Submitted: 17 June, 2022 Accepted: 12 August, 2022 Published: 08 November, 2022 DOI:10.22514/sv.2022.073

Open Access
Signa Vitae

ORIGINAL RESEARCH

Effect of patient end-tidal carbon dioxide levels on cerebral regional oxygen saturation and inflammatory cytokine concentrations in elderly patients undergoing laparoscopic radical gastrectomy: a randomized controlled trial

Yan-lin Yan[1,†], Liu-rong Lin[2,3,†], Kai Zeng[2], Hong-da Cai[2], Cai-zhu Lin[2], Min Liang[2,*], Yan-zhen Li[2,*]

[1]Department of Anesthesiology, Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, 350001 Fuzhou, Fujian, China
[2]Department of Anesthesiology, the First Affiliated Hospital of Fujian Medical University, 350005 Fuzhou, Fujian, China
[3]Anesthesiology Research Institute, the First Affiliated Hospital, Fujian Medical University, 350005 Fuzhou, Fujian, China

***Correspondence**
liyanzhen@fjmu.edu.cn
(Yan-zhen Li);
min.liang@fjmu.edu.cn
(Min Liang)

Abstract

Carbon dioxide levels can affect inflammation and cerebral regional oxygen saturation ($rScO_2$), a pathophysiological indicator of early postoperative cognitive dysfunction (POCD).To compare the cerebral $rScO_2$ and postoperative inflammation based on patient end-tidal carbon dioxide ($P_{ET}CO_2$) levels in elderly patients undergoing laparoscopic radical gastrectomy. Ninety patients were randomly divided into three groups according to $P_{ET}CO_2$ level: group L (low $P_{ET}CO_2$, 36–40 mmHg), group C (control $P_{ET}CO_2$, 41–45 mmHg) and group H (high $P_{ET}CO_2$, 46–50 mmHg). Eighty-four patients (age, range: 60–80 years) scheduled to undergo radical laparoscopic gastrectomy were included in the final analysis. The indicated $P_{ET}CO_2$ was maintained for patients in each group. Their intraoperative cerebral $rScO_2$ was recorded at indicated timepoints (T0–T6) from arrival at the operating room to post-extubation. The Montreal Cognitive Assessment Test (MoCA) and changes in serum concentrations of inflammatory cytokines were measured at 1 h, 1d and 7 d after surgery. The cerebral $rScO_2$ at T3 (1 h post-skin incision)–T5 (completion of skin sutures) was significantly higher in group H than in group L, while the MoCA score was not significantly different between group H and L ($p > 0.05$). At 1 h, 1 d and 7 d after surgery, the concentrations of inflammatory cytokines, including interleukin 6 (IL-6) and S100β, were significantly higher in group L than in group H ($p < 0.05$). At 1 h and 7 d after surgery, the inflammatory cytokines were significantly higher in group C than in group H. Our findings suggest that higher $P_{ET}CO_2$ levels increased cerebral $rScO_2$ and reduced the serum concentrations of IL-6 and S100β but may not affect the MoCA score in elderly patients after radical laparoscopic gastrectomy.

Keywords

Elderly patients; Cerebral oxygenation; Postoperative cognitive dysfunction; Inflammatory cytokines

1. Background

Laparoscopic radical gastrectomy is being increasingly performed on elderly adults (aged $\geq$60 years). Although it is reported that all adult patients are at risk for some level of postoperative cognitive dysfunction (POCD) after major surgery, this risk is significant mainly among elderly adults [1], in whom intraoperative cerebral oxygen desaturation has been associated with early POCD [2, 3].

Frequent changes in intracranial pressure and cerebral blood flow (CBF) may occur during laparoscopic surgery and can affect the cerebral perfusion pressure and cerebral oxygenation [4]. Therefore, intraoperative monitoring of cerebral regional oxygen saturation ($rScO_2$) is a significant determining factor for maintaining postoperative cognitive function.

Cerebral $rScO_2$ may be affected by various factors, including the arterial partial pressure of carbon dioxide ($PaCO_2$), the body's position and intraoperative blood pressure [5]. Although we can control the factors affecting cerebral oxygen supply/demand, such as the $PaCO_2$, cardiac output, perfusion pressure, arterial oxygen content and cerebral metabolic rate, increasing the patient's end-tidal carbon dioxide ($P_{ET}CO_2$) level was shown to be the most powerful and convenient method in managing cerebral desaturation [6]. Therefore, intraoperative CO_2 regulation can improve cerebral $rScO_2$.

A lung-protective ventilation strategy resulting in permis-

sive hypercapnia (PHC) can be used to enhance cerebral perfusion and induce a rightward shift in the oxygen dissociation curve; thus, maintaining a relatively stable $P_{ET}CO_2$ level and improving tissue oxygenation. Further, a previous study reported a strong correlation between $PaCO_2$ and $P_{ET}CO_2$ [7]. Intuitively and conveniently, an increase in $P_{ET}CO_2$can improve CBF. A previous study observed a strong correlation between postoperative cognitive function and intraoperative cerebral $rScO_2$ [8], a parameter that can predict POCD occurrence with a sensitivity and accuracy of 90% and 86.5%, respectively [9].

This current study investigated whether appropriate elevation of $P_{ET}CO_2$ could prevent the incidence of cerebral desaturation in elderly patients undergoing scheduled laparoscopic radical gastrectomy. The primary outcomes were changes in cerebral $rScO_2$ and the incidence of POCD following changes in $P_{ET}CO_2$. The secondary outcomes were changes in the serum concentrations of interleukin (IL)-6, S100β and neuron-specific enolase (NSE), which are associated with the occurrence of POCD.

2. Materials and methods

2.1 Patients and Ethics

This randomized controlled trial enrolled elderly adult patients scheduled to undergo elective radical gastrectomy at our institution between July 2019 and June 2021. All enrolled patients provided written informed consent for participation.

The inclusion criteria for patient selection were: underwent elective radical gastrectomy; older than 60 years; had an American Society of Anaesthesiology physical status of II–III; a stable hematocrit level, $>$35% and; the ability to communicate normally with doctors. Patients who used antidepressants, painkillers, benzodiazepines and other medications that may affect their cognitive functions and those with functional illiteracy and a MoCA score $\leq$13 points, 1–6 years of education with a MoCA score $\leq$19 points, or $\geq$7 years of education with a MoCA score $\leq$24 points; arrhythmia, severe heart valve disease or cerebrovascular disease; a family history of mental or neurological disease and; liver and kidney dysfunction or other serious cardiopulmonary diseases were excluded.

Patients were randomly allocated to three groups using opaque, sequentially numbered envelopes containing the randomization assignments (third-party allocation). The allocation sequence was generated based on random number generation by the designated data manager, who was not otherwise involved in the trial. The patients were allocated to groups L, C or H, which corresponded to lower, control, or higher $P_{ET}CO_2$ levels, respectively, and were treated using a ventilation protocol designed to maintain a respective $P_{ET}CO_2$ of 36–40, 41–45 or 46–50 mmHg throughout the intraoperative period.

The patients, the physicians who provided perioperative care and the $rScO_2$evaluator were blinded to the group assignments and $P_{ET}CO_2$ levels. The anesthesiologist was aware of each participant's assignment due to the need to prevent excessive changes in cerebral $rScO_2$ (absolute value $<$55% or $\geq$20% below baseline level). The cerebral $rScO_2$ data were recorded by a data recorder who was also blinded to the group assignments and the $P_{ET}CO_2$ evaluator.

2.2 Anesthesia and monitoring

Cerebral $rScO_2$ was monitored using two sensors positioned bilaterally on the patient's forehead (INVOS 5100C) upon arrival at the operating room. A bispectral index (BIS) monitor (Aespire 7900 (Datex–Ohmeda s/5), Madison, WI, USA) was also used. Their cardiac output (CO) and rate of variation per stroke (SVV) were monitored using a FloTrac/Vigileo system (Edwards Lifesciences). Their intraoperative blood pressure and arterial blood gas (ABG) were continuously monitored, and their routine hemodynamic parameters, including pulse rate and electrocardiogram, were also monitored.

Anesthesia was induced using propofol (2 mg kg^{-1}), sufentanil (0.2 μg kg^{-1}) and cisatracurium (0.3 mg kg^{-1}). After intubation, ventilation was adjusted using a Datex-Ohmeda 7900 Anesthesia Machine (GE Healthcare, Madison, WI, USA). Anesthesia was maintained using sevoflurane titration to maintain the BIS at 45–55, remifentanil was infused *via* a computerized pump for analgesia, and cisatracurium injection (2.5 μg $kg^{-1}min^{-1}$) was given to maintain muscle relaxation.

A lung-protective strategy of volume-controlled ventilation was used, with a fraction of inspired oxygen (FiO_2) of 0.4 and tidal volume (VT) of 6–8 ml kg^{-1}. The positive end-expiratory pressure (PEEP) was adjusted to 5 cmH_2O. The respiratory rate (RR) was regulated to maintain the $P_{ET}CO_2$ within the indicated range specified for each group.

Upon completion of the surgery, propofol and remifentanil were discontinued. Flurbiprofen axetil (0.2 mg kg^{-1}) was administered *via* intravenous injection for postoperative pain control. Additionally, an intravenous patient-controlled analgesia (PCA) pump containing sufentanil (2 μg kg^{-1}) in a total volume of 100 mL (0.9% saline) was connected at the end of surgery to deliver a basal infusion rate of 0.02 mL kg^{-1} h^{-1} and an on-demand dosage of 0.02 mL kg^{-1} with a 15-min lockout time. After endotracheal extubation, each patient remained under observation in the post-anesthesia care unit (PACU). The surgeon was responsible for decisions regarding postoperative medical treatment according to standard institutional regimens.

2.3 Monitoring protocol

A trained observer, who did not participate in patient care and was blinded to the details of the study protocol, measured and recorded the following indicators: intraoperative indicators, including $rScO_2$, CO, mean arterial pressure (MAP), heart rate (HR), hemoglobin (Hb) and lactic acid (Lac), and serological indicators including IL-6, S100β, Aβ-42 and p-tau protein levels.

(1) The $rScO_2$, CO, MAP and HR values were recorded upon the patient's arrival at the operating room (T_0), 5 min after intubation (T_1), at the beginning of the operation (T_2), 1 h (T_3) and 2 h (T_4) after skin incision, at the end of the operation (T_5) and 5 min after extubation (T_6).

(2) MoCA was administered at 1 h (D_0), 1 d (D_2) and 7 d after surgery (D_3).

(3) Arterial blood samples were drawn for ABG monitoring at T_1, T_2, T_3, T_4 and T_5.

(4) Venous blood samples were obtained to measure the serum IL-6 and S100β concentrations at D_0, 1 h after surgery (D_1), D_2 and D_3.

At T_1, the $P_{ET}CO_2$ was raised to the predetermined value by adjusting the respiratory rate (RR). $P_{ET}CO_2$ and intraoperative ABG monitoring were used to ensure that the CO_2 levels reached the target values and were maintained until the end of the operation (T_1–T_5).

A specific protocol was followed when the anesthesiologist was notified of any cerebral desaturation event (CDE; $rScO_2$ absolute value $<$55% or $\geq$20% less than baseline), which included a change in the depth of anesthesia or a switch to another ventilation set point (*i.e.*, improving $P_{ET}CO_2$ or FiO_2). Patients who did not respond to these changes were excluded from the study. A decrease in the MAP of $>$20% relative to the baseline was treated using fluid therapy guided by the FloTrac/Vigileo system or repeated doses of norepinephrine (5 μg intravenously).

2.4 Outcome measures

The primary outcomes included the cerebral $rScO_2$ in response to changing $P_{ET}CO_2$, which were recorded at each time point (T_0–T_6), and the MoCA scores within 7 days after surgery as a measure of POCD. The secondary outcomes included the serum concentrations of IL-6 and S100β as markers for POCD. The patients' MAP, HR and BIS values were recorded at all time points while their ABG data, including PH, Lac, PaO_2 and $PaCO_2$, were collected at T_2–T_5.

2.5 Statistical analysis

Considering the reported prevalence of POCD among adult patients undergoing noncardiac surgery is as high as 41% [10], with a higher incidence among elderly adults, we set a minimum difference of 30% in the incidence of POCD between the groups as an indicator of clinical significance. To achieve this, we estimated that a sample size of 70 was needed with a power level of 0.8 and an α value of 0.05.

The data were coded and entered using the Statistical Package for the Social Sciences (SPSS) software, (version 25, IBM, Armonk, NY, USA). Quantitative data are presented as mean and standard deviation, and categorical data are presented as frequency (count) and relative frequency (percentage). Comparisons between groups were performed using the unpaired *t*-test. A repeated measures analysis of variance was used to compare serial measurements within each group, together with the Bonferroni post hoc test for pairwise comparison. The chi-square (χ^2) test was used to compare categorical data unless the expected frequency was $<$5, in which case the exact test was used. A p value < 0.05 was considered statistically significant.

3. Results

3.1 Study population

Of the 90 patients initially enrolled in the study, three patients were excluded because of alterations in the surgical treatment. In addition, two patients (or their family members) withdrew from the study and one patient was lost to follow-up. Finally, 84 patients were included in the data analysis. The distributions of patient demographic variables in all groups were found to be comparable among the three groups (Table 1).

3.2 Analysis of changes in cerebral $rScO_2$ and hemodynamic variables

Our results showed no significant differences in the baseline (T_0) of cerebral $rScO_2$ values between the three groups. At T_1 and T_2, significant improvements in $rScO_2$ were observed in response to 100% oxygen compared with T_0 (room air). At T_3–T_5, recorded under the predetermined $P_{ET}CO_2$ values for each group, we found that the cerebral $rScO_2$ of group H was significantly higher than that of group L ($p < 0.05$). However, no significant difference was observed between group H and group C (Table 2). The incidence of cerebral desaturation event (CDE; $rScO_2$ absolute value $<$55% or $\geq$20% less than baseline) was significantly greater in group L than in group H ($p < 0.0125$) (Table 5).

Changes in hemodynamic variables, including mean blood pressure, heart rate and cardiac output, were not significantly different in intergroup analysis (Table 2).

3.3 Analysis of MoCA score

POCD was observed in 36 (42.9%) patients at 1 d, among whom 18 (21.4%) recovered at 7 d. The diagnosis of POCD was based on MoCA scores for all cases at 1 d and 7 d after surgery. Further analysis showed no significant difference in MoCA scores among the three groups ($p > 0.05$) (Table 3).

3.4 Inflammatory cytokine

The levels of IL-6, an anti-inflammatory cytokine, increased from Preop to Postop 7 d in the three groups. The levels of IL-6 in group L were higher than in group H at the timepoint in Postop ($p < 0.05$). In addition, the levels of IL-6 in group C were found to decrease at 1 h and 7 d after surgery ($p < 0.05$).

The levels of S100β increased among all groups and showed a peak level at Postop 1 d. Changes in S100β were significantly smaller in group H than in group L ($p < 0.05$), while a significant difference between group H and group C was observed at Postop 1 d (Table 4).

3.5 Analysis of related complications

Analysis of complications that might be associated with $P_{ET}CO_2$showed no significant difference in the incidence of postoperative nausea and vomit, infection of incision and abdominal cavity infection between the three groups. However, having been compared to group L the incidence of lung infection in group H was significantly greater (Table 5).

4. Discussion

This study showed that a higher level of $P_{ET}CO_2$ was associated with increased cerebral $rScO_2$ in elderly patients undergoing laparoscopic radical gastrectomy. In addition, maintaining an appropriate $P_{ET}CO_2$ level reduced the serum concentrations of inflammatory cytokines IL-6 and S100β in this popu-

TABLE 1. Patients' demographics and risk factors.

	Group L (n = 28)	Group C (n = 28)	Group H (n = 28)	*p* value
Sex (male/female)	20/8	24/4	24/4	0.291
Age	66.29 ± 4.38	68.29 ± 5.74	66.14 ± 4.88	0.199
BMI (m^2/kg)	21.64 ± 2.56	23.00 ± 3.02	22.22 ± 2.73	0.171
HTN	8 (28.6%)	6 (21.4%)	2 (7.1%)	0.115
DM (g/dL)	4 (14.3%)	6 (21.4%)	2 (7.1%)	0.126
Operation duration (min)	118.79 ± 18.19	126.64 ± 24.37	129.93 ± 18.46	0.347
Hb (g/L)	118.79 ± 18.19	126.64 ± 24.37	129.93 ± 18.46	0.347
Crystalloid (mL)	1057 ± 195	1071 ± 243	1135 ± 330	0.702
Colloid (mL)	586 ± 254	586 ± 266	607 ± 256	0.968
UO (mL)	396 ± 155	393 ± 187	403 ± 204	0.988
Blood loss (mL)	156 ± 104	164 ± 93	196 ± 99	0.519
Education years	3.79 ± 4.14	5.71 ± 3.97	3.29 ± 2.49	0.184

Data are presented as counts (%) or means ± standard deviations.
Group L low $P_{ET}CO_2$ (36–40 mmHg), Group C control $P_{ET}CO_2$ (41–45 mmHg), Group H high $P_{ET}CO_2$ (46–50 mmHg); BMI: body mass index; HTN: hypertension; DM: diabetes mellitus; Hb: hemoglobin; UO: urine output.

TABLE 2. The $rScO_2$ and hemodynamic variables.

	Group	Cases	T_0	T_1	T_2	T_3	T_4	T_5	T_6
$rScO_2$ (%)	L	28	64.5 ± 6.1	67.4 ± 5.8	67.8 ± 6.0	69.6 ± 6.5	66.9 ± 6.5	68.7 ± 6.6	69.1 ± 7.7
	C	28	66.2 ± 5.8	69.2 ± 7.1	68.0 ± 6.5	72.4 ± 6.9	71.0 ± 6.9	71.1 ± 6.5	72.8 ± 5.6
	H	28	66.6 ± 5.9	72.4 ± 6.0	68.2 ± 5.9	74.8 ± 4.9*	74.0 ± 5.6*	73.4 ± 4.1*	72.4 ± 4.8
HR (bpm)	L	28	73.5 ± 15.5	64.1 ± 13.3	60.9 ± 10.2	64.2 ± 7.9	63.9 ± 8.0	69.6 ± 11.2	80.1 ± 14.1
	C	28	75.6 ± 11.5	59.5 ± 5.8	57.0 ± 6.62	62.6 ± 7.1	63.0 ± 10.2	63.1 ± 13.9	78.9 ± 18.2
	H	28	70.4 ± 12.2	57.9 ± 10.5	62.3 ± 10.8	65.7 ± 12.8	67.4 ± 11.2	61.1 ± 7.9	72.4 ± 11.3
MAP (mmHg)	L	28	102.4 ± 15.9	80.4 ± 12.1	87.4 ± 9.9	81.6 ± 10.2	81.1 ± 9.4	93.7 ± 13.8	103.0 ± 15.6
	C	28	107.2 ± 15.7	84.1 ± 13.7	89.3 ± 12.1	82.9 ± 9.0	86.1 ± 15.4	90.7 ± 15.8	106.5 ± 14.0
	H	28	107.2 ± 11.2	81.1 ± 11.3	94.6 ± 17.3	82.9 ± 12.4	83.9 ± 8.3	85.5 ± 9.6	107.7 ± 15.1
CO (L/min)	L	28	5.2 ± 1.3	3.5 ± 1.1	3.5 ± 0.9	4.0 ± 1.2	3.9 ± 1.1	4.5 ± 1.7	5.1 ± 1.9
	C	28	4.8 ± 1.1	3.6 ± 0.8	3.4 ± 0.9	3.8 ± 0.9	4.3 ± 1.0	4.8 ± 1.3	5.4 ± 1.1
	H	28	4.7 ± 1.0	3.7 ± 1.2	3.5 ± 0.8	4.1 ± 0.9	4.4 ± 1.1	4.5 ± 1.0	5.4 ± 1.3

Data are presented as means ± standard deviations or counts (%).
*Group L low $P_{ET}CO_2$ (36–40 mmHg), Group C control $P_{ET}CO_2$ (41–45 mmHg), Group H high $P_{ET}CO_2$ (46–50 mmHg), T_0 before induction, T_2 beginning of the operation, T_3 1 hour after skin incision, T_4 2 hours after skin incision, T_6 5 minutes after extubation. *$p < 0.05$ compared with group L.*
HR: heart rate; MAP: mean arterial pressure; CO: cardiac output; $rScO_2$: cerebral regional oxygen saturation.

TABLE 3. MoCA scores.

Group	Cases	MoCA scores		
		D_0	D_2	D_3
L	28	20.9 ± 2.9	18.9 ± 3.0	21.0 ± 2.8
C	28	22.0 ± 2.9	19.9 ± 3.5	21.9 ± 3.5
H	28	21.2 ± 3.5	19.7 ± 3.2	21.4 ± 3.6

Data are presented as mean ± standard deviations or counts (%).
Group L low $P_{ET}CO_2$ (36–40 mmHg), Group C control $P_{ET}CO_2$ (41–45 mmHg), Group H high $P_{ET}CO_2$ (46–50 mmHg), D_0 1 day before surgery, D_2 1 day after surgery, D_3 7 days after surgery, MoCA: the Montreal Cognitive Assessment Test.

TABLE 4. Serum concentrations of IL-6 and S100β.

	cases	D_0	D_1	D_2	D_3
IL-6 (pg/mL)					
L	28	13.14 ± 1.24	14.58 ± 1.46	16.39 ± 1.92	18.72 ± 2.23
C	28	12.82 ± 1.04	14.31 ± 1.71	15.75 ± 1.32	17.53 ± 1.49*
H	28	12.50 ± 1.30	13.09 ± 1.28*#	15.23 ± 1.74*	15.44 ± 1.48*#
S100β (pg/mL)					
L	28	84.22 ± 9.75	110.49 ± 16.75	157.33 ± 23.55	140.52 ± 12.30
C	28	82.97 ± 11.37	105.25 ± 8.06	141.07 ± 8.06	110.39 ± 9.70*
H	28	87.53 ± 8.50	100.55 ± 13.65*	123.26 ± 18.13*#	102.13 ± 21.11*

Data are presented as means ± standard deviations or counts (%).
*Group L low $P_{ET}CO_2$ (36–40 mmHg), Group C control $P_{ET}CO_2$ (41–45 mmHg), Group H high $P_{ET}CO_2$ (46–50 mmHg), IL interleukin, NSE neuron-specific enolase, D_3 7 days after surgery, *$p < 0.05$ compared with group L, #$p < 0.05$ compared with group C. IL-6: including interleukin 6.*

TABLE 5. Incidence of complications.

	L (n = 28)		C (n = 28)		H (n = 28)		*p*
	cases	(%)	cases	(%)	cases	(%)	
cerebral desaturation event	10/28	35.7	4/28	14.3	0	0.0	0.001
nausea and vomit	4/28	14.3	2/28	7.1	6/28	21.4	0.311
lung infection	4/28	14.3	0	0.0	10/28	35.7	0.001
infection of incision	0	0.0	0	0.0	2/28	7.1	0.129
Abdominal cavity infection	4/28	14.3	0	0.0	6/28	21.4	0.042

Data are presented as means ± standard deviations or counts (%).
Group L low $P_{ET}CO_2$ (36–40 mmHg), Group C control $P_{ET}CO_2$ (41–45 mmHg), Group H high $P_{ET}CO_2$ (46–50 mmHg).

lation.

POCD is a well-known clinical phenomenon of multifactorial origin [11, 12]. Unlike other potential causes of POCD, intraoperative cerebral hypoxia can be modified [13]. Several studies have reported a positive correlation between POCD and lower intraoperative $rScO_2$ values in elderly patients[14, 15]. Several other studies investigating the effects of $PaCO_2$ on CBF also focused on $rScO_2$. Nakao *et al.* [11] found that cerebral inflammation due to anesthesia or surgery and perioperative vital sign changes that reduced CBF, such as persistent hypotension and/or hypocapnia, could contribute to the development of POCD, especially in patients whose CBF was already reduced. As CO_2 is the most effective regulator of CBF, cerebral $rScO_2$ should be improved in response to an increase in $PaCO_2$. Zhu *et al.* [12] showed that PHC could enhance CBF, improve the cerebral $rScO_2$ of patients undergoing cardiac surgery and adjust the cerebral oxygen supply balance. Based on these findings, we presumed that an increase in $P_{ET}CO_2$ would improve intraoperative cerebral $rScO_2$ and reduce the incidence of POCD. However, no such conclusion could be deduced from our results, which showed that the increase in $rScO_2$ was observed only when $P_{ET}CO_2$ was increased, while the MoCA scores were unaffected. These indicate that the correlation between $rScO_2$ and POCD remains to be further clarified.

A previous study showed that mild hypercapnia ($PaCO_2$ at 45–55 mmHg) could improve cerebral oxygenation, increase $rScO_2$ and reduce the incidence of POCD [12]. This approach is believed to activate neuronal nitric oxide synthase, thus promoting nitric oxide production and causing cerebrovascular dilatation. The expansion of cerebral blood vessels improves the cerebral oxygen supply, reduces the risk of cerebral ischemia and hypoxia, and effectively protects brain functions. Therefore, in this current study, a lung protective ventilation strategy was applied to explore the effects of different levels of $P_{ET}CO_2$ on $rScO_2$ and postoperative cognitive function in elderly patients undergoing laparoscopic radical gastrectomy. The key finding of this study is that maintaining a high intraoperative $P_{ET}CO_2$ (46–50 mmHg) improved elderly patients' postoperative cognitive scores (MoCA scores). In addition, the results also showed that $P_{ET}CO_2$ significantly improved $rScO_2$, but for $P_{ET}CO_2$ values >45 mmHg, which is similar to the results of previous studies. Further, the association between elevation in $P_{ET}CO_2$ and improvement of cerebral $rScO_2$ suggests that $P_{ET}CO_2$ might be an influential factor of $rScO_2$. However, the premise of this conclusion is that $P_{ET}CO_2$ should be increased to a certain level, *i.e.*, at least up to 45 mmHg. Although the exact reason remains to be clarified, we hypothesized that it might be related to the specific lung protective ventilation strategies used in this study.

At present, the pathogenesis of POCD is unclear. Studies have shown that the infiltration of inflammatory factors into the central nervous system and expansion of immune responses might promote nerve cell apoptosis, necrosis and degenerative changes [16–18]. A meta-analysis showed that peripheral markers of inflammation, especially IL-6 and S100β, were closely associated with POCD [19]. Therefore, in this study, we assessed the levels of these serological factors and found that they decreased with increasing $P_{ET}CO_2$. Compared with groups L and C, the levels of most inflammatory markers

were significantly reduced in group H. Therefore, the increase in $P_{ET}CO_2$ might help reduce these inflammatory factors, including IL-6 and S100β, although it only occurred above a certain $P_{ET}CO_2$ threshold.

Many studies have verified the ability of CO_2 to regulate cerebrovascular and improve CBF [20, 21] and have established the effects of oxygen supply on the brain's cognitive functions. But always experiment is to stop more levels. In a previous experimental research, the effects of changes in $P_{ET}CO_2$ were demonstrated by determining the changes in cognitive function after surgery, and the results not only indicated that cerebral $rScO_2$ could predict POCD but also suggested that it could be used to improve patients' cognitive function after surgery. However, these observations are inconsistent with the results of this present study, possibly due to no direct link between $rScO_2$ and POCD. Here, we observed that the levels of inflammatory markers IL-6 and S100β were significantly decreased with higher $P_{ET}CO_2$ and $rScO_2$, while MoCA scores showed no significant change, indicating that IL-6 and S100β may not be related factors of POCD, or at least not the main influencing factors.

A low BIS value and a prolonged period of deep anesthesia have emerged as risk factors for POCD [22]. In this study, the risk of POCD due to deep anesthesia was avoided by monitoring BIS intraoperatively to guide the depth of anesthesia. The enhanced recovery after surgery (ERAS) program can enhance postoperative recovery and reduce the length of hospital stay and morbidity by applying a series of optimization measures from evidence-based medicine during the perioperative period [23]. All patients in this study were treated with target-directed fluid therapy following the ERAS principle, which might be related to the observed faster recovery with this lung-protective ventilation strategy.

5. Conclusions

In conclusion, this study confirms that an increase in $P_{ET}CO_2$ can increase $rScO_2$ and improve postoperative cognition, but not MoCA scores. However, an insufficient increase in CO_2 levels may increase cerebral $rScO_2$, and an excessive increase in CO_2 may lead to other complications, such as CO_2 accumulation, brain edema and pulmonary inflammation. The specific determination of a safe and effective CO_2 level requires further in-depth research. However, this study is limited by its single-center design, a relatively small sample size and a lack of long-term follow-up data. Additional studies using larger cohort and multicentre settings are needed to validate these findings [24].

ABBREVIATIONS

$P_{ET}CO_2$: end-tidal carbon dioxide; POCD: postoperative cognitive dysfunction; $rScO_2$: mregional cerebral oxygen saturation; MoCA: Montreal Cognitive assessment; IL-6: cytokine interleukin-6; ASA: American Standards of Association; BMI: body mass index; BIS: bispectral index; CO: cardiac output; SV: stroke volume; MAP: mean arterial pressure; HR: heart rate; PCIA: patient-controlled intravenous analgesia.

AUTHOR CONTRIBUTIONS

KZ—Guarantor of integrity of the entire study & Manuscript review; YZL and ML—Study concepts; YLY and LRL—Study design & Clinical studies & Manuscript preparation; CZL and HDC—Definition of intellectual content; KZ and CZL—Literature research; YZL, ML and HDC—Data analysis; YLY, YZL and ML—Statistical analysis; YLY—Manuscript editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This trial was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethical Review Committee for Clinical Trials of the First Affiliated Hospital of Fujian Medical University y (NO. [2018]080). Written Informed consent to participate in the study was obtained from participants.

ACKNOWLEDGMENT

Not applicable.

FUNDING

Grants covering the research: We gratefully acknowledge Fujian Provincial Health Technology Project (No. 2019-1-47 and 2019-2-19) and Startup Fund for Scientific Research of Fujian Medical University (No.2018QH1080 and 2021QH1305).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Monk T, Weldon B, Garvan C, Dede D, van der Aa M, Heilman K, *et al*. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008; 108: 18–30.

[2] de Tournay-Jetté E, Dupuis G, Bherer L, Deschamps A, Cartier R, Denault A. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2011; 25: 95–104.

[3] Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM, *et al*. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. The Annals of Thoracic Surgery. 2009; 87: 36–45.

[4] Lee J, Lee P, Do S, Jeon Y, Lee J, Hwang J, *et al*. The effect of gynaecological laparoscopic surgery on cerebral oxygenation. Journal of International Medical Research. 2006; 34: 531–536.

[5] Denault A, Deschamps A, Murkin JM. A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Seminars in Cardiothoracic and Vascular Anesthesia. 2007; 11: 274–281.

[6] Kim SY, Chae DW, Chun Y, Jeong KH, Park K, Han DW. Modelling of the effect of end-tidal carbon dioxide on cerebral oxygen saturation in beach chair position under general anaesthesia. Basic & Clinical Pharmacology & Toxicology. 2016; 119: 85–92.

[7] 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. Respiratory Care. 2010; 55: 288–293.

[8] Colak Z, Borojevic M, Bogovic A, Ivancan V, Biocina B, Majeric-Kogler V. Influence of intraoperative cerebral oximetry monitoring on neurocognitive function after coronary artery bypass surgery: a randomized, prospective study. European Journal of Cardio-Thoracic Surgery. 2015; 47: 447–454.

[9] Li X, Li F, Liu Z, Shao M. Investigation of one-lung ventilation postoperative cognitive dysfunction and regional cerebral oxygen saturation relations. Journal of Zhejiang University-SCIENCE B. 2015; 16: 1042–1048.

[10] Coburn M, Fahlenkamp A, Zoremba N, Schaelte G. Postoperative cognitive dysfunction: incidence and prophylaxis. Anaesthesist. 2010; 59: 177–185.

[11] Rundshagen I. Postoperative cognitive dysfunction. Deutsches Arzteblatt International. 2014; 111: 119–125.

[12] Tsai TL, Sands LP, Leung JM. An update on postoperative cognitive dysfunction. Advances in Anesthesia. 2010; 28: 269–284.

[13] Murniece S, Soehle M, Vanags I and Mamaja B. Near infrared spectroscopy based clinical algorithm applicability during spinal neurosurgery and postoperative cognitive disturbances. Medicina. 2019; 55: 179.

[14] Babakhani B, Heroabadi A, Hosseinitabatabaei N, Schott M, Yekaninejad S, Jantzen JP, *et al*. Cerebral oxygenation under general anesthesia can be safely preserved in patients in prone position: a prospective observational study. Journal of Neurosurgical Anesthesiology. 2017; 29: 291–297.

[15] Deiner S, Chu I, Mahanian M, Lin HM, Hecht AC, Silverstein JH. Prone position is associated with mild cerebral oxygen desaturation in elderly surgical patients. PLoS One. 2014; 9: e106387.

[16] Barrientos RM, Higgins EA, Biedenkapp JC, Sprunger DB, Wright-Hardesty KJ, Watkins LR, *et al*. Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiology of Aging. 2006; 27: 723–732.

[17] Barrientos RM, Frank MG, Watkins LR, Maier SF. Memory impairments in healthy aging: role of aging-induced microglial sensitization. Aging and Disease. 2010; 1: 212–231.

[18] Di Filippo M, Chiasserini D, Tozzi A, Picconi B, Calabresi P. Mitochondria and the link between neuroinflammation and neurodegeneration. Journal of Alzheimer's Disease. 2010; 20: S369–S379.

[19] Peng L, Xu L, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis. PLoS One. 2013; 8: e79624.

[20] Wong C, Churilov L, Cowie D, Tan CO, Hu R, Tremewen D, *et al*. Randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery. BMJ Open. 2020; 10: e029159.

[21] Nayak S, Jindal A. Permissive hypercapnia: is there any upper limit? Indian Journal of Critical Care Medicine. 2015; 19: 56–57.

[22] Chan MTV, Cheng BCP, Lee TMC, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. Journal of Neurosurgical Anesthesiology. 2013; 25: 33–42.

[23] Kotekar N, Shenkar A, Nagaraj R. Postoperative cognitive dysfunction-current preventive strategies. Clinical Interventions in Aging. 2018; 13: 2267–2273.

[24] Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, *et al*. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Journal of Clinical Epidemiology. 2010; 63: e1–e37.

How to cite this article: Yan-lin Yan, Liu-rong Lin, Kai Zeng, Hong-da Cai, Cai-zhu Lin, Min Liang, *et al*. Effect of patient end-tidal carbon dioxide levels on cerebral regional oxygen saturation and inflammatory cytokine concentrations in elderly patients undergoing laparoscopic radical gastrectomy: a randomized controlled trial. Signa Vitae. 2022; 18(6): 59-65. doi: 10.22514/sv.2022.073.