weighted average of $etCO_2$

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; $etCO_2$, 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 $etCO_2$ 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**).

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 $etCO_2$' and 'normal to high $etCO_2$' patients; (2) compared to 'normal to high $etCO_2$' patients, 'low $etCO_2$' patients developed more often severe PPCs; (3) propensity score matching did not change these findings; and (4) an inverse relationship was observed between lowest $etCO_2$ 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 $etCO_2$, which was associated with the use of a higher V_T and a higher relative minute ventilation. In the 'low $etCO_2$' patients a respiratory rate below 10 breaths per minute was infrequent, possibly due to

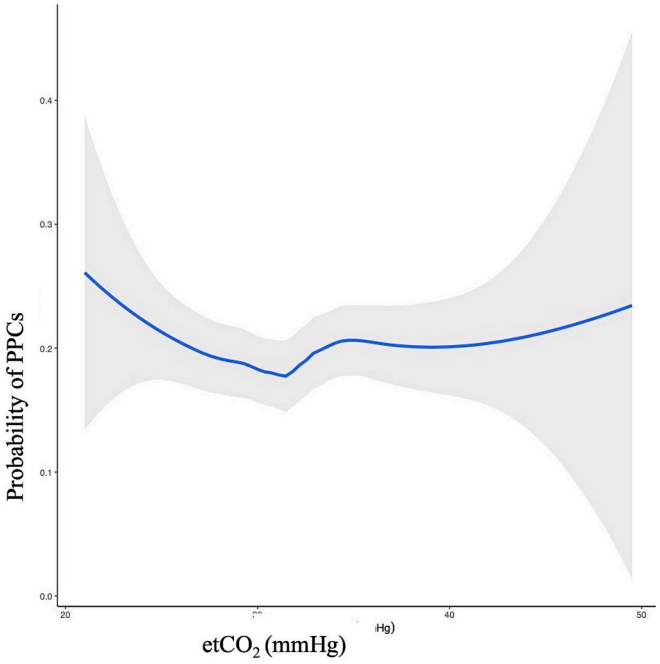

Fig. 2. Relationship between probability of overall PPCs (n/N) and lowest end–tidal carbon dioxide (mm Hg) in unmatched cohort.
PPCs: postoperative pulmonary complications; $etCO_2$**:** end–tidal carbon dioxide. The lowest end–tidal carbon dioxide refers to lowest etCO2 captured intraoperatively for each patient.

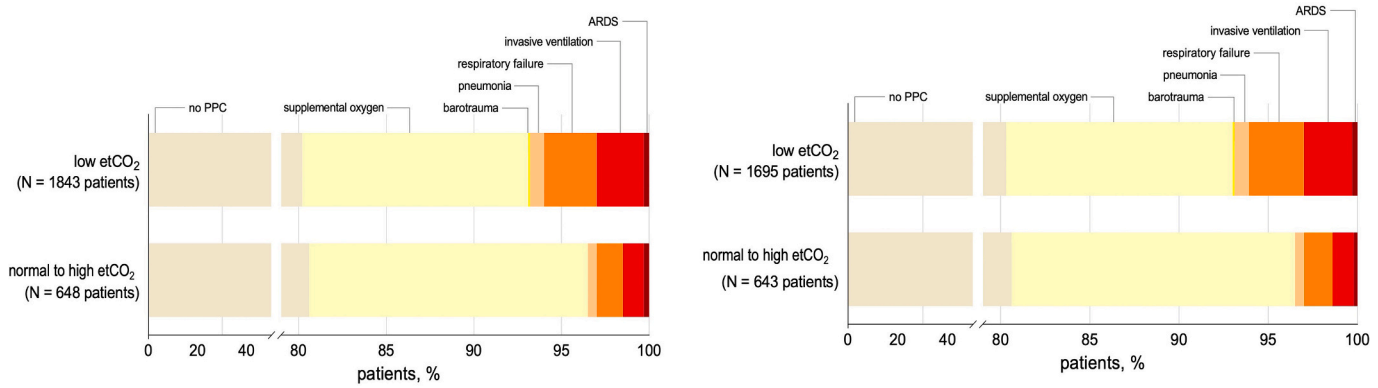

Fig. 1. Distribution plot for postoperative pulmonary complications between 'low $etCO_2$' patients and 'normal to high' $etCO_2$ patients.
Plot left: unmatched cohort.
Plot right: propensity–matched cohort.
$etCO_2$**:** end–tidal carbon dioxide; PPCs: postoperative pulmonary complications; ARDS: acute respiratory distress syndrome

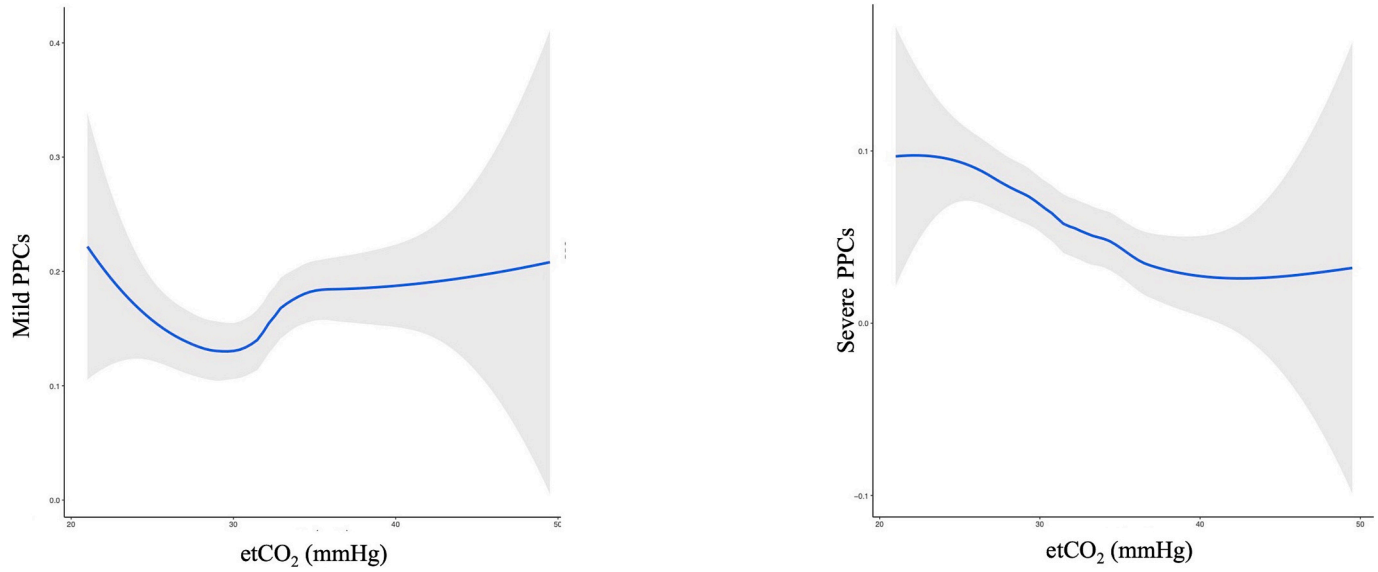

Fig. 3. Relationship between primary outcome divided into probability of mild (left) or severe (right) PPCs (n/N) and lowest end–tidal carbon dioxide (mm Hg) in unmatched cohort.
PPCs: postoperative pulmonary complications; $etCO_2$: end–tidal carbon dioxide.

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; $etCO_2$, 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 $etCO_2$ and outcome, when we restrict our composite endpoint to severe PPCs, by ignoring 'unplanned supplementary oxygen'. This supports previous findings linking intraoperative low $etCO_2$ 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 $etCO_2$' patients more often developed severe PPCs compared to 'normal to high $etCO_2$' 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 $etCO_2$ could also reflect an increased dead space fraction. Patients with higher risk of PPCs may exhibit a higher partial pressure of carbon dioxide ($PaCO_2$)–$etCO_2$ 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 $etCO_2$ 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 $etCO_2$ 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 $etCO_2$ 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 $etCO_2$ reflects true hypocapnia in all patients. Hypotension [19–21], and a not well–fitted supraglottic device [23], could also result in low $etCO_2$ readings. In LAS VEGAS, however, ventilation data including $etCO_2$ 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 $etCO_2$ levels and severe PPCs in the higher range of $etCO_2$ 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 CO_2 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 CO_2 values in our analysis. Future prospective research should investigate whether lung-protective ventilation with higher CO_2 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 $PaCO_2$, $etCO_2$ was a surrogate used for hypocapnia. Expiratory CO_2 is not a precise representation of the milieu interior, as $PaCO_2$ is approximately 2—5 mmHg higher than $etCO_2$. 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 out was not collected in the LAS VEGAS study. Nevertheless, a good correlation exists between $etCO_2$ and $PaCO_2$ 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 $etCO_2$' as in 'normal to high $etCO_2$' patients. Compared to 'normal to high $etCO_2$' patients, 'low $etCO_2$' 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. **Sabrine 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. **Sabrine 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.

References

[1] LAS VEGAS investigators. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - an observational study in 29 countries. Eur J Anaesthesiol 2017;34(8):492–507. https://doi.org/10.1097/EJA.0000000000000646.
[2] Akkermans A, van Waes JAR, Thompson A, Shanks A, Peelen LM, Aziz MF, et al. An observational study of end-tidal carbon dioxide trends in general anesthesia. Can J Anaesth 2019;66(2):149–60. https://doi.org/10.1007/s12630-018-1249-1.
[3] Way M, Hill GE. Intraoperative end-tidal carbon dioxide concentrations: what is the target? Anesthesiol Res Pract 2011;2011:271539. https://doi.org/10.1155/2011/271539.
[4] Bender SP, Paganelli WC, Gerety LP, Tharp WG, Shanks AM, Housey M, et al. Intraoperative lung-protective ventilation trends and practice patterns: a report from the multicenter perioperative outcomes group. Anesth Analg 2015;121(5):1231–9. https://doi.org/10.1213/ANE.0000000000000940.
[5] Dony P, Dramaix M, Boogaerts JG. Hypocapnia measured by end-tidal carbon dioxide tension during anesthesia is associated with increased 30-day mortality rate. J Clin Anesth 2017;36:123–6. https://doi.org/10.1016/j.jclinane.2016.10.028.
[6] Park JH, Lee HM, Kang CM, Kim KS, Jang CH, Hwang HK, et al. Correlation of intraoperative end-tidal carbon dioxide concentration on postoperative hospital stay in patients undergoing pylorus-preserving pancreaticoduodenectomy. World J Surg 2021;45(6):1860–7. https://doi.org/10.1007/s00268-021-05984-x.
[7] Wax DB, Lin HM, Hossain S, Porter SB. Intraoperative carbon dioxide management and outcomes. Eur J Anaesthesiol 2010;27(9):819–23. https://doi.org/10.1097/EJA.0b013e32833cca07.
[8] Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care 2010;14(2):220. https://doi.org/10.1186/cc8926.
[9] McSwain SD, Hamel DS, Smith PB, Gentile MA, Srinivasan S, Meliones JN, et al. End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. Respir Care 2010;55(3):288–93.
[10] Aminiahidashti H, Shafiee S, Zamani Kiasari A, Sazgar M. Applications of end-tidal carbon dioxide (ETCO2) monitoring in emergency department; a narrative review. Emerg (Tehran) 2018;6(1):e5.

[11] Mazo V, Sabaté S, Canet J, Gallart L, de Abreu MG, Belda J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. Anesthesiology 2014;121(2):219–31. https://doi.org/10.1097/ALN.0000000000000334.
[12] Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747–55. https://doi.org/10.1056/NEJMsa1410639.
[13] van Meenen DMP, Algera AG, Schuijt MTU, Simonis FD, van der Hoeven SM, Neto AS, et al. Effect of mechanical power on mortality in invasively ventilated ICU patients without the acute respiratory distress syndrome: an analysis of three randomised clinical trials. Eur J Anaesthesiol 2023;40(1):21–8. https://doi.org/10.1097/EJA.0000000000001778.
[14] Dong L, Takeda C, Kamitani T, Hamada M, Hirotsu A, Yamamoto Y, et al. Association between intraoperative end-tidal carbon dioxide and postoperative organ dysfunction in major abdominal surgery: a cohort study. PloS One 2023;18(3):e0268362. https://doi.org/10.1371/journal.pone.0268362.
[15] Bender SP, Paganelli WC, Gerety LP, Tharp WG, Shanks AM, Housey M, et al. Intraoperative lung-protective ventilation trends and practice patterns: a report from the multicenter perioperative outcomes group. Anesth Analg 2015;121(5):1231–9. https://doi.org/10.1213/ANE.0000000000000940.
[16] Lele EE, Hantos Z, Bitay M, Szívós B, Bogáts G, Peták F, et al. Bronchoconstriction during alveolar hypocapnia and systemic hypercapnia in dogs with a cardiopulmonary bypass. Respir Physiol Neurobiol 2011;175(1):140–5. https://doi.org/10.1016/j.resp.2010.10.004.
[17] Rodarte JR, Hyatt RE. Effect of acute exposure to CO2 on lung mechanics in normal man. Respir Physiol 1973;17(2):135–45. https://doi.org/10.1016/0034-5687(73)90057-1.
[18] Myrianthefs PM, Briva A, Lecuona E, Dumasius V, Rutschman DH, Ridge KM, et al. Hypocapnic but not metabolic alkalosis impairs alveolar fluid reabsorption. Am J Respir Crit Care Med 2005;171(11):1267–71. https://doi.org/10.1164/rccm.200408-998OC.
[19] Nassar BS, Schmidt GA. Estimating arterial partial pressure of carbon dioxide in ventilated patients: how valid are surrogate measures? Ann Am Thorac Soc 2017;14(6):1005–14. https://doi.org/10.1513/AnnalsATS.201701-034FR.
[20] Jin X, Weil MH, Tang W, Povoas H, Pernat A, Xie J, et al. End-tidal carbon dioxide as a noninvasive indicator of cardiac index during circulatory shock. Crit Care Med 2000;28(7):2415–9. https://doi.org/10.1097/00003246-200007000-00037.
[21] Fogagnolo A, Montanaro F, Al-Husinat L, Turrini C, Rauseo M, Mirabella L, et al. Management of intraoperative mechanical ventilation to prevent postoperative complications after general anesthesia: a narrative review. J Clin Med 2021;10(12):2656. https://doi.org/10.3390/jcm10122656.
[22] Sun M, Jia R, Wang L, Sun D, Wei M, Wang T, et al. Effect of protective lung ventilation on pulmonary complications after laparoscopic surgery: a meta-analysis of randomized controlled trials. Front Med (Lausanne) 2023;10:1171760. https://doi.org/10.3389/fmed.2023.1171760.
[23] Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015;32(2):88–105. https://doi.org/10.1097/EJA.0000000000000118.
[24] Morita S, Tsuruta M, Okabayashi K, Ishida T, Shigeta K, Seishima R, et al. Impact of intraoperative hypocapnia on postoperative complications in laparoscopic surgery for colorectal cancer. Surg Today 2022;52(2):278–86. https://doi.org/10.1007/s00595-021-02315-4.
[25] Fuller BM, Mohr NM, Drewry AM, Ferguson IT, Trzeciak S, Kollef MH, et al. Partial pressure of arterial carbon dioxide and survival to hospital discharge among patients requiring acute mechanical ventilation: a cohort study. J Crit Care 2017;41:29–35. https://doi.org/10.1016/j.jcrc.2017.04.033.
[26] Tiruvoipati R, Serpa Neto A, Young M, Marhoon N, Wilson J, Gupta S, et al. An exploratory analysis of the association between hypercapnia and hospital mortality in critically ill patients with Sepsis. Ann Am Thorac Soc 2022;19(2):245–54. https://doi.org/10.1513/AnnalsATS.202102-104OC.
[27] Satoh K, Ohashi A, Kumagai M, Sato MA, Kuji Joh S. Evaluation of differences between PaCO2 and ETCO2 by age as measured during general anesthesia with patients in a supine position. J Anesth 2015;2015:710537. https://doi.org/10.1155/2015/710537.