Cerebrovascular and systemic hemodynamic response to carbon dioxide in humans

Daria V. Kuznetsova and Vladimir P. Kulikov

Background **Arterial partial pressure alteration of CO_2 (P_{aCO_2}) affects not only the cerebral blood flow velocity but also the systemic arterial blood pressure (BP). At the same time, BP can affect the cerebral blood flow. The objective of the present research is to study the impact of the P_{aCO_2} level on cerebrovascular CO_2 reactivity (CVR_{CO_2}) and BP as well as the impact of BP upon CVR_{CO_2} alteration by hypercapnia and hypocapnia.**

Materials and methods **Cerebral blood flow velocity was recorded by means of transcranial Doppler in both middle cerebral arteries (MCAv left and right). The mean arterial pressure (MAP) was studied using the finger photoplethysmography method, arterial blood oxygen saturation was estimated by the pulse oximetry method, and end-tidal P_{CO_2} (P_{ETCO_2}) was measured with an infrared capnograph. After a recording of the reference values of all the parameters, all the volunteers underwent a rebreathing as well as a hyperventilation.**

Results **At rest, P_{ETCO_2} was 33.6 (SD 3.1) mmHg. At rebreathing, MCAv increased at 38 mmHg P_{ETCO_2}, MAP − at 43 mmHg P_{ETCO_2}. By hyperventilation, MCAv decreased at 28 mmHg P_{ETCO_2}, MAP − at 26 mmHg P_{ETCO_2}. When P_{ETCO_2} reached 43 mmHg, CVR_{CO_2} increased from 2.3 (SD 1.4) to 3.3 (SD 1.2)%/mmHg ($P<0.01$). When P_{ETCO_2} decreased to 26 mmHg, CVR_{CO_2} increased from −3.6 (SD 2.5) to −5.9 (SD 3.9)%/mmHg ($P<0.01$).**

Conclusion **Within the alteration of P_{ETCO_2} above 43 and under 26 mmHg, BP increased and decreased, respectively, leading to a change in CVR_{CO_2}.** ***Blood Press Monit*** **19:81–89** © **2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: arterial blood pressure, cerebral blood flow, hypercapnia, hypocapnia, transcranial Doppler

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Introduction

The partial pressure of arterial CO_2 (P_{aCO_2}) plays an important part in cerebral blood flow (CBF) regulation. Elevations in P_{aCO_2} (i.e. hypercapnia) lead to vasodilation of cerebral arterioles and a subsequent increase in CBF, whereas a reduction in P_{aCO_2} (i.e. hypocapnia) leads to vasoconstriction and a subsequent decrease in CBF. The highly sensitive distribution of CBF in response to changes in P_{aCO_2}, termed cerebrovascular CO_2 reactivity (CVR_{CO_2}), is a vital homeostatic function that helps regulate and maintain central pH [1]. The measurement of CVR_{CO_2} has been applied in clinical practice to evaluate cerebrovascular function in patients with carotid atherosclerosis [2–5], stroke [6], hypertension [7], heart failure [8], and vertebral artery hypoplasia [9]. CVR_{CO_2} disorder causes a higher risk of occurrence of cerebral ischemia [2–5].

At the same time, hypercapnia causes an increase in arterial blood pressure [10–13]. An increase in arterial blood pressure, in turn, causes an increase in cerebral perfusion pressure and, according to Poiseuille's law, an increase in CBF velocity. CBF permanency under perfusion pressure alteration is provided by autoregulation mechanisms. Cerebral autoregulation consists of CBF constant volume maintenance when the mean hemodynamic pressure varies within 50–170 mmHg [14]. However, autoregulation becomes ineffective under hypercapnia [15,16]. The increase in arterial pressure caused by hypercapnia can lead to an increase in CBF [17], alongside the direct vasodilatating effect of CO_2, which complicates CVR_{CO_2} estimation and can cause misinterpretation of the results [18]. Considering the prognostic significance of CVR_{CO_2} in patients with vascular pathology, it is essential to estimate the validity of CVR_{CO_2} correctly. There are researches focused on arterial pressure and CBF velocity investigation under hypercapnia [18–20]; however, the problem of CVR_{CO_2} estimation, independent of arterial pressure, is still unsolved. Similar to hypercapnia, the problem of arterial pressure impact on CBF velocity under hypocapnia is unstudied.

The objective of the present research is to investigate the impact of P_{aCO_2} level on CBF velocity and arterial pressure as well as to improve CVR_{CO_2} estimation methods.

Materials and methods

Participants

Eleven (six male) nonsmoking volunteers who were not taking any medicine participated in the research. None of the participants had any cardiovascular or respiratory

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diseases; all of them had normal arterial pressure. None of the volunteers had prolonged exposure to high altitude in the 6 months before participating in the study. Female volunteers were not taking oral contraceptives and were tested in the luteal to early follicular phases of their menstrual cycle. The mean (SD) age, height, weight, and BMI were 21 (3.7) years, 1.74 (0.09) m, 66 (14.2) kg, and 21.7 (3.3) kg/m^2, respectively. The volunteers were informed about the investigation protocol and devices to be used, and provided written acceptance of participation in the research. The studies conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the local Biomedical Ethics Committee of Altai State Medical University. All the participants were instructed not to take any caffeine or alcohol 12 h before the tests and to abstain from eating or performing any sort of vigorous activity 4 h before the tests.

Protocol

The tests were carried out in the afternoon in a quiet, aired laboratory (altitude = 250 m). The participants were in the dorsal position, had a comfortable bolster under the head, and were wearing a face mask connected to the capnograph.

All the volunteers underwent three stages of the tests: baseline, rebreathing, and hyperventilation (Diagram 1). At the baseline, the participants breathed room air (normocapnia). With the help of rebreathing, we created hypercapnia. For this, a breathing circuit (Carbonic 01; Carbonic Ltd, Barnaul, Russia) with 1000 ml of dead space extra volume was connected to the face mask. This led to an increase in end-tidal partial pressure of CO_2 (P_{ETCO_2}) by 10–15 mmHg. Rebreathing was followed by a rest, during which hemodynamic parameters, CBF, and capnogram reverted to initial values. With the help of hyperventilation, we created hypocapnia. For this, the participants were instructed to draw deep and quick breaths, resulting one breathing cycle per 2 s. This led to a reduction in P_{ETCO_2} by 10–15 mmHg.

To create hypercapnia, we used the rebreathing method applied by many other authors [13,19–22]. The application of a breathing circuit requires no additional equipment or gas mixtures, making it accessible and easy to use. Rebreathing causes not only hypercapnia but also hypoxia. However, the CBF reaction for the combined effect of hypoxia and hypercapnia is mostly detected by the P_{aCO_2} level and not by arterial partial pressure of O_2 deficiency [23]; thus, we chose rebreathing to estimate the impact of hypercapnia on CBF velocity. To create hypocapnia, we used the spontaneous hyperventilation method. However, we refrained from applying hyperventilation at a rate higher than one breathing cycle per 2 s, or over a period of time longer than 2 min, as we considered that it could cause respiratory discomfort.

Hypercapnia and hypocapnia created by means of rebreathing and hyperventilation allow us to include a wide range of P_{ETCO_2}. However, we refrained from creating a gradual increase in CO_2 from hypocapnia to hypercapnia, as in the Duffin rebreathing method [21], because we considered the possibility of an increase and reduction in P_{ETCO_2} relative to the initial state of normocapnia to be more physiological.

Instrumentation

To evaluate CBF, we used bilateral transcranial Doppler (TCD) monitoring (Angiodin-Universal; BIOSS, Moscow, Russia). We measured the time–mean maximum blood flow velocity in the M1 segment in middle cerebral arteries left and right (MCAv left and right, cm/s). Using a special helmet, the ultrasonic 2 MHz impulse-wave probes were fixed in the middle temporal acoustic windows area from both sides.

TCD measures blood flow velocity and not CBF *per se*. Nevertheless, studies show that flow velocity in the middle cerebral artery represents a reliable and valid index of CBF [24–28]. TCD enables us to investigate CBF bilaterally and also provides sufficient time resolution to carry out tests without any extra risk for the participants [1,29]. We applied TCD to evaluate CBF and CVR_{CO_2}, relying on its high temporal resolution, noninvasiveness, and relatively low cost in conjunction with safety. Moreover, most of the other authors applied TCD to study CBF and CVR_{CO_2} [19,20,30].

During the entire investigation period, monitoring of mean arterial blood pressure (MAP, mmHg) was carried out by finger photoplethysmography using a continuous beat-to-beat noninvasive measurement (CNAP Monitor 500; CNSystems, Graz, Austria) on the left middle and index fingers.

Capnographic control with P_{ETCO_2} (mmHg) estimation was maintained during the entire investigation period (OEM module; Oridion Systems Ltd, Jerusalem, Israel). P_{ETCO_2} differs from P_{aCO_2} by only 1–2 mmHg and reproduces its value adequately [31].

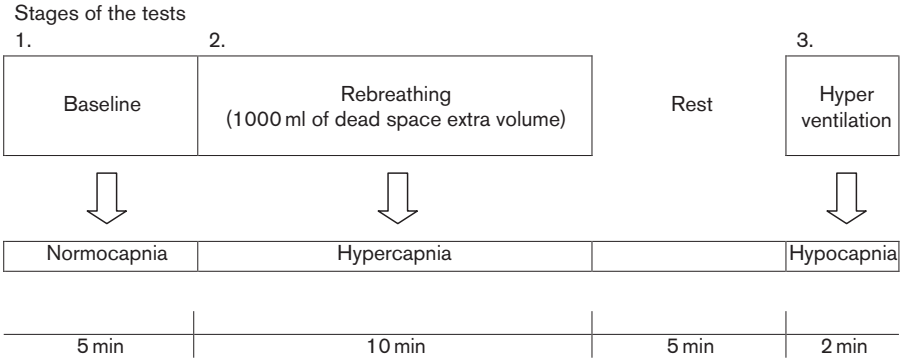
Arterial blood oxygen saturation (SpO_2, %) was measured using the pulse oximetry method (BPM-200; Biosys, Seoul, Korea).

Data and statistical analysis

For every test stage, MCAv left and right, P_{ETCO_2}, MAP, and SpO_2 values were correlated in time and registered every 10 s by statistic programs for further processing.

MCAv left and right, P_{ETCO_2}, MAP, and SpO_2 data were averaged out for each participant within a 5-min period of normocapnia. On this basis, the mean (SD) values of the

Diagram 1



The design of the study.

Table 1 Baseline characteristics of cerebral and systemic hemodynamic parameters, P_{ETCO_2} and SpO_2, in all volunteers

		Parameters				
Participants	Sex	MCAv left (cm/s)	MCAv right (cm/s)	MAP (mmHg)	P_{ETCO_2} (mmHg)	SpO_2 (%)
1	M	62	56.8	86.7	38	99
2	F	68.4	71.3	95.4	32	98.5
3	F	74.2	74.7	101.7	33	98.4
4	M	59.1	–	84.4	35	98.1
5	M	53.2	65.9	93.4	33	98.6
6	M	67.2	71.1	100.9	40	97
7	F	75.7	74.5	86.6	33	99
8	M	74.6	58.6	96.3	30	97.5
9	F	73.4	67.6	94.3	32	98.3
10	F	54.9	51.5	73.7	30	97.4
11	M	60	50.2	76	35	98
Mean (SD)		65.7 (8.3)	64.2 (9.3)	89.9 (9.3)	33.6 (3.1)	98 (0.6)

MAP, mean arterial blood pressure; MCAv, middle cerebral artery flow velocity; P_{ETCO_2}, end-tidal partial pressure of CO_2; SpO_2, saturation of arterial blood O_2.

parameters reported above for all the samples were calculated (Table 1). The maximum alterations in all the parameters during rebreathing and hyperventilation as compared with baseline (Δ) as well as their absolute and percentage values (Table 2) were calculated. MCAv data for every 10 s during the rebreathing and hyperventilation were converted into percentage alteration from the mean value during baseline (%MCAv left and right). Then, %MCAv left and right were correlated with P_{ETCO_2}. Absolute CBF velocity alteration was standardized per 1 mmHg P_{ETCO_2} during rebreathing and hyperventilation.

To estimate vascular cerebral CO_2 reactivity, the cerebrovascular reactivity index common for MCA left and right during hypercapnia ($CVR_{hyperCO_2}$) and hypocapnia (CVR_{hypoCO_2}) [32] was calculated according to the following formulae:

$$CVR_{hyperCO_2} = \frac{(\Delta MCAv\ hyper/MCAv\ norm)}{\Delta P_{ETCO_2}\ hyper} \times 100.$$

$$CVR_{hypoCO_2} = \frac{(\Delta MCAv\ hypo/MCAv\ norm)}{\Delta P_{ETCO_2}\ hypo} \times 100,$$

Table 2 Measured parameters

	Mean (SD)			
	Rebreathing		Hyperventilation	
Parameters	Left	Right	Left	Right
MCAv (cm/s)	100.7 (16.3)	93.8 (36.5)	34.2 (7.3)	34.7 (7.1)
ΔMCAv (cm/s)	35.0 (10.4)	35.4 (16.0)	−31.5 (7.2)	−29.6 (7.1)
%MCAv	53.1 (13.2)	54.3 (21.0)	−47.9 (9.0)	−41.8 (16.0)
MAP (mmHg)	108.7 (13.9)		79.4 (9.0)	
ΔMAP (mmHg)	18.9 (9.6)		−10.1 (4.5)	
%MAP	20.9 (11.2)		−11.2 (4.4)	
P_{ETCO_2} (mmHg)	48.2 (3.7)		18.8 (3.3)	
ΔP_{ETCO_2} (mmHg)	14.6 (2.7)		−14.7 (5.1)	
$\%P_{ETCO_2}$	43.8 (9.3)		−43.4 (12.1)	
SpO_2	93.5 (2.8)		99.0 (0)	
ΔSpO_2	−4.7 (3.2)		0.8 (0.6)	

%, parameter alteration percentage relative to baseline; MAP, mean arterial blood pressure; MCAv, middle cerebral artery flow velocity; P_{ETCO_2}, end-tidal partial pressure of CO_2; SpO_2, saturation of arterial blood O_2; Δ, parameter alteration relative to baseline.

where MCAv norm is the MCAv value during normocapnia, ΔMCAv hyper (ΔMCAv hypo) is the MCAv alteration during hypercapnia (hypocapnia) relative to MCAv norm, and ΔP_{ETCO_2} hyper (ΔP_{ETCO_2} hypo) is

P_{ETCO_2} alteration during hypercapnia (hypocapnia) relative to P_{ETCO_2} during normocapnia.

Statistical data processing was carried out using the statistic program package STATISTICA 6.0 (StatSoft Inc., Tulsa, Oklahoma, USA). We assessed the impact of P_{ETCO_2} on %MCAv left and right, MAP, CVR_{CO_2} during hypocapnia, normocapnia, and hypercapnia using one-way analysis of variance (ANOVA). Bonferroni post-hoc tests were performed to isolate any significant differences. The relationship between selected dependent variables was assessed using a Spearman's rank product–moment correlation. The level of probability for statistical significance was P less than 0.05. All data are represented as mean (SD).

Results

All the volunteers underwent baseline, rebreathing, and hyperventilation stages. MCAv of one of the volunteers was recorded only from one side because of a poor acoustic window.

During the baseline period, cerebral and systemic hemodynamic parameter values, P_{ETCO_2} and SpO_2, corresponded to the age standards in all the volunteers (Table 1). Figure 1 shows an example of typical alterations in cerebral and systemic hemodynamic indices as well as capnography and blood oxygen saturation during the entire test period.

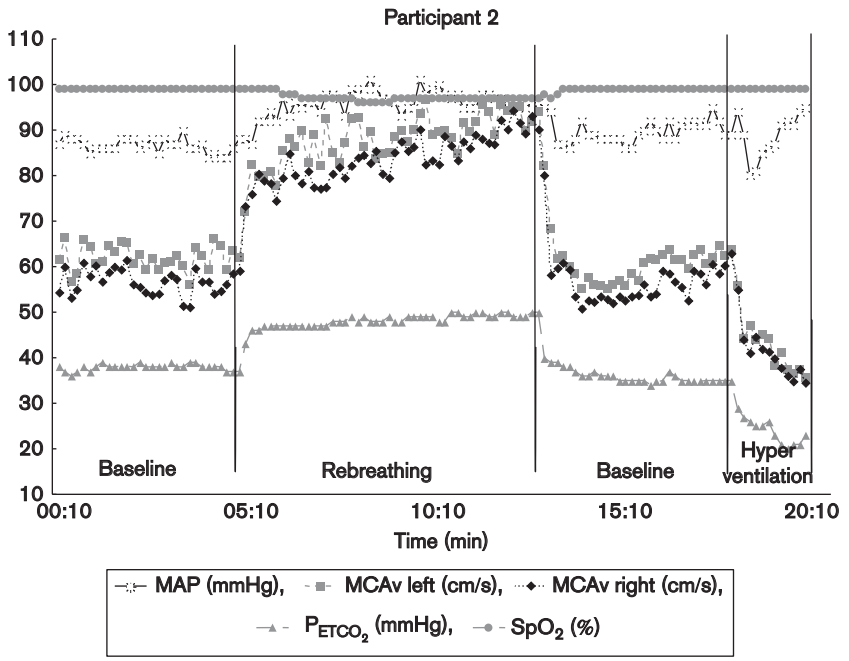
Cerebral and systemic hemodynamics during the rebreathing

During the rebreathing, P_{ETCO_2}, MCAv left, and right started increasing during the first 10 s. P_{ETCO_2} continued to increase for 60 s, then remained at the level reached, with minor alterations. MCAv left and right also increased for 60 s; afterward, the values changed insignificantly, remaining at the level reached. The increase in CBF velocity on both sides during the first 60 s of rebreathing was 2.5 cm/s per 1 mmHg of P_{ETCO_2} increase; after the 60th second the increase was 3.5 cm/s per 1 mmHg P_{ETCO_2}. No sharp MAP growth at the beginning of rebreathing, similar to P_{ETCO_2} and MCAv, was noted. MAP started increasing at about the 30th second of rebreathing, continued increasing up to 2 min, and remained at the level reached, with minor alterations. SpO_2 decreased gradually during 2–3 min and remained reduced until the end of rebreathing. Table 2 shows the maximum alterations in all the parameters during rebreathing and hyperventilation.

Correlation analysis showed a P_{ETCO_2} interconnection with MCAv left and right and with MAP, MAP with MCAv left and right during rebreathing (Table 3).

The results of one-way ANOVA indicated a dependence of CBF velocity left and right and MAP on P_{ETCO_2} level during rebreathing. Post-hoc analysis indicated that %MCAv increased significantly compared with the baseline

Fig. 1



A typical recording of the parameters under study in participant 2 during the baseline, rebreathing, and hyperventilation stages. MAP, mean arterial blood pressure; MCAv, middle cerebral artery flow velocity; P_{ETCO_2}, end-tidal partial pressure of CO_2; SpO_2, saturation of arterial blood O_2.

Table 3 Parameter correlation analysis at rebreathing, hyperventilation, and combined rebreathing–hyperventilation stages

	Rebreathing		Hyperventilation		Rebreathing–hyperventilation	
Parameters	*R*	*P*	*R*	*P*	*R*	*P*
P_{ETCO_2} and MCAv						
Left	0.74	<0.01	0.99	<0.01	0.86	<0.01
Right	0.86	<0.01	0.92	<0.01	0.93	<0.01
P_{ETCO_2} and MAP	0.47	<0.01	−0.29	0.33	0.72	<0.01
P_{ETCO_2} and SpO_2	0.01	0.94	−0.46	0.11	−0.50	<0.01
MCAv left and right	0.88	<0.01	0.92	<0.01	0.94	<0.01
MAP and MCAv						
Left	0.43	<0.01	−0.26	0.40	0.69	<0.01
Right	0.50	<0.01	−0.12	0.69	0.73	<0.01
SpO_2 and MCAv						
Left	−0.04	0.77	−0.46	0.11	−0.49	<0.01
Right	−0.02	0.91	−0.40	0.17	−0.48	<0.01

MAP, mean arterial blood pressure; MCAv, middle cerebral artery flow velocity; P_{ETCO_2}, end-tidal partial pressure of CO_2; SpO_2, saturation of arterial blood O_2.

at P_{ETCO_2} 38 mmHg or more (Fig. 2). MAP increased significantly [by 4.1 (3.8) mmHg] compared with the baseline only at 43 mmHg P_{ETCO_2} (Fig. 3).

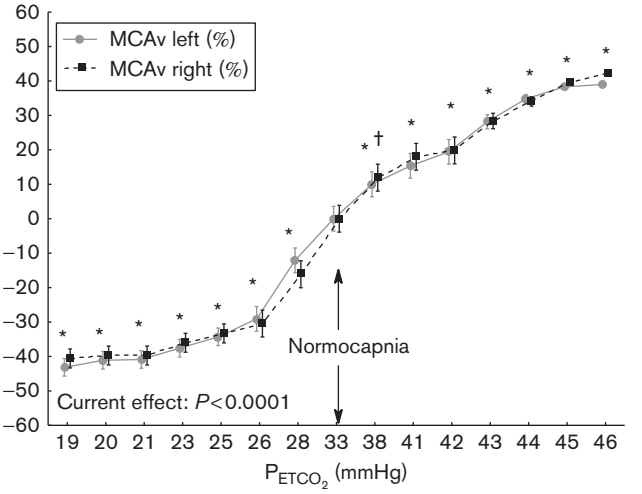
$CVR_{hyperCO_2}$ also altered significantly depending on the P_{ETCO_2} level. According to post-hoc analysis data, when P_{ETCO_2} was under and over 43 mmHg, the $CVR_{hyperCO_2}$ values did not differ. However, significant differences were detected among the $CVR_{hyperCO_2}$ values around 43 mmHg P_{ETCO_2} (Fig. 4). At 38–43 mmHg P_{ETCO_2}, mean (SD) $CVR_{hyperCO_2}$ was 2.3 (1.4)%/mmHg, whereas when P_{ETCO_2} increased over 43 mmHg $CVR_{hyperCO_2}$ reached 3.3 (1.2)%/mmHg ($P < 0.01$).

Cerebral and systemic hemodynamics during hyperventilation

During hyperventilation, the MCAv left and right, as well as P_{ETCO_2}, decreased during the first 10 s. MCAv left and right continued decreasing for 30 s and then remained stable despite the continuous gradual decrease in P_{ETCO_2} during the entire hyperventilation stage. The CBF velocity decreased down to its plateau was ~5.5 cm/s per 1 mmHg P_{ETCO_2}, and then at plateau it reached 3.5–4 cm/s per 1 mmHg P_{ETCO_2}. The maximum decrease in MAP was achieved at the 20th second of hyperventilation. Table 2 shows all the parameter alterations during hyperventilation.

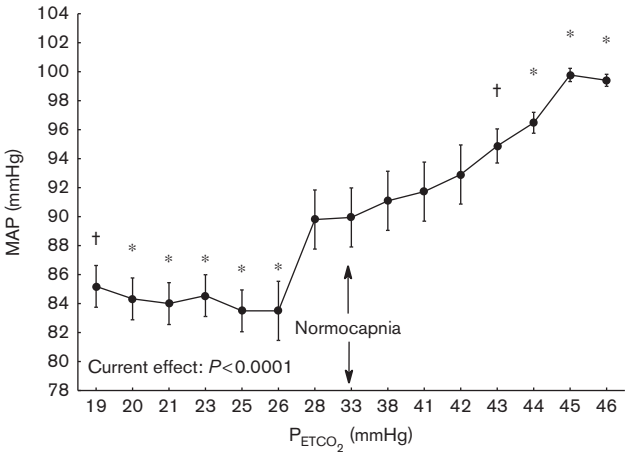
Correlation analysis during the hyperventilation data indicated a correlation of P_{ETCO_2} with MCAv left and right (Table 3). The results of one-way ANOVA indicated a dependence of CBF velocity left and right and MAP on the P_{ETCO_2} level. Post-hoc analysis indicated that %MCAv decreased significantly compared with the baseline at P_{ETCO_2} 28 mmHg or less (Fig. 2). MAP decreased significantly [by 6.8 (4.9) mmHg] compared with the baseline, reaching 26 mmHg P_{ETCO_2}, and remained reduced until the end of the hyperventilation stage (Fig. 3).

Fig. 2



The impact of the end-tidal partial pressure of CO_2 (P_{ETCO_2}) level on alteration flow velocity in the middle cerebral artery percentage relative to baseline (%MCAv) left and right. %MCAv left and right values are given as the least squares means for each P_{ETCO_2} value. Vertical stripes show 0.95 confidence intervals. *$P<0.01$ and †$P<0.05$ for %MCAv left and right at corresponding P_{ETCO_2} hypercapnia and hypocapnia values against %MCAv left and right at normocapnia 33 mmHg P_{ETCO_2}.

Fig. 3



The impact of the end-tidal partial pressure of CO_2 (P_{ETCO_2}) level on the mean arterial blood pressure (MAP) value. MAP data are given as the least squares means for each P_{ETCO_2} value. Vertical stripes show 0.95 confidence intervals. *$P<0.01$ and †$P<0.05$ for MAP at corresponding P_{ETCO_2} values against MAP at normocapnia 33 mmHg P_{ETCO_2}.

CVR_{hypoCO_2} also altered significantly depending on the P_{ETCO_2} level. Post-hoc analysis indicated that, when CVR_{hypoCO_2} increased, P_{ETCO_2} reached 26–25 mmHg, and when P_{ETCO_2} decreased there was also a reduction in CVR_{hypoCO_2}, whereas within a P_{ETCO_2} of 23–19 mmHg the CVR_{hypoCO_2} remained unaltered (Fig. 5). Mean (SD)

CVR_{hypoCO_2} at 28 mmHg P_{ETCO_2} was −3.6 (2.5)%/mmHg, and, at 26–25 mmHg, P_{ETCO_2} was −5.9 (3.9)%/mmHg ($P < 0.01$).

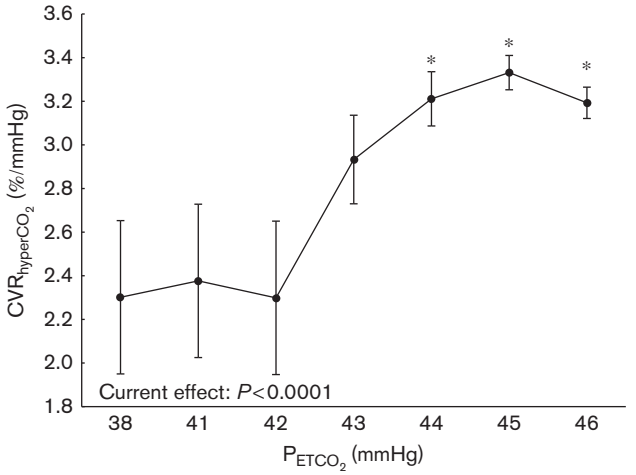
Discussion

The present research aimed to study the impact of the P_{ETCO_2} level on the cerebral and systemic hemodynamics in healthy volunteers. Applying rebreathing and hyperventilation, we studied MCAv, MAP, and CVR_{CO_2} during decrease and increase of P_{ETCO_2}. In earlier studies [19,20,30], the impact of P_{ETCO_2} on CBF and arterial pressure under hypercapnia has already been analyzed. Our research supplements those mentioned previously as we first studied the impact of P_{ETCO_2} and MAP level on CVR_{CO_2} under hypercapnia and hypocapnia.

The application of rebreathing and hyperventilation enabled the observation of cerebral and systemic hemodynamics reaction to CO_2 in the P_{ETCO_2} range from 19 to 48 mmHg. During the baseline period, the P_{ETCO_2} was slightly lower than the classical conception of normocapnia (35–45 mmHg). Moreover, we studied this phenomenon mainly in female volunteers. Such a decrease in P_{ETCO_2} at quiet breathing in healthy women can be attributed to ventilation peculiarities depending on the menstrual cycle phase. We tested women in the lutein phase and at the beginning of the follicular phase of their menstrual cycle, when the estrogen level was at its lowest, to minimize the impact of heightened estrogenic background on cerebrovascular reactivity [33]. During the same menstrual cycle period, functional hyperventilation and P_{aCO_2} decrease by 2.5–3 mmHg [34] were observed because of central neural mechanisms of progesterone action [35].

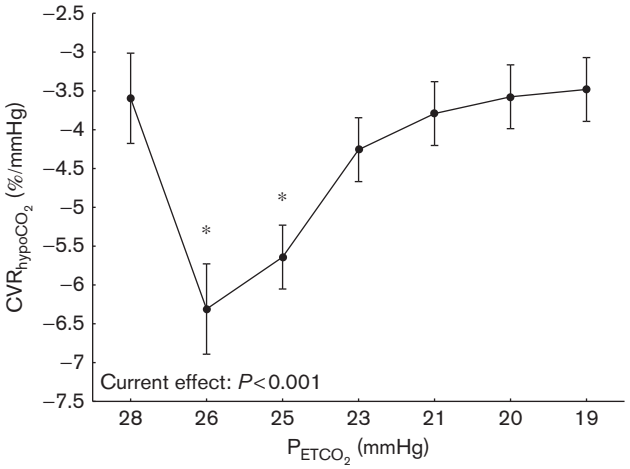
CBF velocity changed from 35 cm/s by hyperventilation to 100 cm/s by rebreathing. This range of CBF velocity alteration is comparable with the data of other investigations studying CBF alteration during hypercapnia and hypocapnia using the TCD method [19,22,36–38]. It is known that the CO_2-impact mechanisms upon CBF vary. Increase in P_{aCO_2} causes a reduction in CO_2-mediated extracellular pH [39,40], activation of K^+-canals in vascular smooth muscle cells [41–43], endothelial and

Fig. 4



The impact of end-tidal partial pressure of CO_2 (P_{ETCO_2}) level on cerebrovascular reactivity to hypercapnia ($CVR_{hyperCO_2}$) values during rebreathing. $CVR_{hyperCO_2}$ values are given as the least squares means for each P_{ETCO_2} value. Vertical stripes show 0.95 confidence intervals. *$P<0.01$ for $CVR_{hyperCO_2}$ at corresponding P_{ETCO_2} values against each $CVR_{hyperCO_2}$ value at P_{ETCO_2} 38, 41, and 42 mmHg.

Fig. 5



The impact of end-tidal partial pressure of CO_2 (P_{ETCO_2}) level on cerebrovascular reactivity to the hypocapnia (CVR_{hypoCO_2}) value during the hyperventilation. CVR_{hypoCO_2} values are given as the least squares means for each P_{ETCO_2} value. Vertical stripes show 0.95 confidence intervals. *$P<0.05$ for CVR_{hypoCO_2} at corresponding P_{ETCO_2} values against CVR_{hypoCO_2} at P_{ETCO_2} 23, 21, 20, 19, and 28 mmHg.

neuronal isoforms of nitric oxide synthase synthesis intensification with nitric oxide, and cyclic GMP accumulation [44,45]. The mechanisms mentioned above result in reductions in intracellular Ca^{2+} values and smooth muscle cells relaxation accompanied by a decrease in vascular tone. CBF velocity reduction and vasoconstriction during hypocapnia, as opposed to hypercapnic vasodilation mechanisms listed above, are conditioned by a decrease in pP and an increase in the intracellular calcium concentration in plain muscle cells exclusively, which leads to intensification of vascular tone [46].

Hypercapnia influences not only cerebral hemodynamics but also systemic blood flow [47]. When P_{aCO_2} increases, the arterial pressure increases by means of sympathoactivation of the central and peripheral chemoreceptors [11,13,48] and, as a result, vascular tone and cardiac output intensification [10,12]. Thereafter, arterial pressure decreases during hypocapnia. In our research, MAP naturally increased during hypercapnia and decreased during hypocapnia. A significant increase in MAP during hypercapnia, compared with normocapnia, occurred only at P_{ETCO_2} 43 mmHg. In the research by Battisti-Charbonney *et al.* [20], P_{ETCO_2} liminal value for MAP during rebreathing was 44.4 mmHg, which is almost identical to our P_{ETCO_2} liminal value results for MAP. Minor variations in P_{ETCO_2} liminal values for MAP in the studies described can be conditioned by the peculiarities of the rebreathing techniques used in them. Our data of MAP study during rebreathing differ from the data obtained by Shoemaker *et al.* [13], who studied the reaction of the cardiovascular system and the sympathetic nervous system (MSNA) during hypercapnia. He detected a significant increase in MAP at P_{ETCO_2} 50 mmHg compared with P_{ETCO_2} 40 mmHg. An absolute increase in P_{ETCO_2}, which caused an increase in MAP in his research, matched ours and reached about 10 mmHg.

P_{ETCO_2} liminal value for MAP during hypocapnia has probably been unstudied earlier. Our research indicated a significant decrease in MAP on reaching the P_{ETCO_2} liminal value of 26 mmHg.

It is known that when arterial pressure increases, cerebral perfusion pressure increases, which can influence CBF velocity [49]. In healthy individuals, CBF stability under perfusion pressure alteration is provided by autoregulation, which consists in maintaining constant CBF volume under a mean hemodynamic pressure alteration within 50–170 mmHg [14]. However, hypercapnia causes weakening and disorders of the autoregulation mechanism [15,16,50]. Under such circumstances, an increase in arterial pressure contributes toward intensification of CBF [17,23], which complicates CVR_{CO_2} assessment and can lead to misinterpretation of the results [18].

The impact of P_{ETCO_2} on cerebrovascular reactivity during rebreathing has also been described by other authors [19,20], but they did not study the threshold of CVR_{CO_2} alterations depending on the P_{ETCO_2} level during hypercapnia and hypocapnia. We found that $CVR_{hyperCO_2}$ alters when the P_{ETCO_2} level increases. When P_{ETCO_2} exceeded 43 mmHg, $CVR_{hyperCO_2}$ increased significantly. As the P_{ETCO_2} threshold for MAP was also 43 mmHg, it became evident that it was precisely the increase in cerebral perfusion pressure conditioned by MAP growth that contributed toward a greater increase in CBF velocity by 1 mmHg P_{ETCO_2} on reaching the P_{ETCO_2} threshold of 43 mmHg.

CVR_{hypoCO_2} also depended on the level of P_{ETCO_2}. CVR_{hypoCO_2} increased significantly on reaching P_{ETCO_2} 26 mmHg, then decreased, and at 23 mmHg P_{ETCO_2} and with a further decrease, CVR_{hypoCO_2} remained constant. These results can be explained, first, by the limits of cerebral vasoconstriction under hypocapnia. Maximum constriction of resistive vessels occurred probably when P_{ETCO_2} decreased to 23 mmHg, as at a greater decrease of P_{ETCO_2} CVR_{hypoCO_2} remained unchanged. Second, CBF velocity and CVR_{hypoCO_2} can be influenced by a decrease in MAP as well, accompanied by an appropriate reduction in cerebral perfusion. A maximum decrease in MAP was detected at 26 mmHg P_{ETCO_2} and a maximum CVR_{hypoCO_2} also occurred at the same value.

Thus, our research proves the impact of MAP on CVR_{CO_2} and the necessity of CVR_{CO_2} estimation only when MAP is constant. CVR_{CO_2} estimation within the range of P_{ETCO_2} from 26 to 43 mmHg appears to be correct. However, taking into consideration the individual ventilation peculiarities, it is preferable to assess CVR_{CO_2} under arterial pressure monitoring control.

The present study has several limitations. First, to evaluate CBF, we applied TCD, which does not have sufficient spatial resolution to study cerebral perfusion, as, for instance, computed tomography perfusion scan and MRI. However, TCD meets the needs of the CVR_{CO_2} study in the optimal way [1]. In addition, to evaluate CVR_{CO_2}, we applied rebreathing without compensating hypoxia with extra oxygen, as some other authors do [19,20]. We were guided by the fact that under the combined effect of hypoxia and hypercapnia, the CBF reaction is mainly defined by the latter [23]. We assume that these limitations could not have affected the results of the study.

Conclusion

The level of P_{ETCO_2} affects MAP and CVR_{CO_2}. Elevation in P_{ETCO_2} over 43 mmHg at rebreathing leads to a significant increase in MAP by 4.1 (3.8) mmHg, whereas a reduction of P_{ETCO_2} over 26 mmHg at hyperventilation leads to a significant decrease in MAP by 6.8 (4.9) mmHg. When P_{ETCO_2} reaches the same liminal values, a significant change in CVR_{CO_2} also occurs. P_{ETCO_2} thresholds for CVR_{CO_2} and MAP during rebreathing and

hyperventilation coincide. Thus, within P_{ETCO_2} alteration from 26 to 43 mmHg, the arterial pressure does not change, which means that the CBF velocity and CVR_{CO_2} are determined by the cerebral vessels' CO_2 reaction, which reflects the 'true' cerebrovascular CO_2 reactivity, independent of arterial pressure.

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Conflicts of interest

There are no conflicts of interest.

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