Effect of permissive hypercapnia on background cerebral electrical activity in premature babies

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BACKGROUND: Permissive hypercapnia is routinely practiced in neonatal intensive care units. The effect of permissive hypercapnia on the preterm brain and brain electrical activity is unknown. In this study, we aimed to determine the effect of chronic changes in partial pressure of blood carbon dioxide (P_{CO_2}) on brain electrical activity in preterm newborn babies born at or before 32 wk gestation.

METHODS: Eighty-three 1-h long digital electroencephalography (EEG) recordings were performed once a week for 4 wk on 25 babies with median gestational age of 29 wk (range: 23–32) after 48 h of age. Capillary blood gas measurements were performed midway through EEG recordings.

RESULTS: There are associations between EEG parameters and blood pH, P_{CO_2} , and blood glucose concentration. However, there are also strong and complex associations with gestational age and substantial individual patient effects that make it difficult to demonstrate predictive associations. P_{CO_2} and bicarbonate are significantly correlated with relative power of θ EEG band and Δ EEG band respectively after adjustment for age and intrababy correlations, but after allowing for multiple testing these relationships are of borderline statistical significance.

CONCLUSION: Compensated respiratory acidosis may affect EEG by increased delta wave activity in preterm babies born before 32 wk gestation.

Hypocapnia before surfactant therapy in preterm infants has been associated with increased risk of bronchopulmonary dysplasia (1). As a result, permissive hypercapnia defined as partial pressure of blood carbon dioxide (P_{CO_2}) of more than 7 kPa is routinely practiced in neonatal intensive care units (2).

The effect of hypercapnia on preterm brain has not been fully evaluated. A small randomized controlled trial showed that minimal ventilation with an aim to maintain P_{CO_2} more than 7 kPa showed an increased trend to adverse neurodevelopmental outcome (3). A review of two randomized controlled trials ($n = 269$) with no neurodevelopmental assessment did

not demonstrate any significant overall benefit on mortality and pulmonary morbidity from permissive hypercapnia (4). An observational cohort study of 425 preterm infants which showed an increased risk of bronchopulmonary dysplasia with permissive hypercapnia did not evaluate the effect of hypercapnia on the preterm brain.

Electroencephalography (EEG) is the record of the brain electrical activity. Preterm EEG is discontinuous with bursts of high voltage slow wave electrical activity interspersed by periods of electrical quiescence called interburst interval (IBI) (5). Prolonged EEG IBIs of more than 30 s in preterm infants born at less than 28 wk gestation and more than 25 s in preterm infants born at more than 28 wk gestation have been associated with increased incidence of death or developmental motor abnormalities (6,7). EEG has been studied in relation to age, hypotension, hypo and hypercapnia, and cardiac output in preterm babies born before 30 wk gestation during the first 72 h after birth (8–11). Lower levels of blood carbon dioxide have been associated with slowing of cerebral electrical activity and increased cerebral fractional oxygen extraction, while hypercapnia was associated with suppression of cerebral electrical activity during the first 48 h after birth (9). However, the incidence of hypercapnia, permissive or otherwise is more common (42.6%) after 7 d of age than during the first 48 h after birth (2). No studies have been performed to evaluate the effect of hypercapnia on brain electrical activity in preterm infants born before 32 wk gestational age after 72 h of age.

In this study, we aimed to determine the effect of chronic changes in P_{CO_2} on brain electrical activity in preterm newborn babies born before 32 wk gestation and more than 48 h of age along with a number of related parameters such as pH and bicarbonate.

RESULTS

Eighty-three EEG recordings were performed on 25 babies (11 males) with a median gestational age at birth of 29 wk (range: 23–32) and median birth weight of 1,224 g (range: 635–1,695) at a single tertiary referral newborn intensive care unit. Their

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median Apgar score at 5 min was 9 (range: 4–10). The condition of the babies at the time of EEG recording was as shown in [Table 1](#). None of the babies were on inotropes, morphine, or antiepileptic medications at the time of the EEG recording. Only two babies had raised C-reactive protein at the time of recording. Only one baby had evidence of periventricular leukomalacia on follow-up cranial ultrasound scans.

There is a strong nonlinear trend in the EEG parameters with corrected gestational age (CGA) with a decrease in relative power of the α , β , and θ EEG bands (RP_{α} , RP_{β} , RP_{θ}) to around 29 wk and an increase thereafter ([Figure 1](#)). The relative power of the Δ EEG band (RP_{Δ}) shows a similar effect but inverted. For all these parameters, the nonlinearity is highly significant ($P < 0.001$). In contrast, IBI shows a linear decrease with CGA. There are also lesser but clear differences between individual babies that are statistically significant (see below and [Table 2](#)).

PcO_2 shows little change with gestational age, whereas pH and bicarbonate significantly increases with CGA and glucose level decreases ([Figure 2](#)).

PcO_2 is significantly correlated with RP in all four frequency bands, but not with IBI ([Figure 3](#); [Table 2](#)), and the association with RP_{θ} remains significant ($P = 0.013$) after adjustment

for age and intrababy correlations. However, this relationship is only of borderline significance after allowance is made for the fact that five frequency parameters have been assessed ($P = 0.063$). We observe that the relationship between PcO_2 and RP_{θ} remains highly significant after adjusting for CGA alone ($P = 0.001$) but is weakened after additionally allowing for individual patient differences. Glucose and pH have significant correlations with EEG parameters, but these are lost on adjustment for CGA. In contrast, bicarbonate levels show significant associations with EEG parameters only after adjusting for CGA, but the relationship between RP_{Δ} and bicarbonate would be considered as significant even after adjustment for the multiple testing ($P = 0.039$). As shown in [Table 2](#), the CGA effect remains highly significant for all EEG components after adjustment for each of the clinical variables, and (with one exception) the interpatient variability likewise remains significant.

Two babies died before discharge. Of the 23 survivors, 9 (39%) babies had chronic lung disease defined as oxygen requirement at 36 wk CGA. Nine babies did not complete neurodevelopment follow-up. Of the remaining 14 babies, 12 infants were noted to have neurodevelopment within normal limits at 2 y

Table 1. Median (range) of corrected gestational age, age, pH, PcO_2 , blood glucose concentration, and bicarbonate at the time of EEG recordings

Characteristics	First EEG (n = 24)	Second EEG (n = 22)	Third EEG (n = 19)	Fourth EEG (n = 18)
Corrected gestational age (wk)	30 (25–33)	31 (26–34)	32 (27–35)	33 (28–36)
Age (days)	6 (3–7)	13 (6–14)	20 (13–22)	27 (21–28)
pH	7.3 (7.2–7.4)	7.3 (7.2–7.4)	7.3 (7.2–7.4)	7.4 (7.2–7.4)
PcO_2 (kPa)	5.8 (3.8–8.5)	6.9 (4.8–10.2)	6.7 (5.3–9.6)	7.0 (5.2–10.5)
Blood glucose (mmol/l)	6.8 (2.3–16.8), (n = 23)	6.2 (4.3–10.7), (n = 20)	5.3 (4.2–10.7), (n = 18)	5.3 (3.5–10.8), (n = 14)
Bicarbonate level (mEq/l)	19.6 (16.7–23.2)	23.2 (17.0–35.9)	25.0 (18.6–28.8)	25.3 (20.0–33.1)
Ventilation (n)				
SIMV	10	8	5	1
CPAP	5	3	3	5
Oxygen	0	1	9	11
Air	9	10	2	2

CPAP, continuous positive airway pressure; EEG, electroencephalography; SIMV, synchronized intermittent mandatory ventilation.

Figure 1. Relationship between electroencephalography parameters and corrected gestational age (CGA). (a) RP_{α} , (b) RP_{β} , (c) RP_{θ} , (d) interburst interval, and (e) RP_{Δ} . Grey lines join repeat measurements from the same babies. Solid line is a regression fit using a quadratic function.

Table 2. Associations between clinical and EEG variables

Component	Clinical variable	Adjusted model					
		Spearman correlation		Clinical variable	Age effect	Between patient	
		ρ	P			CV	P
Log(RP _α)	CGA	0.48	<0.001				
	pH	0.35	0.001	0.34	<0.001	18%	<0.001
	PcO ₂	−0.23	0.035	0.40	<0.001	18%	<0.001
	Bicarbonate	0.04	0.70	0.048	<0.001	18%	<0.001
	Glucose	−0.39	0.002	0.62	<0.001	17%	<0.001
Log(RP _β)	CGA	0.51	<0.001				
	pH	0.25	0.022	0.23	<0.001	27%	<0.001
	PcO ₂	−0.23	0.039	0.21	<0.001	27%	<0.001
	Bicarbonate	0.00	1.00	0.023	<0.001	27%	<0.001
	Glucose	−0.25	0.055	0.56	0.002	26%	0.003
Log(RP _θ)	CGA	0.37	<0.001				
	pH	0.41	<0.001	0.21	<0.001	16%	<0.001
	PcO ₂	−0.30	0.007	0.013	<0.001	16%	0.001
	Bicarbonate	−0.01	0.92	0.039	<0.001	16%	<0.001
	Glucose	−0.37	0.003	0.45	<0.001	14%	0.001
Log(IBM)	CGA	−0.66	<0.001				
	pH	−0.42	<0.001	0.62	<0.001	17%	0.012
	PcO ₂	0.01	0.93	0.23	<0.001	17%	0.006
	Bicarbonate	−0.38	<0.001	0.25	<0.001	17%	0.008
	Glucose	0.33	0.009	0.40	<0.001	19%	0.064
Log(RP _Δ)	CGA	−0.44	<0.001				
	pH	−0.35	0.001	0.79	<0.001	1.1%	<0.001
	PcO ₂	0.29	0.007	0.067	<0.001	1.1%	<0.001
	Bicarbonate	0.03	0.81	0.008	<0.001	1.0%	<0.001
	Glucose	0.33	0.011	0.95	<0.001	1.1%	0.005

Uncorrected Spearman correlations and an adjusted model allowing for a quadratic age effect and inpatient correlations. The adjusted models for each EEG parameter included effects of the clinical variable, an age effect and a patient effect, and P values are given for each effect along with the between-patient CV. P values in the table are not adjusted for multiple testing (but see text).

CGA, corrected gestational age; CV, coefficient of variation; EEG, electroencephalography; IBM, interburst interval.

of age, 1 infant had mild neurodevelopment delay (gestation at birth: 31 wk; twin pregnancy; normal cranial ultrasound scan; no chronic lung disease; PcO₂ range: 5.4–8.1 kPa; IBM range: 2.6–5.3 s), and 1 infant had moderate neurodevelopment delay (gestation at birth: 29 wk; singleton pregnancy; parieto-occipital periventricular leukomalacia on cranial ultrasound scan; no chronic lung disease; PcO₂ range: 5.3–6.2 kPa; IBM range: 1.6–3.3 s).

DISCUSSION

Our results show that there are associations between EEG and pH, PcO₂, bicarbonate, and glucose. However, there are also strong and quite complex associations with gestational age and substantial individual patient effects that make it difficult to demonstrate predictive associations within individual patients. Nevertheless, PcO₂ is correlated with RP_θ after adjustment for age and intrababy correlations although this effect is of borderline significance after allowing for multiple testing. There

is also an association between blood bicarbonate concentrations and RP_Δ, which would be considered significant after all adjustments. In carefully adjusting for CGA and for interpatient variability, the analyses here are conservative and real effects of PcO₂ and bicarbonate will have been absorbed into the age and interpatient effects. Taken as a whole, these data suggest that there may be associations between EEG parameters and compensated respiratory acidosis in babies more than 48 h of age, which warrant further study, but the data here do not allow us to draw any firm conclusions about specific EEG and clinical parameters.

Changes in RP_θ in relation to PcO₂ are likely to be due to the inverse effect of the changes in RP_Δ. RP_Δ increases with increase in PcO₂ (not statistically significant) and increase in blood bicarbonate concentrations (statistically significant). As 39% of our cohort had chronic lung disease, the changes in PcO₂ and bicarbonate are likely to be chronic. Together, this indicates an increased level of EEG Δ wave activity with

Figure 2. Relationship between clinical parameters and corrected gestational age (CGA). Solid lines are a linear regression fit. (a) PCO_2 ($P = 0.76$), (b) pH ($P < 0.001$), (c) glucose ($P = 0.014$), and (d) bicarbonate ($P < 0.001$).

Figure 3. Relationship between electroencephalography parameters and PCO_2 levels after adjustment for corrected gestational age (quadratic fit) and interbaby effects. Solid lines are a linear regression fit. (a) RP_α ($P = 0.40$), (b) RP_β ($P = 0.21$), (c) RP_θ ($P = 0.013$), (d) interburst interval (IBI) ($P = 0.23$), and (e) RP_Δ ($P = 0.07$).

compensated respiratory acidosis. Indeed, Scher *et al.* (12) showed that babies with chronic lung disease had a significant reduction in the percentage of active sleep. In addition, they noted significant differences in relation to the number (0.29/min vs. 0.13/min) and duration (4.8 vs. 2.94 s) of arousals as well as the total number of body movements (1.57/min vs. 0.74/min) (12). These data suggest that chronic changes in blood gases in babies more than 48 h old may be associated with unfavorable EEG background warranting further study on the effects of permissive hypercapnia on the preterm brain.

The effects of pH, PCO_2 , and blood glucose concentration on EEG when babies are more than 48 h old differ from those noted in previous studies conducted during the first 48 h after birth. Victor *et al.* (9) showed that lower levels of PCO_2 were associated with increased cerebral fractional oxygen extraction and slowing of EEG, while higher levels of PCO_2 were associated with suppression of EEG during the first 48 h of age. Granot *et al.* (13) using amplitude integrated EEG on 65 preterm babies born before 28 wk gestational age showed that

respiratory acidosis and hyperglycemia during the first 72 h after birth was associated with suppressed electrical activity. Wikström *et al.* (14) using one-channel EEG reported that in a cohort of 32 babies born before 28 wk gestation higher levels of PCO_2 were associated with suppressed cerebral electrical activity. Wikström *et al.* (14) showed that high plasma glucose and low plasma glucose were both associated with suppressed electrical activity during the first 72 h after birth. Eaton *et al.* (15) using continuous EEG monitoring conducted from 3.5 to 165 h of age showed that metabolic and respiratory acidosis were associated with prolonged IBIs. It appears that the pre-term brain responds differently to acute and chronic changes in PCO_2 with suppression of EEG activity with acute hypercapnia and increased EEG activity with chronic hypercapnia.

The strong trends in EEG parameters in relation to CGA noted in our cohort are consistent with the results of other studies (16,17). Indeed, in our study, IBIs decrease with increased CGA (17). In our study, RP_Δ shows slight increase until 30 wk gestational age possibly due to the decrease in IBI

and thereafter decreases sharply possibly due to an overall increase in frequency and decrease in amplitude of the EEG waves. Much of the changes in the relative power of other EEG bands (θ , α , and β) are more likely to be due to the inverse of the effects of RP_{Δ} than due to absolute changes in the EEG bands themselves.

The nonlinear energy operator method was used to detect bursts as has been shown in previous publications (18). However, we performed the EEG burst detection optimization using our own IBI markings. We found that by performing our own independent markings along with burst detection and artifact removal, we were able to achieve an automated burst detector that ascertained interburst values. When comparing the averaged values of the IBIs against the gestational ages of the babies, a strong and significant regression was confirmed.

The artifact detection consisted of a method similar to that which detected bursts. The method used a threshold that was based on signal epochs that were agreed to be artifact between two clinical neurophysiologists. Therefore, EEG signals that were both large in amplitude and high in frequency could be detected automatically using this method. The relative powers were detected using a window length of 2 s with a 1 s overlap.

The strong relationships with gestational age and substantial individual patient variability in EEG measurements in this study, combined with the large interval between measurements make it difficult to robustly demonstrate effects of PcO_2 and related variables on the EEG parameters. Here, in the analysis, we have been conservative in only claiming effects which led to significant associations after adjustment for CGA and patient. Since the clinical parameters themselves are confounded with CGA, this adjustment is likely to be overconservative. The results here suggest that further work is required with shorter time periods between measurements and with more measurements per baby, which will allow comparisons within the same babies at essentially the same gestational age.

In conclusion, this study suggests that compensated respiratory acidosis affect EEG in preterm babies born before 32 wk gestation and more than 48 h old. The suppression of EEG noted in acute respiratory acidosis is not seen in chronic compensated respiratory acidosis. Further research is required in assessing the effects of permissive hypercapnia on preterm brain injury.

METHODS

A prospective observational study was performed at the Newborn Intensive Care unit, St Mary's Hospital for Women and Children, Manchester, UK. The study was approved by the Oldham Local Research Ethics Committee. Infants born at or before 32 wk gestation were recruited to the study following informed parental consent. Infants with significant intraventricular hemorrhages (defined as hemorrhages extending beyond the germinal matrix) have abnormally prolonged periods of EEG discontinuity and were therefore excluded (19).

Digital EEG recordings were performed for 60 min once a week for up to 4 wk with the first EEG recording being at least 48 h postbirth. The electrodes were placed at Fp1, C3, T3, O1, Fp2, C4, T4, O2, and Cz by trained clinical neurophysiologists. Disposable cup-shaped silver-silver chloride electrodes were placed on the scalp and secured using EEG paste.

The nine channels were arranged in a standard 12 signal observation pattern. These signals included the following channel differences: Fp2-T4, T4-O2, Fp2-C4, C4-O2, Fp1-T3, T3-O1, Fp1-C3, C3-O1, T4-C4, C4-Cz, Cz-C3, and C3-T3.

These 12 signals were used for all channel EEG analysis. The sampling frequency of the signals, across all channels, was 200 Hz. EEG was automatically analyzed to determine the relative powers of EEG frequency bands, EEG IBI, and the presence of artifact.

Relative Powers of EEG Frequency Bands

The relative powers of selected EEG frequency bands were calculated with an initial fourth order high pass Butterworth IIR filter with a cut off of 0.3 Hz in place. The length of the reduced relative power window was 400 samples with a window overlap of 200 samples. A Hanning window was convolved with each signal epoch to reduce spectral leakage between frequency bins. The relative powers were calculated by dividing the value of their associated frequency range by the total of the frequency bins up to and including 30 Hz. The spectrum was divided as follows: Δ band (0.5–3.5 Hz), θ band (4–7.5 Hz), α band (8–12.5 Hz), and β band (13–30 Hz). The relative power values were calculated for each individual channel, and the mean of the values was found by averaging over all 12 channels. The median relative power values over the entire 1 h EEG recording were used for statistical analysis to account for sleep-wake cycling and minimize the effects of handling for blood sampling on EEG. Relative power values that contained signal artifact (as defined below) were not included in the calculation of the median.

IBIs

A fourth order high pass Butterworth IIR filter with a cut off of 0.4 Hz and a sixth order low pass Butterworth IIR filter with a 30 Hz cutoff were initially applied to the EEG channels. The EEG IBIs were calculated by using the nonlinear energy operator method and the equation $E(n) = x(n) x(n-3) - x(n-1) x(n-2)$, where $E(n)$ is the operator and $x(n)$ is the input signal (20). A smoothing window of 203 samples was applied to the nonlinear energy operator values to obtain an overall value of $E(k)$. An $E(k)$ value greater than 5.932 was used to determine whether a burst was occurring. A minimum criterion of 1 s in length was defined for burst and IBIs. The median IBI over the entire 1 h EEG recording was used for statistical analysis to account for sleep-wake cycling. IBI values that contained signal artifact were not included in the calculation of the median.

Artifact Detection

The artifact detection was performed using a method similar to the burst detection. However, a fourth order Butterworth IIR band stop filter was used with cutoff frequencies of 49 and 51 Hz to remove noise. Additionally, a different equation was used for artifact detection as compared to the burst detection nonlinear energy operator method, $E(n) = x(n)^2 - x(n+1) x(n-1)$, where $E(n)$ is the operator and $x(n)$ is the input signal (21). A smoothing window of 203 samples with an $E(k)$ threshold of 2.88949×10^6 was used. An artifact detection would cause the burst detection process to be paused while an artifact was occurring. Burst detection and interburst length counting continued once the artifact was no longer present.

Clinical Measurements

The primary measure, PcO_2 , along with secondary measures pH, bicarbonate, and blood glucose concentration using capillary blood were measured midway through the EEG recording using ABL 835 Flex (Radiometer, Copenhagen, Denmark). Cranial ultrasound scans were performed as deemed clinically necessary until discharge from the neonatal unit. The images from these scans were examined for periventricular leukomalacia.

Clinical Management

The clinical management of the babies in this study was according to local clinical guidelines. In babies more than 48 h old, PcO_2 was allowed to increase, provided the pH was maintained above 7.2. If two consecutive blood glucose measurements more than 2 h apart were more than 12 mmol/L, insulin infusion was commenced to maintain blood glucose concentrations below 12 mmol/L.

A formal neurodevelopmental assessment was not performed. However, follow-up was offered by the clinical team until 2 y of age. The outcome of this follow-up was recorded.

Statistical Methods

Correlations between clinical and EEG variables were assessed using Spearman correlations. Mixed linear models were used to assess the associations between EEG and clinical variables, with the EEG variables being log-transformed. CGA in weeks was included as a quadratic function, and the significance of the nonlinearity tested by comparison with a linear representation using likelihood ratio tests. Patient identifiers were added as random effects to allow for correlations within babies, and the magnitude of the interbaby differences expressed as coefficient of variation (CV). Significance of these effects was assessed using a restricted likelihood ratio test based on simulated values from the finite posterior distribution (22). As five EEG parameters were tested, the Holm test was used to generate multiplicity-adjusted *P* values. Models were fitted using R (23) and the lme4 and RLRsim (22) packages.

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