ORIGINAL ARTICLES

Cerebral autoregulation of preterm neonates – a non-linear control system?

B Zernikow, E Michel, G Kohlmann, J Steck, R M Schmitt, G Jorch

Abstract

The low frequency cerebral blood flow velocity (CBFV) oscillations in neonates are commonly attributed to an underdamped immature linear type cerebral autoregulation, and the 'instability' is regarded as causative for peri-intraventricular haemorrhage/periventricular leukomalacia. In contrast, oscillations susceptible to frequency entrainment are a fundamental part of the *stable* function of non-linear control systems. To classify the autoregulation an observational study was done on the relationship between CBFV oscillations, heart rate variability, and artificial ventilation. In 10 preterm neonates (gestational age 26 to 35 weeks) we serially Doppler traced arterial CBFV continuously for 12 minutes between days 1 and 49 of life. The individual time series of CBFV and heart rate were subjected to spectral analysis. Forty six of 47 tracings showed significant low frequency CBFV oscillations. Low frequency heart rate oscillations were not a prerequisite thereof. All patients with <30% of total power in the low frequency band of CBFV oscillations were on the ventilator. Three of them demonstrated a shift of spectral power from low frequency to a frequency equal or harmonic to the ventilator rate indicating entrainment. The findings of CBFV oscillations combined with entrainment classify the autoregulation as a *non-linear* system. It is suggested that entrainment by periodic high amplitude stimuli might challenge the regulatory capacity to its limits thus increasing the risk for cerebral damage.

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In preterm infants, cyclical variations of cerebral blood flow velocity (CBFV), assessed by Doppler sonography, and fluctuations of the cerebral blood volume detected by near infrared spectroscopy have a frequency of 1 to 5/min (0.02 to 0.08 Hz).^{1–4} This slow variability pattern was attributed to the instability of a presumably underdamped immature cerebral autoregulation system.⁴ No correlations were found between heart rate or blood pressure and CBFV oscillations if these parameters were obtained simultaneously.¹

Hence, mainly local factors such as rhythmical changes in cerebral vascular tone were assumed to cause the observed effect. According to Coughtrey *et al*, CBFV oscillations are negatively correlated with the postnatal age.³ Only 25% of all recordings obtained in children older than 37 weeks' gestation showed this phenomenon, which was totally absent during continuous cerebral Doppler measurements in adults.^{5,6} Positive pressure ventilation has been described as having a major impact on cerebral blood flow.^{7–9} In newborns, Cowan observed CBFV variations in phase with intermittent positive pressure ventilation (IPPV).¹⁰ These were strongly correlated with the application of a high positive inspiratory pressure (PIP) and could be diminished by PIP reduction.¹⁰ The importance of beat to beat variability in CBFV of ventilated preterms with respiratory distress syndrome in respect to the development of peri-intraventricular haemorrhage/periventricular leukomalacia (PIVH/PVL) remains unclear.^{7,9,11–13}

In control theory, control systems are subdivided into linear and non-linear types. In biology, most known control systems are non-linear. The thermal and blood pressure control systems are well characterised in the human. Both systems show endogenous oscillations that can be synchronised to rhythmical external stimuli.^{14,15} This process qualifies non-linear systems and is called selective *frequency entrainment*.¹⁶ Entrainment occurs more easily the smaller the difference of the original oscillatory frequency and the stimulatory frequency, and its occurrence is also dependent on the amplitude of the stimulating signal. Thus, entrainment is a function of both frequency and amplitude of the stimulus.¹⁵ Although the ability for selective frequency entrainment represents an obligatory characteristic of a non-linear control system, the entrained system can express stable as well as unstable dynamic behaviour depending on its individual composition.

In general, oscillations of non-linear systems do not reflect underdamping of the system as they do in linear systems, and thus by no means are an *a priori* sign of instability. Instead, they are a fundamental part of the control system comparable with the on-off periodicity observed in a properly working home refrigerator.

University Children's
Hospital, Muenster,
Germany
B Zernikow
E Michel
G Jorch

IBMT, Fraunhofer
Institut, St Ingbert,
Germany
G Kohlmann
J Steck
R M Schmitt

Correspondence to:
Dr Boris Zernikow,
University Children's
Hospital, Department of
Haematology/Oncology,
'Innere Oben',
Adenauerallee 119, 53113
Bonn, Germany.

(Reprint requests to:
Professor G Jorch, University
Children's Hospital, W19B,
Albert-Schweitzer-Str 33,
48149 Muenster, Germany.)

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Table 1 Detailed clinical data of the patients

Patient No	Sex	Gestational age (weeks)	Mode of delivery	Apgar score (1/5/10 min)	Birth weight (g)	Pathology*
1	M	29	Caesarean section	4/8/8	940	RDS grade III, PIVH grade I (left)/grade 2 (right), PVL, posthaemorrhagic hydrocephalus, NEC
2	M	30	Caesarean section	9/9/9	1160	RDS grades I–II, PIVH grade 2
3	F	26	Vaginally	6/8/9	940	RDS grade I
4	F	30	Caesarean section	8/8/7	1250	RDS grade III, PIVH grade 2, congenital AV block degree III
5	F	27	Vaginally	9/10/10	1040	RDS grade I
6	F	35	Caesarean section	8/10/10	1900	Gastroschisis after surgery
7	M	29	Caesarean section	5/7/8	970	RDS grades III–IV, PIVH grade 3, posthaemorrhagic hydrocephalus
8	M	28	Caesarean section	4/8/8	880	RDS grade III
9	F	29	Caesarean section	5/8/10	990	RDS grades II–III, PIVH grades 1–2, posthaemorrhagic hydrocephalus, 3rd triplet
10	F	29	Caesarean section	3/5/7	1140	RDS grade II, 2nd twin

*AV=atrioventricular; NEC=necrotising enterocolitis; PIVH=peri-intraventricular haemorrhage; PVL=periventricular leukomalacia; RDS=respiratory distress syndrome.

Continuous Doppler tracings of CBFV in the internal carotid artery of preterm neonates and computerised processing of data were used to try and answer the following questions: (1) Is the cerebral autoregulation a non-linear control system? (2) What are the interdependencies between ventilation and the control systems of cerebral blood flow and heart rate variability? (3) What is the physiological and clinical significance of the cycling phenomenon?

Patients and methods

Data were collected on a group of 10 preterm neonates admitted to the neonatal intensive care unit of the University Children's Hospital Muenster between April and June 1992. Recordings were obtained in the clinical setting.

We have chosen the design of a longitudinal study. No attempt was made to shield the study patients from external stimuli like IPPV as alterations in external disturbance followed by reactive changes in CBFV oscillations should yield information about regulatory processes and their maturational state in preterm neonates. A certain lack of homogeneity of the patient group in regard to PIVH/PVL and other conditions was accepted, and even a preterm with a congenital third degree atrioventricular heart block of unknown origin was included in order to study the relationship of heart rate variability and CBFV oscillations. Detailed clinical data of each child are listed in table 1. The study was approved by the local neonatal intensive care unit ethics committee.

CEREBRAL BLOOD FLOW MEASUREMENTS

Using the anterior fontanelle as an acoustic window, we insonated one internal carotid artery with a miniaturised 5 MHz pulsed Duplex Doppler probe (size 13×9×20 mm³).¹⁷ The sample volume was placed at the basis of the clivus to give an angle of insonation

of less than 5 degrees. The sample volume was set to 5 mm and a 100 Hz high pass filter was used to reject the components of the Doppler signal due to oscillations of the arterial vessel wall. In fixing the probe we used a recently developed vacuum rubber hood.¹⁸ After fixation, under direct visual and acoustic control, the depth of the sample volume could be readjusted both mechanically by usage of the hood's special properties and electronically. Attachment and positioning of the probe typically took two to three minutes. The probe was connected to a Hewlett Packard HP SONOS 500 device by a super flexible cable. The SONOS 500 was interfaced to an AT compatible personal computer.¹⁷ Custom software derived the maximum frequency envelope from the spectra online. Data for systolic, mean, and diastolic velocity as well as heart rate were calculated beat by beat and electronically stored. The Doppler unit was mounted on a trolley and could be wheeled to the cot side.

PROTOCOL

Recordings of CBFV oscillations were obtained in the 10 infants when they had stabilised for the first time (typically day 1 or 2 of life) and at about weekly intervals thereafter until discharge (table 2). We obtained a total of 47 recordings. There were one to 10 measurements on each infant. Each recording lasted 12 to 15 minutes. As each recording was analysed by fast Fourier transformation as an entire period later on, and the sleep state changed several times during the tracing, data on behavioural states were excluded from evaluation.

The quality of the Doppler signal was controlled acoustically during the whole measurement period and the recording was terminated in case of deposition of the sample volume indicated by a sudden change in Doppler sound. Only 12 to 15 minute segments free of artifacts were used for analysis. Before each measurement each patient had a complete cerebral ultrasound scan for hydrocephalus, PIVH, and PVL done by a skilled operator. Standard views as well as the total Doppler measurements were videotaped for later assessment if necessary. There was no attempt made to obtain systematically continuous blood pressure measurements as only a minority of the patients had indwelling arterial catheters. In the ventilated infants, transcutaneously monitored blood gases (oxygen tension (PaO₂), carbon dioxide tension (PaCO₂) by TCM2 (Radiometer), and oxygen saturation by oximeter (Radiometer)) were in the normal range. All measurements were made under the usual clinical conditions with ventilator settings prescribed by independent clinicians (table 2).

ANALYSIS AND STATISTICS

Two types of data have been studied: heart rate variability and CBFV oscillations. The instantaneous heart rate and corresponding values

Table 2 Details of recordings of CBFV oscillations

Day of life	Ventilator rate (l/min)	PIP/PEEP (cm H ₂ O)	Low frequency		Drugs
			V _S (%)*	HR (%)†	
Patient 1					
1	43	19/2.5	47.0‡	4.4	—
3	12	14/2.5	29.4‡	19.7	Phenobarbitone, pethidine, diazepam
6	—	—/3	28.6‡	4.4	Phenobarbitone
8	—	—/3	35.0‡	17.7	Phenobarbitone
10	—	—/3	59.9‡	20.8	—
17	—	—/3	68.7‡	17.0	Phenobarbitone, dopamine
24	—	—/—	43.5‡	62.7‡	Phenobarbitone
36	—	—/—	75.9‡	34.6‡	Phenobarbitone
43	—	—/—	45.4‡	32.7‡	Phenobarbitone
49	—	—/—	57.2‡	87.4‡	Phenobarbitone
Patient 2					
3	8	14/2	23.6‡	25.9‡	Dopamine, dobutamine
5	—	—/3	30.7‡	27.5‡	—
8	—	—/3	35.2‡	23.9‡	—
13	—	—/—	52.2‡	59.5‡	—
20	—	—/—	42.7‡	63.5‡	—
31	—	—/—	55.3‡	77.6‡	—
34	—	—/—	73.4‡	65.9‡	—
42	—	—/—	55.2‡	42.0‡	—
Patient 3					
6	27	21/3	54.4‡	19.5	Phenobarbitone
8	15	20/3	43.5‡	62.7‡	Phenobarbitone
13	33	20/2	78.9‡	22.1	—
15	20	26/3	78.6‡	13.9	Dopamine, chloral hydrate
20	16	20/2	87.7‡	68.4‡	—
24	—	—/—	80.4‡	61.4‡	—
34	—	—/—	73.6‡	58.6‡	—
40	—	—/—	81.0‡	75.0‡	—
Patient 4					
1	45	22/3	64.4‡	11.3	Phenobarbitone, pethidine, dopamine, dobutamine, pancuronium
3	35	17/3	39.7‡	8.0	Phenobarbitone, dopamine, dobutamine
7	35	15/3	46.3‡	31.0‡	Phenobarbitone
8	25	13/3	26.4‡	15.7	Phenobarbitone
14	35	15/3	63.4‡	16.4	Phenobarbitone
21	—	—/3	47.5‡	12.2	Phenobarbitone
29	—	—/3	39.9	44.4‡	Phenobarbitone
38	—	—/—	58.1‡	34.9‡	—
Patient 5					
2	—	—/3	76.4‡	35.8‡	—
4	—	—/3	50.6‡	34.0‡	—
8	—	—/3	85.6‡	47.9‡	—
15	—	—/—	75.2‡	68.4‡	—
22	—	—/—	64.3‡	27.7‡	—
32	—	—/—	76.5‡	54.6‡	—
40	—	—/—	71.6‡	49.4‡	—
Patient 6					
1	28	22/3	33.8‡	34.4‡	—
Patient 7					
29	53	24/4	20.7	34.4‡	—
42	—	—/3	34.2‡	4.1	—
Patient 8					
11	—	—/3	70.6‡	26.1‡	—
73	—	—/—	58.5‡	23.3	—
Patient 9					
2	24	17/4	29.1‡	21.7‡	Phenobarbitone, dopamine, dobutamine
Patient 10					
16	—	—/—	33.5‡	18.2	Theophylline

*Low frequency VS=proportion of total spectral power in low frequency band of CBFV oscillations.

†Low frequency HR=proportion of total spectral power in the low frequency band of heart rate variability.

‡Significantly raised, $p < 0.001$.

Bold=corresponding figure presented; bold/italic=CBFV oscillation entrainment.

for systolic/diastolic mean velocities were individually averaged over each one second period to give an equidistant time series (one value every one second). The resulting time series in heart rate and Doppler velocity were subjected to spectral analysis using the fast Fourier transformation to determine the spectral power distribution of heart rate variability and CBFV oscillations in various frequency bands (Statgraphics, STSC Inc). The frequency band between 0.0 and 0.02 Hz was truncated according to Baldzer *et al* as both a trend as well as slight instabilities in recording quality could increase the spectral power of this region without evidence of any well defined peak.¹⁹ The spectral power estimates of heart rate variability and CBFV oscillations were calculated as cumulated spectral ordinates for a low

frequency band from 0.02 to 0.08 Hz according to prior investigations^{1,3} and for a band greater 0.08 Hz up to the Nyquist limit of 0.5 Hz.¹⁹ The one sample z test²⁰ was used to decide whether the local power content was disproportionately increased. (The more common χ^2 test would have been an alternative choice. For the comparison of single proportions, Shott recommends the one sample z test.²⁰)

We performed a cross correlation between heart rate and systolic CBFV on all measurements.

Results

In all but one recording, systolic CBFV oscillations showed a significantly increased spectral power content in the low frequency region relative to the 12.5% of total spectral power expected from a flat spectrum ($p < 0.0001$, one sample z test). Expressed as percentage of the total power spectrum, the values are given in table 2.

A typical plot of systolic velocity and diastolic velocity is shown in fig 1. The synchronous slow variation in the two graphs with a periodicity of about 20 seconds corresponding to a frequency of 0.05 Hz is obvious. The Doppler measurement of diastolic CBFV is more susceptible to disturbances and errors than that of the systolic CBFV.^{1,21} Although qualitatively the same results were obtained for systolic CBFV as for diastolic CBFV ($p < 0.0006$, one sample z test), we will focus on systolic CBFV in this study.

In each of three infants once a distinct CBFV oscillation power spectrum was obtained that indicated the presence of entrainment by respiration. As shown in table 2, these preterm neonates belonged to the group of infants that were intubated and artificially ventilated with ventilator rates of 25, 12, and 24/min and corresponding pressures of PIP/positive end expiratory pressure (PEEP) of 13/3, 14/2.5, and 17/4 cm H₂O.

Figure 2 illustrates these findings in respect to patient 4, the newborn with third degree atrioventricular block of unknown origin. On the first day of life, the patient required assisted ventilation at a rate of 45/min (pressure 22/3 cm H₂O). Although heart rate modulations in the low frequency range were absent (11.3% of total power, not significant by one sample z test), she expressed low frequency oscillations in CBFV (64.4% of total power, fig 2A, B). On day 8 the ventilator settings were changed to a rate closer to the typical spontaneous frequency of CBFV oscillations of 0.02 to 0.08 Hz, and as figs 2C and D depict clearly, entrainment occurred. The spectral content of the low frequency region was diminished to 26.4% of total power and a new frequency appeared at 0.42 Hz identical to the ventilator rate of 25/min. Spectral analysis of the heart rate variability showed a relative low frequency power of only 15.7% and harmonic entrainment. During spontaneous breathing at day 38, the patient expressed high power in the low frequency region of CBFV oscillations

Figure 1 (A) Part of a simultaneous heart rate, systolic (V_s) and diastolic (V_d) CBFV tracing in a preterm neonate (patient 2, table 1) at day 34 of life. (B) and (C) are the power spectra of the CBFV oscillations shown in (A); the power is given in arbitrary units. The low frequency band between 0.02–0.08 Hz (hatched) contains 73.4% of total power for the systolic and 54.9% of total power for diastolic velocity.

(59.1%) and heart rate variability (34.9%) again (figs 2E and F).

Similar CBFV oscillation patterns were present in patient 1 (fig 3) who at day 2 of life suffered from PIVH (grade I left, II right) and later developed hydrocephalus and PVL. The ventilator rate of 43/min (pressure 19/2.5 cm H_2O) did not affect the CBFV oscillations at day 1 (fig 3A), whereas diminished power of the low frequency band of both CBFV oscillations and heart rate variability at day 3 may be attributed to a ventilator rate of 12/min (pressure 14/2.5 cm H_2O) and a connected process of entrainment. Two peaks in the power spectra within the same frequency range as the ventilator rate were observed (figs 3B and C). Finally, patient 9 (fig 4) appeared with identical patterns of entrainment behaviour at day 2 of life. In contrast to patient 1, only CBFV oscillations but not heart rate variability was entrained by mechanical ventilation with a frequency of 24/min (pressure 17/4 cm H_2O). This patient had no intracranial or other obvious pathology except prematurity and respiratory distress syndrome, and this is consistent with the premise that entrainment of CBFV oscillations by artificial ventilation cannot be accounted for by intracranial pathology.

In another five recordings, the amplitude of the stimulus was not high enough to entrain the CBFV oscillations completely and to diminish the low frequency region to values below the spectral power attributable to the stimulus. One of these five recordings is given as an example in fig 5. Patients 3 and 6 displayed power spectra of CBFV containing peaks at the ventilation frequency of 15, 16, 20, 27 (patient 3) and 28/min (patient 6).

In the five infants with more than seven consecutive CBFV measurements each, individual linear regression analyses of relative power of CBFV oscillations in the low frequency region with postnatal age showed no significant correlation coefficient for any baby ($p > 0.05$, data not shown).

Heart rate variability will be addressed in depth in a separate paper; suffice to say that a newborn with third degree congenital heart block five of eight heart rate variability power spectra showed less than 30% of total power in the low frequency band. Surprisingly, infants with an evenly distributed heart rate variability power spectrum without high power density in the low frequency region showed CBFV oscillations identical to infants with high spectral power content in this particular region. Cross correlation revealed no time correlation between heart rate variability and CBFV oscillations.

Discussion

OSCILLATIONS

Fast Fourier analysis of our recordings of CBFV showed significantly increased power content of the low frequency CBFV oscillations band in 46 of 47 tracings. This band is similar in shape and analogous to the low frequency of heart rate variability thought to be

due to the non-linear nature of the central thermoregulation in adults.²²

The presence of CBFV oscillations is compatible with our postulate of a non-linear central cerebral blood flow control system comparable with both the blood pressure control system and the central thermoregulation. Indeed the entire neural autoregulation system is assumed to consist of a central 'bang-bang' element that might be understood as a discrete element as well as the

sum of a number of operators in the central nervous system autonomous afference and efference fibres, smooth muscle receptors, and vascular (vessel wall) muscles.²³ It probably acts in parallel with the metabolic dependent autoregulation system, or it functions as a modulator thereof. The fact that recent reports give clear evidence that in adults there are the same CBFV oscillations that are independent of oscillations in systemic blood pressure²⁴ further supports the concept of

Figure 2 Power spectra of simultaneous heart rate and systolic (V_s) CBFV tracings in patient 4 at day 1, 8, and 38 of life. (A) and (B) day 1. Ventilation frequency 45/minute (0.75 Hz); no entrainment. (C) and (D) day 8. Ventilation frequency 25/minute (arrow indicates 0.42 Hz). The low frequency CBFV oscillations are entrained by the ventilator rate. Spectral analysis of heart rate variability is suggestive of harmonic entrainment. (E) and (F) day 38. The patient is breathing spontaneously; no entrainment.

Figure 3 Patient 1. Power spectra of systolic (Vs) CBFV oscillations at day 1 and day 3 and heart rate variability at day 3 of life. (A) Day 1. The low frequency region contains 47% of total power. The ventilation frequency of 43/minute (0.72 Hz) is above the Nyquist limit (0.5 Hz). If present, spectral analysis should alias it to 0.2 Hz. However, such a peak is missing, and the power of the low frequency region is undiminished; no entrainment. (B) Day 3. Both heart rate variability and (C) CBFV oscillations show strong spectral components at the ventilation frequency of 12/minute (arrow indicates 0.2 Hz). The 0.43 Hz peak in the systolic CBFV power spectrum is compatible with harmonic entrainment.

a non-linear cerebral blood flow control system. Improvements in technology might explain the discrepancy with former observations.^{5 6}

Which neuronal pathways could represent the afferences and efferences of a central feed-back loop? Several authors showed that there is a reflex arc of vasomotor neurons that originate in the ventral and posterior part of the hypothalamus, the stimulation of which leads to dilatation of cerebral vessels.²⁵ Moreover, cholinergic dilator receptors have been found on smooth muscles and intracerebral arteries, and they can be inhibited by atropine. Purves reported the finding of axoaxonal junctions between sympathetic and parasympathetic intravascular fibres/neurons and hypothesised that the release of noradrenaline from the adrenergic terminals could be reduced or abolished by acetylcholine acting through nicotinic receptors.²⁵ This neural composition seems to fit well into the postulated model of an antagonistic acting system capable of producing rhythmical oscillations in blood flow.

The existence of a central cerebral blood flow regulation element would also explain the appearance of CBFV oscillations within the same frequency band in different intracranial arteries.^{1 3 4}

ENTRAINMENT

Like Cowan and Thoresen¹⁰ we showed that CBFV oscillations are susceptible to entrainment (figs 2D, 3C, 4B). The CBFV oscillations are entrained by cerebral blood flow disturbances due to mechanical ventilation. As according to Minorsky entrainment is a typical characteristic of non-linear systems,¹⁶ its presence indicates that cerebral autoregulation is non-linear. It has been suggested that by varying the amplitude and frequency of the disturbing stimulus the properties of such a regulatory system and its characteristic range of entrainment can be investigated.²⁶ In our setting, we could vary neither the frequency nor the amplitude of disturbance delivered to the system by the mechanical ventilation, and entrainment was observed under common clinical conditions. As entrainment is a function of the amplitude of the disturbing stimulus that varies considerably depending on lung compliance and PIP used, the range of entrainment will probably differ slightly in different experimental settings. The range of entrainment of 12 to 25/min periodicity observed by us and reflected by the ventilator rate gives us an idea of the range to be expected.

The mechanism of beat to beat variability in CBFV during mechanical ventilation has been discussed in detail elsewhere.¹⁰ It has been stressed that both central blood pressure¹ as well as CBFV show remarkable variations with ventilator inflations, especially if the ventilated child's own breathing is unsynchronised to the machine.⁸ It is consistent with non-linear control theory that these rhythmical disturbances make the central cerebral blood flow control system counteract in order to maintain homeostasis in cerebral blood flow,

Figure 4 Power spectra of (A) heart rate variability and (B) systolic (V_s) CBFV oscillations of patient 9 at day 2 of life. The peak at 0.4 Hz indicates CBFV oscillation entrainment by the ventilatory stimulus.

and the system no longer expresses its original rhythmical oscillation but that of the stimulus.¹⁶ At least it might reduce the system's spontaneous periodicity as reflected by a diminished power content of the low frequency band.

OTHER SOURCES OF CBFV OSCILLATIONS

Changes in CBFV in preterm neonates have been explained by fluctuations in PaCO_2 and mean arterial blood pressure.^{21–27} To the best of our knowledge there are no studies on rhythmical changes in PaCO_2 within the low frequency band, but there might be a relationship between metabolic and neural regulation of cerebral blood flow. Purves noticed that the vascular response to carbon dioxide can be markedly influenced by stimulation of neural regions in the pontine area.²⁵ Hence, the neural part of the autoregulatory system could act as a modulator of the meta-

bolic regulatory system, and even fluctuations could better reflect modulated PaCO_2 reactivity than a direct impact on vessel smooth muscle cells.

As there is a striking parallelism between low frequency heart rate variability and CBFV oscillations, it is tempting to speculate that the latter is the intracranial observable sign of left ventricular output changes at a frequency of 0.02 to 0.08 Hz. Two arguments obviously contradict this explanation. (1) CBFV oscillations were observed by us and others despite the fact that these patients showed no signs of low frequency heart rate variability or variability of mean arterial blood pressure.¹ (2) Winberg and Ergander recently studied the relationship between heart rate, left ventricular output, and stroke volume during fluctuations in heart rate in preterm newborns with postnatal ages of 1 to 21 days.²⁸ They found the heart rate changes inversely related to changes in stroke volume. Heart rate variability produced a minimal effect on left ventricular output. To summarise, it appears unlikely that heart rate variability is the cause of CBFV oscillations.

NON-LINEAR CONTROL SYSTEM AND PIVH

Although not undisputed,¹³ several authors have suggested that cerebral blood flow beat to beat variability in respiratory distress syndrome triggers severe PIVH in preterm neonates.^{7–9} One study has convincingly shown that paralysing the infants at risk decreased the overall incidence of PIVH, and to an even greater extent decreased the rate of severe grade 3 to 4 PIVH.¹¹ Pancuronium seemed to abolish the beat to beat variability of CBFV in ventilated infants with respiratory distress syndrome¹¹ and also decreased the variability of arterial blood pressure from 5% down to 1.9%.²⁹ Although a second study could not reproduce the results of Perlman *et al.*,¹¹ it may be that pancuronium is capable of preventing severe PIVH in a selected high risk patient group (29 to 32 weeks' gestation) in which the main pathophysiological cause of PIVH is (associated with?) CBFV beat to beat variability.¹¹ The reason why variability of both blood pressure and CBFV probably causes PIVH in that particular patient group remains unclear. Furthermore, mechanistic explanations regarding the fragility of germinal matrix vessels have been discussed.⁹ Considering that Anthony *et al* observed a degree of slow CBFV variability of up to 64% in the middle cerebral artery of healthy preterm neonates,¹ the single factor of a fluctuating CBFV pattern is probably not harmful enough to lead to catastrophic cerebral events.

CLINICAL IMPLICATIONS AND PERSPECTIVES

Taking our model of a non-linear cerebral blood flow control system, we speculate that disturbances within the range of entrainment provided with a high amplitude, as is usually the case in ventilation for respiratory distress syndrome, challenge the regulatory capacity of this system to its limits as is reflected by the

Figure 5 Power spectrum of systolic (V_s) CBFV oscillations for patient 3 at day 6 of life. Spectral component corresponding to the ventilator rate (arrow) can be clearly identified at $27/\text{min} = 0.45 \text{ Hz}$.

diminished power of the low frequency region of CBFV oscillations. There might be no reserve to counteract further disturbing stimuli. Consequently this state could allow cerebral events like PIVH if accompanied by the prerequisites of severe blood pressure changes, fragile vascular elements, high PaCO_2 and low PaO_2 . The recent findings of Pryds *et al*³⁰ who by the xenon-133 clearance method showed an absent global cerebral blood flow reactivity to changes in PaCO_2 and mean arterial blood pressure in mechanically ventilated preterm infants who subsequently developed PIVH, would well fit into that theory. Pryds *et al* explained their findings with 'functional disturbances of CBF regulation', and by different methodology might have observed the same phenomenon as we did, namely entrainment presumably blocking the control system.

SUMMARY

The presence of spontaneous oscillations and selective frequency entrainment gives evidence that cerebral autoregulation is a non-linear type control system. The increased risk for PIVH/PVL in mechanically ventilated preterm neonates might find its explanation in interactions between autoregulation and the periodic external disturbing stimulus thus reducing the autoregulatory capacity. In consequence, the fragile cerebral anatomy is left at the mercy of coincidental fluctuations in blood pressure or blood gases.

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- 1 Anthony MY, Evans DH, Levene MI. Cyclical variations in cerebral blood flow velocity. *Arch Dis Child* 1991; **66**: 12-6.
- 2 Livera LN, Wickramasinghe YABD, Spencer SA, Rolfe P, Thorniley MS. Cyclical fluctuations in cerebral blood volume. *Arch Dis Child* 1992; **67**: 62-3.
- 3 Coughtrey H, Rennie JM, Evans DA. Postnatal evolution of slow variability in cerebral blood flow velocity. *Arch Dis Child* 1992; **67**: 412-5.
- 4 Cowan F. Cerebral blood flow velocity in the sleeping normal newborn infant. Studies on the cerebral circulation of the newborn infant. [Thesis.] Oslo: A/S Holstad-Trykk, 1983.
- 5 Hauge A, Thoresen M, Walloe L. Changes in cerebral blood flow during hyperventilation and CO_2 -breathing measured transcutaneously in humans by a bidirectional, pulsed, ultrasound Doppler blood velocity meter. *Acta Physiol Scand* 1980; **110**: 167-73.
- 6 Elligsen I, Hauge A, Nicolaysen M, Thoresen M, Walloe L. Changes in human cerebral blood flow due to step changes in PaO_2 and PaCO_2 . *Acta Physiol Scand* 1987; **129**: 157-63.
- 7 Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome: relation to the development of intraventricular hemorrhage. *N Engl J Med* 1983; **309**: 204-9.
- 8 Rennie JM, South M, Morley CJ. Cerebral blood flow velocity variability in infants receiving assisted ventilation. *Arch Dis Child* 1987; **62**: 1247-51.
- 9 Volpe JJ. Intraventricular hemorrhage in the premature infant – current concepts. Part 1. *Ann Neurol* 1989; **25**: 3-11.
- 10 Cowan F, Thoresen M. The effect of intermittent positive-pressure ventilation on cerebral arterial and venous blood velocities in the newborn infant. *Acta Paediatr Scand* 1987; **76**: 239-47.
- 11 Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *N Engl J Med* 1985; **312**: 1353-7.
- 12 Miall-Allen VM, de Vries LS, Dubowitz LMS, Whitelaw AGL. Blood-pressure fluctuation and intraventricular hemorrhage in the preterm infant of less than 31 weeks' gestation. *Pediatrics* 1989; **83**: 657-61.
- 13 Miall-Allen VM. Letter to the editor. *Pediatrics* 1990; **85**: 621-2.
- 14 Hyndman BW. The role of rhythms in homeostasis. *Kybernetik* 1974; **15**: 227-36.
- 15 Kitney RI. An analysis of the nonlinear behaviour of the human thermal vasomotor control system. *J Theor Biol* 1974; **52**: 231-48.
- 16 Minorsky. *Nonlinear oscillations*. New York: Van Nostrand, 1962: 4-27.
- 17 Rabe H, Grohs B, Bresser BW, Jorch G. Continuous Doppler sonography: a new method of monitoring cerebral circulation in very low birthweight infants. *Klin Padiatr* 1990; **202**: 383-6.
- 18 Michel E, Zernikow B, Rabe H, Jorch G. Adaptive multi-purpose probe fixation device for use on newborns. *Ultrasound Med Biol* 1993; **19**: 581-6.
- 19 Baldzer K, Dykes FD, Jones SA, Brogan M, Carrigan TA, Giddens DP. Heart rate variability analysis in full-term infants: spectral indices of neonatal cardiorespiratory control. *Pediatr Res* 1989; **26**: 188-95.
- 20 Shott S. *Statistics for health professionals*. Philadelphia: Saunders, 1990: 106-9.
- 21 Menke J, Michel E, Rabe H, *et al*. Simultaneous influence of blood pressure, pCO_2 and PO_2 on cerebral blood flow velocity in preterm infants less than 33 weeks gestation. *Pediatr Res* 1993; **34**: 173-7.
- 22 Sayers BM. Analysis of heart rate variability. *Ergonomics* 1973; **16**: 17-32.
- 23 Kitney RI. A nonlinear model for studying oscillations in the blood pressure control system. *J Biomed Eng* 1979; **1**: 89-90.
- 24 Klingelhöfer J, Sander D. Transcranial Doppler ultrasonography in sleep. In: Babikian VL, Wechsler LR, eds. *Transcranial Doppler ultrasonography*. St Louis: Mosby, 1993: 150-9.
- 25 Purves MJ. Do vasomotor nerves significantly regulate cerebral blood flow? *Circ Res* 1978; **43**: 485-93.
- 26 Hyndman BW, Kitney RI, McSayers BA. Spontaneous rhythms in physiological control systems. *Nature* 1971; **233**: 339-41.
- 27 Van de Bor M, Walter FJ. Cerebral blood flow regulation in preterm infants. *Biol Neonate* 1991; **59**: 329-35.
- 28 Winberg P, Ergander U. Relationship between heart rate, left ventricular output and stroke volume in preterm infants during fluctuations in heart rate. *Pediatr Res* 1992; **31**: 117-20.
- 29 Miall-Allen VM, Whitelaw AGL. Effect of pancuronium and pethidin on heart rate and blood pressure in ventilated infants. *Arch Dis Child* 1987; **62**: 1179-80.
- 30 Pryds O, Greisen G, Lou H, Friis-Hansen B. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation. *J Pediatr* 1989; **115**: 638-45.