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Cerebral blood flow and cerebral oxygen consumption in patients with COPD on mechanical ventilation

A. Sari, S. Oshiata, T. Toriumi, S. Yamashita, S. Kojima, S. Kakumoto and A. Yonei

Department of Anesthesia, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki Okayama, 710 Japan

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Abstract. *Objective:* To investigate the effect of $PaCO_2$ on cerebral blood flow (CBF) in chronic obstructive pulmonary disease (COPD).
Design: Before-after trial.
Setting: General ICU in a regional hospital.
Patients: 7 patients undergoing mechanical ventilation because of an exacerbation of COPD.
Intervention: CBF and cerebral metabolic rate of oxygen ($CMRO_2$) of COPD were measured before and after hyperventilation and were compaired by those of normal patients. CBF was measured by the Kety-Schmidt technique using 15% N_2O.
Measurements/results: Hyperventilation produced a significant reduction in CBF in COPD with no concomitant change in $CMRO_2$. $CMRO_2$ in COPD was significantly lower than those in normal patients. The regression equation was shifted significantly more to the right in COPD.
Conclusion: The sensitivity of CBF in CO_2 remained but $CMRO_2$ was reduced markedly in COPD patients.

Key words: Chronic obstructive pulmonary disease (COPD) – Cerebral blood flow (CBF) – Cerebral metabolic rate for oxygen ($CMRO_2$) – CO_2 response

Patients with chronic obstructive pulmonary disease (COPD) have a low cerebral blood flow (CBF) due to an increase in blood viscosity produced by increases in both the hematocrit (Hct) and the hemoglobin (Hb) concentration [1–5]. In such patients, CBF was found to increase and return to normal range with phlebotomy when the Hct, and thereby viscosity was reduced significantly. However, the relationship between CBF and the cerebral metabolic rate of oxygen ($CMRO_2$), or the cerebrovascular response to $PaCO_2$ remain unknown. Knowledge of the response to CO_2, in particular, is important in managing COPD patients under mechanical ventilation.

In this study, we examined CBF, $CMRO_2$, and CO_2 reactivity of CBF in patients with COPD and compared them to normal awake patients examined in a previous study [6, 7].

Patients and methods

This study was approved by the Ethics Committee at Kurashiki Central Hospital, and written informed consent was obtained from each patient's relatives. We studied 7 male patients with COPD ranging in age from 42–79 years (63 ± 15 years, mean ± SD) (Table 1). Each patient was admitted to the ICU from the medical ward requiring mechanical ventilation because of an exacerbation of COPD associated with unconsciousness. Each patient was intubated and placed on controlled mechanical ventilation (Siemens Elema Servo ventilator, 900 C), which was facilitated by pancuronium bromide and diazepam intravenously as needed.

Cerebral blood flow was measured in 7 patients, and 7 observations of the CO_2 response were made in the same patient during mechanical ventilation. Each measurements was performed when the patient could be ventilated easily, and settings of the ventilator during measurements were as follows: tidal volume, 8 ml/kg; respiratory rate, 10 breaths/min; inspiratory to expiratory ratio: 1:2; and FiO_2, 0.85 (15% N_2O). Peak airway pressure was maintained below 30 cmH_2O by controlling the tidal volume and/or respiratory rate. Diazepam for sedation and aminophylline for bronchoconstriction were discontinued at least 24 h prior to this study. In each patient, an electroencephalogram was recorded using frontoparietal silversilver choride electrodes (DM 610G, Nihon Kohden, Tokyo). The radial artery was cannulated to measure arterial blood pressure and to collect blood. An 18-gauge catheter was placed in the left jugular bulb for blood collection and CBF measurement. The vein was cannulated under ultrasound guidance (Echo Camera, Model SSD-255, Aloka, Tokyo) [8] and the position of the catheter was confirmed by radiograph. Cerebral blood flow was measured by the Kety-Schmidt technique using 15% N_2O [9]. After taking arterial and

Table 1. Cases of COPD

No.	Age	Sex	Diagnosis	Consciousness	Outcome
1	67	M	Emphysema	Confusion	died in ICU
2	53	M	Emphysema Old TB	Somnolence	discharged
3	50	M	Emphysema	Somnolence	discharged
4	79	M	Pneumoconiosis	Somnolence	died in ICU
5	42	M	Bronchial asthma	Confusion	discharged
6	73	M	Emphysema	Confusion	discharged
7	79	M	Emphysema	Stupor	died in ICU

M = male, TB = pulmonary tuberculosis, discharged = discharged from ICU

jugular bulb venous blood samples, N_2O was added to the inspired oxygen and simultaneous arterial and jugular bulb venous blood samples were obtained at 1, 3, 5, 7, 10, 12, and 15 min after initiating N_2O inhalation. The blood level of N_2O was measured by gas chromatography (Shimazu, GC4APTF, Tokyo) and the CBF was calculated using a modification of the Kety-Schmidt method [10], which included prolongation of the N_2O saturation phase and extrapolation of the arteriovenous difference of the N_2O concentration to infinity.

The difference between mean arterial pressure (MAP) and the internal jugular venous pressure (JVP) was defined as the cerebral perfusion pressure (PP). Cerebral vascular resistance (CVR) was calculated as the ratio of CPP to CBF. The PO_2, PCO_2, and pH were measured with a blood gas analyzer (178 pH/Blood Gas Analyzer, Corning Medical and Scientific, MA). Oxygen saturation (SaO_2, SvO_2) and hemoglobin (Hb) were measured with a Hemoximeter (OSM2, Radiometer, Copenhagen). Hematocrit (Hct) was measured with a centrifugal machine for Hct (Hematocrit MC-201, Hitachi Koki Co. Ltd., Tokyo).

During CBF measurement end-tidal CO_2 was monitored with a CO_2 analyzer (CCD300, Datex, Helsinki) to keep the $PaCO_2$ constant and SaO_2 was monitored with a pulse oximeter (Oxypal OLV 1100, Nihon Kohden, Tokyo) to maintain an adequate oxygenation. These values were measured before and at 7 and 15 min after the beginning of N_2O inhalation and the mean value of the three determinations was calculated. Oxygen content was calculated from the Hb oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from PO_2 and oxygen solubility. The $CMRO_2$ was calculated as the product of CBF and the oxygen content difference ($C(a\text{-}jv)O_2$) between arterial blood (CaO_2) and jugular bulb venous blood ($JCvO_2$).

In preparing for the second set of measurements, the mechanical ventilation rate was increased to reduce the in $PaCO_2$ as shown by a decrease in end-tidal CO_2. Measurement of CBF was repeated after 10 min had elapsed to permit stabilization of the blood gases. During each of the two measurements, arterial pressure, temperature, blood gases, and Hb were determined to preclude the possibility that CBF may have changed due to factors other than the alteration in $PaCO_2$.

The data were analyzed using the Wilcoxon signed rank test to compare cerebral hemodynamics and metabolism, the intercepts, and the slopes of these equations between the ventilated patients with COPC and the control subjects. Any difference between before and after hyperventilation in COPD was evaluated using the two-tailed Wilcoxon test for paired data. A p-value < 0.05 was considered significant.

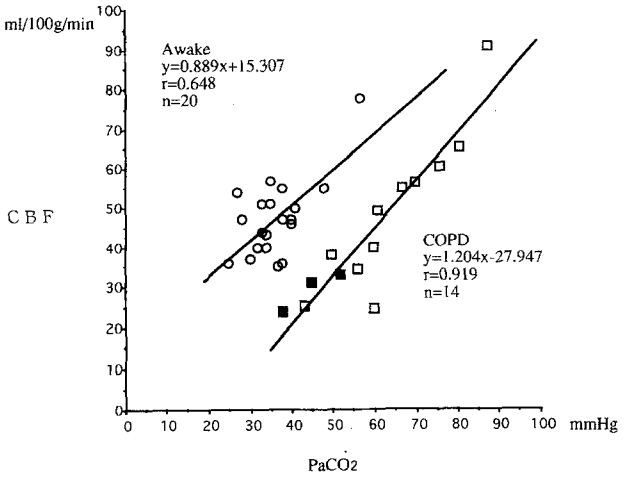

Fig. 1. Comparison of the cerebrovascular responses to changes in the $PaCO_2$ in ventilated COPD (open square) and awake control (open circles) subjects. Three solid sqaures indicate values below 55 mmHg of MAP following hyperventilation. There is no significant difference in the slopes of the regression line between the COPD and control groups, however, the line for COPD patients is shifted significantly to the right. Data for the awake control subjects was originally published in references [6] and [7]

Table 2. Comparison of cerebral hemodynamics and metabolism between awake and COPD subjects

	Awake ($n = 20$)	COPD ($n = 7$)		Before vs after HV
		Before HV	After HV	
Age	45±2	63±15[a]		
MAP	92±3	84±8	70±17	NS
JVP	5±3	5±1	5±1	NS
CPP	87±12	79±7	65±17	NS
CBF	48±10	53±22	36±17	0.025
CVR	1.9±0.7	1.7±0.8	1.8±0.6	NS
FiO_2	1.0	0.85	0.85	
Arterial				
PO_2	490±41	251±80[a]	288±79[b]	NS
PCO_2	35±5	67±16[a]	54±11[b]	0.025
pH	7.45±0.02	7.40±0.07	7.42±0.04	NS
Hct	43±3	38±5	39±5	NS
Hb	14±2	13±1	13±1	NS
Jugular				
PO_2	41±5	50±23	38±9	NS
PCO_2	48±6	82±19[a]	69±14[b]	0.025
pH	7.37±0.03	7.34±0.07	7.34±0.06	NS
$JCvO_2$	13.7±1.8	12.4±4.4	11.8±3.3	NS
$C(a\text{-}jv)O_2$	6.4±1.7	4.5±1.9	6.0±2.0	0.025
$CMRO_2$	2.94±0.59	2.09±0.6	2.02±0.44[c]	NS
$CBF/CMRO_2$	16±4	27±12	18±6	0.025

HV = hyperventilation, see text for other abbreviations
Age years, MAP mmHg, JVP mmHg, CPP mmHg, CBF ml/100 g/min, PO_2 mmHg, PCO_2 mmHg, Hb mg/dl, Hct%, $JCvO_2$ vol%, $C(a\text{-}jv)O_2$ vol%, $CMRO_2$ ml/100 g/min, $CBF/CMRO_2$ ml blood/ml O_2.
Before HV = before hyperventilation
After HV = after hyperventilation
[a] $p < 0.02$ awake vs before hyperventilation
[b] $p < 0.02$ awake vs after hyperventilation
[c] $p < 0.05$ awake vs after hyperventilation

Results

All data are summarized in Table 2 and are compared to the findings in a total of 20 awake control subjects studied in two previous studies [7, 8]. Of 7 patients 4 were discharged from the ICU after weaning from mechanical ventilation and 3 died of multiple organ failure while under mechanical ventilation in the ICU (Table 1). There was no significant difference in CBF, both before and after hyperventilation, between the awake controls and COPD patients, although the COPD group had a significantly higher $PaCO_2$ (67±16 mmHg before hyperventilation and 54±11 mmHg after hyperventilation vs 35±5 mmHg) ($p < 0.05$). Cerebral blood flow in COPD patients decreased significantly from 53±22 to 36±17 ml/100 g/min following hyperventilation. However, three of 7 COPD patients in the hyperventilation group experienced a reduction in MAP below 55 mmHg with concomitant reduction in $PaCO_2$ (Fig. 1 three solid squares). Their MAP after hyperventilation were 53, 53, and 54 mmHg, respectively.

A positive linear relationship was observed between CBF (y) and $PaCO_2$ (x) in both the control and COPD groups, with the regression equation being

$y = 0.889x + 15.307$ ($r = 0.648$, $n = 20$) for the control group and $y = 1.204x - 27.947$ ($r = 0.919$, $n = 14$) for the COPD group (Fig. 1). There was no significant difference in the slope of the either equation between the COPD and control group, however, the equation was shifted significantly more to the right in the COPD group.

In ventilated COPD patients, the mean of 14 $CMRO_2$ measurements was 2.06 ± 0.5 ml/100 g/min, which was significantly lower than in awake controls ($2.94 + 0.59$ ml/100 g/min) ($p < 0.01$). The $CBF/CMRO_2$ ratio after hyperventilation was significantly lower than that before hyperventilation in the COPD group ($p < 0.01$). The venous-arterial difference in $PaCO_2$ ($V\text{-}aDCO_2$) was 13 mmHg in awake control subjects and 15 mmHg in COPD patients, however, there was no significant difference in $V\text{-}aDCO_2$ between awake and COPD patients. There was a significant difference in age between the control and COPD groups (45 ± 2 years vs 63 ± 15 years; $p < 0.01$).

Discussion

A relation between reduced $CMRO_2$ and cerebral function has been described in many clinical conditions, including organic dementia [11] and hepatic or septic coma [12]. Although many studies concerning the relationship between CBF and blood viscosity in COPD have been reported [1–5], we are not aware of any previous studies of $CMRO_2$ in COPD patients. The measurements of CBF and $CMRO_2$ in awake control subjects were obtained in our two previous studies [6, 7] and were compared to the findings in COPD patients described presently. However, a significant ($p < 0.01$) difference in age was observed between awake control and COPD patients. In our COPD patients, $CMRO_2$ was reduced, this may have been caused by advanced age, sedatives to facilitate controlled mechanical ventilation, and/or primary event of COPD. Ther cerebral metabolism of oxygen decreases up to 9% with age [11] in proportion to the progressive age-related decrease in neurons. In our study, patients with COPD were significantly older than were control subjects, therefore, aging may have caused the reduction in $CMRO_2$. However, $CMOR_2$ in the COPD group was significantly lower than that reported by Lassen et al. [11], who demonstrated that the $CMRO_2$ was 9% lower in the elderly than in young normal subjects (mean $CMRO_2$; 2.71 ± 0.12; mean age; 72 years). Diazepam decreased the $CMRO_2$ by a maximum of 17% and returned to baseline within 120 min in the dog [13]. Although our patients were sedated with diazepam during mechanical ventilation, all drugs having any effect on the central nervous system were discontinued at least 24 h prior to the study. Factors other than aging or diazepam may, therefore, contribute to reducing the $CMRO_2$ in COPD.

Although the response to CO_2 the CBF was maintained in COPD patients as well as in awake controls, the relationship of CBF to $PaCO_2$ was shifted to the right, whereas the sensitivity to CO_2 was unchanged in COPD when compared to the awake group (Fig. 1). With chronic changes in the CO_2 levels, CBF returns gradually toward normal over a period of 24 to 36 hours in the hypocapnic state [14]. The shift to the right of the CO_2 response suggests that in the hypercapnic state, the phenomenon described above may occur. This slow compensation is accounted for by the gradual return to normal of the cerebrospinal fluid (CSF) pH via the secondary adjustment of the CSF bicarbonate concentration which does not readily cross the blood-brain barrier. The normal CO_2 response of CBF may be accounted for by abrupt changes in hydrogen ion concentration which occur secondary to either hypercapnia or hypocapnia in the extracellular fluid of vascular smooth muscle cells of resistance vessels. Responsiveness to CO_2 of the cerebral circulation was absent during hypotension at a mean blood pressure of 50 mmHg [15]. Three of seven patients experienced a reduction in MAP below 5 mmHg following hyperventilation to 53 mmHg, 53 mmHg, and 54 mmHg. Therefore, the loss of autoregulation, and not hypocapnia, may contribute the reduction in the CBF (Fig. 1, solid squares). The venousarterial PCO_2 difference was larger than that in awake control subjects, however, there was no significant difference in $V\text{-}aDCO_2$ between awake and COPD subjects (15 mmHg in COPD vs. 13mHg in awake). This increase in $V\text{-}aDCO_2$ is most likely due to the high absolute $PaCO_2$ level in COPD patients and not due to a greater CO_2 production rate.

In conclusion, our study confirms that the $CMRO_2$ was reduced and that cerebrovascular response to CO_2 was preserved in COPD patients during mechanical ventilation.

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Dr. A. Sari
Department of Anesthesiology
and Intensive Care Medicine
Kawasaki Medical School
577 Matsushima, Kurashiki
Okayama, 701-01
Japan