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REPORTS OF ORIGINAL INVESTIGATIONS

Difference between arterial and end-tidal carbon dioxide and adverse events after non-cardiac surgery: a historical cohort study

Différence entre le dioxyde de carbone artériel et le dioxyde de carbone télé-expiratoire et événements indésirables après une chirurgie non cardiaque : une étude de cohorte historique

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Abstract

Purpose *The difference between arterial and end-tidal partial pressure of carbon dioxide (ΔCO_2) is a measure of alveolar dead space, commonly evaluated intraoperatively. Given its relationship to ventilation and perfusion, ΔCO_2 may provide prognostic information and guide clinical decisions. We hypothesized that higher ΔCO_2 values are associated with occurrence of a composite outcome of re-intubation, postoperative mechanical ventilation, or 30-day mortality in patients undergoing non-cardiac surgery.*

Methods *We conducted a historical cohort study of adult patients undergoing non-cardiac surgery with an arterial line at a single tertiary care medical centre. The composite outcome, identified from electronic health records, was re-intubation, postoperative mechanical ventilation, or 30-day mortality. Student's t test and Chi-squared test were used for univariable analysis. Logistic regression was used for multivariable analysis of the relationship of ΔCO_2 with the composite outcome.*

Results *A total of 19,425 patients were included in the final study population. Univariable analysis showed an association between higher mean (standard deviation [SD]) intraoperative ΔCO_2 values and the composite outcome (6.1 [5.3] vs 5.7 [4.5] mm Hg; $P = 0.002$). After adjusting for baseline subject characteristics, every 5-mm Hg increase in the ΔCO_2 was associated with a nearly 20% increased odds of the composite outcome (odds ratio, 1.20; 95% confidence interval, 1.12 to 1.28; $P < 0.001$).*

Conclusions *In this patient population, increased intraoperative ΔCO_2 was associated with an increased odds of the composite outcome of postoperative mechanical ventilation, re-intubation, or 30-day mortality that was independent of its relationship with pre-existing pulmonary disease. Future studies are needed to determine if ΔCO_2 can be used to guide patient management and improve patient outcomes.*

Résumé

Objectif *La différence entre la pression partielle artérielle et télé-expiratoire en dioxyde de carbone (ΔCO_2) est une mesure de l'espace mort alvéolaire couramment évaluée en période peropératoire. Compte tenu de sa relation avec la ventilation et la perfusion, la ΔCO_2 pourrait fournir des informations pronostiques et guider les décisions cliniques. Nous avons émis l'hypothèse que des valeurs de ΔCO_2 plus élevées seraient associées à l'apparition d'un résultat composite de réintubation, de ventilation mécanique postopératoire ou de mortalité à 30 jours chez les patients bénéficiant d'une chirurgie non cardiaque.*

Méthode *Nous avons mené une étude de cohorte historique de patients adultes bénéficiant d'une chirurgie non cardiaque dans un seul centre médical de soins tertiaires et chez lesquels une canule artérielle était installée. Le résultat composite, identifié à partir des dossiers de santé électroniques, était la réintubation, la ventilation mécanique postopératoire ou la mortalité à 30 jours. Le test t de Student et le test du chi carré ont été*

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utilisés pour l'analyse univariée. La régression logistique a été utilisée pour l'analyse multivariée de la relation entre la ΔCO_2 et le résultat composite.
Résultats *Au total, 19 425 patients ont été inclus dans la population finale à l'étude. L'analyse univariée a montré une association entre des valeurs peropératoires moyennes plus élevées (écart type [ET]) de ΔCO_2 et le résultat composite (6,1 [5,3] vs 5,7 [4,5] mmHg; P = 0,002). Après ajustement pour tenir compte des caractéristiques de base des sujets, chaque augmentation de 5 mmHg de la ΔCO_2 a été associée à une augmentation de près de 20 % de la probabilité du résultat composite (rapport de cotes, 1,20; intervalle de confiance à 95 %, 1,12 à 1,28; P < 0,001).*
Conclusion *Dans cette population de patients, une augmentation peropératoire de la ΔCO_2 était associée à une probabilité accrue du résultat composite de ventilation mécanique postopératoire, de réintubation ou de mortalité à 30 jours, indépendamment de sa relation avec une maladie pulmonaire préexistante. D'autres études sont nécessaires à l'avenir pour déterminer si la ΔCO_2 peut être utilisée pour guider la prise en charge des patients et améliorer les devenirs des patients.*

Keywords dead space · arterial to end-tidal carbon dioxide difference · end-tidal carbon dioxide (CO_2) · delta carbon dioxide (CO_2)

Postoperative respiratory complications are common and significant postoperative adverse events. Patients affected by complications such as pulmonary edema, postoperative respiratory failure, and pneumonia tend to have longer hospital stays, higher costs, and increased 30-day mortality.[1–4] Recent studies indicate that ventilator settings contribute to postoperative pulmonary complications, even in healthy patients.[5–8] These studies have focused primarily on the impact of inspiratory pressures and tidal volume (TV), with little data collected on ventilation efficiency. Dead space ventilation (VD) is affected by both lung function and perfusion,[9] and its intraoperative measurement may provide prognostic information and aid in optimizing ventilation management during surgery.

Dead space is the portion of TV that does not participate in gas exchange. Total dead space (VD_{phys}) is composed of anatomic (VD_{ana}) and alveolar dead space (VD_{alv}), represented by the equation $VD_{phys} = VD_{ana} + VD_{alv}$. The division between VD_{ana} and VD_{alv} is not a strictly anatomic division, but depends on the interface between inspired air and alveolar gas. Dead space associated with conducting airways (endotracheal tube, trachea, proximal bronchi) is described as VD_{ana} and dead space associated with non-perfused alveoli (distal airways) is described as VD_{alv}.[10] While VD_{ana} is relatively fixed in an intubated patient undergoing general anesthesia, VD_{alv} can be influenced by perfusion (heart rate [HR], mean arterial pressure [MAP], cardiac output [CO], volume status, patient positioning), ventilation (respiratory rate [RR], TV, positive end-expiratory pressure [PEEP]), and metabolic (CO_2 production)[11–13] variables, many of which are monitored and modified under general anesthesia.

Evaluation of VD_{phys} is useful in assessment and management in some clinical settings. An elevated VD_{phys} predicts an increased risk for mortality in acute respiratory disease syndrome (ARDS).[14–16] Through its relationship to atelectasis and ventilation/perfusion (V/Q) matching, VD_{phys} is also useful for choosing the optimal level of PEEP in mechanically ventilated patients.[17–19] As VD_{ana} is often a relatively fixed component, evaluation and management based on VD_{phys} or VD_{alv}, might be useful in other patient populations undergoing mechanical ventilation.

There are multiple ways to calculate or estimate VD_{phys}, VD_{ana}, and VD_{alv}, but these are often not available in many clinical settings. The difference between arterial partial pressure of carbon dioxide ($PaCO_2$) and partial pressure of end-tidal CO_2 ($PetCO_2$), ΔCO_2, is one of the most readily available methods to estimate VD_{alv} as the difference between these two values is attributed primarily to VD_{alv}.[13,20–28] Increased ΔCO_2 has been associated with poor outcomes in trauma[29] and critically ill patients requiring major surgery.[13]

The objective of this study was to evaluate if ΔCO_2 is independently associated with worse outcomes in patients undergoing non-cardiac surgery. We hypothesized that, in patients undergoing general anesthesia, greater ΔCO_2 is associated with an increased odds of the postoperative composite outcome of postoperative mechanical ventilation, re-intubation, or 30-day mortality.

Methods

Following approval from the Institutional Review Board, we conducted a historical cohort study at University of Michigan Medical Center (Ann Arbor, MI, USA); the requirement for patient consent was waived. We queried the electronic anesthesia records for all adult cases from 23 July 2009 to 31 January 2019 for which general endotracheal anesthesia was performed and at least one arterial blood gas (ABG) was recorded during the procedure. Exclusion criteria were an American Society of Anesthesiology (ASA) Physical Status classification of

VI, preoperative mechanical ventilation, sodium bicarbonate administration within 15 min prior to ABG measurement, cardiopulmonary bypass or extracorporeal membrane oxygenation, absent $PetCO_2$ or $PaCO_2$ data, or intraoperative one-lung ventilation.

Patient and perioperative data

Demographic information was collected from the preoperative history and physical documentation. This comprised age, sex, height, weight (actual and ideal), body mass index (BMI), ASA Physical Status score, smoking status (current or former), chronic obstructive pulmonary disease (COPD), and asthma. Preoperative values for albumin, blood urea nitrogen, creatinine, and peripheral oxygen saturation (SpO_2) were obtained. Creatinine clearance was calculated using the Cockcroft–Gault formula. Procedure variables included (i) type, (ii) duration, and (iii) emergent *vs* elective procedure. Other intraoperative variables were the total transfusion requirement including volume of packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate; estimated blood loss; total crystalloid administration; and grams of albumin administered.

Blood gas, ventilator, and hemodynamic data

For all patients, the first ABG obtained in the operating room after induction of general anesthesia was utilized in our analysis and pH, $PaCO_2$, arterial partial pressure of oxygen (PaO_2), and arterial oxygen saturation (SaO_2) were collected. Ventilator parameters (TV, RR, minute ventilation, pressure support, peak airway pressure, PEEP, and fraction of inspired oxygen), hemodynamic data (HR and MAP), and $PetCO_2$ were collected for the ten-minute epoch surrounding the ABG time and the median values were utilized in the analysis.

Outcome

Our study outcome was a composite of the postoperative complications, postoperative mechanical ventilation, re-intubation, or mortality, as identified from the electronic health record (EHR). Postoperative mechanical ventilation was defined as any patient who required mechanical ventilation after the procedure for any duration not associated with another procedure. We defined re-intubation as a period of time in the EHR without receipt of mechanical ventilation subsequently followed by the documented presence of mechanical ventilation. Mortality was included as an outcome since it would act to censor future pulmonary complications. Patients were assumed to be alive at 30 days unless noted to be deceased in the medical record.

Statistics

We calculated descriptive statistics for each variable. Continuous variables that were normally distributed were presented as mean (standard deviation [SD]). Continuous variables that were non-normally distributed were summarized as median [interquartile range (IQR)]. Categorical variables were summarized using counts and proportions.

Preoperative characteristics and ΔCO_2 were compared between those with and without the composite outcome using Chi square tests for categorical variables and *t* tests or Mann–Whitney U tests for continuous variables. Multivariable logistic regression models were generated to evaluate whether ΔCO_2 was associated with the composite outcome while adjusting for other patient and surgical factors based on clinical and statistical significance. For entry into the model, we chose clinically relevant variables that were selected by two anesthesiologists based on the literature. Additionally, we considered variables with standardized differences greater than 0.2 using Cohen's d. We also collapsed several variables into one variable, or chose a representative variable from a group, when the groups of variables were similar or highly correlated ($\rho > 0.8$). Upon constructing the multivariable model, we removed, collapsed, or grouped variables with variance inflation factors > 2.5.

For each of the continuous variables included in the model (age, creatinine clearance, preoperative albumin, total albumin, case duration, total volume blood products, percent inspired oxygen, TV, RR, MAP, HR, and ΔCO_2), the following potential transformations were considered: X^{-2}, X^{-1}, $X^{-0.5}$, $\ln(X)$, $X^{0.5}$, X^1, and X^2. The continuous variables were binned and plotted as the proportion within each bin with the outcome. Variables with values of zero were shifted by one or one plus their minimum to use all the listed transformations. Univariate regressions with the composite outcome as the outcome and each transformation of each continuous variable were then used to predict values at the median of the bins and plot the predicted outcome for the transformation. These transformations were inspected visually and used to determine that no non-linear terms were necessary.

Additionally, all variables that were significant predictors in the initial multivariable model were also considered for interactions with the primary predictor, ΔCO_2. Each significantly associated variable was centred and an interaction between it and ΔCO_2 was added individually to the initial full regression. All interactions that were significant individually were used together in a full regression. Interactions that were not significant at a level of $P < 0.05$ in this new full regression were removed. Even though multiple interactions remaining in the model had $P < 0.05$, most interaction terms had a small magnitude of association with the outcome, none changed the direction of the relationship between ΔCO_2 and the primary outcome, and none of the variables were conceptually thought to have a multiplicative effect for any of the variables with the ΔCO_2. Based on this, none of the interactions were added to the final, clinically relevant model.

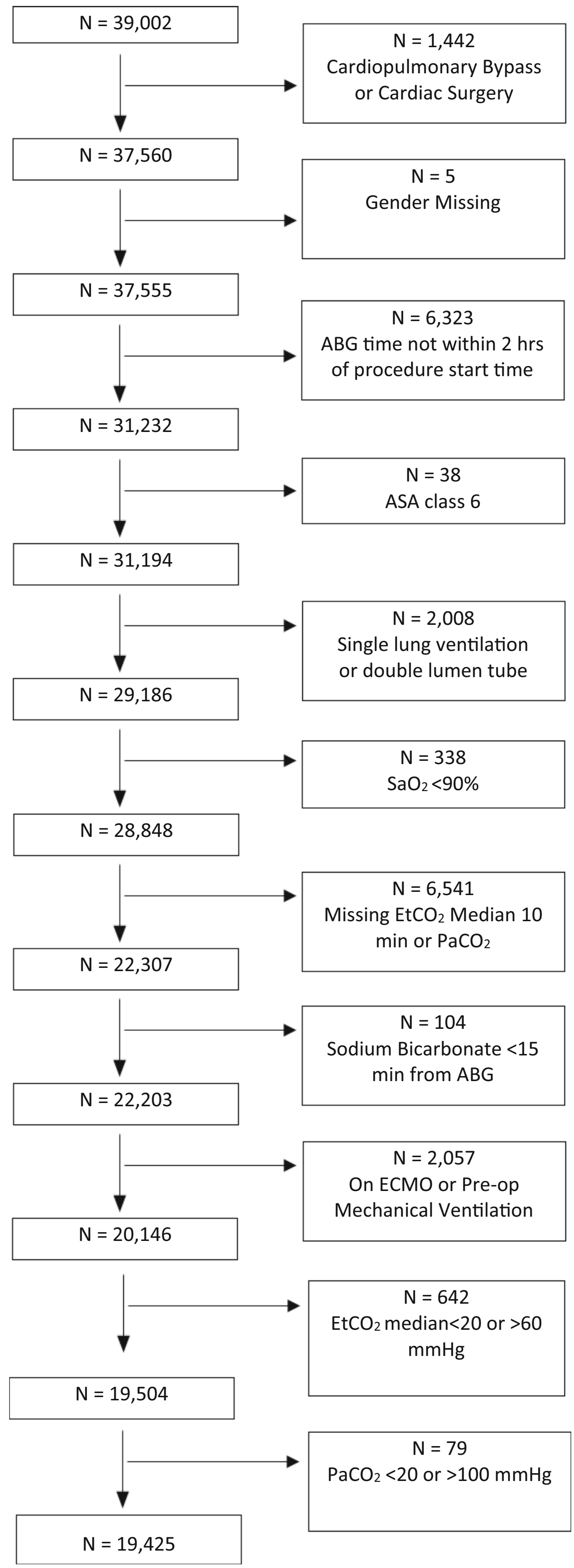
Akaike Information Criteria, Bayes Information Criteria, -2 log likelihood, and area under the receiver operating characteristic curve (95% confidence interval [CI]) were used to evaluate the model. P values < 0.05 and CIs excluding 1 were considered statistically significant. Analyses were performed in R version 3.6.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

After excluding patients with missing data or data concerning for errant manual entry, 19,425 patients remained for analysis (Fig. 1). The mean (SD) time from anesthesia start to ABG was 73 (26) min. In our patient population, 15% (n = 2,830) had COPD, 10% (n = 1,951) had asthma, and 7% (n = 1,274) were on supplemental oxygen preoperatively (Table 1). The mean values for $PaCO_2$ and $PetCO_2$ were 40.2 (5.8) mm Hg and 34.3 (4.0) mm Hg, respectively, with a mean ΔCO_2 of 5.8 (4.6) mm Hg. A total of 3,006 patients (16%) had the composite outcome: 85 (0.4%) required postoperative re-intubation, 2,769 (14%) required postoperative mechanical ventilation, and 452 (2%) had 30-day mortality.

Preoperative and intraoperative variables and outcomes

Many of the evaluated variables were significantly different between groups of patients who did and did not experience the composite outcome (Table 2). Notably, patients who had the composite outcome were more likely to use preoperative supplemental oxygen (19% *vs* 4%; $P < 0.001$) and have COPD (17% *vs* 14%; $P < 0.001$), and less likely to have asthma (8% *vs* 10%; $P < 0.001$). Similar smoking rates (55% *vs* 55%; $P = 0.386$) were present in each cohort. Patients who had the composite outcome had a significantly higher mean (SD) ΔCO_2 (6.1 [5.3] *vs* 5.7 [4.5] mm Hg; $P = 0.002$).



◀ **Fig. 1** Exclusion criteria: Using initial query parameters, information for 39,002 patients were included. Patients were excluded based on pre-determined exclusion criteria. After initial exclusions, box plots of patient data were reviewed, and outliers were eliminated if data were determined to be entered in error (venous blood gas charted as arterial) or unlikely based on known physiologic variables. Ultimately, 19,425 patients were included in the final analysis.

Multivariable regressions

After adjusting for other factors, ΔCO_2 was associated with an increased occurrence of re-intubation, postoperative mechanical ventilation, or 30-day mortality (Table 3). In our regression, every 5-mm Hg increase in the ΔCO_2 was associated with a nearly 20% increased odds of the composite outcome (odds ratio [OR], 1.20; 95% CI, 1.12 to 1.28; $P < 0.001$). For our multivariable regression, at $\Delta CO_2 = 0$, the median [IQR] risk of re-intubation, postoperative mechanical ventilation, or 30-day mortality was 9.2 [7.9–10.5]%, at $\Delta CO_2 = 5$ mm Hg, the risk was 10.8 [9.5–12.2]%, and at $\Delta CO_2 = 10$ mm Hg, the risk was 12.7 [11.0–14.4]%. For the rare patient with $\Delta CO_2 = 20$ mm Hg, the risk was 17.2 [13.8–20.6]% (Fig. 2).

Several other variables were independently associated with the composite outcome (Table 3). The use of preoperative supplemental oxygen was associated with the composite outcome (OR, 2.37; 95% CI, 1.97 to 2.84; $P < 0.001$), while higher albumin levels were associated with a decrease in the incidence of the composite outcome (OR, 0.53; 95% CI, 0.48 to 0.58; $P < 0.001$ per $g \cdot dL^{-1}$). Chronic obstructive pulmonary disease was not associated with re-intubation, postoperative mechanical ventilation, or 30-day mortality (OR, 1.16; 95% CI, 0.99 to 1.36; $P = 0.06$). The model had good discrimination (C statistic, 0.87; 95% CI, 0.86 to 0.88).

Discussion

In this historical cohort study, we found that increased ΔCO_2 was associated with an increase in the composite outcome of postoperative mechanical ventilation, re-intubation, or 30-day mortality in patients undergoing general anesthesia for a non-cardiac surgical procedure. This relationship remained significant even when we adjusted for other relevant pre-existing clinical factors, including COPD, preoperative oxygen use, dialysis, and age. Since the magnitude of association for a 5 mm Hg of change is nearly 20%, even relatively small changes in ΔCO_2 produce clinically important changes to the risk of the composite outcome. For a patient with a ΔCO_2 of 2–4 mm Hg, consistent with normal healthy levels, the median [IQR] predicted risk of pulmonary complications or death in this patient population was between 9.9 [9.6–10.1]% and 10.5 [10.1–11.2]%. For a ΔCO_2 of 10, 15, and 20 mm Hg, the risk increased to 12.7 [11.0–14.4]%, 14.8 [12.9–17.1]%, and 17.2 [13.8–20.6]%, respectively.

The magnitude of ΔCO_2 is affected by both ventilated but unperfused alveoli (true dead space) and alveoli with high ventilation/perfusion ratios (V/Q inequality). Shunt (perfusion without ventilation) will cause a small increase in ΔCO_2 by raising the $PaCO_2$ as mixed venous blood, which is higher in PCO_2, crosses the pulmonary circulation and mixes with the systemic arterial circulation. True dead space and V/Q inequality are markers of disease severity and increase with COPD severity or low CO states. ΔCO_2 is also influenced by dynamic, modifiable, and clinically important variables of ventilation (RR, TV, PEEP), perfusion (HR, MAP, CO, volume status, patient positioning), and metabolism (CO_2 production).[11–13,30] Some of these are under the control of the anesthesiologist, and studies should be conducted to determine how anesthesiologists' manipulation of these parameters affects both ΔCO_2, and more importantly, patient outcome.

Clinically, ΔCO_2 has been utilized as a surrogate for VD_{alv}, primarily in the intensive care unit, where levels correlate with the amount of VD_{alv}.[31] In addition, ΔCO_2 has been shown to correlate with disease severity in ARDS patients, with a higher ΔCO_2 being associated with more severe ARDS[32] and with death.[33] Similarly, elevated ΔCO_2 in patients who have survived cardiac arrest is associated with high hospital mortality.[34] Nevertheless, use of ΔCO_2 as an intraoperative prognostic measure is less common but is supported by our findings.

Tyburski *et al.* studied 501 trauma patients undergoing emergency surgery. In patients who died (n = 147 [29%]), ΔCO_2 was higher at all three time points evaluated (initial, post-resuscitation, and final). In those who died, lower values were predictive of longer survival with a final mean (SD) ΔCO_2 of 22.25 (14.32) mm Hg in patients who died intraoperatively, 19.96 (14.91) mm Hg in patients who died within 24 hr after surgery, and 10.90 (10.13) mm Hg in patients who died after 24 hr but before hospital discharge. Survivors had a ΔCO_2 of 7.37 (6.30) mm Hg (all $P < 0.006$ compared with non-survivors).[29] In another study of critically ill or injured patients requiring major surgery with 41% mortality, Domsky *et al.* found highest mortality rates in patient with the highest ΔCO_2, and highest estimated VD_{alv} fraction.[13]Our study is in agreement with these two studies. While these studies are limited to trauma and critically ill surgery patients, our study is more generalizable as it includes a large variety of non-cardiac operations. To our knowledge, our study is the first large study showing that increased ΔCO_2 is associated with our

Table 1 Patient and demographic characteristics

		Total *N*	*n*	(%)
Male		19,355	10,981	(56.7%)
Comorbidities				
Supplemental oxygen		19,355	1,274	(6.6%)
Current or former smoker		19,355	10,669	(55.2%)
COPD		19,355	2,830	(14.6%)
Asthma		19,335	1,951	(10.1%)
Dialysis		19,354	554	(2.9%)
ASA Physical Status score III, IV, or V		19,334	15,627	(81%)
BMI	Normal	18,724	4,905	(26.2%)
	Underweight	18,724	498	(2.7%)
	Overweight	18,724	5,848	(31.2%)
	Obesity class I	18,724	3,943	(21.1%)
	Obesity class II	18,724	1,979	(10.6%)
	Obesity class III	18,724	1,551	(8.3%)
Emergent		19,334	2,624	(13.6%)
Postoperative re-intubation		19,355	85	(0.4%)
30-day mortality		19,355	452	(2.3%)
Postoperative ventilator		19,355	2,769	(14.3%)
Procedure type				
General surgery		19,355	3,145	(16.2%)
Gynecologic surgery		19,355	329	(1.7%)
Head and neck surgery		19,355	2,339	(12.1%)
Neurosurgery		19,355	4,676	(24.2%)
Orthopedic surgery		19,355	1,441	(7.4%)
Plastic surgery		19,355	231	(1.2%)
Thoracic surgery		19,355	800	(4.1%)
Transplant surgery		19,355	1,099	(5.7%)
Urologic surgery		19,355	1,546	(8.0%)
Vascular surgery		19,355	2,315	(12.0%)
Other surgery		19,355	1,434	(7.4%)

	N	Mean (SD)		Median [IQR]	
Demographics					
Age (yr)	19,355	59	(16)	61	[51–70]
Weight (kg)	19,086	86	(24)		
Height (cm)	19,019	170	(11)		
Preoperative labs/vitals					
Creatinine ($mg \cdot dL^{-1}$)	18,753	1.1	(1.0)		
Blood urea nitrogen ($mg \cdot dL^{-1}$)	18,646	20.1	(12.5)		
Creatinine clearance ($mL \cdot min^{-1}$)	18,490	104.7	(56.8)		
SpO_2 (%)	18,842	97	(2)		
Albumin ($g \cdot dL^{-1}$)	16,649	4.0	(0.7)		
Intraoperative variables					
Case duration (min)	19,354	357	(171)		
Time of ABG from anesthesia start (min)*	19,355	73	(26)		
Fluids†					
Total albumin (g)	4,382	46	(32)	37	[25–50]
Hetastarch (mL)	370	705	(311)	500	[500–1000]

continued

	N	Mean (SD)		Median [IQR]	
Total crystalloid (mL)	19,355	2,690	(1,524)		
Total volume blood products (mL)	3,699	2,093	(4,815)	700	[350–1600]
Total pRBC (mL)	3,224	1,289	(2,264)	700	[350–1400]
Total FFP (mL)	1,184	1,885	(2860)	825	[550–2200]
Total platelets (mL)	830	676	(612)	550	[275–825]
Total cryoprecipitate (mL)	332	270	(196)	200	[100–400]
Estimated blood loss (mL)	17,231	593	(1,546)	200	[100–500]
Hemodynamics					
Heart rate (beats·min^{-1})	19,179	72	(16)		
Mean arterial pressure (mm Hg)	18,179	79	(14)		
Ventilator					
Tidal volume (mL·kg^{-1})	18,296	7.7	(1.6)		
Respiratory rate (breaths·min^{-1})	18,610	12	(3)		
Minute ventilation (L·min^{-1})	18,532	5.8	(1.4)		
Peak airway pressure (mm Hg)	18,922	19	(6)		
PEEP (mm Hg)	18,842	5	(2)		
End-tidal CO_2 (mm Hg)	19,355	34	(4)		
Inspired oxygen percent (%)	18,900	61	(23)		
Blood gas					
pH	19,293	7.41	(0.06)		
PaO_2 (mm Hg)	19,024	215	(108)		
$PaCO_2$ (mm Hg)	19,355	40	(6)		
$PaCO_2$ – $PetCO_2$ (mm Hg)	19,355	**6**	**(5)**		
Composite outcome	19,355	3,006	(16)		

Body mass index (BMI) was subdivided into World Health Organization categories: underweight (BMI < 18.5 kg·m^{-2}), normal (BMI 18.5–24.9 kg·m^{-2}) overweight (BMI 25–29.9 kg·m^{-2}), obesity class I (BMI 30–34.9 kg·m^{-2}), obesity class II (BMI 35.0–39.9 kg·m^{-2}), and obesity class III (BMI ≥ 40 kg·m^{-2}). Tidal volume calculated by dividing tidal volume by ideal body weight.

*The median [interquartile range] time of arterial blood gas from anesthesia start was 71 [54–91] min. †As most patients did not receive transfusions or colloid, numbers reflect only those patients who received a particular product with the corresponding means (standard deviations)/medians [interquartile ranges].

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FFP = fresh frozen plasma; IQR = interquartile range; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2 = arterial partial pressure of oxygen; PEEP = positive end expiratory pressure; $PetCO_2$ = end-tidal partial pressure of carbon dioxide; pRBC = packed red blood cells; SD = standard deviation; SpO2 = peripheral oxygen saturation.

composite outcome in a broad patient population of adults undergoing general anesthesia with arterial lines. Our results indicate that high intraoperative ΔCO_2 should not be ignored in patients undergoing general anesthesia. Additional studies are necessary to better understand the clinical utility of our results.

There are a few important limitations to this study. As a single-centre study, it might not be generalizable to other centres with different intraoperative ventilator strategies or practice surrounding $PaCO_2$ measurement indications or timing. At our institution, 97.7% of patients who had an arterial line placed for their procedure had an ABG measured with a mean (SD) time from anesthesia start to ABG measurement of 73 (26) min. This limits our findings to patients and procedures for which arterial lines are utilized and likely explains the wider ΔCO_2 found in this study compared with previous studies that excluded ASA III–V patients or patients with "respiratory or cardiac abnormalities."[35,36] Second, $PaCO_2$ and $PetCO_2$ are dynamic as patients undergo hours of anesthesia. The first ABG was selected to facilitate comparability of patients undergoing anesthesia as a baseline since many patients had only one ABG at the beginning of the case. Selecting the first ABG allowed for analysis of a large patient population; it also minimized bias. Nevertheless, this measure was more representative of the initial clinical

Table 2 Univariable analysis for study variables

		No composite outcome			Composite outcome			*P* value	Cohen's *d*
		n	Total *N*	(%)	*n*	Total *N*	(%)		
Male		9,184	16,349	(56.2%)	1,797	3,006	(59.8%)	0.001	0.07
Preoperative supplemental O_2		712	16,349	(4.4%)	562	3,006	(18.7%)	< 0.001	0.46
Comorbidities:									
Current or former smoker		9,035	16,349	(55.3%)	1,634	3,006	(54.4%)	0.36	0.02
Diagnosis of COPD		2,333	16,349	(14.3%)	497	3,006	(16.5%)	0.002	0.06
Diagnosis of asthma		1,708	16,349	(10.4%)	243	3,006	(8.1%)	< 0.001	0.08
Preoperative dialysis		355	16,349	(2.2%)	199	3,005	(6.6%)	< 0.001	0.22
BMI	Normal	4,154	15,926	(26.1%)	751	2,798	(26.8%)	< 0.001	0.02
	Underweight	387	15,926	(2.4%)	111	2,798	(4.0%)		0.09
	Overweight	5,031	15,926	(31.6%)	817	2,798	(29.2%)		0.05
	Obesity class I	3,396	15,926	(21.3%)	547	2,798	(19.5%)		0.04
	Obesity class II	1,681	15,926	(10.6%)	298	2,798	(10.7%)		< 0.01
	Obesity class III	1,277	15,926	(8.0%)	274	2,798	(9.8%)		0.06
ASA Physical Status score III, IV, or V		12,946	16,335	(79.3%)	2,681	2,999	(89.4%)	< 0.001	0.28
Emergent		1,295	16,335	(7.9%)	1,329	2,999	(44.3%)	< 0.001	0.91
Procedure type									
General surgery		2,470	16,349	(15.1%)	675	3,006	(2.5%)	< 0.001	0.19
Gynecologic surgery		284	16,349	(1.7%)	45	3,006	(1.5%)	0.39	0.02
Head and neck surgery		1,944	16,349	(11.9%)	395	3,006	(13.1%)	0.06	0.04
Neurosurgery		4,267	16,349	(26.1%)	409	3,006	(13.6%)	< 0.001	0.32
Orthopedic surgery		1,294	16,349	(7.9%)	147	3,006	(4.9%)	< 0.001	0.12
Plastic surgery		201	16,349	(1.2%)	30	3,006	(1.0%)	0.32	0.02
Thoracic surgery		726	16,349	(4.4%)	74	3,006	(2.5%)	< 0.001	0.11
Transplant surgery		626	16,349	(3.8%)	473	3,006	(15.7%)	< 0.001	0.41
Urologic surgery		1,432	16,349	(8.8%)	114	3,006	(3.8%)	< 0.001	0.21
Vascular surgery		2,020	16,349	(12.4%)	295	3,006	(9.8%)	< 0.001	0.08
Other surgery		1,085	16,349	(6.6%)	349	3,006	(11.6%)	< 0.001	0.17

	No composite outcome			Composite outcome				
	Mean (SD)	Median [IQR]	*n*	Mean (SD)	Median [IQR]	*n*	*P* value*	Cohen's *d*
Demographic								
Age (yr)	59.4	(15.6)	16,349	59.1	(15.2)	3,006	0.39	0.02
Weight (kg)	85.3	(23.2)	16,215	86.4	(26.2)	2,871	0.03	0.05
Height (cm)	170	(11.1)	16,120	170.4	(11.2)	2,899	0.04	0.04
Preoperative labs/vitals								
Preoperative Cr ($mg{\cdot}dL^{-1}$)	1.0	(0.9)	15,811	1.3	(1.2)	2,942	< 0.001	0.24
Preoperative BUN ($mg{\cdot}dL^{-1}$)	19.2	(10.9)	15,723	25.2	(18.2)	2,923	< 0.001	0.24
Creatinine clearance ($mL{\cdot}min^{-1}$)	105.3	(54.5)	15,682	101.5	(68.3)	2,808	0.006	0.06
Preoperative albumin ($g{\cdot}dL^{-1}$)	4.1	(0.6)	13,946	3.5	(0.8)	2,703	< 0.001	0.90
Preoperative SpO_2 (%)	96.8	(2.2)	16,033	96.5	(2.6)	2,809	< 0.001	0.10
Intraoperative variables								
Case duration (min)	350.3	(159.7)	16,348	390.8	(220.6)	3,006	< 0.001	0.21

continued

	No composite outcome					Composite outcome						
	Mean (SD)		Median [IQR]		*n*	Mean (SD)		Median [IQR]		*n*	*P* value*	Cohen's *d*
Time of ABG from anesthesia start (min)	73.4	(26.1)			16,349	70.9	(27.1)			3,006	< 0.001	0.09
Fluids§												
Total crystalloid (mL)	2,651	(1,394)			16,349	2,904	(2,087)			3,006	0.28‡	0.14
Total albumin (g)	41.3	(24.8)	25	[25–25]	3,196	59.5	(44.4)	50	[50–75]	1,186	< 0.001‡	0.49
Hetastarch (mL)	689	(296)	500	[500–1000]	307	780	(364)	800	[500–1,000]	63	0.41‡	0.03
Total volume blood products (mL)	861	(893)	700	[350–1050]	2,221	3,942	(7,151)	1,400	[700–4,213]	1,478	< 0.001‡	0.48
Total pRBC (mL)	727	(518)	700	[350–700]	1,884	2,080	(3,300)	1,050	[700–2,100]	1,340	< 0.001‡	0.49
Total FFP (mL)	734	(649)	550	[275–825]	395	2,462	(3,328)	1,340	[550–3,300]	789	< 0.001‡	0.44
Total platelets (mL)	446	(315)	275	[275–550]	272	787	(686)	550	[275–1,100]	558	< 0.001‡	0.46
Total cryoprecipitate (mL)	174	(87)	200	[100–200]	30	280	(201)	200	[200–400]	302	< 0.001‡	0.37
Estimated blood loss (mL)	394	(584)	200	[75–400]	14,755	1,776	(3,601)	450	[100–1706]	2,476	< 0.001‡	0.54
Hemodynamics†												
Heart rate (beats·min^{-1})	71	(15)			16,193	81	(20)			2,986	< 0.001	0.58
Mean arterial pressure (mm Hg)	79	(14)			15,366	76	(15)			2,813	< 0.001	0.20
Ventilator †												
Tidal volume (mL·kg^{-1})	7.7	(1.6)			15,507	7.5	(1.7)			2,789	< 0.001	0.12
Respiratory rate (breaths·min^{-1})	12	(3)			15,720	12	(3)			2,890	< 0.001	0.22
Minute ventilation (L·min^{-1})	5.7	(1.4)			15,662	5.9	(1.6)			2,870	< 0.001	0.11
Peak airway pressure (mm Hg)	18.5	(5.6)			16,027	20.5	(6.0)			2,895	< 0.001	0.34
PEEP (mm Hg)	4.8	(1.8)			15,954	5.1	(2.1)			2,888	< 0.001	0.14
End-tidal CO_2 (mm Hg)	34.4	(3.8)			16,349	34.8	(4.8)			3,006	< 0.001	0.11
Inspired oxygen (%)	60	(22)			16,010	70	(24)			2,890	< 0.001	0.41
Blood gas												
pH	7.4	(0.1)			16,298	7.4	(0.1)			2,995	< 0.001	0.41
PaO_2 (mm Hg)	215.0	(107.0)			16,061	217.5	(113.2)			2,963	0.28	0.02
$PaCO_2$ (mm Hg)	40.1	(5.7)			16,349	40.9	(6.7)			3,006	< 0.001	0.13
$PaCO_2$ – $PetCO_2$ (mm Hg)	**5.7**	**(4.5)**			**16,349**	**6.1**	**(5.3)**			**3,006**	**0.002**	**0.07**

Body mass index (BMI) was subdivided into World Health Organization categories: underweight (BMI < 18.5 kg·m^{-2}), normal (BMI 18.5–24.9 kg·m^{-2}), overweight (BMI 25–29.9 kg·m^{-2}), obesity class I (BMI 30–34.9 kg·m^{-2}), obesity class II (BMI 35.0–39.9 kg·m^{-2}), and obesity class III (BMI ≥ 40 kg·m^{-2}).

* *t* test *P* value unless otherwise indicated; † Median values from the 10 min epoch surrounding arterial blood gas analysis were utilized in calculation; ‡ Mann–Whitney U test *P* value. § As most patients did not receive transfusions or colloid, numbers reflect only those patients who received a particular product with the corresponding means (standard deviations)/medians [interquartile ranges].

ABG = arterial blood gas; ASA = American Society of Anesthesiologist ; BMI = body mass index; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; Cr = creatinine; FFP = fresh frozen plasma; IQR = interquartile range; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2 = arterial partial pressure of oxygen; PEEP = positive end expiratory pressure; $PetCO_2$ = end-tidal partial pressure of carbon dioxide; pRBC = packed red blood cells; SD = standard deviation; SpO2 = peripheral oxygen saturation.

Table 3 Multivariable regression for composite outcome

	Odds ratio	(95% CI)	*P* value
(Intercept)	0.01	(0.004 to 0.024)	< 0.001
Preoperative variables			
Emergent procedure	5.45	(4.69 to 6.33)	< 0.001
Age (yr)	1.01	(1.00 to 1.01)	0.007
Male	1.03	(0.90 to 1.17)	0.71
Supplemental O_2	2.37	(1.97 to 2.84)	< 0.001
Current or former smoker	0.91	(0.81 to 1.03)	0.15
COPD	1.16	(0.99 to 1.36)	0.06
ASA Physical Status III–IV or V	1.21	(1.01 to 1.45)	0.04
Asthma	0.75	(0.61 to 0.93)	0.007
Preoperative dialysis	1.45	(1.08 to 1.95)	0.01
BMI category			
Normal	1		
Underweight	1.03	(0.74 to 1.44)	0.85
Overweight	1.01	(0.87 to 1.18)	0.89
Obesity class I	1.14	(0.96 to 1.35)	0.15
Obesity class II	1.12	(0.90 to 1.39)	0.32
Obesity class III	1.34	(1.06 to 1.71)	0.02
Procedure type			
Head and neck + plastic surgery	1.32	(1.09 to 1.60)	0.004
Neurosurgery	0.57	(0.48 to 0.68)	< 0.001
Orthopedic surgery	0.58	(0.45 to 0.75)	< 0.001
Urologic surgery	0.62	(0.48 to 0.80)	< 0.001
General/gynecologic/thoracic/transplant surgery	0.69	(0.57 to 0.85)	< 0.001
Other surgery	1.56	(1.21 to 2.03)	0.001
Creatinine clearance ($mL·min^{-1}$)	1.00	(1.00 to1.00)	0.001
Preoperative albumin ($g·dL^{-1}$)	0.53	(0.48 to 0.58)	< 0.001
Intraoperative variables			
Albumin transfused (g)	1.01	(1.01 to 1.01)	< 0.001
Case duration (min)	1.29	(1.24 to 1.34)	< 0.001
Total volume blood products (mL)	1.81	(1.68 to 1.94)	< 0.001
Inspired oxygen (%)	1.01	(1.01 to 1.02)	< 0.001
Tidal volume ($mL·kg^{-1}$)	1.05	(1.00 to 1.09)	0.046
Respiratory rate ($breaths·min^{-1}$)	1.07	(1.05 to 1.10)	< 0.001
Mean arterial pressure (mm Hg)	1.0	(0.99 to 1.00)	0.243
Heart rate ($beats·min^{-1}$)	1.02	(1.01 to 1.02)	< 0.001
$PaCO_2$ - $PetCO_2$ (5 mm Hg)	1.20	(1.12 to 1.28)	< 0.001

BMI was subdivided into World Health Organization categories: underweight (BMI < 18.5 $kg·m^{-2}$), normal (BMI 18.5–24.9 $kg·m^{-2}$), overweight (BMI 25–29.9 $kg·m^{-2}$), obesity class I (BMI 30–34.9 kg^2), obesity class II (BMI 35.0–39.9 $kg·m^{-2}$), and obesity class III (BMI $\geq$ 40 $kg·m^{-2}$). Akaike Information Criteria = 8356.444, Bayes Information Criteria = 8599.658, -2logLikelihood = 928292.444, and C statistic = 0.87 (95% CI, 0.86 to 0.88).

ASA = American Society of Anesthesiologists; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; $PaCO_2$ = arterial partial pressure of carbon dioxide; $PetCO_2$ = end-tidal partial pressure of carbon dioxide.

condition, rather than the final clinical condition, of patients undergoing anesthesia. Furthermore, we did not evaluate whether ΔCO_2 changes over the course of surgery and how that is associated with outcomes. Evaluating these changes and whether they can predict outcome needs further investigation.

Previous studies have investigated risk factors for postoperative respiratory failure and have developed

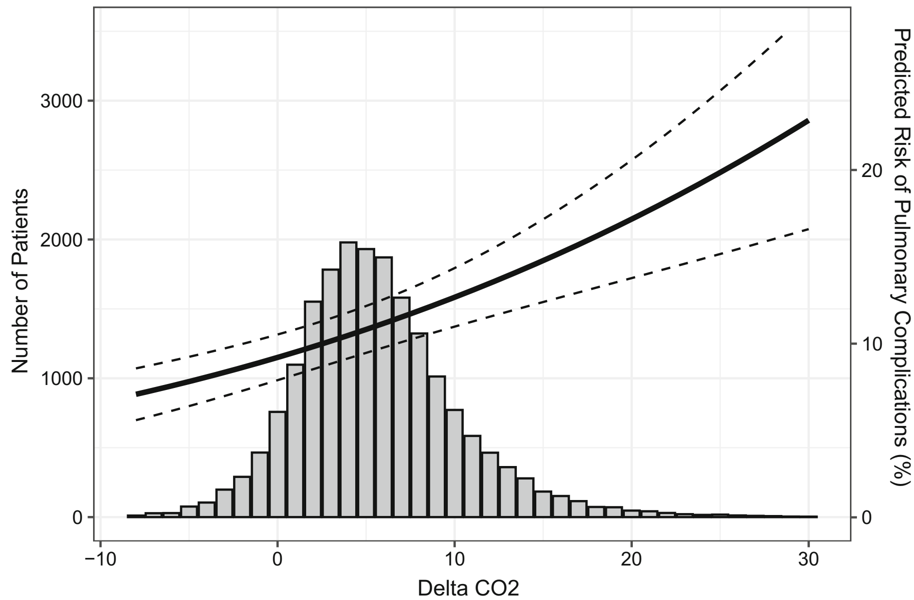


Fig. 2 Predicted risk of pulmonary complications for different ΔCO_2 values overlaid on a histogram showing the distribution of ΔCO_2 values included in this study. The ΔCO_2 range spanned values of -10 mm Hg to 30 mm Hg with most being between 0 mm Hg and 10 mm Hg. After adjusting for all factors in the multivariable model, a curvilinear relationship can be seen between ΔCO_2 values and postoperative pulmonary complications with higher ΔCO_2 values predicting greater risk. ΔCO_2 = difference between arterial and end-tidal partial pressure of carbon dioxide.

clinically predictive models.[37] Some of these clinically significant variables were not included in our analysis because they were not collected in our EHR. For example, New York Heart Association heart failure class has been shown to be a risk factor for postoperative pulmonary complications,[37] but this variable is not present in our anesthesia preoperative history. Where a previous study found that lower preoperative SpO_2 levels were associated with postoperative pulmonary complications,[38] our patients with low values had been placed on supplemental oxygen. Additionally, risk scores developed on a more general surgical population may not be applicable to our unique patient population, specifically patients with an arterial catheter who underwent non-cardiac surgery.

Despite these limitations, our findings support the need for future research on the relationship between ΔCO_2 and postoperative adverse events. This study was retrospective and must be evaluated prospectively in patients undergoing non-cardiac surgery with a study design to address some of the limitations encountered in this patient population. Next, additional patient populations, such as those undergoing anesthesia without mechanical ventilation, pediatric patients, or those undergoing one-lung ventilation should be evaluated. Patients who require one-lung ventilation might represent a specific population risk of ventilation efficiency and where ΔCO_2 might have clinical predictive value.

In addition to evaluating the ΔCO_2 in other patient populations, additional research is needed to determine if specific therapies are beneficial when elevated ΔCO_2 is detected. For example, one animal study of ARDS found that the PEEP value that minimized capnography-measured VD_{alv} also maximized CO and mixed venous oxygen saturation.[39] Further study is needed to determine if individualizing care, through ventilator adjustments or manipulation of hemodynamics, based on minimizing ΔCO_2 reduces adverse events.

Conclusions

Our study shows an independent association between increases in ΔCO_2 and a composite outcome of re-intubation, postoperative mechanical ventilation, or 30-day mortality in patients undergoing non-cardiac surgery. Future research is needed to determine if the ΔCO_2 can be used for risk stratification or as a target for the optimization of intraoperative ventilator and hemodynamic management.

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