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Response of Cerebral Blood Volume to Changes in Arterial Carbon Dioxide Tension in Preterm and Term Infants

J. S. WYATT, A. D. EDWARDS, M. COPE, D. T. DELPY, D. C. McCORMICK, A. POTTER, AND E. O. R. REYNOLDS

Departments of Paediatrics and Medical Physics and Bioengineering, University College, London, WC1E 6JJ, England

ABSTRACT. The response of cerebral blood volume (CBVR) to a small induced change in arterial carbon dioxide tension was studied by near-infrared spectroscopy in 17 newborn infants born from 26 wk of gestation to term. All 17 infants were undergoing mechanical ventilation but had apparently normal brains. The CBVR per kPa change in arterial carbon dioxide tension within the range 3.9 to 9.6 kPa was calculated from the change in total cerebral Hb concentration ([TCHb]) using the equation: $\Delta CBV = \Delta[TCHb] \times 0.89/[H]$ where [H] is the large vessel Hb concentration. A least-squares regression line with 95% confidence limits was derived for CBVR against gestational age. A highly significant linear increase in CBVR was found: mean CBVR from the regression increased from 0.07 mL·100 g^{-1}·kPa^{-1} at 26 wk to 0.51 mL·100 g^{-1}·kPa^{-1} at 40 wk. (*Pediatr Res* 29: 553–557, 1991)

Abbreviations

CBV, cerebral blood volume
CBVR, response of cerebral blood volume to changes in $Paco_2$
[Hb], cerebral deoxyhemoglobin concentration
[HbO_2], cerebral oxyhemoglobin concentration
MABP, mean arterial blood pressure
NIRS, near-infrared spectroscopy
$Paco_2$, arterial carbon dioxide tension
[TCHb], total cerebral Hb concentration
TCHbR, total cerebral Hb response to changes in $Paco_2$

The sensitivity of the intracranial blood vessels to changes in $Paco_2$ was first demonstrated by Wolff and Lennox (1) in 1930 using a pial window technique. Quantitative data on the response of cerebral blood flow to changes in $Paco_2$ were initially obtained by Kety and Schmidt (2) using the nitrous oxide clearance method. Since then, numerous studies in adults (3, 4), newborn infants (5, 6), and experimental animals (7–10) have confirmed the positive relationship between cerebral blood flow and $Paco_2$ in normal individuals. Information on the response of CBV to changing $Paco_2$ is more limited (11–14), and only one report has been published involving newborn infants (15). That study, using NIRS, did not provide absolute quantitative data on CBV changes because of uncertainties about optical path length.

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Correspondence and reprint requests: Dr. J. S. Wyatt, Department of Paediatrics, Rayne Institute, 5 University Street, London WC1E 6JJ, England.
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Fluctuations in $Paco_2$ are common in infants undergoing intensive care. Information on the response of the cerebral circulation may be of considerable significance for improved understanding of the pathogenesis of hypoxic-ischemic brain injury and periventricular hemorrhage in these infants. NIRS, first described by Jobsis (16) in 1977, allows continuous, noninvasive, quantitative monitoring of cerebral blood volume (17, 18) in sick newborn infants. It is thus possible to determine at the bedside the response of the cerebral vasculature to changing $Paco_2$. The purpose of our present study was to measure by NIRS the effect on CBV of small alterations in $Paco_2$ in preterm and term infants with apparently normal brains who were undergoing intensive care. CBVR was defined as the change in CBV in mL·100 g^{-1}·kPa^{-1} resulting from an induced change in $Paco_2$ of 0.5 to 2 kPa.

MATERIALS AND METHODS

Subjects. Seventeen newborn infants who had been admitted to the Neonatal Unit of University College Hospital were studied; 12 were male and five were female. Their gestational ages ranged from 26 to 41 (median 29) wk and their birth weights from 856 to 3825 (median 1350) g. Their principle diagnoses are listed in Table 1. All infants were thought to have normal brains on the basis of clinical history and cranial ultrasound examination using Diasonics DS1 (Diasonics Inc., Sunnyvale, CA) or ATL Ultramark 4 (Advanced Technology Laboratories, Germany). None was receiving medication likely to have an effect on the cerebral circulation. One of the infants subsequently died of chronic lung disease before discharge from hospital. Normality was confirmed in the remaining infants by clinical and ultrasound examination after discharge.

NIRS. Measurements of CBVR by NIRS were performed at the bedside at a postnatal age of 7 to 97 (median 21) h and continued for 1 to 6 (median 2.5) h. All infants were receiving mechanical ventilation at the time of the study. We previously described the portable apparatus we built for NIRS of the infant brain (19). This apparatus was used for studies in six infants, and a commercial prototype of this instrument (NIR1000; Hamamatsu Photonics KK) was used for the remaining 11 infants. The original instrument used near-infrared light at four wavelengths (778, 813, 867, and 904 nm), and the commercial prototype used six wavelengths (797, 803, 831, 849, 867, and 908 nm). A flexible fiberoptic bundle conveyed near-infrared light from laser diodes to the head. The end of the fiber bundle (the optode) was applied to the scalp at a site equidistant from the anterior fontanelle and the external auditory meatus. An identical bundle on the opposite side of the head conveyed transmitted light to a sensitive photomultiplier tube. In the six infants whose biparietal diameter exceeded 7 to 8 cm, insufficient signals were obtained with this positioning, and the transmitting optode was

therefore attached to the scalp just lateral to the anterior fontanelle, making an angle of approximately 90° with the receiving fiber (orthogonal transmission). The distance between the optodes was measured using mechanical callipers. With orthogonal positioning of the fibers, the interoptode spacing was measured as the chord of the arc. To prevent interference from background illumination, the head was wrapped in a light-tight bandage. The total light power density emitted from the end of the transmitting fiber bundle was about 130 $W \cdot m^{-2}$, and the calculated power density at the skin surface was more than one order of magnitude below British Standards Institute safety limits (BS 4803), and considerably less at the brain surface.

A controlling computer calculated the changes in optical absorption at each wavelength and converted these into changes of [HbO_2] and [Hb]. The Hb absorption coefficients, the derivation of appropriate algorithms, and the physical basis for this process have been described previously (20, 21). Data from the NIR1000 were analyzed in a similar manner except that a standard least-squares curve-fitting technique was used. Measurements were obtained at intervals of 15 to 20 s and were displayed instantaneously at the bedside and recorded on computer disk for subsequent analysis.

Due to the intense scattering of light in tissue, the optical path length was considerably greater than the interoptode spacing. On the basis of previous studies in postmortem infants (22), an optical path length of 4.4 times the measured interoptode distance was assumed. Arterial O_2 tension and $PaCO_2$ were estimated continuously using a transcutaneous monitor [Novametrix 850 (Novametrix Medical Systems, Wallingford, CT) or Hewlett-Packard 78834A (Hewlett-Packard Co., Palo Alto, CA)] calibrated against arterial blood gas measurement. An arterial or venous blood sample was taken for Hb estimation on the day of study. MABP was measured continuously from an indwelling arterial cannula or obtained using an oscillometric technique from an inflatable cuff (Dinamap 1846SX; Critikon, Irvine, CA).

After a period of baseline observations, an alteration in $PaCO_2$ of 0.5–1.8 kPa was induced over 5 to 20 min by a small change in ventilator rate. Whenever possible, the $PaCO_2$ was maintained within the clinically accepted range (4–7 kPa). If the $PaCO_2$ was outside this range at the start of the study, the ventilator rate was altered to change the $PaCO_2$ in the direction of normality. The inspired oxygen concentration was varied when necessary to keep the arterial O_2 tension as constant as possible between 8 and 12 kPa. CBVR was estimated only if an adequate change in $PaCO_2$ (>0.5 kPa) was observed and if the clinical condition of the infant remained stable during the maneuver.

Changes from baseline in [HbO_2] and [Hb] measured by NIRS (Fig. 1) were analyzed by computer. Changes in [TCHb] in $\mu mol \cdot L^{-1}$ could be calculated from the sum of [HbO_2] and [Hb]:

$$\Delta[TCHb] = \Delta([HbO_2] + [Hb])$$

Changes in [TCHb] were plotted against $PaCO_2$ for each study (Fig. 2), and a least-squares regression was performed to calculate the mean change in total Hb concentration per kPa change in $PaCO_2$. In one infant, there appeared to be a flattening of the straight-line relationship between CBV and $PaCO_2$ at higher $PaCO_2$ values. In this infant, only the linear portion of the curve was used.

Changes in CBV in $mL \cdot 100\ g^{-1}$ were calculated from [TCHb] in $\mu mol \cdot L^{-1}$ from the formula:

$$\Delta CBV = \Delta[TCHb] \cdot MW/([H] \cdot D \cdot R \cdot 10^5)$$

where MW is the molecular weight of Hb, [H] is the large vessel Hb concentration in $g \cdot dL^{-1}$, D is brain density in $g \cdot mL^{-1}$, and R is the large vessel:cerebral hematocrit ratio. For this study, we assumed values of 64 500 for MW, 1.05 for D (23) and 0.69 for R (24). These values give the formula:

$$\Delta CBV = \Delta[TCHb] \times 0.89/[H]$$

The CBVR (change in CBV per kPa change in $PaCO_2$) in $mL \cdot 100\ g^{-1} \cdot kPa^{-1}$ could then be calculated.

Our study was approved by the University College London Faculty of Clinical Science Committee on the Ethics of Clinical Investigation, and parental consent was obtained before each investigation.

RESULTS

Representative changes in [HbO_2], [Hb], and [HbO_2] + [Hb] during a transient alteration in $PaCO_2$ are shown in Figure 1. Changes in [TCHb] plotted against $PaCO_2$ in the same infant, together with the derived regression line to calculate CBVR, are shown in Figure 2. Values for TCHbR and CBVR in the 17 infants studied are given in Table 2. TCHbR ranged from 1.16 to 11.37 $\mu mol \cdot L^{-1} \cdot kPa^{-1}$, whereas CBVR ranged from 0.06 to 0.68 $mL \cdot 100\ g^{-1} \cdot kPa^{-1}$.

When CBVR was plotted against gestational age at birth, it was apparent that there was a highly significant trend for CBVR to increase with gestational age, as illustrated in Figure 3. It was assumed that there was a linear relationship between these two variables, and the regression line and 95% confidence limits (2.5 and 97.5 percentiles) were calculated using the method of Armitage (25) (Table 3). The mean CBVR calculated from the regression increased from 0.07 $mL \cdot 100\ g^{-1} \cdot kPa^{-1}$ at 26 wk of

Table 1. *Clinical details*

Infant no.	Gestation (wk)	Birth wt (g)	Postnatal age at study (h)	Principle diagnosis	MABP (mm Hg)	Initial $PaCO_2$ (kPa)
1	26	879	9	Hyaline membrane disease	33	9.1
2	27	856	24	Hyaline membrane disease	38	5.0
3	27	890	24	Hyaline membrane disease	36	6.6
4	27	1020	7	Hyaline membrane disease	30	4.9
5	27	1030	28	Hyaline membrane disease	41	9.6
6	28	1000	10	Hyaline membrane disease	32	6.1
7	28	1137	7	Hyaline membrane disease	30	4.4
8	28	1500	23	Hyaline membrane disease	43	4.9
9	29	1350	8	Hyaline membrane disease	35	5.7
10	31	1178	10	Hyaline membrane disease	28	6.2
11	34	2100	10	Hyaline membrane disease	33	7.5
12	36	2552	39	Meconium aspiration	55	7.0
13	36	3080	97	Hyaline membrane disease	50	7.2
14	38	2700	65	Listeria infection	29	3.9
15	40	2700	29	Listeria infection	59	6.8
16	40	3825	21	Meconium aspiration	27	5.1
17	41	3130	12	Diaphragmatic hernia	49	5.7

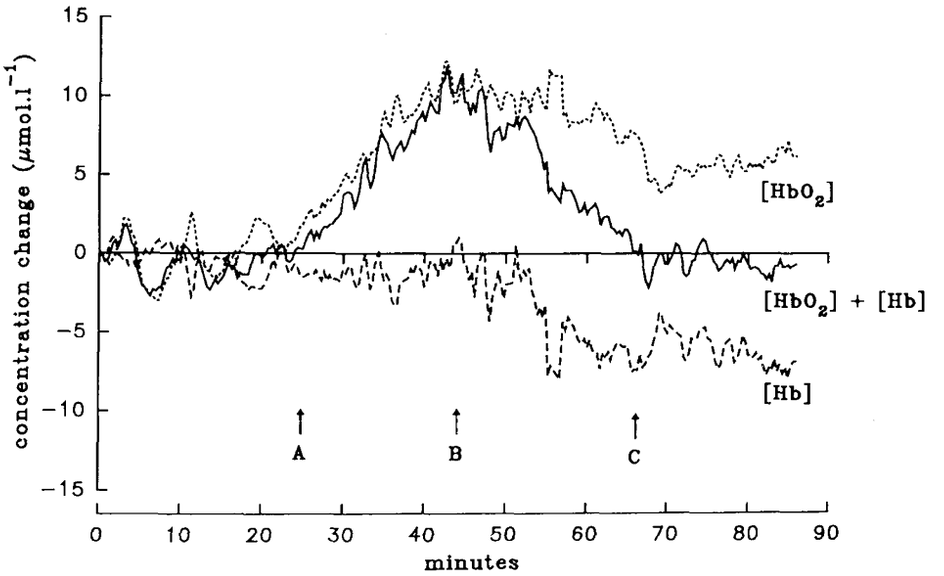

Fig. 1. Changes in $[HbO_2]$, [Hb], and $[HbO_2]$ + [Hb] during a transient alteration in $PaCO_2$ in infant no. 17. The $PaCO_2$ was 5.8 kPa at *A* and rose to 6.8 kPa at *B*, returning to 5.9 kPa at *C*. Arterial O_2 tension rose slightly at *C*, causing a rise from baseline in $[HbO_2]$ and a fall in [Hb].

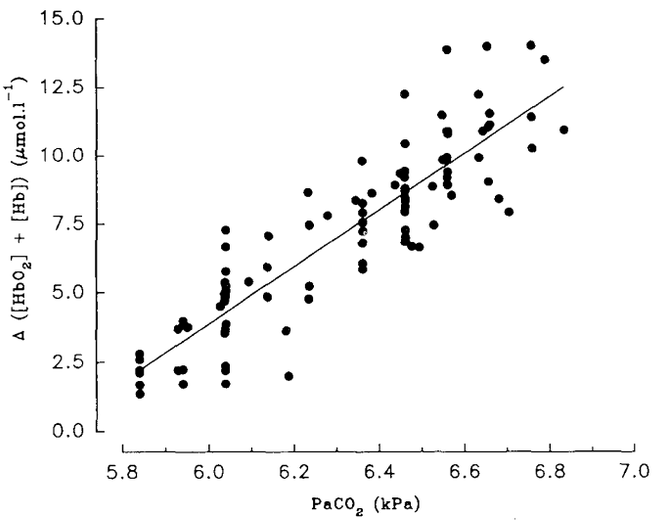

Fig. 2. Relation between changes in $[HbO_2]$ + [Hb] and $PaCO_2$ in the same infant as in Figure 1, together with the derived regression line to calculate TCHbR, which was 11.37 $\mu mol \cdot L^{-1} \cdot kPa^{-1}$. The points represent 20-s averages from the continuous records.

Table 2. *TCHbR and CBVR in infants*

Infant no.	TCHbR ($\mu mol \cdot L^{-1} \cdot kPa^{-1}$)	CBVR ($mL \cdot 100\ g^{-1} \cdot kPa^{-1}$)
1	2.85	0.17
2	3.02	0.16
3	4.09	0.19
4	1.16	0.06
5	4.74	0.35
6	2.90	0.14
7	1.45	0.09
8	1.40	0.09
9	2.42	0.18
10	5.25	0.25
11	3.00	0.15
12	5.68	0.30
13	6.04	0.32
14	9.66	0.68
15	9.94	0.55
16	7.12	0.38
17	11.37	0.63

gestation to 0.51 $mL \cdot 100\ g^{-1} \cdot kPa^{-1}$ at 40 wk (CBVR = 0.031 × gestational age − 0.745; $r = 0.82$, $p < 0.0001$).

Multiple stepwise regression analysis of the contributions of postnatal age and MABP to CBVR revealed no significant independent effect of either variable.

DISCUSSION

Validity of NIRS measurements. We have obtained the first quantitative data on the response of CBV to alterations in $PaCO_2$ in newborn infants. However, the use of NIRS to measure CBV involves several simplifying assumptions. The head is regarded as an optically homogeneous compartment with a constant spatial distribution of Hb and a fixed mean hematocrit. Although Hb concentration is well known to vary in different regions of the brain, this will not have contributed a significant error to our calculation because of the highly light-scattering nature of brain tissue and the extended path taken by each photon.

We have assumed that the relation between optical path length and interoptode spacing was the same in infants with linear (180°) and orthogonal (90°) positioning of the optical fibers. This has been substantiated by recent data from time of flight measurement through the postmortem infant head (26). The possible error in path length is entirely negligible compared with the magnitude of the differences we have observed between term and preterm infants. We have also assumed that the relation between optical path length and interoptode distance was constant at different gestational ages. Although a small increase in path length with increasing gestational age might be anticipated (because of increased myelination), this is unlikely to cause an overestimation in CBVR of more than 10%. This is negligible in comparison with the observed increase in CBVR of approximately 700% between 26 and 40 wk of gestation.

A further assumption was that optical path length remained constant during each study despite the observed changes in [TCHb]. In experimental animals, the optical path length at near-infrared wavelengths has been found to be remarkably constant despite gross changes in oxygenation and perfusion, and before and after death (27). The maximum variation in path length during these extreme changes of condition was <9%. Small fluctuations in [TCHb] can therefore be assumed to have exercised a negligible effect on path length.

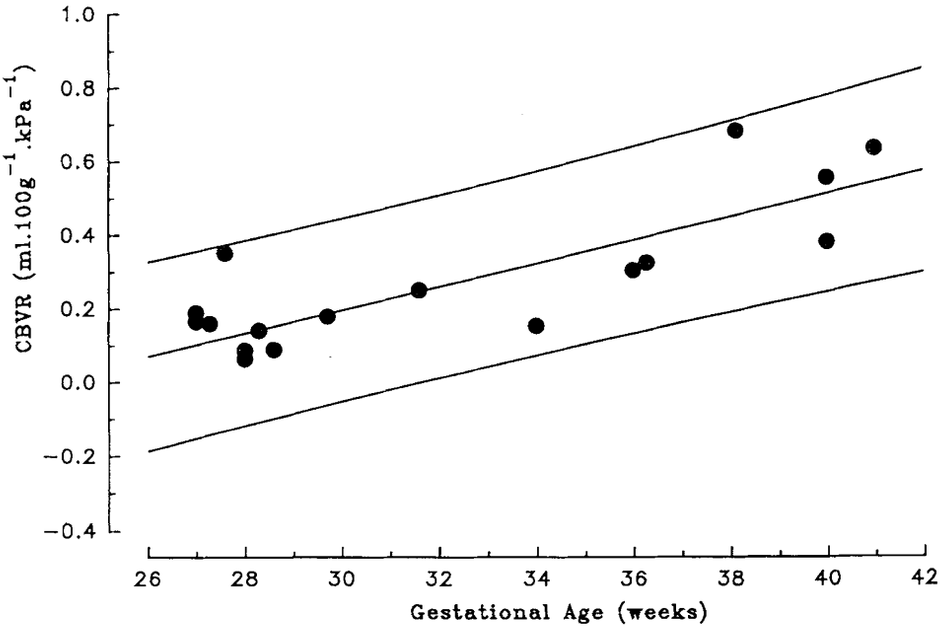

Fig. 3. CBVR in mL·100 g^{-1}·kPa^{-1} in the 17 infants plotted against gestational age. Least-squares regression line and 95% confidence limits (2.5 and 97.5 percentiles) are shown.

Table 3. *Calculated regression and 95% confidence limits for TCHbR and CBVR with increasing gestational ages*

	TCHbR (μmol·L^{-1}·kPa^{-1})			CBVR (mL·100 g^{-1}·kPa^{-1})		
Gestation (wk)	Mean	Upper limit	Lower limit	Mean	Upper limit	Lower limit
26	1.58	5.09	−1.94	0.07	0.33	−0.19
28	2.62	6.06	−0.83	0.13	0.38	−0.12
30	3.65	7.06	0.25	0.20	0.44	−0.05
32	4.69	8.09	1.30	0.26	0.51	0.01
34	5.73	9.15	2.32	0.32	0.57	0.07
36	6.77	10.23	3.31	0.38	0.64	0.13
38	7.81	11.35	4.27	0.45	0.71	0.19
40	8.85	12.48	5.21	0.51	0.78	0.24
42	9.88	13.64	6.12	0.57	0.85	0.30

The large vessel:cerebral hematocrit ratio has been demonstrated to change slightly with alterations in $PaCO_2$ (28). We have estimated that this introduced an error of less than 3% in the conversion of changes in [TCHb] to changes in CBV.

Hb saturation varies with changing $PaCO_2$ due to an alteration in blood pH (the Bohr effect). This did not influence our calculations, however, as a change in Hb saturation would not affect the total Hb concentration. Although there were unknown and variable proportions of fetal and adult Hb in the blood of the infants studied, this had no significant effect on the results, inasmuch as the absorption spectra of fetal and adult Hb are virtually identical in the near-infrared region (29).

CBVR measurement. For quantification of CBVR, we have made the simplifying assumption that the relation between CBV and $PaCO_2$ is linear within the range of $PaCO_2$ observed. Linearity in CBF response over a wide range of $PaCO_2$ has been found by a number of workers (3, 4, 8, 9, 12), but flattening of the response at extremes of $PaCO_2$ has been observed (6, 7), suggesting a sigmoid relationship. It is likely that the relation between CBV and $PaCO_2$ will be broadly similar.

In this study, we aimed to remain within the linear portion of the response curve. In one infant, we did observe apparent flattening of the curve at high $PaCO_2$ values. In no infant was flattening of the CBVR observed at low $PaCO_2$. This may have been because $PaCO_2$ levels below 4 kPa were not observed. Deliberate reduction of $PaCO_2$ below this level was not attempted because of the possible risk from reduced cerebral oxygen delivery.

CBVR in newborn infants. We have confirmed the physiologic response of CBV to changing $PaCO_2$ and have demonstrated an increase in cerebrovascular reactivity with gestational age. In a previous study, we found no obvious relationship between total CBV in newborn infants and gestational age (18). Thus, the calculated percentage change in CBV per kPa increased from about 4% at 26 wk to about 25% at 40 wk of gestation. This effect is not apparent in data indicating normal CO_2 responsivity of CBF (6) and CBF velocity (30) in extremely preterm infants. Thus, Greisen and Trojaborg (6) observed a mean CBF response to an induced change in $PaCO_2$ of 67% per kPa. The cerebrovascular response to changing $PaCO_2$ is known to be attenuated by hypotension (8, 31, 32). Inasmuch as MABP is frequently lower in very preterm infants than in more mature infants, the reduction in CBVR at younger gestational ages might be secondary to hypotension. However, multiple analysis of variance of our data failed to reveal any independent effect of MABP on CBVR.

The values for CBVR obtained in full-term infants correspond closely with those obtained by Greenberg *et al.* (14) from adult human volunteers using radiolabeled erythrocytes. This group determined a mean value for CBVR of 0.049 mL·100 g^{-1}·torr^{-1}, equivalent to 0.37 mL·100 g^{-1}·kPa^{-1}.

The physiologic mechanisms underlying the cerebrovascular response to carbon dioxide tension have not yet been fully elucidated, despite numerous investigations. The direct action of CO_2 and various other mediators, such as perivascular pH and bicarbonate ion, on the cerebral vessel wall remains controversial, and prostanoids have been recently implicated (33). Indomethacin, a prostaglandin synthetase inhibitor, has been found to abolish this response in preterm infants (34), as well as in rats (35) and gerbils (36), although not in some other experimental animals (37). It is possible that alterations in the concentrations of prostanoids in brain tissue or vessel wall may account for the effect of gestational age on CBVR, but to our knowledge no data are available from human infants.

It is not known what are the relative contributions of the arterial, capillary, and venous compartments to the change in CBV induced by carbon dioxide. Inasmuch as increased $PaCO_2$

was invariably associated with a rise in [HbO_2] but little change in [Hb], it is likely that the principle change in blood volume occurs in the arteriolar and capillary circulation. Further studies will be necessary to address this question.

Hypoxic-ischemic brain injury may occur in newborn infants if the $PaCO_2$ is excessively low, causing reduced cerebral perfusion (38). Our data suggest that full-term infants have much greater cerebrovascular sensitivity to $PaCO_2$ than preterm infants, and thus they may be particularly at risk of brain injury from hypocapnia. Inadvertent hypocapnia can readily occur in infants undergoing mechanical ventilation, especially when the lungs are relatively normal, allowing good gas exchange.

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