Transcranial Doppler: response of cerebral blood-flow velocity to carbon dioxide in anaesthetized children

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To determine the effect of carbon dioxide on the cerebral circulation in anaesthetized infants and children, 13 healthy children, ASA physical status I or II, between three months and seven years of age and scheduled for urologic surgery, were studied. Anaesthesia was induced with thiopentone and vecuronium. After tracheal intubation, anaesthesia was maintained with 70 per cent nitrous oxide in oxygen, fentanyl 2 $\mu g \cdot kg^{-1}$, vecuronium 0.05 mg $\cdot kg^{-1}$ and 0.8–1.0 per cent end-tidal isoflurane. A caudal block was performed before surgery. Systolic arterial pressure, heart rate, oxygen saturation, temperature, and end-tidal isoflurane were maintained constant. Ventilation was adjusted to achieve an end-tidal PCO_2 ($P_{ET}CO_2$) of 20 mmHg. The $P_{ET}CO_2$ was then randomly adjusted between 20 and 80 mmHg by the addition of carbon dioxide from an exogenous source. Cerebral blood flow velocity increased logarithmically and directly with the $P_{ET}CO_2$ ($r^2 = 0.56$). There were no complications associated with the use of transcranial Doppler sonography. These data indicate that CO_2 has a direct effect on the velocity of blood in the middle cerebral artery in infants and children anaesthetized with isoflurane.

La présente étude a pour but de déterminer l'effet du dioxyde de carbone (CO_2) sur la circulation cérébrale de treize enfants,

ASA I ou II âgés entre trois mois et sept ans, subissant une intervention chirurgicale urologique. L'induction anesthésique a été pratiquée à l'aide de thiopentone et de vécuronium. Après l'intubation trachéale, le maintien de l'anesthésie a été assurée par la respiration d'un mélange de 70 pour cent de protoxyde d'azote dans de l'oxygène, fentanyl 2,0 $\mu g \cdot kg^{-1}$, vécuronium 0,05 mg $\cdot kg^{-1}$ et l'emploi d'isoflurane 0,8–1,0 pour cent. Un bloc caudal était administré avant le début de la chirurgie. La pression artérielle systolique, le rythme cardiaque, la saturation en oxygène, la temperature et la concentration d'isoflurane en fin d'expiration étaient maintenus constants. La ventilation mécanique était ajustée afin de produire une tension de CO_2 de 20 mmHg en fin d'expiration ($P_{ET}CO_2$). Utilisant une source exogène de CO_2, la $P_{ET}CO_2$ était aléatoirement ajustée entre 20 et 80 mmHg. La vélocité du débit sanguin cérébrale s'est accrue d'une façon logarithmique et parallèle à l'augmentation de la $P_{ET}CO_2$ ($r^2 = 0,56$). Aucune complication n'est survenues de l'utilisation d'un sonographe Doppler transcranien. Ces résultats démontrent que le CO_2 possède un effet direct sur la vélocité du sang dans l'artère moyenne cérébrale chez les enfants anesthésiés avec de l'isoflurane.

Key words

ANAESTHESIA: paediatric;
BRAIN: blood flow, carbon dioxide tension;
MEASUREMENT TECHNIQUES: transcranial Doppler ultrasound;
VENTILATION: carbon dioxide tension.

Transcranial doppler sonography (TCD), as described first by Aaslid in 1982, is a non-invasive technique that measures cerebral blood flow velocity using the Doppler principle.[1] This principle is based on the fact that ultrasonic waves penetrate and scatter in two tissues of different densities. When these waves encounter an interface, that is tissues of different densities, the waves are reflected back to the source at frequencies that differ from the emitted frequency. The difference between the emitted and reflected ultrasonic frequencies is used to calculate the velocity of the moving tissue – in this instance, blood.

Although Doppler techniques have been applied to peripheral limb arteries for many years, investigators have only recently measured the blood velocity in intracranial arteries.[1] Since the bones of the skull both absorb and reflect ultrasound in the 4–9 MHz frequency

range, ultrasonography of the intracerebral vessels has been limited to infants with open fontanelles. In order to facilitate ultrasound studies in older children with closed fontanelles, the Doppler technique has been modified. Investigators restricted the site of application of the ultrasound probe to those areas of the skull where the bone is relatively thin, i.e., the temporal window. To augment further the transmission of ultrasound waves through the skull, the frequency of the Doppler signal was decreased from the 4–9 MHz to 1–2 MHz.

An additional modification was the use of pulsed wave rather than continuous wave ultrasound signals. The former senses lower frequency signals reflected from red cells and enables reconstruction of a pulse signal whereas the latter senses higher frequency signals reflected from the walls of blood vessels. All of these modifications greatly improved the quality of Doppler measurements of the velocity of blood in the large basal intracranial arteries particularly those in the Circle of Willis in older children with closed fontanelles.[2]

Carbon dioxide (CO_2) affects the cerebral circulation by dilating the cerebral arteries and increasing cerebral blood flow (CBF).[3] In adults, this arterial dilatation occurs only at the level of the small resistance vessels or arterioles.[4] Carbon dioxide has no direct effect on the diameter of the large basal arteries.[4] Changes in the diameter of the small resistance vessels directly affect both the cerebral blood flow velocity and the cerebral blood flow.[5,6] Carbon dioxide rapidly equilibrates across biological membranes and alters the perivascular pH. Since the perivascular pH is an important determinant of cerebrovascular reactivity, CO_2 exerts a rapid and considerable effect on CBF.[3] Although CO_2 is believed to act in a similar manner in children, studies in anaesthetized children are not available.

In order to investigate this effect, we designed the following study: (1) to evaluate the applicability of TCD monitoring perioperatively in an aesthetized infants and children, and (2) to determine the effect of CO_2 on cerebral blood flow velocity in anaesthetized healthy infants and children.

Methods

Practical procedure
Following approval from the human subjects review committee, written informed consent was obtained from the parents of 13 healthy ASA physical status I or II infants and children, three months to seven years of age, who were scheduled for elective urological surgery. All children were fasting and unpremedicated. Patients with cardiac or neurologic disease were excluded. All patients were supine and horizontal throughout the study.

Anaesthesia was induced with thiopentone 5 mg·kg⁻¹ and vecuronium 0.1 mg·kg⁻¹ intravenously. After tracheal intubation, the lungs were ventilated with intermittent positive-pressure ventilation with peak inspiratory pressures of 20–25 cmH₂O. Ventilation was adjusted to maintain a $P_{ET}CO_2$ of 40 mmHg. Positive end–expiratory pressure was avoided. Fresh gas flow remained unchanged throughout the study. Anaesthesia was maintained with 70 per cent N_2O/O_2, fentanyl 2 μg·kg⁻¹, vecuronium 0.05 mg·kg⁻¹ and 0.8–1.0 per cent end–tidal isoflurane. The end–tidal concentration of isoflurane was age-adjusted to 1 MAC.[7] A caudal block (1 ml·kg⁻¹, 0.25 per cent bupivacaine without epinephrine) was administered to all patients before surgical incision. Normothermia was maintained. All patients received lactated Ringer's solution (2 ml·kg⁻¹·hr⁻¹) as maintenance fluid, and 3 ml lactated Ringer's solution for each ml of blood loss. Systolic arterial pressure, heart rate, oxygen saturation, end–tidal isoflurane concentration, and the inspired N_2O and O_2 fractions were unchanged throughout the study period. The end–tidal concentrations of isoflurane and CO_2 were measured from the distal end of the tracheal tube[8] and analyzed with a calibrated Puritan-Bennett Datex 254 airway gas monitor (Datex Instrumentation Corp., Helsinki, Finland). The gas monitor was calibrated before each use using a reference gas mixture.

After baseline measurements were recorded at a $P_{ET}CO_2$ of 40 mmHg, the lungs were hyperventilated to a $P_{ET}CO_2$ of 20 mmHg. The mean intrathoracic pressure was maintained constant throughout the study. All measurements were recorded at $P_{ET}CO_2$ values between 20 and 80 mmHg using an exogenous source of carbon dioxide. Random values of $P_{ET}CO_2$ were assigned prior to the case. After administration of CO_2 for five minutes, three consecutive measurements of mean cerebral blood flow velocity (CBFV) and pulsatility index (PI), a resistance index, in the middle cerebral artery (MCA) were recorded at one-minute intervals. The PI was calculated for each MCA velocity measurement according to the formula: (end–systolic flow velocity – end–diastolic flow velocity)/end–systolic flow velocity, as adapted from Pourcelot's index of resistance.[9] At each steady-state condition, systolic arterial pressure, heart rate, oxygen saturation, temperature, end–tidal isoflurane concentration and inspired N_2O and O_2 fractions were recorded.

Doppler instrumentation
The TCD monitor (TC2-64B, EME, Carolina Medical Electronics Inc., King NC) was used to determine the CBFV. This monitor has the following characteristics: pulsed wave ultrasonic frequency, 2 MHz; emitting area,
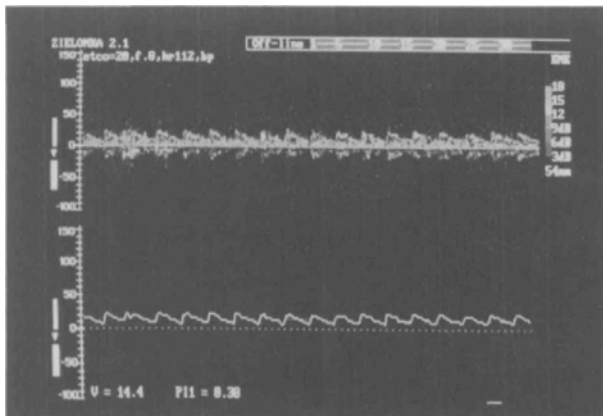
FIGURE 1 Spectral display of the Doppler signal from the middle cerebral artery at $P_{ET}CO_2$ of 20 mmHg. The numeric display in the bottom left quadrant is the mean CBFV and one harmonic of the Fourier PI value (PI) corresponding to the spectra on the lower graph. CBFV was 14.4 cm·sec^{-1} and PI was 0.38.

FIGURE 2 Spectral display of the Doppler signal from the middle cerebral artery at $P_{ET}CO_2$ of 36 mmHg. In this child, the mean CBFV was 29.8 cm·sec^{-1} and the PI was 0.35. Note the increase in mean CBFV from 14.4 in Figure 1 to 29.8 cm·sec^{-1} in this figure.

1.5 cm^2; effective depth range, 3.0–10.0 cm; emitted maximum ultrasonic power, 100 mW. The frequency spectra of the Doppler signals were displayed on a real time spectrum analyzer which allowed a clear visual representation of flow for unambiguous interpretation of the CBFV waveform.

The pulsed wave range-gated TCD probe was placed over the temporal window of the skull just cephalad to the zygomatic arch, approximately 2 cm in front of the tragus. Once positioned over the temporal window, the TCD probe was secured using a telescopic device to facilitate continuous measurements of CBFV in the MCA. The Doppler signal was optimized for clear and accurate determinations by adjusting the depth of the signal, scale and gain of the measurement and the angle of insonation.

The CBFV, PI, and the graphic display of systolic and diastolic cerebral velocities in the MCA were obtained during haemodynamic steady-state periods at each P_{ET}-CO_2 value. The Doppler frequency spectrum was displayed on a frequency analyzer and then reconstructed following fast Fourier transformation. Doppler waveforms with low signal-to-noise ratios or those that included signals from adjacent vessels were excluded from analysis. The outline or envelope of the spectra was used to determine the CBFV within the MCA by positioning the cursor on the individual frequency outlines. The mean velocity was determined by the weighted average velocity. The relative contribution of the Fourier coefficients were compared and the velocity profile was reconstructed to provide more accurate estimates of the mean velocity and pulsatility measurements. The Fourier pulsatility index provided a precise analysis of the pulsatility of displayed waveforms.
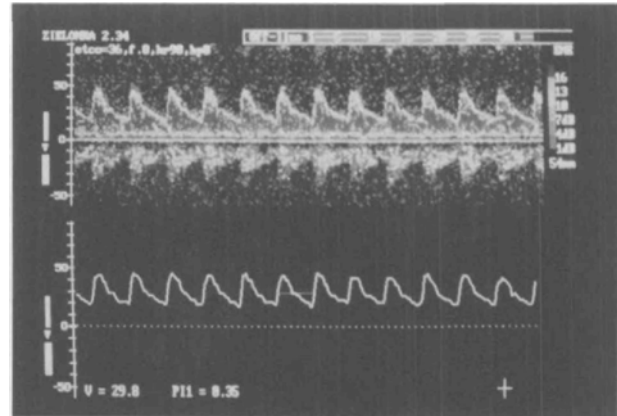
Statistical analysis

The mean ± standard deviation (SD) age and weight were determined. The relationships between $P_{ET}CO_2$ and both CBFV and PI were determined using non-linear regression analysis. The dependence of both TCD variables on the $P_{ET}CO_2$ was determined using the coefficient of determination (r^2). The slope of the semi-logarithmic transformation of the $P_{ET}CO_2$-CBFV data was compared with horizontal using Student's t test. Statistical significance ($P < 0.05$) was accepted.

Results

The mean ± SD age and weight of the 13 infants and children was 3.5 ± 2.0 yr and 18.6 ± 8.9 kg respectively. Systolic arterial blood pressure, heart rate, arterial oxygen saturation and end–tidal isoflurane concentration did not change significantly during the study. The haemoglobin concentration for the 13 patients was between 120 and 143 g·L^{-1}. Doppler recordings of MCA blood velocity were completed in all infants and children at $P_{ET}CO_2$ values between 20 and 80 mmHg. Figures 1–3 illustrate the spectral display of the doppler signal from the MCA of one child anaesthetized at $P_{ET}CO_2$ values of 20, 36 and 74 mmHg respectively. The CBFV increased logarithmically as the $P_{ET}CO_2$ increased ($r^2 = 0.56$) (Figure 4). The slope of the semi-logarithmic transformation of the data was significantly different from horizontal (i.e., slope = 0) ($P = 0.001$). The PI decreased logarithmically as the $P_{ET}CO_2$ increased ($r^2 = 0.41$) (Figure 5). There were no complications from the use of the TCD in this study.

Discussion

Physiological factors extrinsic to the brain can alter its local chemical environment. Carbon dioxide rapidly
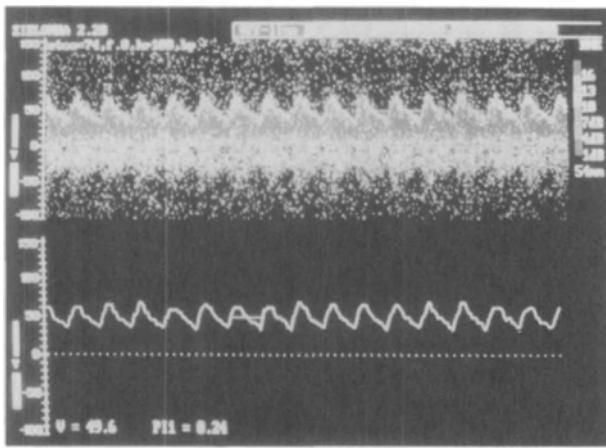
FIGURE 3   Spectral display of the Doppler signal from the MCA at $PETCO_2$ of 74 mmHg. Note the increase in mean CBFV from 29.8 to 49.6 cm·sec^{-1} with a reciprocal decrease in PI from 0.35 to 0.24 as $PETCO_2$ increased from 36 mmHg (Figure 2) to 74 mmHg in this figure.

FIGURE 4   Logarithmic relationship between the $PETCO_2$ and the CBFV of the MCA (r' = 0.56).

equilibrates across biological membranes, thereby altering the local chemical environment. Our results demonstrate that CBFV changes logarithmically and directly with $PETCO_2$ in anaesthetized infants and children. The relationship between $PETCO_2$ and the per cent change in CBFV is a sigmoid curve that is linear for $PETCO_2$ values between 25 and 75 mmHg. In this study, CBFV increased approximately 1.6 cm·sec^{-1}·mmHg^{-1} CO_2 with a coefficient of determination (r^2) of 0.56. This is consistent with previously published values for adults, 1.4 cm·sec^{-1}·mmHg^{-1}. The intermediate r^2 value probably reflects the large interindividual variability in the CBFV in the range of PCO_2 30–50 mmHg.

The cerebral vascular resistance is difficult to measure non-invasively. However, several expressions based on the Fourier transformed transcranial Doppler frequency spectra have been developed to estimate vascular resistance. One such expression is the ratio of the difference between corresponding systolic and diastolic velocities, and the systolic velocity.[9] This expression, also known as the pulsatility index or Pourcelot index (PI) has been shown to correlate closely with the cerebrovascular resistance. We found that PI increased logarithmically as the $PETCO_2$ decreased from 80 to 20 mmHg. This relationship is consistent with our understanding of the effects of CO_2 on the resistance of cerebral vasculature. However, we were surprised that the r^2 for PI was only 0.41. We attributed the low r^2 value to the large interindividual variability in the effect of $PETCO_2$ on cerebrovascular reactivity.

Several studies have compared the relationship between the CBFV as measured with the TCD and CBF.
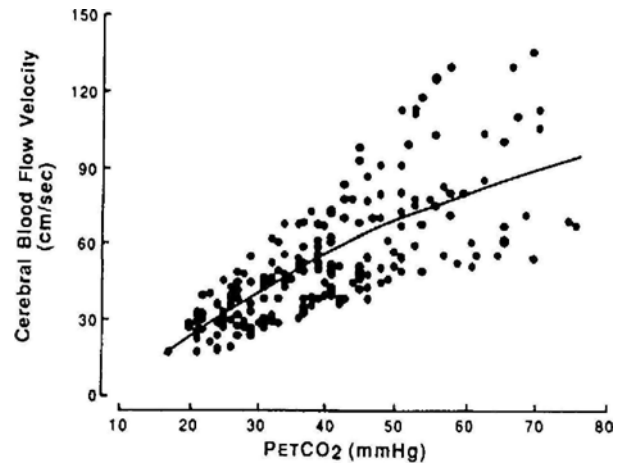
They found the CBFV measurements obtained with pulsed wave range-gated transcranial sonography in both neonates and adults correlated with standard methods used to measure CBF, with correlation coefficients between 0.70 and 0.93.[10–12] Furthermore, the correlation between TCD and Xe^{133} measurements of CBFV and PI were consistently greater for the range gated than for continuous wave Doppler technique.[11] These close correlations in patients of varied ages suggest that changes in the CBFV as measured by TCD sonography over a large range accurately reflect changes in CBF.

Since the TCD is non-invasive, and applied only using landmarks on the skull, there are several assumptions when evaluating the effectiveness of this methodology. The Doppler shift is expressed by the following formula:

$$F = 2 \cdot FO \cdot v \cdot \cos a/c$$

Where F = the doppler shift (Hz), FO = the mean frequency of the emitted ultrasound, v = the blood flow velocity (cm·sec^{-1}), a = the angle between the direction of the transmitted sound beam and the axis of the blood flow, and c = the velocity of sound in tissue (1,550 m/sec). The Doppler shift is proportional to the blood flow velocity when the emitting frequency FO and the angle a remain constant.

It is difficult to determine the angle between the ultrasonic beam and the intracranial arteries, i.e., the insonating angle. If the angle is sharp, then accurate measurements of velocity are possible. If the angle is between 0° and 30°, then its cosine will vary between 1 and 0.86. Thus the maximum error is less than 15 per cent. Under such conditions, one can assume the true velocity v (cm·sec^{-1}) is given by the relation: v = 0.039·f where f is the doppler frequency shift.[3,7,13]
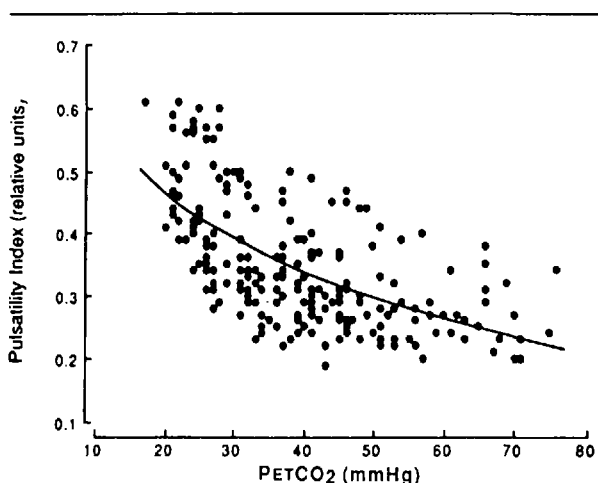
FIGURE 5   Logarithmic relationship between the $P_{ET}CO_2$ and the Fourier PI of the MCA (r' = 0.41).

We assumed that the angle of insonation remained constant during the study. The angle of the MCA at its site of origin from the internal carotid artery is almost perpendicular to the temporal window used in this study. Therefore, the column of blood in the MCA would move directly towards the ultrasound probe. If the Doppler probe is positioned axial to the blood flow, then the magnitude of this error is minimized. In order to minimize the intraindividual variability of CBFV measurements, the probe was fixed in position for the duration of the study once the probe position had been optimized.

Another assumption underlying the relationship between CBFV and CBF is that the diameter of the middle cerebral artery remains constant throughout the study period.[3] Angiographic studies of the basal cerebral arteries in adults have shown that the diameter of these arteries remains constant despite large changes in the PCO_2 or other extrinsic physiological factors as demonstrated by direct observation of pial vessels.[4,14] If the diameter of the MCA were to increase marginally as $P_{ET}CO_2$ increased, then the measured increase in CBFV would underestimate the true effect of CO_2 on CBF.

We were surprised to observe a large dispersion in CBFVs at high $P_{ET}CO_2$ values. Markwalder *et al.* noted a similar finding in awake adults breathing seven per cent CO_2.[5] They attributed this large dispersion to restlessness and dyspnoea in their patients. However, our patients were anaesthetized and therefore demonstrated none of these behaviours. Several factors could explain the observed dispersion: (1) an increase in the error in CBFV measurement at high $P_{ET}CO_2$ values, (2) interindividual variability in the CBFV response to high CO_2 levels on the diameter of the MCA (as discussed above).

The time constant for the acute effects of CO_2 on

cerebral arterial circulation is approximately one minute.[2] We administered CO_2 for five minutes before commencing the study to ensure the cerebral arteriolar response to CO_2 was complete. This exceeds the equilibration period used by others.[5] If the five-minute equilibration period had been inadequate, then CBFV would have changed between the first and third measurements of CBFV in any individual patient. However, the intraindividual coefficient of variation of these repeated measurements was only five per cent. This small coefficient supports our contention that the arteriolar response to CO_2 is complete within five minutes in anaesthetized children.

The cerebrovascular response to carbon dioxide also depends on the arterial blood pressure.[16-17] Although Markwalder *et al.* reported small increases in mean arterial blood pressure during profound hypercapnia in adults, they did not discuss the effects these changes may have on the CBFV measurements.[5] A caudal block was administered to all children to attenuate the sympathetic response to surgical stimulation. To obviate any possible effects of changes in arterial pressure in this study, the systolic arterial blood pressure was maintained constant throughout.

Intrathoracic pressure is an important determinant of the right atrial pressure and therefore cerebral venous pressure. A constant mean intrathoracic pressure was maintained for each patient by initially adjusting the ventilator settings to produce a $P_{ET}CO_2$ of 20 mmHg. The $P_{ET}CO_2$ was then randomly adjusted to values between 20 and 80 mmHg by the addition of exogenous carbon dioxide. Thus, a constant mean intrathoracic pressure was maintained throughout in the present study.

We used end-tidal CO_2 measurements to estimate the arterial PCO_2 based on previous studies in which we showed that both single-breath 16 and continuous distal[7] $P_{ET}CO_2$ closely approximate the $PaCO_2$ in healthy infants and children.

In summary, we have found the TCD to be a reliable device to measure CBFV in anaesthetized children. We have demonstrated that in healthy anaesthetized children, the $P_{ET}CO_2$ directly affects the CBFV in the MCA. Since CBFV has been shown to correlate with the CBF, this device may be used to estimate changes in CBF within the physiologic range in anaesthetized children.

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