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REPORTS OF ORIGINAL INVESTIGATIONS

Intraoperative end-tidal carbon dioxide and postoperative mortality in major abdominal surgery: a historical cohort study

Dioxyde de carbone télé-expiratoire peropératoire et mortalité postopératoire en chirurgie abdominale majeure : une étude de cohorte historique

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Abstract

Purpose *There is a paucity of data on the effect of intraoperative end-tidal carbon dioxide ($EtCO_2$) levels on postoperative mortality. The purpose of this study was to investigate the relationship between intraoperative $EtCO_2$ and 90-day mortality in patients undergoing major abdominal surgery under general anesthesia.*

Methods *We conducted a historical cohort study of patients undergoing major abdominal surgery under general anesthesia at Kyoto University Hospital. We measured the intraoperative $EtCO_2$, and patients with a mean $EtCO_2$ value < 35 mm Hg were classified as low $EtCO_2$. The time effect was determined based on minutes below an $EtCO_2$ of 35 mm Hg, and cumulative effects were evaluated by measuring the area under the threshold of 35 mm Hg for each patient.*

Results *Of 4,710 patients, 1,374 (29%) had low $EtCO_2$ and 55 (1.2%) died within 90 days of surgery. Multivariable Cox regression analysis—adjusted for age, American Society of Anesthesiologists Physical Status classification, sex, laparoscopic surgery, emergency surgery, blood loss, mean arterial pressure, duration of surgery, type of surgery, and chronic obstructive pulmonary disease—revealed an association between low $EtCO_2$ and 90-day mortality (adjusted hazard ratio, 2.2; 95% confidence interval [CI], 1.2 to 3.8; P = 0.006). In addition, severity of low $EtCO_2$ was associated with an increased 90-day mortality (area under the threshold; adjusted hazard ratio; 2.9, 95% CI, 1.2 to 7.4; P =0.02); for long-term exposure to an $EtCO_2$ < 35 mm Hg (≥ 226 min), the adjusted hazard ratio for increased 90-day mortality was 2.3 (95% CI, 0.9 to 6.0; P = 0.08).*

Conclusion *A mean intraoperative $EtCO_2$ < 35 mm Hg was associated with increased postoperative 90-day mortality.*

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Résumé

Objectif *Il n'existe que très peu de données s'intéressant à l'effet du niveau peropératoire télé-expiratoire du dioxyde de carbone ($EtCO_2$) sur la mortalité postopératoire. L'objectif de cette étude était d'examiner la relation entre l'$EtCO_2$ peropératoire et la mortalité à 90 jours chez des patients subissant une chirurgie abdominale majeure sous anesthésie générale.*

Méthode *Nous avons réalisé une étude de cohorte historique portant sur des patients subissant une chirurgie abdominale majeure sous anesthésie générale à l'Hôpital universitaire de Kyoto. Nous avons mesuré l'$EtCO_2$ peropératoire, et les patients avec une valeur moyenne d'$EtCO_2 < 35$ mmHg ont été catégorisés comme $EtCO_2$ faible. L'effet temps a été déterminé en fonction de la durée, en minutes, avec une $EtCO_2$ inférieure à 35 mmHg, et les effets cumulatifs ont été évalués en mesurant l'aire sous le seuil de 35 mmHg pour chaque patient.*

Résultats *Sur 4710 patients, 1374 (29 %) avaient une $EtCO_2$ faible et 55 (1,2 %) sont décédés dans les 90 jours suivant la chirurgie. Une analyse de régression multivariée de Cox, ajustée pour tenir compte des facteurs suivants : âge, statut physique selon l'American Society of Anesthesiologists, sexe, chirurgie par laparoscopie, chirurgie d'urgence, pertes de sang, tension artérielle moyenne, durée de la chirurgie, type de chirurgie et maladie pulmonaire obstructive chronique, a révélé une association entre une $EtCO_2$ faible et la mortalité à 90 jours (rapport de risque ajusté, 2,2; intervalle de confiance [IC] à 95 %, 1,2 à 3,8; P = 0,006). De plus, la sévérité de l'$EtCO_2$ basse était associée à une augmentation de la mortalité à 90 jours (aire sous le seuil; rapport de risque ajusté; 2,9, IC 95 %, 1,2 à 7,4; P =0,02); pour une exposition à long terme à une $EtCO_2 < 35$ mmHg ($\geq$ 226 minutes), le rapport de risque ajusté pour une mortalité accrue à 90 jours était de 2,3 (IC 95 %, 0,9 à 6,0 ; P = 0,08).*

Conclusion *Une $EtCO_2$ peropératoire moyenne < 35 mmHg était associée à une augmentation de la mortalité postopératoire à 90 jours.*

Keywords End-tidal carbon dioxide · Intraoperative hypocapnia · Major abdominal surgery · Postoperative mortality

With an increasing number of surgeries worldwide, approximately 4.2 million people die within 30 days of surgery each year, accounting for 7% of all deaths globally.[1]

The International Standards for a Safe Practice of Anesthesia recommend monitoring of end-tidal carbon dioxide ($EtCO_2$) with a capnograph during general anesthesia.[2] Although mild hypocapnia, defined as an $EtCO_2$ of 30-35 mm Hg, was traditionally used to reduce the requirements for sedatives, analgesics, and neuromuscular blocking drugs,[3] a recent review suggested that mild hypercapnia ($EtCO_2 \geq 40$ mm Hg) should be the standard for anesthesia management,[3] based on evidence of the risks of hypocapnia[4,5] and the benefits of mild hypercapnia.[6-9] Nevertheless, most of these studies were conducted in animals,[8] patients undergoing neurosurgery,[10] and intensive care patients with traumatic brain injury[11] or acute respiratory distress syndrome (ARDS).[9,12] Furthermore, an eight-year observational study of 317,445 adult patients receiving general anesthesia reported that $EtCO_2$ levels varied significantly between hospitals and providers.[13] Thus, there is no consensus on the recommended target intraoperative $EtCO_2$ level in clinical practice.

In the general surgery literature, three studies have shown an association between low $EtCO_2$ and poor postoperative outcomes, including higher mortality[14] and prolonged postoperative length of stay (PLOS).[14-16] Nevertheless, no studies have evaluated the association between duration and degree of low $EtCO_2$ and postoperative outcomes. In addition, the one study that investigated the association between $EtCO_2$ and postoperative mortality did not adjust for important confounding factors like laparoscopic surgery, chronic obstructive pulmonary disease (COPD) status, and surgery type.[14]

Therefore, we explored the effects of the duration and degree of hypocapnia exposure after adjusting for important confounding factors. We aimed to investigate the relationship between intraoperative $EtCO_2$ levels and 90-day mortality (the primary outcome) and in-hospital mortality and PLOS (secondary outcomes).

Methods

Ethics

The Kyoto University Certified Review Board (Kyoto, Japan) approved the study protocol (approval number: R1272-3, 23 January 2020) and waived the requirement for informed consent because of the retrospective nature of the study.

Study design, setting, and population

This retrospective single-centre historical cohort study included data from the Kyoto University Hospital Improve Anesthesia Care and Outcomes (Kyoto-IMPACT) database. The Kyoto-IMPACT database was designed to identify the relationships between intraoperative respiratory and circulatory parameters and postoperative outcomes. We selected patients who underwent surgery under the supervision of an anesthesiologist at the Kyoto University Hospital—a Japanese teaching hospital with 1,121 beds. We have published several papers using data from the Kyoto-IMPACT database.[17,18] We included consecutive patients aged 18 yr or older who underwent major abdominal surgery under general anesthesia at Kyoto University Hospital from March 2008 to December 2017. We targeted the abdominal surgery population because we assumed that there would be a large number of cases in the database, long surgical durations, and a high incidence of recorded outcomes. The major abdominal surgeries in this study included liver, colorectal, gastric, pancreatic, or esophageal resections by either laparoscopic or non-laparoscopic approaches. We excluded cases with missing $EtCO_2$ data or one-lung ventilation.

Data collection

We collected data from the Kyoto-IMPACT database, which was built from an anesthesia information management system and an electronic medical records system. We measured $EtCO_2$ by continuously using a sidestream gas analyzer (GF-220R Multigas/Flow Unit, Nihon Kohden®, Japan) that automatically uploaded data to the anesthesia information management system every 60 sec. The intraoperative $EtCO_2$ was defined as the mean $EtCO_2$ level from skin incision to closure. If the $EtCO_2$ level was less than 20 mm Hg, it was deleted as an artifact (occurring, for example, during aspiration or position change). Definitions of variables, including minimum and maximum $EtCO_2$, are listed in eTable 1 in the Electronic Supplementary Material (ESM). We obtained data on causes of all deaths that occurred within 90 days from the date of surgery by reviewing all clinical data contained within the electronic medical record.

Exposure

To determine how $EtCO_2$ is related to postoperative mortality, we defined exposure by calculating the dose, time, and cumulative effects of $EtCO_2$. Dose effects were evaluated using the mean $EtCO_2$. We divided patients into two groups based on a cut-off level of 35 mm Hg, as suggested by Way and Hill[3]. Patients with low $EtCO_2$ were defined as patients with a mean $EtCO_2 < 35$ mm Hg, whereas patients with normal $EtCO_2$ had a mean $EtCO_2 \geq 35$ mm Hg. Classification into one of these groups was used as the main exposure for further analysis. Furthermore, we considered that the relationship between $EtCO_2$ and mortality may not be linear, so we categorized the mean $EtCO_2$ into quartiles (i.e., < 35, 35-37, 37-39, and ≥ 39 mm Hg). To assess the effects of the duration and degree of low $EtCO_2$ exposure, the time effect was determined based on minutes below an $EtCO_2$ of 35 mm Hg, and cumulative effects were evaluated by measuring the area under the threshold of an $EtCO_2$ of 35 mm Hg. We further categorized minutes and area under the threshold of an $EtCO_2$ of 35 mm Hg into quartiles, with the lowest quartile as the reference category.

Outcomes

We focused on three outcome variables. The primary outcome was 90-day mortality, which was defined as any mortality within 90 days of surgery, because it includes postoperative deaths occurring after 30 days or after discharge.[19-21] For patients who were discharged within 90 days of surgery, post-discharge survival was confirmed from the outpatient visit records. In addition, follow-up information registered by the surgeon was used for patients whose outpatient visit records were discontinued within 90 days. Secondary outcomes were defined as in-hospital mortality and PLOS. In-hospital mortality was defined as any mortality during the index hospitalization. Postoperative length of stay was defined as the duration of hospitalization after surgery for patients who survived until hospital discharge.

Statistical analysis

Analyses of the relationship between $EtCO_2$ and postoperative mortality were planned before data collection. We compared groups using the Mann-Whitney test and the Chi square test. We expressed continuous variables as medians [interquartile ranges (IQRs)] and categorical variables as counts and proportions (%).

First, we performed a Cox proportional hazard regression model to calculate the hazard ratios for low $EtCO_2$ (mean $EtCO_2 < 35$ mm Hg) and 90-day mortality, with the reference category of normal $EtCO_2$ (mean $EtCO_2 \geq 35$ mm Hg). In addition, the hazard ratios for the mean $EtCO_2$ of the first quartile (mean $EtCO_2 < 35$ mm Hg), third quartile (mean $EtCO_2$ 37-39 mm Hg), and fourth quartile (mean $EtCO_2 \geq 39$ mm Hg), were compared with the reference category of the second quartile (mean $EtCO_2$ 35-37 mm Hg) because the latter is considered as normocapnia. Furthermore, to examine the cumulative and time effects, we evaluated how each quartile affected 90-day mortality, with the first quartile of the area below the threshold $EtCO_2$ of 35 mm Hg and minutes under an $EtCO_2$ of 35 mm Hg as the reference category. We created a directed acyclic graph (eFigure, ESM), and further created a model using covariates that affect both $EtCO_2$ and 90-day mortality to show the relationship between $EtCO_2$ and 90-day mortality. In the model, we adjusted for age, sex, American Society of Anesthesiologists Physical Status (I or II *vs* III or VI), laparoscopic surgery, emergency surgery, COPD, blood loss (mL), type of surgery, mean of mean arterial pressure (MAP) (mm Hg), and surgery duration (hr). Moreover, we used a logistic regression model to investigate whether dose, time, or cumulative effects of $EtCO_2$ affected in-hospital mortality, adjusted using the model above. Further, to evaluate the relationship between $EtCO_2$ and PLOS, a linear regression analysis was performed with adjustment for the possible confounders in the model above.

The relationship between $EtCO_2$ and postoperative outcomes may depend on patient characteristics and surgical factors. Thus, we performed subgroup analysis to assess this potential heterogeneity. In addition, we used the same Cox proportional hazard regression model in the following subgroups: (i) type of surgery (hepato-pancreatic surgery or gastrointestinal surgery); (ii) blood loss ($\geq$ 500 or $<$ 500 mL); (iii) laparoscopic surgery (yes or no); (iv) emergency surgery (yes or no); (v) COPD (yes or no); (vi) duration of surgery ($\geq$ or $<$ 4 hr) and (vii) epidural anesthesia (yes or no). We calculated the crude hazard ratio for 90-day mortality in each subgroup and tested the interaction between subgroups and $EtCO_2$. When performing subgroup analysis, subgroup covariates were included in the model as covariates.

A sensitivity analysis was used to assess the robustness of our findings. We used sensitivity models as a Cox proportional 90-day regression model after adjusting for the aforementioned confounders to assess the veracity of the primary analysis: (i) patients limited to a single surgery during the follow-up period; (ii) excluded patients whose follow-up information was registered by surgeons; and (iii) where the outcome was defined as 30-day mortality. We also added an analysis of the partial pressure of arterial carbon dioxide ($PaCO_2$)-$EtCO_2$ gradient and 90-day mortality for patients who had arterial gas measurements taken during surgery. Finally, propensity score matching analysis was performed to balance the aforementioned confounders and further potentially important confounders.

To maximize statistical power, we included all eligible patients in the Kyoto-IMPACT database. To determine study power, we predicted 4,500 eligible surgeries in our database in the nine-year time period, a hazard ratio of 2.5 with a postoperative 90-day mortality of 1%[22,23] and low $EtCO_2$ proportion of 50%,[13] resulting in an estimated power of 87%. We carried out a complete case analysis because the missing data were 0.1%. All statistical tests were two-tailed. We used Stata/SE 15.1 (StataCorp LLC, College Station, TX, USA) for statistical analyses.

Results

Baseline patient characteristics

From the 4,781 major abdominal surgical patients treated between 2008 and 2017, 4,718 met our inclusion criteria and were included in the analyses (4,710 had complete case report forms; Figure).

Low $EtCO_2$ (defined as a mean $EtCO_2$ of less than 35 mm Hg) was found in 29% of the patients. Table 1 displays the characteristics of the study participants. The median [IQR] $EtCO_2$ level was 33 [32-34] mm Hg for patients with low $EtCO_2$ and 38 [36-40] mm Hg for patients with normal $EtCO_2$.

Association between low EtCO2 and 90-day mortality

Table 2 presents the main results of the study. The overall 90-day mortality was 1.2% (55 of 4,710), compared with 2.2% (30 of 1,374) in the low $EtCO_2$ group and 0.8% (25 of 3,336) in the normal $EtCO_2$ group. The adjusted hazard ratio for the low $EtCO_2$ group (mean $EtCO_2 < 35$ mm Hg) after multivariable adjustments indicated an association between low $EtCO_2$ and 90-day mortality (adjusted hazard ratio, 2.2; 95% confidence interval [CI], 1.2 to 3.8; P = 0.006) compared with the normal $EtCO_2$ group. For further analysis, $EtCO_2$ was divided into quartiles, and the second quartile (mean $EtCO_2$ 35-37 mm Hg) was used as the reference. The first quartile (mean $EtCO_2 < 35$ mm Hg) was associated with an increased 90-day mortality (adjusted hazard ratio, 2.9; 95% CI, 1.3 to 6.4; P = 0.008; Table 2). Nevertheless, the third quartile (mean $EtCO_2$ 37-39 mm Hg) and fourth quartile (mean $EtCO_2 \geq$ 39 mm Hg) were not associated with increased 90-day mortality.

Regarding the cumulative effects of $EtCO_2$, the fourth quartile (408-7,206) of the area under the threshold $EtCO_2$ of 35 mm Hg was associated with an increased 90-day mortality compared with the first quartile (0-13; adjusted hazard ratio, 2.9; 95% CI, 1.2 to 7.4; P = 0.02). Finally, regarding the time effects of $EtCO_2$ on 90-day mortality, the adjusted hazard ratio for long-term exposure to $EtCO_2$ levels $<$ 35 mm Hg (the fourth quartile of exposure time to $EtCO_2 <$ 35 mm Hg, 226-1,069 min) compared with short-term exposure (the first quartile of exposure time to $EtCO_2$ $<$ 35 mm Hg, 0-21 min) was 2.3 (95% CI, 0.9 to 6.0; P = 0.08). We reported the causes of death in patients who died within 90 days after surgery in the ESM, eTable 2.

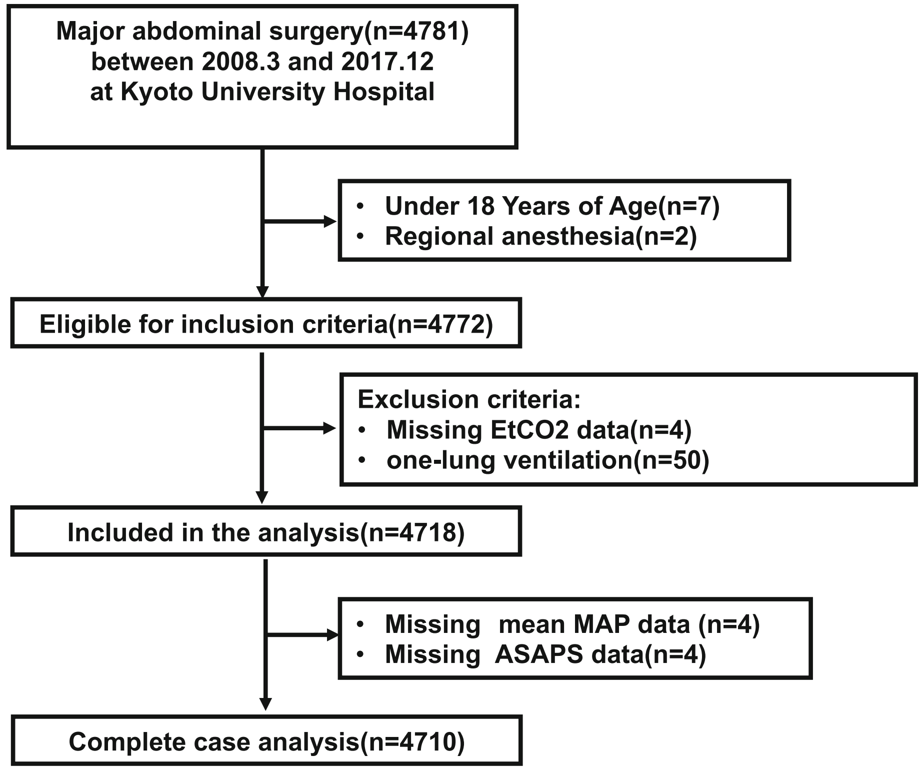

Figure 1 Flow chart for the study. We consecutively included patients aged ≥ 18 yr who underwent major abdominal surgery under general anesthesia at the Kyoto University Hospital from March 2008 to December 2017. Then, we selected the cases that met the eligibility criteria and analyzed them as complete cases.

Association between low EtCO2 and in-hospital mortality

The in-hospital mortality was 1.3% (61 of 4,710) overall, 2.3% (32 of 1,374) in the low $EtCO_2$ group, and 0.9% (29 of 3,336) in the normal $EtCO_2$ group. Compared with the patients with normal $EtCO_2$, patients with low $EtCO_2$ were more likely to have higher in-hospital mortality rates (adjusted odds ratio, 2.0; 95% CI, 1.2 to 3.5; P = 0.01, Table 3). In addition, both time and cumulative effects of low $EtCO_2$ (< 35 mm Hg) were associated with increased in-hospital mortality (Table 3).

Association between low $EtCO_2$ and PLOS

The median [IQR] PLOS was 21 [5-33] days (Table 4). The median [IQR] PLOS in patients with low $EtCO_2$ was longer than in patients with normal $EtCO_2$ (24 [17-39] days *vs* 20 [15-30] days; P < 0.001). Linear regression analysis revealed a significant association between low $EtCO_2$ and PLOS (adjusted difference in PLOS, 1.7; 95% CI, 0.2 to 3.1; P = 0.02).

Subgroup analysis

Subgroup analysis involved type of surgery, blood loss, laparoscopic surgery, emergency surgery, COPD diagnosis, duration of surgery, and epidural anesthesia. These broadened the CIs but did not significantly alter the effects of low $EtCO_2$ on 90-day mortality. There were no interactions between these variables and 90-day mortality (Table 5).

Sensitivity analysis

In the sensitivity analysis, we observed the relationship between low $EtCO_2$ and 90-day mortality (eTable 3, ESM) as well as the relationship between low $EtCO_2$ and 30-day mortality (eTable 4, ESM). The $PaCO_2$-$EtCO_2$ gradient was also significantly associated with increased 90-day mortality (eTable 5, ESM). In the propensity score matched analysis, low $EtCO_2$ was also associated with increased 90-day mortality (eTable 6, ESM).

Discussion

Overview of results

In this retrospective cohort study of over 4,000 abdominal surgery patients undergoing general anesthesia, we found that low intraoperative $EtCO_2$ was associated with a 2.2-fold increase in postoperative 90-day mortality. In addition, low $EtCO_2$ was associated with increased in-hospital mortality and prolonged PLOS.

Table 1 Patient characteristics (N = 4,710)

Characteristics	Low $EtCO_2$ N = 1,374	Normal $EtCO_2$ N = 3,336	P value
Age (yr)	68 [58-75]	66 [56-73]	< 0.001
Male sex	810 (59%)	2,095 (63%)	0.01
ASA Physical Status			< 0.001
I	310 (23%)	910 (27%)	
II	926 (67%)	2,200 (66%)	
III	132 (10%)	222 (7%)	
IV	6 (0.4%)	4 (0.1%)	
BMI ($kg·m^{-2}$)	22 [20-24]	22 [20-24]	0.14
COPD	141 (10%)	271 (8%)	0.02
Type of surgery			< 0.001
Colorectal	383 (28%)	1,029 (31%)	
Liver	558 (41%)	1,001 (30%)	
Gastric	147 (11%)	664 (20%)	
Pancreatic	236 (17%)	444 (13%)	
Esophageal	40 (3%)	179 (5%)	
Complex	10 (0.7%)	19 (0.5%)	
Laparoscopic surgery	606 (44%)	21,24 (64%)	<0.001
Emergency surgery	20 (1.4%)	36 (1.1%)	0.27
Epidural anesthesia	575 (42%)	1,102 (33%)	<0.001
Duration of surgery (hr)	6 [4-8]	6 [4-8]	0.30
Mean MAP (mm Hg)	73 [68-79]	74 [69-80]	< 0.001
Blood loss (mL)	286 [50-700]	110 [20-412]	< 0.001
Transfusion volume (mL)	0 [0-0]	0 [0-0]	< 0.001
Infusion volume (mL)	3,400 [2,300-4,650]	2,900 [2,050-4,200]	< 0.001
Charlson Risk Index	4 [2-6]	4 [2-6]	< 0.001
Mean $EtCO_2$ (mm Hg)	33 [32-34]	38 [36-40]	< 0.001
Minimum $EtCO_2$ (mm Hg)	28 [25-29]	32 [29-33]	< 0.001
Maximum $EtCO_2$ (mm Hg)	38 [36-40]	44 [42-47]	< 0.001

Values are given as median [interquartile range] or count (%).

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; MAP = mean arterial pressure; $EtCO_2$ = end-tidal carbon dioxide level

Possible mechanisms

There are two hypotheses regarding the mechanisms underlying an association between low intraoperative $EtCO_2$ and increased postoperative mortality. One hypothesis is that a low $EtCO_2$ reflects hypocapnia, which has deleterious effects including hypotension due to peripheral vasodilation,[24] reduced tissue perfusion[4], arrhythmia,[25] cerebral vasoconstriction,[26,27] cognitive decline,[28,29] increased intrapulmonary shunt, and pulmonary cellular dysfunction.[5] Another hypothesis is that low $EtCO_2$ may reflect an increased $PaCO_2$-$EtCO_2$ gradient, which indicates pathological conditions such as increased V/Q mismatch, increased alveolar dead space, increased shunting rates, reduced pulmonary blood flow, and hemodynamic instability, rather than systemic hypocapnia. An increase in the $PaCO_2$-$EtCO_2$ gradient above 10 mm Hg is associated with increased ARDS severity,[30] increased mortality in patients with trauma,[31,32] and poor outcomes in patients with sepsis.[33] Furthermore, low $EtCO_2$ may reflect lower cardiac output and lower pulmonary blood flow when ventilation is constant during surgery.[34-37] Whether systemic hypocapnia itself is associated with worse outcomes needs to be clarified in future studies.

Table 2 Multivariable analysis of the relationship between $EtCO_2$ and 90-day mortality

	n	90-day mortality	Crude hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Mean $EtCO_2$						
Normal $EtCO_2$	3,336	25 (0.8%)	1	-	1	-
Low $EtCO_2$	1,374	30 (2.2%)	2.9 (1.7 to 5.0)	<0.001	2.2 (1.2 to 3.8)	0.006
Mean $EtCO_2$ (mm Hg)						
< 35	1,374	30 (2.1%)	3.2 (1.5 to 7.0)	0.004	2.9 (1.3 to 6.4)	0.008
35-37	1,154	8 (0.7%)	1	-	1	-
37-39	992	10 (1.0%)	1.5 (0.6 to 3.7)	0.42	1.7 (0.7 to 4.3)	0.26
≥ 39	1,190	7 (0.6%)	0.9 (0.3 to 2.3)	0.75	1.5 (0.5 to 4.2)	0.47
Minutes below $EtCO_2$ 35 mm Hg						
Quartile value 1 [0-21 min]	1,199	6 (0.5%)	1	-	1	-
Quartile value 2 [22-96 min]	1,167	9 (0.8%)	1.5 (0.6 to 4.3)	0.40	1.5 (0.5 to 4.2)	0.45
Quartile value 3 [97-225 min]	1,172	9 (0.8%)	1.5 (0.5 to 4.3)	0.41	1.1 (0.4 to 3.1)	0.90
Quartile value 4 [226-1,069 min]	1,172	31 (2.7%)	5.3 (2.2 to 12.8)	<0.001	2.3 (0.9 to 6.0)	0.08
Area under the threshold of $EtCO_2$ 35 mm Hg						
Quartile value 1 [0-13 mm Hg·min^{-1}]	1,184	6 (0.5%)	1	-	1	-
Quartile value 2 [14-106 mm Hg·min^{-1}]	1,180	8 (0.7%)	1.3 (0.5 to 3.9)	0.58	1.4 (0.5 to 4.2)	0.50
Quartile value 3 [107-407 mm Hg·min^{-1}	1,180	9(0.8%)	1.5 (0.5 to 4.2)	0.43	1.0 (0.3 to 2.9)	0.99
Quartile value 4 [408-7,206 mm Hg·min^{-1}]	1,166	32(2.7%)	5.5 (2.3 to 13.1)	<0.001	2.9 (1.2 to 7.4)	0.02

CI = confidence interval; $EtCO_2$ = end-tidal carbon dioxide level

Clinical implications

In our study, 29% of the patients had low mean intraoperative $EtCO_2$ levels. A previous study indicated that more than half of the patients who underwent general anesthesia had a low intraoperative $EtCO_2$.[13] Extremely low $EtCO_2$ should be observed carefully as it may be associated with higher postoperative mortality and longer hospital stays. If the $PaCO_2$-$EtCO_2$ gradient increases, before targeting a lower $EtCO_2$, anesthesiologists should consider assessing and stabilizing the circulatory and respiratory status. In addition, our results suggested that a low $EtCO_2$ is associated with poor outcomes independent of blood pressure, which may reflect a condition that compensates for low cardiac output by increasing peripheral vascular resistance and stabilizing blood pressure. Low $EtCO_2$ without low MAP may indicate a decreased cardiac output and pulmonary blood flow; therefore, cardiovascular stabilization should be considered in this scenario.

Hypercapnia can elicit beneficial effects, including increased cardiac index,[6] increased tissue perfusion,[6,7] decreased postoperative surgical site infection,[38] and lung protection.[8,9] A review revealed that mild hypercapnia ($EtCO_2$ ≥ 40 mm Hg) was beneficial and should be accepted as a standard treatment.[3] Conversely, some recent reports show deleterious effects of hypercapnia, including immunosuppression,[39,40] decreased diaphragm contractility[41] and skeletal muscle atrophy.[42] The effects of hypercapnia on postoperative mortality are unclear since it has both beneficial and harmful effects. We did not observe beneficial effects of mild hypercapnia (mean $EtCO_2$ ≥ 39 mm Hg) compared with an $EtCO_2$ of 35-37 mm Hg. We, therefore, recommend that further studies should be undertaken on the effect of hypercapnia on surgical outcomes.

Strengths

Our research has several strengths. First, our research extends beyond $EtCO_2$ by exploring the effects of duration and degree of exposure to a low intraoperative $EtCO_2$ < 35 mm Hg (median duration > 225 min) and an increased 90-day mortality and in-hospital mortality. The two studies that have examined the association between low $EtCO_2$ and outcome have both evaluated the dose effect only,[14,15] whereas only one study assessed the association between the dose effect of low $EtCO_2$ and postoperative mortality.[14] Second, we designed a regression model to adjust for important confounding factors related to postoperative

Table 3 Multivariable analysis of the relationship between $EtCO_2$ and in-hospital mortality

	n	In-hospital mortality	Crude odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Mean $EtCO_2$						
Normal $EtCO_2$	3,336	29 (0.9%)	1	-	1	-
Low $EtCO_2$	1,374	32 (2.3%)	2.7 (1.6 to 4.5)	< 0.001	2.0 (1.2 to 3.5)	0.01
Mean $EtCO_2$ (mm Hg)						
< 35	1,374	32 (2.3%)	2.1 (1.1 to 4.0)	0.02	1.9 (1.0 to 3.9)	0.06
35-37	1,154	13 (1.1%)	1	-	1	-
37-39	992	8 (0.8%)	0.7 (0.3 to 1.7)	0.45	0.8 (0.3 to 2.1)	0.69
≥ 39	1,190	8 (0.7%)	0.6 (0.2 to 1.4)	0.24	1.1 (0.4 to 2.8)	0.88
Minutes below $EtCO_2$ 35 mm Hg						
Quartile value 1 [0-21 min]	1,193	6 (0.5%)	1	-	1	-
Quartile value 2 [22-96 min]	1,158	9 (0.8%)	1.5 (0.5 to 4.3)	0.41	1.4 (0.5 to 4.1)	0.54
Quartile value 3 [97-225 min]	1,172	10 (0.9%)	1.7 (0.6 to 4.7)	0.30	1.22 (0.4 to 3.6)	0.71
Quartile value 4 [226-1,069 min)}	1,172	36 (3.1%)	6.3 (2.6 to 15.0)	< 0.001	2.9 (1.1 to 7.6)	0.03
Area under the threshold of $EtCO_2$ 35 mm Hg						
Quartile value 1 [0-13 mm Hg·min^{-1}]	1,184	6 (0.5%)	1	-	1	-
Quartile value 2 [14-106 mm Hg·min^{-1}]	1,180	8 (0.7%)	1.3 (0.5 to 3.9)	0.58	1.4 (0.5 to 4.3)	0.51
Quartile value 3 [107-407 mm Hg·min^{-1}]	1,180	11 (0.9%)	1.8 (0.7 to 5.0)	0.22	1.3 (0.4 to 3.6)	0.65
Quartile value 4 [408-7,206 mm Hg·min^{-1}]	1,166	36 (3.1%)	6.3 (2.6 to 14.9)	< 0.001	3.3 (1.3 to 8.4)	0.01

CI = confidence interval; $EtCO_2$ = end-tidal carbon dioxide level

Table 4 Multivariable analysis of the relationship between $EtCO_2$ and postoperative length of stay

	n	Median [IQR]	*P* value	Crude difference in PLOS (95% CI)	*P* value	Adjusted difference in PLOS (95% CI)	*P* value
postoperative length of stay							
Normal EtCO2	3,336	20 [15-30]		1	-		
Low EtCO2	1,374	24 [17-39]	< 0.001	5.1 (3.4 to 6.6)	< 0.001	1.7 (0.2 to 3.1)	0.02

CI = confidence interval; $EtCO_2$ = end-tidal carbon dioxide level; IQR = interquartile range; PLOS = postoperative length of stay

mortality, including type of surgery, laparoscopic surgery, COPD, and blood loss. Third, we effectively captured 90-day mortality data in 98.9% of the patients. We did this by accessing 90-day follow-up outpatient records (4,553/4,710, 96.7%) and information registered by surgeons for patients whose outpatient visit records were discontinued within 90 days (99/4,710, 2.1%), leaving loss of follow-up in 53/4,710 (1.1%) of patients.

Limitations

There are several limitations to our study. First, there are likely unknown or unmeasured confounders. These may include the potential reasons for anesthesiologists to aim for a specific $EtCO_2$ level and the missing source data on smoking status, hypothermia, anesthetic depth, and ventilation parameters. Second, this study evaluated the effect of the $PaCO_2$-$EtCO_2$ gradient on 90-day mortality using the first intraoperative measured $PaCO_2$ level, but it did not consider the effect of variations over time in either $PaCO_2$ level or $PaCO_2$-$EtCO_2$ gradient. Third, the study design employed was observational so could not infer causality. Furthermore, it is not clear whether the association between $EtCO_2$ and 90-day mortality is due to hypocapnia or the $PaCO_2$-$EtCO_2$ gradient. Therefore, future randomized controlled trials are needed.

Table 5 Subgroup analyses stratified by patient and operative variable

	n	90-day mortality	Crude hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value	*P* for interaction
Overall	4,710	55 (1.2%)	2.9 (1.7 to 5.0)	< 0.001	2.2 (1.2 to 3.8)	0.006	
Type of surgery							0.2
Hepato-pancreatic surgery	2,239	39 (1.7%)	2.1 (1.1 to 4.0)	0.01	1.7 (0.9 to 3.2)	0.12	
Gastrointestinal surgery	2,442	15 (0.6%)	5.0 (1.8 to 14.0)	0.002	4.4 (1.5 to 13.1)	0.007	
Blood loss (mL)							0.7
≥ 500	1,198	40 (3.3%)	2.1 (1.1 to 3.9)	0.02	2.11(1.1 to 4.1)	0.02	
< 500	3,512	15 (0.4%)	2.6 (0.9 to 7.1)	0.06	2.2 (0.8 to 6.3)	0.14	
Laparoscopic surgery							0.9
Yes	2,730	13 (0.5%)	2.2 (0.7 to 6.7)	0.16	1.6(0.5 to 5.5)	0.42	
No	1,980	42 (2.1%)	2.4 (1.3 to 4.4)	0.007	2.2 (1.2 to 4.2)	0.01	
Emergency surgery							0.6
Yes	56	8 (14.3%)	2.0 (0.5 to 8.0)	0.32	-	-	
No	4,654	47 (1.0%)	3.0 (1.7 to 5.4)	< 0.001	2.1 (1.1 to 3.8)	0.01	
COPD							0.6
Yes	412	6(1.5%)	1.9 (0.4 to 9.5)	0.42	1.1 (0.2 to 6.8)	0.94	
No	4,298	49 (1.1%)	3.1 (1.8 to 5.4)	< 0.001	2.4 (1.3 to 4.2)	0.004	
Duration of surgery (hr)							0.3
≥ 4	3,809	49 (1.3%)	2.6 (1.5 to 4.6)	< 0.001	1.8 (1.0 to 3.3)	0.04	
< 4	951	7 (0.7%)	6.5 (1.3 to 33.3)	0.02	-	-	
Epidural anesthesia							0.3
Yes	1,677	23 (1.4%)	2.1 (0.9 to 4.8)	0.07	1.9 (0.8 to 4.4)	0.14	
No	3,033	32 (1.1%)	3.6 (1.8 to 7.3)	< 0.001	2.6 (1.2 to 5.5)	0.01	

Hepato-pancreatic surgery included liver and/or pancreatic resection.

Gastrointestinal surgery was defined as colorectal, gastric, or esophageal resection.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; $EtCO_2$ = end-tidal carbon dioxide level

Conclusions

In patients undergoing major abdominal surgery, intraoperative low $EtCO_2$ was associated with increased postoperative 90-day mortality, in-hospital mortality, and hospital stay.

Author contributions *Li Dong* conceptualized the study. *Li Dong*, *Chikashi Takeda*, *Toshiyuki Mizota*, and *Yosuke Yamamoto* designed the study. *Li Dong* and *Toshiyuki Mizota* collected data. All authors analyzed and interpreted data. *Li Dong* drafted the manuscript. All authors edited and approved the manuscript.

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