Relationship between middle cerebral artery blood velocity and end-tidal PCO2 in the hypocapnic-hypercapnic range in humans

Kojiro Ide, Michael Eliasziw, and Marc J. Poulin

Departments of Physiology and Biophysics, Clinical Neurosciences, and Community Health Sciences, Faculties of Medicine and Kinesiology, University of Calgary, Calgary, Alberta, Canada T2N 4N1

Submitted 23 December 2002; accepted in final form 12 March 2003

CEREBRAL BLOOD FLOW (CBF) is highly sensitive to alterations in arterial PCO2 (PaCO2). In studies of anesthetized animals, the CBF response to PaCO2 has been described by exponential (12, 35) or sigmoidal (8, 27) functions, depending on the range of PaCO2 investigated. In general, the animal studies report that the CBF response to alterations in PaCO2 appears to level off at extreme levels of hypocapnia (less than ~20 Torr) and hypercapnia (greater than ~100 Torr), whereas the CBF-PaCO2 relationship appears to be rather linear in the range of PaCO2 from ~20 to ~60 Torr (27). In humans, some studies have been consistent with a linear CBF response across both the hypocapnic and hypercapnic ranges of PETCO2 (9), whereas other studies have not (7, 26) and have instead suggested that the relationship is better described by exponential (15) or sigmoidal (28) functions. Although CBF is reduced with acute hypocapnia (23), CBF returns toward normal values over a period of minutes despite PaCO2 or end-tidal PCO2 (PETCO2) being kept constantly low (23, 32). The presence of a slow adaptive process in the CBF response to hypocapnia (23) may help explain why there is uncertainty as to whether the CBF response is linear with variations in PETCO2 from ~20 to ~50 Torr in humans.

The previous studies in humans were based on two or three distinct levels of PETCO2, and did not provide a complete description of the CBF response over the range of PETCO2 from ~20 to ~50 Torr. Thus the aim of this study was to further extend the previous findings in human studies by measuring the CBF sensitivity to variations in PETCO2 throughout the range of PETCO2 from hypocapnia to hypercapnia. Furthermore, Poulin et al. (22, 23) previously reported the presence of an undershoot or an overshoot in CBF when PETCO2 is returned to eucapnic levels after a sustained period of hypercapnia (22) and hypocapnia (23), respectively. The reason for the overshoot and undershoot is unclear but may reflect an alteration or adaptation in the mechanisms underlying the vasodilation and vasoconstriction of cerebral vessels by hypercapnia and hypocapnia, respectively. Thus a secondary objective of this study was to investigate the hypothesis that the CBF response to alterations in PETCO2 is different when PETCO2 is incremented from hypocapnia to hypercapnia (22) and when PETCO2 is decremented from hypercapnia to hypocapnia.

Cerebral perfusion was evaluated by using transcranial Doppler ultrasound (TCD), and end-tidal gases were controlled by using the technique of dynamic end-tidal forcing. TCD is a noninvasive tool for the evaluation of cerebral perfusion with the advantage of near-continuous recordings. Moreover, use of the dynamic end-tidal forcing technique enables the control of end-tidal PCO2 during steady-state conditions.
of PetCO2 and end-tidal Po2 (PetO2) precisely, despite the variations in the ventilatory responses resulting from changes in the arterial blood gases. Therefore, this allows the examination of steady-state CBF responses to each level of PetCO2. Together, these techniques are well-suited for the evaluation of CBF responses to alterations in PetCO2 in humans.

METHODS

Subjects. The study involved eight young adults (2 women, age 27.4 ± 5.7 yr, body weight 67.2 ± 8.9 kg, and height 174.7 ± 7.8 cm). The study requirements were fully explained to all participants, and each gave informed consent before participating in the study. The research study was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Participants were not taking any medication, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease.

Protocols. The laboratory is located at 1,103 m above sea level, and the average barometric pressure for the study days in this experiment was ~660 Torr. The subjects visited the laboratory on three occasions. The first day served as a session for familiarization to the apparatus for all participants. On the second and third visits, the main study was conducted. On each of these visits, the subject’s normal PetCO2 and PetO2 were measured before the experiment, while the subject was sitting quietly and comfortably for ~10 min. In brief, respired gas was sampled via a fine catheter held at the opening of one nostril by an adapted nasal O2 therapy kit. The gas was sampled continuously at a rate of 20 ml/min and analyzed for PO2 and PCO2 by mass spectrometer (AMIS 2000, Innovision, Odense, Denmark). Values for PO2 and PCO2 were sampled by computer every 10 ms. PetO2 and PetCO2 were identified and recorded for each breath by using a computer and dedicated software (Chamber version 1.00, University Laboratory of Physiology, Oxford, UK).

For the main study, two protocols were employed on each day: a CO2-incrementing protocol (protocol I) and a CO2-decrementing protocol (protocol D). Both protocols were performed on each subject, with the order randomly assigned and a 45-min recovery period between each protocol. The technique of dynamic end-tidal forcing was used to control PetCO2 and PetO2 (see Hyperventilation and control of PetCO2). In both protocols, PetO2 was held constant at 100 Torr throughout the experiments. Initially, PetCO2 was held at 1.5 Torr above the subject’s normal value for 8 min. This was done because the technique of dynamic end-tidal forcing can add but cannot remove CO2 from the inspirate. Thus, by adding a small amount of CO2 to the inspirate, it is possible to regulate PetCO2 to hold it at the desired level. Otherwise, if the actual PetCO2 rises slightly above the desired level (for example, if the normal PetCO2 value is underestimated) and if there is no CO2 in the inspirate, the control of PetCO2 becomes ineffective. In protocol I, PetCO2 was then decreased in one step by 16 Torr and was stabilized for 2 min. PetCO2 was then increased in stepwise increments of 2 Torr every 2 min up to 10 Torr above the subject’s normal value. In protocol D, PetCO2 was increased in one step by 10 Torr and was stabilized for 4 min. PetCO2 was then reduced in a stepwise manner by 2 Torr every 2 min to a value of 16 Torr below the subject’s normal value. Finally, PetCO2 was returned in one step to its initial near-eucapnic value and maintained at this value for a further 5 min.

Hyperventilation and control of PetCO2. Each experimental protocol was initiated with a 3-min period with the subject breathing normally through a mouthpiece with the nose occluded by a nose clip. Thereafter, the subject followed a constant pattern of hyperventilation. This controlled hyperventilation enabled the technique of dynamic end-tidal forcing to stabilize the subject’s PetCO2 at the desired level by changing the inspired PCO2 level. A frequency of one breath every 3 s was dictated by an audio alarm, and visual feedback was provided with an oscilloscope that reflected the inspired tidal volume to keep the volume relatively constant throughout. Subjects were allowed to breathe at their own pace only if it was difficult to keep the pace during the highest level of hypercapnia. After the cessation of hypocapnia or hypercapnia, subjects were allowed to breathe normally for the remainder (i.e., 5 min) of the experiment.

The inspired and expired gases were sampled at a rate of 20 ml/min and analyzed by mass spectrometer for fractional concentrations of O2 and CO2. Respiratory volumes and flow information were obtained by using a pneumotachograph and differential pressure transducer (RSS100-DR, Hans Rudolph, Kansas City, MO). Respiratory flow direction and timing information were measured with a turbine volume transducer (VMM-400, Interface Associates). A computer sampled the experimental variables every 10 ms. Accurate control of the end-tidal gases was achieved by using the technique of dynamic end-tidal forcing (BreatheM version 2.07, University Laboratory of Physiology, Oxford, UK). A controlling computer generated the inspired partial pressure of O2 and CO2 predicted to give the desired end-tidal partial pressures by using a fast gas-mixing system (11, 23, 29). The controlling computer received feedback of the measured end-tidal partial pressures on a breath-by-breath basis as the experiment progressed. These measured end-tidal values were compared with the desired values, and the computer then adjusted the initial predicted inspired gas mixture by using an integral proportional feedback algorithm based on the deviations of the measured end-tidal values from the desired end-tidal values (11, 23, 29).

TCD. Backscattered Doppler signals from the right MCA were measured by using a 2-MHz pulsed Doppler ultrasound system (TC22, SciMed, Bristol, UK). The MCA was identified by an insonation pathway through the right temporal window just above the zygomatic arch by using search techniques described previously (22, 23). This procedure was repeated on each visit. The insonation depth (the distance from the probe to the start of the Doppler sample volume) was set initially at a depth of ~50 mm, and then a short search procedure began by varying the angle and position of the probe to identify a window that provided Doppler spectra from the MCA. The sample depth was then increased in an increment of 1 mm until the quality of the Doppler spectra from the MCA became poor (~65 mm). At this point, the sample depth was decreased in an increment of 1 mm to a depth of ~45 mm. At each depth, a short search was performed by making small adjustments to the angle and position of the probe to assess the relative magnitude of the total Doppler power along with the quality of the Doppler spectra. The sample was then returned to the depth at which the Doppler signal was maximal, and at that depth the angle and position of insonation was adjusted to provide the signal with maximum power. The center of this position was identified with a waterproof marker directly on the skin. The Doppler probe was removed, and ultrasonic gel (Aquasonic 100, Parker Laboratories, Fairfield, NJ) was reapplied to the probe, which was then secured with a headband device (Müller and Moll Fixation, Nicolet Instruments, Madison, WI). The Doppler probe was securely positioned in this headband device to maintain the optimal insonation position and angle.
During a first visit (familiarization), the optimal position of the Doppler probe was identified, and a tracing of this position was made by using a plastic transparency with the marker to delineate the contour of the Doppler probe fixture and the headband device. This tracing served to establish the precise position of the headband device for the subsequent visits. To maintain the insonation position and angle between the experimental sessions within each visit, the Doppler probe was not removed from or adjusted within the headband device. The Doppler system was adapted by the manufacturer to make the Doppler signals available as analog signals sampled every 10 ms. Signals for maximum and intensity-weighted mean Doppler frequency shifts were available as analog signals and were updated each time a new spectrum was calculated every 10 ms. In this study, the maximum frequency of Doppler shift, namely, peak blood velocity \( V_p \) was taken as the primary index of CBF (24).

**Analysis.** To average \( V_p \) over larger periods of time, \( V_p \) was first averaged over each heart beat to give the beat-by-beat values \( (V_p) \). Likewise, the data for PETCO2 were determined for each breath to give breath-by-breath values. The beat-by-beat and breath-by-breath data were further averaged to give one value over each 15-s period. For the statistical analysis, the 15-s data were averaged to give values for a 3-min baseline period before the onset of the CO2 stimulus and for the last 30 s of each 2-min PETCO2 step. In addition to calculating absolute values, normalized beat-by-beat and breath-by-breath values were calculated for \( V_p \) and PETCO2, respectively. For \( V_p \), the 3-min baseline period was normalized to 100% and used to calculate the percent change over time in \( V_p \) for the duration of the experiment. For PETCO2, the data over the 3-min baseline period expressed as deviations from the baseline value and used to calculate the difference between the measured PETCO2 and the baseline eucapnic PETCO2 (\( \Delta \text{PETCO2} \)). The beat-by-beat and breath-by-breath normalized data were also averaged to give one value every 15 s. Similar to the absolute data, the 15-s normalized data were averaged to give values for baseline and for the last 30 s of each step in PETCO2.

**Regression models.** To determine the mathematical model that best described the CBF-PETCO2 relationship, several regression equations were fit with \( V_p \) as the dependent variable and \( \Delta \text{PETCO2} \) as the independent variable. Before fitting the equations, the mean of the two repetitions for each subject was calculated for both protocol I and protocol D, thus providing one set of data for each subject per protocol. Calculating the mean to reduce the number of observations was a reasonable approach because the level of agreement (i.e., reproducibility) between the repetitions among subjects was very high. The level of agreement was assessed by the intra-class correlation coefficient, which has a range of values from 0 (no agreement) to 1 (perfect agreement). The level of agreement was 0.93 for \( V_p \) and 0.99 for \( \Delta \text{PETCO2} \) in protocol I and 0.95 for \( V_p \) and 0.99 for \( \Delta \text{PETCO2} \) in protocol D. Thus the means for \( V_p \) and PETCO2 of the last 30 s of each of the 14 PETCO2 steps were determined for each subject, and the data set for the regression analyses consisted of 112 pairs (14 steps by 8 subjects) of normalized values of \( V_p \) and \( \Delta \text{PETCO2} \) for each protocol.

Three regression models were considered. The first was a simple linear model, written as

\[
y = a + b \cdot x
\]

where \( y \) is \( V_p \) (\%), \( x \) is \( \Delta \text{PETCO2} \) (Torr), and \( a \) and \( b \) are regression parameters (\( a = \text{intercept}, b = \text{slope} \)).

The CBF-PETCO2 relationship has previously been described as consisting of two different components, one above and the other below eucapnia. Thus the second regression model consisted of a piecewise linear model, with the first piece corresponding to the data in the eucapnia-hypocapnia range and the second piece in the eucapnia-hypercapnia range. Both pieces were written in the form of Eq. 1 above.

Finally, a nonlinear exponential regression model was considered. This model was written as

\[
y = y_0 + ae^{(x-b)}
\]

where \( y \) is \( \% \), \( x \) is \( \Delta \text{PETCO2} \) (Torr), and \( a \) and \( b \) are regression parameters. In this model, the sensitivity of CBF for a given \( \Delta \text{PETCO2} \) was described by the first derivative, which can be written as

\[
\frac{dy}{dx} = b \cdot e^{(x-b)}
\]

**Statistics.** A Student’s t-test was performed to assess differences in the steady-state levels of PETCO2 between protocols I and D. To assess the effect of protocol on the relationship between \( V_p \) and PETCO2, a multiple-parital F test was performed. An indicator variable was added to the regression model to differentiate between data from protocols I and D. The strength of the relationship between \( V_p \) and \( \Delta \text{PETCO2} \) in each of the three regression models was evaluated by using a coefficient of determination (\( R^2 \)). A statistical test of coincidence and of parallelism (17) was used to assess whether the regression models describing protocols I and D were coincidental and parallel. The very nature of the test of parallelism is to determine whether the two slopes (i.e., curves) are equal. Therefore, if the two slopes are different, then the two curves are not parallel. The nature of the test of coincidence is to determine simultaneously whether the two slopes and intercepts are equal. Therefore, if the two slopes and intercepts are different, then the two curves do not cross the y-axis at the same point and are not parallel.

**RESULTS**

**Control of PETCO2 and PETO2.** Figure 1 shows sample experimental tracings of real-time recordings during protocol I (Fig. 1A) and protocol D (Fig. 1B) in one of the experiments. The figure illustrates typical recordings of inspiratory (\( V_T \)) and expiratory tidal volumes (\( V_T \)), \( P_{CO2} \), \( P_{O2} \), and \( V_p \) during protocols I and D. Each protocol began with 3 min of normal breathing and then volume- and rate-controlled hyperventilation followed. Combined with controlled hyperventilation, the dynamic end-tidal forcing technique was successful in keeping \( P_{ETO2} \) constant at 100 Torr while controlling PETCO2 at the desired levels throughout the experiment. During baseline measurements, \( V_p \) was stable, and during the variations in PETCO2, \( V_p \) followed the change in PETCO2.

**CBF responses to \( \Delta \text{PETCO2} \).** Table 1 shows the group means for PETCO2, \( \Delta \text{PETCO2} \), PETO2, \( V_p \) (absolute values in cm/s; normalized values in % of baseline) at baseline eucapnia, the lowest PETCO2 in hypocapnia, and the highest PETCO2 in hypercapnia during protocols I and D. Figure 2 illustrates temporal profiles of the percent change from baseline in \( V_p \) and PETCO2. Figure 3 illustrates the individual data of the percent changes (from baseline) in \( V_p \) as a function of \( \Delta \text{PETCO2} \). Figure 4 illustrates the relationship between percent change from baseline in \( V_p \) as a function of \( \Delta \text{PETCO2} \) during
protocols I and D for all subjects. In protocol I, $\bar{V}_p$ at baseline eucapnia was 58.3 ± 7.8 cm/s and decreased to 60.8 ± 4.9% (35.2 ± 4.6 cm/s) with the lowest $\text{P}_{\text{ETCO}_2}$ (38.4 ± 2.3 to 23.0 ± 1.4 Torr; Table 1). Then, the increases in $\bar{V}_p$ followed the increases in $\text{P}_{\text{ETCO}_2}$. With the highest $\text{P}_{\text{ETCO}_2}$ (48.7 ± 1.8 Torr), $\bar{V}_p$ was increased to 151.8 ± 8.9% (88.3 ± 13.5 cm/s). In protocol D, $\bar{V}_p$ was increased to 149.2 ± 12.1% (59.1 ± 8.3 to 88.1 ± 15.4 cm/s) with the highest $\text{P}_{\text{ETCO}_2}$ (38.3 ± 2.3 to 48.9 ± 2.0 Torr; Table 1). Then, the decrease in $\bar{V}_p$ followed the decreases in $\text{P}_{\text{ETCO}_2}$. With the lowest $\text{P}_{\text{ETCO}_2}$ (22.4 ± 1.7 Torr), $\bar{V}_p$ was decreased to 69.1 ± 5.3% (40.7 ± 5.2 cm/s). With the lowest $\text{P}_{\text{ETCO}_2}$, the absolute value for $\bar{V}_p$ was smaller in protocol I than it was in protocol D ($P = 0.005$), although the level of $\text{P}_{\text{ETCO}_2}$ was comparable between protocols.

A test of carry-over effect (30) was used to assess whether a subject's response in the second protocol was

![Figure 1](http://jap.physiology.org/)

**Fig. 1.** Sample tracings of real-time recordings of the respiratory and vascular data during the CO2-incrementing protocol (protocol I; A) and the CO2-decrementing protocol (protocol D; B) in one of the experiments. $V_T$, inspiratory tidal volume (in liters); $V_T$, expiratory tidal volume (in liters); $V_p$, blood velocity in the middle cerebral artery associated with the maximum frequency of the Doppler shift (in cm/s).
altered by lingering aftereffects from the first protocol. A test of carry-over effect yielded \( P \) values of 0.74 for \( V_p \) and 0.94 for \( \Delta P_{\text{ETCO}_2} \), implying the absence of a carry-over effect. In other words, the order in which protocols \( I \) and \( D \) were administered to the subjects did not affect the results.

Comparison of coefficients of determination for the regression models describing the CBF-P\( \text{ETCO}_2 \) relationship. Table 2 shows the coefficients of determination and regression parameter estimates for the one-linear, two-linear, and exponential regression models for the CBF-P\( \text{ETCO}_2 \) relationship in protocols \( I \) and \( D \). On the basis of \( R^2 \), the exponential model was the best-fitting model and is illustrated in Fig. 4. A test of coincidence and of parallelism using a multiple-partial \( F \) test indicated that the regression models describing protocols \( I \) and \( D \) were noncoincident (\( P \) \( < 0.001 \)) and were not parallel (\( P = 0.003 \)). This is evident from Fig. 4, where the fitted regression lines share a common point in hypocapnia and then diverge as \( \text{PETCO}_2 \) increases.

Comparison of coefficients of determination for the regression models describing the CBF-P\( \text{ETCO}_2 \) relationship. Table 2 shows the coefficients of determination and regression parameter estimates for the one-linear, two-linear, and exponential regression models for the CBF-P\( \text{ETCO}_2 \) relationship in protocols \( I \) and \( D \). On the basis of \( R^2 \), the exponential model was the best-fitting model and is illustrated in Fig. 4. A test of coincidence and of parallelism using a multiple-partial \( F \) test indicated that the regression models describing protocols \( I \) and \( D \) were noncoincident (\( P \) \( < 0.001 \)) and were not parallel (\( P = 0.003 \)). This is evident from Fig. 4, where the fitted regression lines share a common point in hypocapnia and then diverge as \( \Delta \text{PETCO}_2 \) increases.

**CBF-P\( \text{ETCO}_2 \) sensitivity: predictions based on models.** Table 3 shows the predicted CBF-P\( \text{ETCO}_2 \) sensitivity determined from one- and two-linear, and exponential models at \( \text{PETCO}_2 \) of \( -20 \), \(-16 \), \(-10 \), \( 10 \), and \( 20 \) Torr. The two-linear regression model implies that the CBF-P\( \text{ETCO}_2 \) sensitivity would be altered with the transition at eucapnia, i.e., CBF-P\( \text{ETCO}_2 \) sensitivity above eucapnia is higher than that below eucapnia. With the exponential model, the CBF-P\( \text{ETCO}_2 \) sensitivity would change continuously throughout the range of \( \text{PETCO}_2 \). The exponential model indicates that the CBF-P\( \text{ETCO}_2 \) sensitivity would increase from 2.1 to 4.7%/Torr in protocol \( I \) and from 1.9 to 4.0%/Torr in protocol \( D \) in the range of \( \text{PETCO}_2 \) from 16 Torr below eucapnia to 10 Torr above eucapnia.

**DISCUSSION**

**Major findings.** This study provides continuous beat-by-beat measurement of MCA blood velocity throughout the range of \( \text{PETCO}_2 \) (i.e., \( \text{PaCO}_2 \)) from \(-20 \) to \(-50 \) Torr in humans. The major findings are that 1) CBF closely follows the alterations in \( \text{PETCO}_2 \) throughout the range of \( \text{PETCO}_2 \) studied; 2) the sensitivity of CBF to the changes in \( \text{PETCO}_2 \) is nonlinear, with a greater sensitivity in the hypercapnic range compared with the hypocapnic range, and the relationship between CBF and \( \Delta \text{PETCO}_2 \) appears to be best described by an exponential regression model; and 3) there is evidence of hysteresis in the CBF-P\( \text{ETCO}_2 \) relationship, with the sensitivity of
CBF being greater during an incremental protocol compared with a decremental protocol for a given \( \text{PETCO}_2 \).

**CBF response curve in the range of \( \text{PCO}_2 \) from 20 to 50 Torr.** In a study by Reivich (27), the CBF response in the range of \( \text{PaCO}_2 \) from 5 to 400 Torr was evaluated by using a mathematical model based on the cross-sectional data of 10 anaesthetized monkeys. The CBF responses to alterations in \( \text{PaCO}_2 \) appear to have levelled off at low levels of hypocapnia (i.e., \(<20\) Torr) and hypercapnia (i.e., \(>60\) Torr). However, in the range of \( \text{PaCO}_2 \) from 20 to 60 Torr, a range over which measurements can be made in humans, the CBF-PETCO\(_2\) relationship was described as a straight line (27). In humans, the data in the study by Hauge et al. (9) showed that the relationship between CBF (blood velocity in the internal carotid artery and the vertebral artery) and PETCO\(_2\) was described as linear in the range of PETCO\(_2\) from 25 to 55 Torr, and the CBF sensitivity to PaCO\(_2\) (CBF-PaCO\(_2\) sensitivity) levelled off only at low levels of hypocapnia (i.e., \(<20\) Torr). In the present study, judging by the \( R^2 \), both the one- and the two-linear regression models were relatively poor models. This was not unexpected based on a previous report of

**Fig. 4. Relationship between the changes in middle cerebral artery \( V_p \) (% change from baseline) and \( \text{PETCO}_2 \) for all subjects.** The solid line denotes the fitted exponential regression equation for protocol I, and the dashed line denotes the fitted exponential regression equation for protocol D.

**Fig. 3. Relationship between the changes in \( V_p \) (% change from baseline) in the middle cerebral artery and changes in \( \text{PETCO}_2 \) (\( \text{PETCO}_2 \)) during protocols I (●; incremental \( \text{PETCO}_2 \)) and D (○; decremental \( \text{PETCO}_2 \)) for each subject.**
a slow adaptation in CBF in response to hypocapnia (23). Fitting by a linear regression assumes that there would be no change in CBF-PETCO2 sensitivity. In this study, and on the basis of the $R^2$ value, the exponential model was the best-fit model to describe the CBF-PETCO2 relationship in the range of PETCO2 from ~20 to ~50 Torr. This observation is supported by a study in humans (15) and by studies in animals (12, 35). In a study by Tominaga et al. (34), it was shown that the CBF responses in the range of PETCO2 from ~20 to ~50 Torr were described by two exponential models separating the CBF responses between a hypocapnic-euoxic region and a euoxic-hypocapnic region rather than by one exponential model.

**CBF-PETCO2 sensitivity in hypocapnia.** The response of CBF to alterations in PaCO2 is thought to be associated with a change in cerebral extracellular pH (18, 33). However, the exact mechanism by which extracellular pH might be involved in the process of cerebral vessels dilatation in response to PaCO2 remains unclear. In hypocapnia, a lower CBF-PETCO2 sensitivity might be associated with a metabolic adaptation associated with lactate acid formation in the brain (3). An increase in cerebral lactate production in response to respiratory alkalosis has been observed in humans (2). A facilitated lactate production may be caused by an increase in phosphofructokinase activity associated with an increase in pH (20), an excess uptake of glucose associated with cerebral tissue hypoxia caused by a reduction in CBF and/or associated with the Bohr effect (2). In rats it has been reported that cerebral tissue lactate progressively increases with decreases in PaCO2 in a hypocapnic environment, but cerebral tissue lactate does not appear to change with an increase in PaCO2 in a hypercapnic environment (16).

**Effect of protocols on CBF-PETCO2 sensitivity.** A statistical test of coincidence and parallelism indicated that the exponential regression models describing protocols I and D were not coincidental and not parallel. This implies that the CBF-PETCO2 sensitivity depends on which protocol is used. Not only is the CBF-PETCO2 sensitivity corresponding to protocol I higher than in protocol D, but the difference between the two is accentuated with increasing values of PETCO2 (as shown in Fig. 4). It is unlikely that an adaptation process can explain a difference between protocols. The duration of the PETCO2 steps was selected on the basis of the knowledge of time constants of CBF responses to alterations in PETCO2 (22) to ensure that the steps in both protocols were long enough for CBF to reach steady state yet short enough to avoid any influence of an adaptive process. However, previous studies have reported the presence of an undershoot and overshoot in CBF when PETCO2 is returned to prestimulus levels after 20 min of euoxic hypercapnia and euoxic hypocapnia, respectively (22). The difference in CBF-PETCO2 sensitivity between the protocols observed in this study is consistent with those findings. The mechanisms underlying these processes are unclear but may involve, at least in part, changes in the levels of lactate and bicarbonate (1, 5).

**CBF-PETCO2 sensitivity at altitude.** The present study was conducted at a mild level of altitude (i.e., 1,103 m above sea level). It has been reported that the CBF-PETCO2 sensitivity is increased in an acute exposure to moderate altitude (13). In a recent study by Poulin et al. (21), exposure to hypoxia in a purpose-built chamber for 48 h, in which PETO2 was held at 60 Torr, equivalent to ~2,800 m (unacclimatized) and ~3,400 m (acclimatized) (25), increased CBF-PETCO2 sensitivity

### Table 2. Coefficient of determination, constants and slopes for the 1- and 2-compartment linear, and exponential models

<table>
<thead>
<tr>
<th></th>
<th>1 Linear</th>
<th></th>
<th>2 Linear</th>
<th></th>
<th>3 Linear</th>
<th></th>
<th>4 Linear</th>
<th></th>
<th>5 Linear</th>
<th></th>
<th>6 Linear</th>
<th></th>
<th>7 Linear</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypocapnia</td>
<td>Hypercapnia</td>
<td>Hypocapnia</td>
<td>Hypercapnia</td>
<td>Hypocapnia</td>
<td>Hypercapnia</td>
<td>Hypocapnia</td>
<td>Hypercapnia</td>
<td>Hypocapnia</td>
<td>Hypercapnia</td>
<td>Hypocapnia</td>
<td>Hypercapnia</td>
<td>Hypocapnia</td>
<td>Hypercapnia</td>
</tr>
<tr>
<td>$R^2$</td>
<td>$a$</td>
<td>$b$</td>
<td>$R^2$</td>
<td>$a$</td>
<td>$b$</td>
<td>$R^2$</td>
<td>$a$</td>
<td>$b$</td>
<td>$R^2$</td>
<td>$a$</td>
<td>$b$</td>
<td>$R^2$</td>
<td>$a$</td>
<td>$b$</td>
</tr>
<tr>
<td>Protocol I</td>
<td>0.94</td>
<td>110.3</td>
<td>3.21</td>
<td>0.93</td>
<td>105.6</td>
<td>2.67</td>
<td>0.82</td>
<td>104.6</td>
<td>4.34</td>
<td>0.88</td>
<td>94.4</td>
<td>4.85</td>
<td>0.85</td>
<td>95.9</td>
</tr>
<tr>
<td>Protocol D</td>
<td>0.88</td>
<td>105.1</td>
<td>2.89</td>
<td>0.84</td>
<td>94.4</td>
<td>1.74</td>
<td>0.85</td>
<td>95.9</td>
<td>4.85</td>
<td>0.85</td>
<td>95.9</td>
<td>4.85</td>
<td>0.85</td>
<td>95.9</td>
</tr>
</tbody>
</table>

$R^2$, coefficient of determination. Equation of the linear model: $y = a + b \cdot x$. Equation of the exponential model: $y = e^{a+b \cdot x}$.  

### Table 3. Sensitivity of cerebral blood flow to alterations in PETCO2 determined by 1- and 2-linear, and exponential models at ΔPETCO2 of −20, −16, −10, 10, and 20 Torr

<table>
<thead>
<tr>
<th></th>
<th>Protocol I</th>
<th></th>
<th>Protocol D</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPETCO2, Torr</td>
<td>−20</td>
<td>−16</td>
<td>−10</td>
<td>10</td>
</tr>
<tr>
<td>1 linear, %/Torr</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>2 linear, %/Torr</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Exponential, %/Torr</td>
<td>1.8</td>
<td>2.1</td>
<td>2.5</td>
<td>4.7</td>
</tr>
</tbody>
</table>

ΔPETCO2 change in PETCO2. Equation of the linear model: $y = a + b \cdot x$. Equation of the exponential model: $y = e^{a+b \cdot x}$. Constants and slopes are given in Table 2.
CEREBROVASCULAR REACTIVITY TO CO2

by 28%. Likewise, a 5-day exposure to moderate altitude was reported to increase CBF-PetCO2 sensitivity from 4% /Torr at sea level to 5.2% /Torr (13), although CBF-PetCO2 sensitivity was estimated to remain unchanged after “correcting” for a lower cerebrospinal fluid HCO3 caused by hypocapnia. In the present study, the CBF-PetCO2 sensitivity calculated from the exponential model was estimated to be 5.3 and 4.8% /Torr at 55 Torr in protocols I and D, respectively. This observation is comparable to the data obtained at sea level by Tominaga et al. (34) in which a CBF sensitivity of 6%/Torr was observed at a PetCO2 of 55 Torr. Yet it is not clear whether there is an effect of long-term exposure to mild altitude on the CBF-PetCO2 sensitivity. This remains to be investigated.

Technical considerations. A critical issue for the TCD technique is the extent to which blood velocity reflects volume flow. Any changes in diameter of the insonated artery will change blood velocity even when blood flow is constant. In the study by Bishop et al. (4), CBF responses determined by 133Xe clearance technique were compared with changes in Vp determined by TCD in response to hypercapnia, and there was a good linear relationship between these measurements. On the other hand, in the study by Clark et al. (7), decreases in Vp in response to hypocapnia were relatively smaller compared with decreases in CBF determined by 133Xe clearance technique, indicating that there may have been dilatation of the MCA with hypocapnia. Poulin and colleagues (22, 23) studied relative changes in MCA diameter by using the Doppler power signal and demonstrated that MCA diameter remained relatively constant at levels of hypocapnia (23) or hypercapnia (22) comparable to those employed in this study. In support, in the study by Serrador et al. (31), MCA diameter determined by MRI was unchanged during hyperperventilation, hypercapnia, and lower body negative pressure.

Another important consideration is whether 2 min was long enough to obtain steady-state CBF responses at each level of PetCO2. This was assessed in a preliminary study (unpublished observations) based on the previously reported values of 14–45 and 6–7 s for the on and off time constants for the MCA blood flow response to step increases and decreases in PetCO2 (22, 23), respectively. In two subjects, we examined the responses of MCA velocity to several separate 5-min step changes in PetCO2. With step increases in PetCO2 of 2, 4, 6, 8, and 10 Torr, the increases in Vp were 7, 20, 32, 39, and 46%, respectively, at 2 min and 7, 16, 26, 37, and 51% at 5 min, respectively, suggesting that 2 min at each PetCO2 step was long enough to allow Vp to reach steady-state values in the present study.

Changes in blood pressure with alterations in Paco2 must also be considered. In healthy subjects, several studies have reported increases in mean arterial blood pressure (range of 6 to 13 mmHg; 7–14%) (15, 19, 26) and an increase in sympathetic nerve activity (19) with hypercapnia (PetCO2 range = 36–54 Torr). On the other hand, studies have shown little (6) or no change (14) in mean arterial blood pressure with hypocapnia. However, in the normal range of autoregulation (range of 60 to 150 mmHg), the CBF response to Paco2 may be independent of changes in mean arterial blood pressure (10), but this has not yet been extensively studied. Because we did not specifically address the question of how changes in arterial blood pressure might affect differences in CBF-PetCO2 sensitivity in hypocapnia and hypercapnia or the differences in CBF-PetCO2 sensitivity between the protocols, we cannot exclude an effect of changes in blood pressure on the results reported in this study.

In summary, this study described the CBF-Pco2 relationship in the range of PetCO2 from ~20 to ~50 in humans. Over this range, a nonlinear exponential model provided a reasonably good fit, suggesting that the CBF-PetCO2 sensitivity is nonlinear and varies depending on the level of PetCO2. However, it was also shown that the CBF response to alterations in PetCO2 was affected by the direction of the stimulus. The mechanisms underlying these responses require further investigation.

We thank J. S. Vantanalaj and C. T. Debert for excellent technical assistance, and Drs. W. A. Whitelaw, J. E. Remmers, and K. L. Dorrington for revision of the manuscript.

This study was supported by the Alberta Heritage Foundation for Medical Research (AHFMR), the Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Alberta North West Territories and Nunavut. K. Ide was recipient of a Fellowship from the AHFMR.

REFERENCES

11. Howson MG, Khamnei S, McIntyre ME, O’Connor DF, and Robbins PA. A rapid computer controlled binary gas mixing system.


34. Waltz AG. Effect of P\textsubscript{ACO\textsubscript{2}} on blood flow and microvasculature of ischemic and nonischemic cerebral cortex. Stroke 1: 27–37, 1970.