Relationship Between Blood Pressure, Cerebral Electrical Activity, Cerebral Fractional Oxygen Extraction, and Peripheral Blood Flow in Very Low Birth Weight Newborn Infants

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ABSTRACT: There is uncertainty about the level of systemic blood pressure required to maintain adequate cerebral oxygen delivery and organ integrity. This prospective, observational study on 35 very low birth weight infants aimed to determine the mean blood pressure (MBP) below which cerebral electrical activity, peripheral blood flow (PBF), and cerebral fractional oxygen extraction (CFOE) are abnormal. Digital EEG, recorded every day on the first 4 d after birth, were analyzed a) by automatic spectral analysis, b) by manual measurement of interburst interval, and c) qualitatively. CFOE and PBF measurements were performed using near-infrared spectroscopy and venous occlusion. MBP was measured using arterial catheters. The median (range) of MBP recorded was 32 mm Hg (16–46). The EEG became abnormal at MBP levels below 23 mm Hg: a) the relative power of the delta (0.5–3.5 Hz) frequency band was decreased, b) interburst intervals were prolonged, and c) all four qualitatively abnormal EEG (low amplitude and prolonged interburst intervals) from four different patients were recorded below this MBP level. The only abnormally high CFOE was measured at MBP of 20 mm Hg. PBF decreased at MBP levels between 23 and 33 mm Hg. None of the infants in this study developed cystic periventricular leukomalacia. One infant (MBP, 22 mm Hg) developed ventricular dilatation after intraventricular hemorrhage. The EEG and CFOE remained normal at MBP levels above 23 mm Hg. It would appear that cerebral perfusion is probably maintained at MBP levels above 23 mm Hg. (*Pediatr Res* 59: 314–319, 2006)

Several authors have described an association between systemic hypotension in premature infants and neurologic morbidity (1–3), and, in some centers, clinical practice is to support blood pressure by inotropes and volume expanders when the MBP level falls below 30 mm Hg. The likely mechanism by which hypotension causes neurologic damage is by diminished oxygen delivery through decreased cerebral perfusion. However, the relationship between MBP and cerebral blood flow is unclear in premature infants (4–8). Some authors have argued that cerebral blood flow is pressure passive and dependent on MBP in infants between 28 and 39

wk gestation (5,7). Others, who have studied infants between 24 and 34 wk gestation, observed that cerebral blood flow is independent of MBP (4,8). Furthermore, the critical level of MBP at which cerebral perfusion becomes compromised has not been clearly determined.

In spite of a lack of evidence linking systemic hypotension to brain damage in very low birth weight infants, it is well known that older subjects lose consciousness when MBP falls to a seriously low level. A change in the level of consciousness may not be recognized in sick newborn infants who are heavily sedated while being ventilated, but it may be associated with recognizable changes in the EEG pattern. Using a cerebral function monitor, Greisen *et al.* (9) showed that reduced blood flow to the neonatal brain correlated with decreased amplitude of the EEG. There have been no other studies that have investigated the relationship between background cerebral electrical activity and hemodynamic variables in very low birth weight infants. Nevertheless, the EEG pattern of infants between 26 and 30 wk gestation has been well characterized (10). It is markedly discontinuous and consists of long periods of quiescence, called interburst intervals, interspersed with bursts of high-voltage activity of mixed frequency. With increasing gestation, the interburst intervals decrease and the record becomes more continuous (11). Abnormal background EEG activity characterized by prolonged interburst intervals has been linked to death and adverse neurologic outcome in preterm babies (12).

The largest portion of the brain oxygen consumption is used to maintain transmembrane ion gradient (13). Decreased cerebral oxygen delivery therefore leads to a sequence of alterations in the transmembrane electrochemical gradients, and hence in surface EEG patterns (13). Tissue oxygen deprivation is determined by the dynamic relationship between oxygen supply and oxygen demand. A balance between cerebral oxygen delivery and utilization would therefore be expected to

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Abbreviations: CFOE, cerebral fractional oxygen extraction; MBP, mean blood pressure; PBF, peripheral blood flow; P₉₀, 90th centile

provide an indication of this energy balance at the time of EEG recording (14,15). At lower levels of MBP (23–27 mm Hg), PBF would be expected to diminish (16).

The purpose of this study was to determine the relationship between MBP, cerebral electrical activity, CFOE, and PBF in premature newborn infants, with an intention of establishing the level of MBP at which management of hypotension is to be instituted.

METHODS

This was a prospective observational study performed on 35 very low birth weight infants of less than 30 wk gestation born at Liverpool Women's Hospital. Measurements were performed every day on the first 4 d after birth. Ethical approval was obtained from the Liverpool Children's Research Ethics Committee and informed parental consent was obtained. An upper gestational age limit of 30 wk was chosen as sleep-wake cycling is typically not seen below this gestation (17). Infants with serious intraventricular hemorrhage (defined as any hemorrhage extending beyond the germinal matrix) on the first 2 d after birth were excluded from the study.

EEG. Digital EEG and ECG recordings were performed for 75 min using a Micromed 16-channel system (Micromed Electronics Ltd., UK). Six electrodes were placed on the frontopolar (Fp1, Fp2), central (C3, C4), and occipital (O1, O2) positions bilaterally according to the International 10-20 System (18). A reference electrode was placed at the vertex (Cz). Skin impedance of <2 k Ω was maintained for all recordings. A sampling rate of 256 Hz was used for digitization.

The EEG was analyzed qualitatively and quantitatively. M.B. and R.A., both experienced at reporting neonatal and pediatric EEG, undertook the qualitative reporting. They were blind to MBP and cranial ultrasound scan findings. The EEG was displayed on a computer screen as four bipolar channels (Fp1 – C3, C3 – O1, Fp2 – C4, and C4 – O2) using a high-pass filter of 0.3 Hz, a low-pass filter of 70 Hz, a notch filter of 50 Hz, a base time of 10 s, and a gain of 100 μ V. The EEG recordings were analyzed for degree of discontinuity, amplitude, presence of abnormal transients, and synchrony.

Quantitative analysis of EEG was by a) spectral analysis and b) manual calculation of the interburst interval. To calculate the interburst intervals, gross artifacts (activity with no identifiable normal EEG activity) were identified by eye and removed. The interburst interval was defined as a period between electrical bursts during which activities were lower than 30 μ V in all leads and calculated manually (19). The 90th centile (P_{90}) for interburst interval was then calculated for the first 60 min of artifact-free recording for each baby. The normal range (10th to 90th centile) of P_{90} interburst interval in infants between 24 and 30 wk gestation is 7–25 s during the first 2 d after birth (20).

Spectral analysis using Fast Fourier transformation was performed using the manufacturer's software (Micromed) and is described in detail elsewhere (20). The 75 min of EEG recorded from six monopolar channels (Fp1, Fp2, C3, C4, O1, and O2) was subjected to spectral analysis. The spectrum was subdivided into delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz), and beta (13–30 Hz) frequency bands. The absolute power of a frequency band was defined as the integral of the power values within the frequency range and expressed as μ V². The relative power (RP) of a frequency band was defined as the ratio of the absolute power of that frequency band to the total power of the EEG signal and expressed as a percentage. The absolute and relative powers of each frequency band were calculated for every 10-s epoch. Gross artifacts (activity with no identifiable normal EEG activity) were identified by eye and removed manually in 10-s epochs. The first 60 min of artifact-free EEG was then used to calculate the median absolute and the median relative powers of each frequency band. For very low birth weight infants, the relative power of the delta frequency band is the most discriminatory and repeatable (coefficient of repeatability of 8%) spectral measurement (20). The normal range (10th to 90th centile) of the relative power of the delta frequency band in infants between 24 and 30 wk gestation is 62–82% during the first 2 d after birth (20).

CFOE. CFOE measurements were made during each EEG recording. Cerebral venous oxygen saturation (CSvO₂) was measured by partial jugular venous occlusion and the Hamamatsu NIRO 500 (Hamamatsu Corp., Bridgewater, NJ) with a pulse oximeter in beat-to-beat mode (Datex-Ohmeda, Madison, WI) (14,15). The mean of five partial jugular venous occlusions made over a 5–10 min period was taken (15). Cerebral arterial oxygen saturation (CSaO₂) was assumed to be equal to peripheral arterial oxygen saturation. CFOE was calculated using the formula: CFOE = CSaO₂ – CSvO₂/CSaO₂ (15). The mean $\pm$ SD of CFOE in

clinically stable infants between 27 and 31 wk gestation was 0.29 ± 0.06 (14). The coefficient of repeatability of CFOE measurements was 0.05.

PBF. Measurements of PBF were made during each EEG recording, using a method that has been described in detail elsewhere (21). The Hamamatsu NIRO 500 and a pulse oximeter in beat-to-beat mode (Datex-Ohmeda) were used to measure total tissue Hb concentration (Δ HbT) in the forearm. Hb flow was then calculated by the slope of a line through the Δ HbT values during the first 2 s of occlusion using a least squares method. PBF (mL/100 mL/min) was calculated by dividing Hb flow by venous Hb concentration. The normal range (minimum–maximum) of PBF in infants between 28 and 32 wk gestation is 6.1–13.4 mL/100 mL/min (21).

Clinical data. Demographic details and the use of inotropes and sedatives were recorded. MBP measurements were recorded from an indwelling arterial catheter every 4 min during each EEG recording. The mean of these measurements was used for analysis. Arterial blood gas measurement was performed midway through the EEG recording. Histologic evidence of chorioamnionitis (defined as presence of polymorphonuclear leukocytes in the chorion and amnion) was also recorded.

Clinical management. MBP monitoring was done by Nova-dome pressure transducer (Micromed) attached to the indwelling arterial catheter. The attending physician, who was not a member of the research group, determined the management of hypotension. It was generally aimed to keep the MBP above the 10th centile for the birth weight (22). This was achieved by volume expansion using blood transfusion or normal saline or inotropes such as dopamine, dobutamine, or hydrocortisone used singly or in combination. All infants who received morphine were prescribed a dose of 20 μ g/kg/h.

Follow-up measurements. Cranial ultrasound scans were performed on all infants on the first 4 d, after birth and repeated at regular fortnightly intervals before discharge.

Statistical analysis. The purpose of this study was to investigate the cerebrovascular effects of hypotension. This invariably occurred during the first 48 h. Therefore, the measurements of PBF, CFOE and EEG made at the lowest MBP during this period [within a preset range of arterial carbon dioxide partial pressure between 35 and 50 mm Hg (20)] were selected for each infant for further analysis.

The EEG was analyzed in relation to MBP. For analysis of the quantitative EEG results, univariate analysis was performed with the relative power of each frequency band and interburst interval duration as the dependent variables with MBP as the independent variable. For significant univariate relationships, a stepwise regression using gestation, MBP, dopamine infusion rate (μ g/kg/h) at the time of recording, pH, and Pco₂ as predictor variables was performed to rule out any confounding factors.

Curve fitting was done where appropriate using the F-test provided by SPSS version 10 (SPSS Inc., Chicago, IL). Linear, quadratic, and cubic regression curves were fitted. F-ratios were calculated to determine which model provided the best fit.

Regression curves with 95% confidence intervals were plotted on graphs that also included the normal ranges for the relative power of delta band and for the P_{90} interburst interval. The highest MBP at which the 95% confidence intervals of the regression curve intercepted the normal range for the relative power of delta band or the P_{90} interburst interval was chosen as the critical point of MBP at which EEG became abnormal.

The demography and condition of the infants with qualitatively normal and abnormal EEG records were compared using the Mann-Whitney *U* test (Table 1).

RESULTS

The demography and condition of infants at the time of EEG recordings are described in Table 1. Thirty-four infants were ventilated at the time of measurement. All infants had normal blood glucose concentrations at the time of recording. The daily measurements of peripheral blood flow, CFOE, MBP, and EEG have been summarized in Table 2.

The lowest MBP during the first 48 h for each baby was related to the corresponding EEG, CFOE, and PBF measurements.

The EEG was recorded in all cases. Using qualitative analysis, 31 EEG records were normal: all four abnormal EEG were recorded at MBP levels below 23 mm Hg. The abnormal qualitative reports and their corresponding levels of MBP are described in Table 3. Examples of EEG traces from three

Table 1. Demography and condition of infants in the study group and the four infants with abnormal EEG records

	All infants (n = 35)	Normal EEG (n = 31)	Abnormal EEG (n = 4)	p Value
Gestation (wk)	27 (23–30)	27 (23–30)	27 (24–28)	0.979
Birth weight (g)	935 (470–1495)	935 (470–1495)	857 (534–1160)	0.604
IUGR (BW <10th centile)	9	8	1	0.973
No. of males	15	13	2	0.762
Chorioamnionitis (no. of infants)	6 (n = 25)	6 (n = 22)	0 (n = 3)	0.309
Apgar at 5 min	8 (4–10)	8 (4–10)	8 (5–10)	0.674
Cord base deficit (mmol/L)	3.5 (–1.3 to 9.6)	3.5 (–1.3 to 9.6)	3.3 (1–5.9)	0.938
Age at the time of recording (h)	14 (5–48)	14 (5–48)	13 (7–14)	0.467
Morphine infusion (no. of infants)	28	24	4	0.295
Arterial Po ₂ (mm Hg)	59 (35–143)	59 (35–143)	71 (40–87)	0.534
Arterial pH	7.33 (7.23–7.45)	7.33 (7.27–7.45)	7.31 (7.23–7.37)	0.251
Arterial Pco ₂ (mm Hg)	42 (36–49)	42 (36–49)	43 (38–46)	0.776
CRIB score	3 (0–17)	3 (0–17)	8 (2–14)	0.177
MBP (mm Hg)	32 (16–46)	33 (20–46)	22 (16–22)	<0.001

Values are median (range), unless stated otherwise. *p* Values were obtained by comparing infants with normal and abnormal EEG using Mann-Whitney *U* test.

Table 2. Changes in MBP, CFOE, PBF, and relative power of EEG delta frequency band and EEG interburst interval during the first 4 d after birth

	Day 1	Day 2	Day 3	Day 4
MBP (mm Hg)	32 (16–46) [35]	37 (20–51) [35]	41 (27–56) [24]	42 (27–57) [16]
CFOE	0.33 (0.25–0.43) [21]	0.28 (0.14–0.49) [23]	0.3 (0.2–0.49) [19]	0.3 (0.2–0.35) [14]
PBF (mL/100 mL/min)	4.2 (2.2–12.8) [14]	6.1 (2.7–25.3) [16]	6.4 (1.4–19.2) [14]	6.5 (3.1–23.1) [9]
RP delta (%)	69 (20–80) [35]	73 (60–87) [35]	78 (66–88) [35]	78 (58–89) [27]
P90 IBI (s)	15 (7–53) [35]	12 (6–31) [35]	10 (5–16) [35]	9 (3–16) [27]

Values are median (range) [no.].

Table 3. Qualitative EEG reports and cranial ultrasound scan findings in the four infants with abnormal EEG

Case no.	Age (h)	MBP (mm Hg)	RP delta (%)	P90 IBI (s)	EEG report	CFOE	Cranial ultrasound
1	13	16	20	33	↓ Amplitude, ↑ interburst interval		Subependymal bleed
	35	30	73	15	Normal		Subependymal bleed
	60	32	79	13	Normal		Subependymal bleed
	86	41	88	6	Normal		Subependymal bleed
2	13	22	75	9	Slowing +, ↓ amplitude, seizure +		Normal
	34	34	64	26	↑ Interburst interval	0.18	Subependymal bleed
	58	44	75	12	↑ Interburst interval	0.22	IVH with parenchymal bleed
	73	57	70	15	↑ Interburst interval	0.26	IVH with parenchymal bleed
3	7	22	56	51	↑ Interburst interval	0.31	Normal
	24	38	80	28	↑ Interburst interval	0.18	Normal
	48	42	71	11	Normal	0.32	Normal
4	14	22	59	29	↓ Amplitude, ↑ interburst interval		Normal
	38	26	71	15	↓ Amplitude, improved		Subependymal bleed
	52		87	9	↓ Amplitude, improved		Subependymal bleed
	74		86	9	↓ Amplitude, near normal		Subependymal bleed

IVH, intraventricular hemorrhage.

different infants at different levels of MBP are shown in Figure 1. Only MBP was significantly different between the two groups (Table 1). Only one normal EEG was recorded at MBP levels below 23 mm Hg and clinical details of this infant (Case No. 5) are described below.

Exploration of the relationship between the relative power of each EEG frequency band and MBP showed that only the relative power of the delta frequency band had a significant relationship with MBP. The best-fit curve was a cubic regression curve (Fig. 2). The F-ratio comparing the linear model with the quadratic model was 14.5 ($p < 0.001$), and the F-ratio comparing the quadratic model with the cubic model was 14 ($p < 0.001$). The highest point of intercept between the 95% confidence intervals of the cubic regression curve and the lower

limit of the normal range of the relative power of the delta band was at 23 mm Hg (Fig. 2). Three infants had abnormally low (<10th centile) relative power of the delta band, resulting in leverage of the regression curve by these three points. Stepwise regression confirmed the relationship between MBP and the relative power of the delta frequency band.

Univariate analysis between the P₉₀ interburst interval and MBP was statistically significant (Pearson's correlation: -0.501 ; $p = 0.002$). The curve of best fit was a linear regression model (Fig. 3). The highest point of intercept between 95% confidence intervals of the linear regression curve and the upper limit of the normal range of the interburst interval was at 23 mm Hg (Fig. 3). Only three infants had abnormally prolonged interburst intervals, resulting in lever-

Figure 1. EEG traces from three infants at different levels of MBP. (A) Trace 1: gestation: 24 wk; age: 6 h; MBP: 26 mm Hg. (B) Trace 2: gestation: 24 wk; age: 14 h; MBP: 22 mm Hg. (C) Trace 3: gestation: 27 wk; age: 13 h; MBP: 16 mm Hg.

Figure 2. Relationship between MBP and the relative power (RP) of the delta band, showing line of best fit with 95% confidence interval ($n = 35$; $R_{sq} = 0.627$; $p < 0.001$). The horizontal dotted lines indicate normal range of the relative power of the delta band (10th–90th centile). Vertical dotted line indicates the point of intercept. Abnormal EEG records are circled. Square indicates an infant where the CFOE was abnormal (0.44).

age of the regression line by these three points. Stepwise regression confirmed the relationship between MBP and interburst interval.

CFOE was measured in 19 infants. Of the four infants with abnormal EEG, only one infant had CFOE (value: 0.31) measured. Loss of CFOE measurements was due to equipment failure and difficulty in gaining access to patients with severe hypotension in whom clinical management took priority. Eighteen infants had normal CFOE (median, 0.31; range, 0.25–0.40). Only one infant had an abnormally high CFOE (0.44). This infant (case no. 5) is described in detail below. CFOE did not show a statistically significant relationship with MBP (Spearman's ρ : -0.31 , $p = 0.19$, $n = 19$).

PBF was measured in 14 infants (median, 5.2 mL/100 mL/min; range, 2.2–12.8). None of the infants with abnormal EEG and MBP below 23 mm Hg had PBF measurements. The

Figure 3. Relationship between MBP and the 90th percentile of interburst interval, showing line of best fit with 95% confidence interval ($n = 35$; $R_{sq} = 0.251$; $p = 0.002$). The horizontal dotted lines indicate normal range of the P₉₀ interburst interval (10th–90th centile). Vertical dotted line indicates the point of intercept. Circles indicate abnormal EEG records. Square indicates a baby where the CFOE was abnormal (0.44).

losses of measurements were again due to equipment failure and difficulty in gaining access to patients with severe hypotension. PBF decreased with decrease in MBP (Spearman's ρ : 0.56 , $p = 0.036$, $n = 14$) (Fig. 4) and was abnormally low at MBP levels below 33 mm Hg. Low levels of PBF were associated with normal CFOE in all infants except for the one infant (case no. 5) described in more detail below (Fig. 5).

One female infant (case no. 5) of 26 wk gestation and birth weight 612 g (below 10th centile) had a normal EEG at a MBP level of 20 mm Hg. Her PBF was abnormally low (2.68 mL/100 mL/min) and the CFOE (0.44) was abnormally high (Fig. 4).

Figure 4. Relationship between PBF and MBP ($n = 14$; $\rho = 0.56$; $p = 0.036$). Dotted lines show normal ranges of peripheral blood flow. Straight lines indicate regression line with 95% confidence intervals. Square indicates a baby where the CFOE was abnormal (0.44).

Figure 5. Relationship between MBP, PBF, and CFOE. Numbers next to points indicate MBP (mm Hg). Infants with low PBF [<6.1 mL/100 mL/min (25)] mostly have normal CFOE at MBP range of 23–33 mm Hg (quadrant B). One infant (case no. 5) with MBP of 20 mm Hg and low PBF had high CFOE (quadrant A).

Sixteen infants received dopamine infusions [$20 \mu\text{g/kg/min}$ ($n = 4$), $15 \mu\text{g/kg/min}$ ($n = 1$), $10 \mu\text{g/kg/min}$ ($n = 8$), $5 \mu\text{g/kg/min}$ ($n = 3$)]. Of these 16 infants, two infants were also treated with dobutamine and one received dobutamine and hydrocortisone. Use of dopamine did not affect any of the outcome variables and was consistently excluded by the multiple regression analyses.

None of the cranial ultrasound scans on any of the 35 infants showed persistent echogenicity or cystic periventricular leukomalacia. The cranial ultrasound scans of the four infants with abnormal EEG records are described in Table 2. One infant with an abnormal EEG (case no. 2 in Table 2) showed gross ventricular dilatation on later cranial ultrasound scans.

Of the remaining 31 infants with normal EEG, 26 infants had normal or subependymal hemorrhages on later cranial ultrasound scans. Four infants developed intraventricular hemorrhages and one other case developed bilateral intraventricular hemorrhage with parenchymal extension during the third and fourth day after birth. Later ultrasound scans showed that two of these infants developed mild ventricular dilatation (rate of increase in head circumference measurements was along the centiles for the normal population) and hydrocephalus in one other case.

EEG was abnormal in five infants on d 3 and 4. The five EEG abnormalities were related to development of intraventricular hemorrhage ($n = 4$) and hypercarbia ($n = 1$) and not to MBP.

DISCUSSION

There is variation in the clinical management of hypotension in very low birth weight infants. The recommendation of the British Association of Perinatal Medicine that MBP levels in mm Hg should not fall below the gestational age in weeks is a consensus opinion, which is unsupported by scientific

evidence (23). The other common practice of maintaining MBP levels above 30 mm Hg using volume expansion and inotropes is based on statistical associations between MBP levels below 30 mm Hg and periventricular hemorrhage, cerebral ischemic lesions, and death (1–3). A third approach is to maintain the MBP above the 10th centile of a normal range based on birth weight or gestation and postnatal age (3,22).

In this study, the level of MBP below which cerebral electrical activity became abnormal was found to be 23 mm Hg. At MBP levels between 23 and 33 mm Hg, PBF was abnormally low while EEG patterns and CFOE remained normal. The EEG abnormalities in most (three out of four) of these babies whose MBP was below 23 mm Hg during the first 48 h after birth were transient and none developed cystic periventricular leukomalacia. Even at a MBP below 23 mm Hg, one infant maintained a normal EEG, but CFOE was increased, implying decreased cerebral oxygen delivery. The increases in MBP (22) and relative power of delta band (20) and decreases in CFOE (24) and P_{90} interburst interval (24) that are reported in Table 3 followed a similar pattern to that reported by other studies.

The observation that normal cerebral electrical activity is maintained at MBP levels below 30 mm Hg is consistent with other studies. Tysczuk *et al.* (8) showed that infants between 24 and 34 wk gestation undergoing neonatal intensive care were able to maintain normal cerebral blood flow at a MBP range of 23.7–39.3 mm Hg. Munro *et al.* (25) showed that in 12 hypotensive (MBP: 25 ± 1 mm Hg) extremely low birth weight infants also maintained normal cerebral blood flow (14 ± 1 mL/100 g/min). Pryds and Greisen (26) recorded single-flash visual evoked potentials in 32 preterm infants (mean gestational age: 29 wk) during the first day of life. Amplitude and latency of the signal were unchanged during episodes of low cerebral blood flow and correspondingly low cerebral oxygen delivery and severe arterial hypotension (MBP: 10 mm Hg), provided that the arterial oxygen tension was greater than 5 kPa (26).

In this study, the EEG did not become normal at the same time as the recovery of MBP. The cellular and biochemical events that underlie the recovery of EEG following anoxia are not well understood. Restoration of circulation and substrate supply are necessary for repletion of cellular ATP stores and return to normal levels of pH and ion concentrations. Mac-Millan (27) reported that EEG recovered in parallel with the recovery of Na-K-ATPase activity over 72 h after global ischemia in rat forebrain. Thus, although metabolic recovery is necessary for electrophysiological recovery, the two are not necessarily contemporaneous and there are numerous experimental models in which the EEG recovers more slowly than cerebral energy metabolism, as reflected by brain oxygen consumption, high-energy phosphate content, and intracellular pH (28).

As observed in a previous study, PBF diminished with decreasing systemic MBP (16). Abnormally low levels of PBF were measured at MBP levels between 23 and 33 mm Hg, although simultaneous measurements of CFOE were normal. Two inferences can be drawn from these observations. First, that peripheral perfusion diminishes at MBP levels higher than

the critical level of MBP below which cerebral electrical activity becomes abnormal. Second, that in these infants cerebral oxygen delivery is maintained at MBP levels between 23 and 33 mm Hg, probably by diminished peripheral perfusion.

The critical level of MBP below which permanent brain damage occurs is of interest to clinicians. Watanabe *et al.* (29) showed that 95% of infants with normal EEG patterns had normal neurodevelopmental outcome. The remaining 5% of infants were able to walk and exhibited only minimal signs of cerebral palsy (29). It may therefore be reasonable to assume that preservation of normal EEG between MBP levels of 23 and 30 mm Hg indicates normal cerebral perfusion. However, the prolonged periods of electrical discontinuity that were noted in relation to MBP levels below 23 mm Hg have been associated with adverse neurologic outcome (12). Nevertheless, the EEG abnormalities noted in this study do not necessarily represent evidence of irreversible brain damage because the EEG abnormalities recovered and became normal by the fourth day in most infants. In the only infant that the EEG abnormality did not recover (case no. 2 in Table 2), there was an intraventricular hemorrhage and the persistent EEG abnormality may have been a consequence of the extensive nature of this hemorrhage. It should be noted that none of the infants studied developed cystic periventricular leukomalacia.

There are two methodological concerns with this study. First, the relationship between low MBP and abnormal cerebral electrical activity remains an association. However, several other variables (Table 1) that may cause EEG abnormalities were considered and hypotension remained the single most prominent cause. Second, because the management of hypotension was left to the clinical team, only five infants with seriously low MBP below 23 mm Hg could be studied. The results of the present study cannot therefore be interpreted as sufficient support for a recommendation that MBP levels between 23 and 30 mm Hg do not require treatment. However, the results of this study generate hypotheses that need to be further addressed. They raise the possibility that these immature infants may maintain cerebral perfusion at lower levels of systemic blood pressure than has hitherto generally been thought to be the case.

In only one infant was there a lack of agreement between the qualitative EEG reporting and quantitative methods: the EEG recording was reported by the neurologist to show low amplitude slow wave activity (Table 2, case no. 2, d 1), but the quantitative analysis was normal. This lack of agreement was probably due to the poor sensitivity of spectral analysis in detecting this moderately abnormal EEG: a combination of slowing of the EEG waveforms (which would increase the relative power of the delta band) and a decrease in their amplitude (which would decrease the relative power of the delta band) may have resulted in little or no net change in the relative power of delta band.

In conclusion, cerebral electrical activity remained normal at MBP levels between 23 and 30 mm Hg and was found to be abnormal at MBP levels below 23 mm Hg. Cerebral electrical activity and CFOE were maintained at lower MBP levels than currently accepted by most clinicians.

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