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Near-infrared Spectrophotometry (NIRS)-Monitored Circadian Variation of Preterm Infants' Cerebral Blood Volume and Neurological Outcome

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Abstract: Objectives. Using near-infrared spectrophotometry (NIRS), the circadian variation in cerebral blood volume of preterm infants is assessed and its characteristics are related to neurological outcomes at 6 years of age.

Design. Cerebral blood volume and oxygenation, determined by NIRS, blood gases (pO_2 and pCO_2), blood pressure and heart rate were monitored around the clock for 25 hours in eight infants (6 male and 2 female) between the ages of 2 and 14 days. None had serious neurological problems at birth. At 6 years of age, these children underwent a psychoneurological examination on the basis of which they were classified into 2 groups, one of 5 children with the more severe abnormalities, the other of 3 children with a lesser deficit.

Setting. All infants were examined at the Institute of Pediatrics, Scientific Center for Children's Health, Academy of Medical Sciences, in Moscow, Russia.

Results. All neonates had a detectable circadian rhythm of cerebral blood volume, blood pressure, heart rate and transcutaneous pO_2 and pCO_2 ($P<0.001$). Circadian characteristics at birth differed between children who at 6 years of age had more vs. less severe psychoneurological abnormalities.

Main findings. A lower circadian trough (estimated as the bathymetron) of blood pressure and a higher circadian peak (estimated as the acrometron) of pO_2 were predictive of future neurological deficit.

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Conclusions. These results illustrate the putative merits of a chronobiological approach that assesses the dynamic characteristics of change in pertinent variables and their interaction.

Zusammenfassung: *Nahe-Infrarot Spektrophotometrie (NIRS) – Aufzeichnung der zirkadianen Schwankungen bei Frühgeborenen.* Zielsetzung: Durch die Verwendung der Nahe-Infrarot Spektrophotometrie (NIRS) wird die zirkadiane Schwankung im zerebralen Blutdurchfluß des Hirns bei Frühgeborenen bestimmt und die Charakteristika werden mit neurologischen Befunden mit 6 Jahren verglichen.

Untersuchungsanordnung: Das Volumen des zerebralen Blutdurchflusses und die Sauerstoffsättigung des Blutes – Bestimmung durch NIRS –, Blutdruck und Herzfrequenz wurden rund um die Uhr für 25 Stunden bei 8 Säuglingen (6 männlichen und 2 weiblichen) im Alter zwischen 2 und 14 Tagen gemessen. Keiner der Säuglinge hatte bei der Geburt ernste neurologische Probleme. Im Alter von 6 Jahren wurden diese Kinder psychoneurologisch untersucht und daraufhin in zwei Gruppen geteilt, eine von fünf Kindern mit schwereren Störungen eine andere mit drei Kindern mit geringeren Defiziten.

Untersuchungsrahmen: Alle Kinder wurden am Institut für Kinderheilkunde untersucht, dem wissenschaftlichen Zentrum für die Gesundheit der Kinder an der Akademie der medizinischen Wissenschaften in Moskau. Alle Neugeborenen hatten einen deutlichen zirkadianen Rhythmus der zerebralen Blutdurchflussmenge, des Blutdrucks, der Herzfrequenz und der transkutanen Sauerstoff- und Kohlendioxydsättigung ($p<0.001$). Die zirkadianen Charakteristika bei der Geburt unterschieden sich bei den Kindern mit schwereren psychoneuerologischen Störungen von denen mit leichteren Störungen. Hauptergebnisse: Eine geringere zirkadiane Schwankung des Blutdruckes und eine höherer zirkadianer Gipfel der Sauerstoffsättigung waren prädiktiv für ein späteres neurologisches Defizit.

Schlußfolgerungen: Diese Ergebnisse illustrieren den möglichen Nutzen eines chronobiologischen Vorgehens, das die dynamischen Charakteristika der Veränderungen bei zugehörigen Variablen und ihren Interaktionen bestimmt.

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Introduction

Near-infrared spectrophotometry (NIRS) is a method for non-invasive monitoring of tissue oxygenation and blood volume at the bedside, applicable by an apparatus introduced by Wyatt et al. (1986) to record indices of cerebral oxygenation and hemodynamics, including oxygenated hemoglobin, reduced hemoglobin, oxidized cytochrome aa3, and total hemoglobin concentration. Cerebral blood volume, mixed cerebral venous saturation, and changes in cerebral blood flow can be derived therefrom. Wyatt et al. (1986) reported that abnormal responses could be detected in cerebral edema following birth asphyxia, patent ductus arteriosus and cystic encephalomalacia.

The validity of measurements obtained by NIRS has been assessed by different investigators. Benaron et al. (1992) compared different non-invasive methods for estimating oxygenation in vivo, discussing the strengths and weaknesses of each. The methods reviewed include pulse oximetry and transcutaneal oximetry used in clinical practice; NIRS, magnetic resonance spectroscopy, magnetic resonance saturation imaging, and time-of-flight absorbance spectrophotometry from an experimental viewpoint. Finding that the optical path length is not independent of wavelength, Benaron et al. (1995) caution that quantitative NIRS

measurements in the clinic may require the concurrent measurement of both absorbance and optical path length at each wavelength. Different measures of cerebrovascular responses to carbon dioxide as detected by NIRS are also compared from a methodologic viewpoint by Brun and Griesen (1994). While finding NIRS useful to provide continuous bedside information about cerebral oxygenation and metabolism in sick preterm infants by measurements of oxyhemoglobin and deoxyhemoglobin, Pryds et al. (1990) and Skov et al. (1990) question whether the cytochrome aa3 signal may be artifactual due to an interference from oxyhemoglobin. In their studies on newborn piglets, Brun et al. (1997) find NIRS valuable to monitor changes in cerebral tissue oxygenation but not in cerebral blood volume. Good agreement of changes in cerebral blood volume measured by NIRS versus jugular venous occlusion plethysmography was, however, reported by Wickramasinghe et al. (1992). In conjunction with partial jugular venous occlusion, the measurement of cerebral venous oxyhemoglobin saturation by NIRS was validated against an invasive method applied during cardiac catheterization by Yoxall et al. (1995) (see also Yoxall and Weindling, 1996).

NIRS has numerous applications for clinical use and from a research viewpoint in the experimental laboratory. In the rat, NIRS was used to study mechanisms of epilepsy (Hoshi and Tamura 1993b). In this rat model, wherein seizures are induced chemically, the authors conclude that cellular hypoxia may be responsible for epileptic brain damage based on the measurement of dynamic changes in cerebral oxygenation assessed by NIRS. In healthy human adults, Hoshi and Tamura (1993a) investigated the changes in the oxygenation state of brain hemoglobin during mental work, monitored in real time by NIRS.

Many clinical studies in adults have focused on changes in cerebral blood volume and oxygenation following surgery. Yamane et al. (1994) find that patients who experience a decrease in oxygenated hemoglobin without recovery following cross-clamping of the internal carotid artery may have poor collateral circulation and therefore may develop cerebral ischemia. Nollert et al. (1995a) report that the main causes of impaired cerebral oxygenation are the decrease in hemoglobin with hemodilution, vasoconstriction due to hypocapnia, and the leftward shift of the hemoglobin-binding curve due to alkalosis and hypothermia. Studying cerebral oxygenation during cardiac surgery, Nollert et al. (1995b) conclude that neuropsychological deficits in patients after cardiac surgery can be caused by intraoperative cerebral hypoxia. Studying electroconvulsive therapy, Saito et al. (1996) conclude that this approach may initially increase the cerebral metabolic rate of oxygen more than cerebral blood flow, and that rapidly increasing blood pressure transiently may overwhelm cerebral pressure autoregulation.

NIRS has been used to measure concentration changes of cerebral hemoglobin and cytochrome in neonates, children and adults, to study cerebral oxygenation and hemodynamics (Duncan et al. 1996). In children, NIRS was used to study childhood moyamoya disease, a form of childhood encephalopathy (Itoh et al. 1994). Skov and Griesen (1994) caution, however, that the interesting possibility of monitoring cytochrome oxygenation by near-infrared spectrophotometry requires further validation.

Most important applications of NIRS can be found in the neonatal intensive care unit. According to Delpy et al. (1987), NIRS (and phosphorus magnetic res-

onance spectroscopy, MRS) "show promise of providing important information about the mechanisms and prognostic significance of hypoxic-ischemic damage to the brain – the most important cause of permanent neurodevelopmental disabilities in infants who require intensive care". In their review, von Siebenthal et al. (1992) write that "Neonatal encephalopathy of early onset, plausibly related to hypoxia and ischemia, remains one of the main problems in perinatal medicine" and that "Various studies have shown the feasibility of NIRS in preterm infants" (see also Bernert et al. 1995). In the opinion of Wyatt (1994): "Haemodynamic abnormalities frequently precede the delayed failure of energy metabolism. NIRS (and MRS) provide unique information on deranged cerebral energy metabolism following hypoxia-ischemia and will guide the introduction of new cerebroprotective interventions."

Applications of NIRS in the neonatal intensive care unit have been forthcoming. Investigating the effects of crying on cerebral blood volume and cytochrome aa3, Brazy (1988) found that crying altered cerebral blood volume in neonates in a pattern consistent with cyclic obstruction to cerebral venous return, decreasing cerebral oxygenation in infants with respiratory problems. During crying episodes, Brazy (1988) observed that cerebral blood volume and oxidized cytochrome aa3 demonstrated oscillatory fluctuations every 10 to 20 seconds. Changes of oxygenated and deoxygenated hemoglobin, of arterial oxygen saturation and of heart rate were reportedly greater during crying episodes than during quiet spans (Bernert et al. 1997). Munger et al. (1998) caution that studies on cerebral hemodynamics should take sleep state into account. An increase in cerebral blood flow over the first three days of life in extremely pre-term babies is reported by Meek et al. (1998).

Clinical applications of the technique have included, with the monitoring of the high-risk newborn, cerebral measurements in the intrapartum fetus (Rolfe et al., 1992; Doyle et al., 1994; Hamilton et al., 1996), the infant undergoing extracorporeal membrane oxygenation (Liem et al., 1995a and b) and hypothermic cardiac surgery (Nomura et al., 1996) (for review, see du Plessis, 1995). Wyatt (1994) and Saliba et al. (1997) used NIRS along with MRS to study the brain of newborn infants after perinatal asphyxia. Jenni et al. (1996) further report obstructive apnea to have a strong impact on cerebral total hemoglobin concentration. The authors note that as such alterations may exacerbate or cause intraventricular hemorrhage, efforts should be made to prevent obstruction of upper airways and to focus monitoring on cerebral perfusion. Based on their NIRS studies, Liem et al. (1997) note that in newborn infants blood transfusion in anemia results in improvement of cerebral oxygenation but hemodilution in polycythemia does not improve cerebral oxygenation despite a possible improvement of cerebral perfusion. In a different context, Akiyama and Yamauchi (1994) use NIRS for the early diagnosis of biliary atresia.

Other important applications of NIRS relate to the assessment of interventions. Fahnenstich et al. (1991) and Skov et al. (1992) used the technique to monitor relative changes in cerebral oxygenation and cerebral blood volume during surfactant replacement therapy. Bucher et al. (1994) studied the effect of aminophylline on cerebral haemodynamics and oxidative metabolism in mechanically ventilated premature infants, the treatment being given to facilitate their weaning from the

Table 1. Characteristics of infants investigated

Child ID	Birth date (day.mo.yr)	Time	GA*	Gender	BW**	Apgar score 1/5 min	PA***	Hb#
ch	02.04.92	23:55	35	m	2080	6/7	2	245
de	24.02.92	14:35	37	m	2100	6/8	3	231
iv	27.03.92	06:10	37	m	1750	6/7	6	243
ku	10.12.91	00:00	35	m	2400	6/8	4	231
ru	21.03.92	10:20	36	m	2350	7/8	11	158
rt	21.03.92	10:25	36	f	2040	6/8	10	203
sh	21.02.92	08:00	37	f	2350	6/7	4	154
vo	05.02.92	17:40	37	m	2400	6/7	14	223

* gestational age (weeks)
** birthweight (g)
*** postnatal age (days) at NIRS examination
\# hemoglobin concentration in blood (g/L) at NIRS study.

respirator. Liem et al. (1994), Benders et al. (1995) and Mosca et al. (1997a) assessed the effect of treatment of preterm infants with indomethacin. The authors point out that low arterial oxygen content, either caused by low arterial oxygen saturation or by a lower hemoglobin concentration, may be a contraindication for treatment with indomethacin in preterm infants. Pellicer et al. (1998) assess the effect of systemic dexamethasone administration on cerebral hemodynamics while Mosca et al. (1997b) compared effects of closed vs. open endotracheal suctioning in preterm infants on cerebral oxygenation and blood volume. Effects of positive and negative pressure ventilation on cerebral blood volume were studied by Palmer et al. (1995). Cerebral hemodynamics during pediatric cardiopulmonary bypass have been studied by Baris et al. (1995), Van Bel et al. (1996) and Chow et al. (1997).

As reviewed above, NIRS has provided some insight into cerebrovascular physiology and pharmacology. Pryds and Edwards (1996) note, however, that the precise relation between cerebral blood flow and cerebral damage remains elusive. Since cerebral injury remains a substantial problem in neonatal intensive care, these authors stress the urgent need for research in the field. Against this background, the present study attempts to evaluate the about-daily (circadian) variation in the cerebral blood volume of preterm infants and to relate its characteristics to neurological outcomes.

Subjects and Methods

The first part of the study was done from December 1991 to April 1992. Six male and 2 female infants (including one twin pair, "ru" and "rt"; gestational ages 35–37 weeks; birthweight 1750–2400 g) were examined each for 25 hours, between the ages of 2 and 14 days (Table 1). All infants were clinically stable; none had serious neurological problems or abnormal ultrasound findings. Infants were nursed in a neonatal unit with lights on from 07:00 to 19:00, and breathed spontaneously. Oxygen concentration in incubators was increased up to 30–40%.

Cerebral blood volume and oxygenation were determined by NIRS (Reynolds et al., 1991). The instrument was specially designed in-house, using wavelengths of 740, 790, 830, 870 and 940 nm to assess the absorption of cerebral oxyhemoglobin (HbO) and deoxyhemoglobin (Hb), from which cerebral blood volume (BV, in ml/100 g) was calculated (Yatsyk et al. 1994; Syutkina et al. 1996). These variables were monitored continuously for 25 hours.

Concomitantly, blood gases (pO_2 and pCO_2) were continuously recorded transcutaneously using the TCM-222 monitor from Radiometer (Denmark). Paper speed was 0.5 cm/min. The records were digitized for consecutive 2-minute intervals. Systolic (S), mean arterial (MA) and diastolic (D) blood pressure (BP) as well as heart rate (HR) were measured noninvasively at 20- to 30-min intervals with the BX5 monitor from Colin Medical Instruments (Komaki, Japan).

After subtraction of a linear trend, each data series was analyzed by single cosinor (Halberg, 1969). This method involves the least-squares fit of one (or several) cosine curve(s) with anticipated period(s). A 24-hour period was used for assessing the circadian component. Estimates of the double amplitude (2A, a measure of the extent of change within one cycle predictable by the fitted model) and of the acrophase (a measure of the timing of overall high values recurring in each cycle) were obtained. The MESOR (M, a rhythm-adjusted mean) was estimated as the ordinate of the linear trend at the midpoint of the monitoring span. The acrometron (AM = M + A) and the bathymetron (BM = M – A) were calculated to approximate the anticipated highest and lowest values predictably assumed by each variable during each cycle. The amplitude was expressed both in original units and as a percentage of the MESOR.

The second part of the study was done from December 1997 to April 1998. The same children were examined by a neurologist (MAK) and a psychologist (IDG) at the age of 6 years. The results of the psychoneurological examination are shown in Table 2. All children had DAMCP (deficit of attention, motor control and perception; Aicardi 1998). Play skills, tidiness, self-service and movement as well as movement volume were normal in all children. One child (iv) had generalized tonic-clonic seizures at the age of 3 years. Physical development of all children was normal.

Electroencephalography (EEG) revealed delay of bioelectrical activity formation (in 50% of the children), dysfunction of subcortical structures (62%), paroxysmal activity (12.5%) and pathological irritation (25%). Only one child had a normal EEG. All had normal MRIs.

The results of the psychoneurological examination were quantified as a number of "normal functions", expressed as a score in arbitrary units, denoted as "score #1".

For the estimation of mental functions, we used Computerized Test Systems (CTS) (Dzuba and Nemkovsky 1997; Maslova et al. 1997a,b). This method makes it possible to quantify perception, attention, memory, psychomotor activity, and level of analytic and synthetic processes, summarized as "score #2". The results of the CTS examination are shown in Table 3. CTS includes the set of relatively difficult tests adapted for a specific age. A low score does not indicate severe mental retardation but rather minimal deficit of mental functions supporting primary neurological diagnosis of DAMCP.

Table 2. Results of psychoneurological examination at 6 years of age*

Test exam	Child ID ku	vo	ch	iv	rt	sh	ru	de
Behavior	euphoria	N	N	N	N	N	N	N
Speech	DD	dysarthria	dyslalia	dysarthria	DD	dysthymia	dyslalia	N
Area of interest	Dec	N	Dec	N	Dec	N	N	N
Cooperativeness	formal	N	difficilt	N	N	N	N	N
Emotions	primitive	labile	labile	labile	primitve	labile	labile	labile
Mental development	infantile	AA	AA	AA	AA	AA	AA	AA
Cranial nerve abnormalities	III,IV, VI,VII	III,IV, VI,IX	III,IV, VI,IX	III,IV, VI,IX	III,IV, VI	III,IV, VI	XII	III,IV, VI
Muscle tone:								
– upper extremities	Inc	Dec	dystonis	Dec	Dec	N	N	N
– lower extremities	Inc	Inc	dystonia	dystonia	Dec	N	N	N
Tendon reflexes:								
– upper extremities	Inc	Inc	Dec	N	N	N	N	N
– lower extremities	Inc	Inc	Dec	Inc	N	N	N	N
Tics	+	–	+	–	–	–	–	–
Coordination:								
– static tests	AN	N	N	AN	N	N	N	AN
– locomotor tests	AN	AN	N	N	N	N	N	N
Fine motor functions	insufficient	insufficient	N	insufficient	N	N	N	N
Pathological reflexes	foot clonus	–	–	–	–	–	–	foot clonus
Pelvic functions:								
– enuresis	–	–	–	–	–	–	–	–
– encopresis	–	–	+	–	–	–	–	–
EEG:								
– rest	AN	AN	AN	AN	N	N	N	N
– hyperventilation	AN	AN	AN	AN	AN	AN	N	AN
Test "Score #1" (number of normal functions)	2	9	7	10	13	16	17	15

* See Table 1 for child identification.
AA = appropriate for age; AN = abnormal; DD = delay of development; Dec = decreased; Inc = increased; N = normal.

On the basis of routine psychoneurological examination, EEG and CTS at the age of 6 years, infants were classified into two groups: with more (group 1) and less (group 2) severe abnormalities. Group 1 included 5 children ("ku", "vo", "ch", "iv", "rt"); group 2 included 3 children ("ru", "sh" and "de").

Results

Table 4 shows that the neurological status at 6 years of age indeed differed with statistical significance between the two groups, while the clinical state during the neonatal stage was similar.

All neonates had a detectable circadian rhythm of cerebral blood volume, SBP, MAP, DBP and HR, transcutaneous pO_2 and pCO_2 ($P < 0.001$). The circadian double amplitudes of SBP, MAP and DBP (but not of HR) tended to be (numerically) larger and their MESOR tended to be lower in group 1 than in group 2 (Table 5). As a consequence, the predictable daily low value (BM) of these variables was lower among the infants found 6 years later to have more neurological abnormalities ($P < 0.05$ for SBP and DBP). A similar tendency was observed for the concentrations of cerebral oxyhemoglobin and deoxyhemoglobin and for cere-

Table 3. Characteristics of mental functions at 6 years of age, evaluated by CTS (expressed as a percentage of usual value)

Mental function	Child ID							
	ku	vo	ch	iv	rt	sh	ru	de
Volume of visual memory	17	17	34	34	34	51	68	85
Volume of attention	17	17	34	34	34	51	85	85
Volume of sensory memory	17	17	17	34	34	68	68	68
Visual-motor coordination	34	34	68	68	100	100	100	100
Spatial orientation	17	17	34	34	68	85	85	68
Perception	17	17	17	34	34	51	51	68
Ability to concentrate attention	17	17	34	51	51	85	85	68
Distribution of attention	17	17	17	17	51	85	85	85
Ability to fix attention	17	17	34	34	34	51	51	51
Ability to switch attention	34	34	51	34	68	85	85	85
Rhythmic sensomotor activity	17	17	34	34	68	85	85	68
Conceptual thinking	17	17	17	34	51	68	68	68
Level of attention and thinking	17	17	17	17	51	68	68	68
Abstract and concrete thinking	17	34	34	34	68	68	68	68
Total score								
Mean	19.4	20.6	31.5	35.2	53.2	71.5	75.1	73.9
±SD	6.2	7.2	14.7	12.4	19.5	16.3	14.2	12.3

Table 4. Comparison of characteristics between infants with more or less severe neurological abnormalities*

Abnormality	Neonatal span					at 6 years of age	
	GA	BW	Apgar-1 min	Apgar-5 min	PA	score #1	score #2
more severe	36.0±0.4	2134±123	6.0±0.0	7.4±0.2	7.2±2.2	8.2±1.8	32.0±6.1
less severe	36.7±0.3	2267±83	6.3±0.3	7.7±0.3	6.0±2.5	16.0±0.6	73.5±1.1
Student t	1.034	0.760	1.369	0.655	0.352	3.154	5.057
P	NS	NS	NS	NS	NS	0.020	0.002

* For a description of scores #1 and #2, see Tables 2 and 3; children with more severe abnormalities include ku, vo, ch, iv and rt; children with less severe abnormalities include ru, sh and de.
GA = gestational age (weeks); BW = birthweight (g); PA = postnatal age (days) at NIRS examination; NS = not statistically significant ($P > 0.05$).

bral blood volume (Table 6), especially when the amplitudes were expressed as a percentage of the MESOR, but the results are not statistically significant.

In group 1, the MESOR of $tcpO_2$ was slightly higher as compared with that of group 2 (Table 7). In view of the difference in circadian double amplitudes, which were larger in group 1 than in group 2, no difference was found in terms of the bathymetron, but well in terms of the acrometron.

Table 5. Comparison of cardiovascular characteristics between infants with more or less severe neurological abnormalities*

Child ID	2A	2A (%)	M	AM	BM
			SBP (mmHg)		
ku	1.88	2.68	70.24	71.18	69.30
vo	16.04	24.58	65.23	73.25	57.21
ch	4.66	6.76	68.84	71.17	66.51
iv	6.76	9.66	70.05	73.43	66.67
rt	25.84	34.70	74.47	87.39	61.55
mean±SE	11.04±4.40	15.68±6.02	69.77±1.48	75.28±3.07	64.25±2.16
sh	7.30	8.60	84.88	88.53	81.23
ru	4.40	4.92	89.33	91.53	87.13
de	6.86	9.26	74.09	77.52	70.66
mean±SE	6.19±0.90	7.59±1.35	82.77±4.52	85.86±4.26	79.67±482
Student t	0.822	0.999	3.377	2.059	3.393
P	NS	NS	0.015	0.085	0.015
			MAP (mmHg)		
ku	5.08	8.92	56.95	59.49	54.41
vo	13.70	28.58	47.89	54.74	41.04
ch	1.08	1.92	56.68	57.22	56.14
iv	3.42	6.26	54.52	56.23	52.81
rt	19.98	33.62	59.42	69.41	49.43
mean±SE	8.65±3.54	15.86±6.37	55.09±1.96	59.42±2.62	50.76±2.67
sh	5.40	8.66	62.44	65.14	59.74
ru	3.94	5.70	69.21	71.18	67.24
de	5.58	9.76	57.08	59.87	54.29
mean±SE	4.97±0.52	8.04±1.21	62.91±3.51	65.40±3.27	60.43±3.75
Student t	0.776	0.915	2.135	1.416	2.151
P	NS	NS	0.077	NS	0.075
			DBP (mmHg)		
ku	1.26	3.08	40.97	41.60	40.34
vo	11.64	30.50	38.17	43.99	32.35
ch	2.06	4.98	41.36	42.39	40.33
iv	9.00	20.68	43.52	48.02	39.02
rt	16.24	32.38	50.15	58.27	42.03
mean±SE	8.04±2.85	18.32±6.17	42.83±2.02	46.85±3.06	38.81±1.68
sh	5.04	10.08	50.04	52.56	47.52
ru	2.52	4.54	55.50	56.76	54.24
de	5.34	11.54	46.31	48.98	43.64
mean±SE	4.30±0.89	8.72±2.13	50.63±2.67	52.77±2.25	48.47±3.10
Student t	0.969	1.147	2.343	1.345	3.029
P	NS	NS	0.058	NS	0.023

Table 5. (continued)

Child ID	2A	2A (%)	M	AM	BM
			HR (beats/min)		
ku	17.44	14.32	121.77	130.49	113.05
vo	15.30	11.96	127.90	135.55	120.25
ch	12.48	10.42	119.75	125.99	113.51
iv	26.98	19.16	140.81	154.30	127.32
rt	21.44	15.62	137.20	147.92	126.48
mean±SE	18.73±2.53	14.30±1.51	129.49±4.15	138.85±5.32	120.12±3.05
sh	12.46	10.18	122.23	128.46	116.00
ru	14.82	11.04	134.20	141.61	126.79
de	34.88	26.10	133.62	151.06	116.18
mean±SE	20.72±7.11	15.77±5.17	130.03±3.90	140.37±6.56	119.66±3.57
Student t	0.321	0.345	0.084	0.179	0.095
P	NS	NS	NS	NS	NS

* See Table 1 for child identification: ku, vo, ch, iv, rt are children with more severe abnormalities; ru, sh, de are children with less severe abnormalities.
SBP = systolic blood pressure; MAP = mean arterial pressure; DBP = diastolic blood pressure; HR = heart rate
M = MESOR (midline-estimating statistic of rhythm), a rhythm- adjusted mean, estimated as the ordinate of the linear trend at the midpoint of the monitoring span; 2A = double amplitude, expressed in original units, a measure of the extent of predictable change within one cycle; 2A (%) is 2A expressed as a percentage of M; AM and BM are acrometron and bathymetron, calculated as AM = M + A and BM = M – A.
SE = standard error; P = P-value from test of equality of group means.

Discussion

Preterm infants are considered to be especially susceptible to ischemic cerebral injury, often secondary to systemic hypotension, because of the occurrence of a pressure-passive cerebral circulation (Lou et al. 1979a). The results herein confirm that spans of relative ischemia tend to occur regularly as part of the circadian variation of cerebral blood volume in infants who are to develop moderate neurological abnormalities by 6 years of age. In other infants, a difference was also documented by 1 year of age (Syutkina 1994). It was previously shown that $20\,ml \cdot 100\,g^{-1} \cdot min^{-1}$ is a critical value for cerebral blood flow, associated with severe brain damage in newborns (Lou et al. 1979b). The present study provides the range of acceptability for another variable, cerebral blood volume; values below that range may lead to minimal cerebral dysfunction later in life.

Multiple regression analyses suggested a direct association between the circadian variation in cerebral blood volume and that of blood pressure, notably that of SBP and MAP. An indirect relation with the circadian rhythm in pO_2 was also observed, thus pointing to the occurrence of vasoconstriction at high pO_2 and dilatation at low pO_2.

The continuous noninvasive monitoring of cerebral blood volume along with cerebral oxygenation by NIRS at the bedside offers itself as a useful tool to better understand mechanisms leading to periventricular-intraventricular hemorrhage,

Table 6. Comparison of cerebral oxygenation and blood flow between infants with more or less severe neurological abnormalities*

Child ID	2A	2A (%)	M	AM	BM
		Reduced hemoglobin concentration (mcmol/L)			
ku	1.0	5.18	19.3	19.8	18.8
vo	2.0	16.00	12.5	13.5	11.5
ch	1.2	5.20	23.1	23.7	22.5
iv	7.0	40.94	17.1	20.6	13.6
rt	1.2	3.22	37.2	37.8	36.6
mean±SE	2.5±1.1	14.11±7.08	21.8±4.2	23.1±4.0	20.6±4.4
sh	1.6	8.60	18.6	19.4	17.8
ru	4.6	12.26	37.5	39.8	35.2
de	2.2	14.76	14.9	16.0	13.8
mean±SE	2.8±0.9	11.87±1.79	23.7±7.0	25.1±7.4	22.3±6.6
Student t	0.192	0.235	0.241	0.261	0.219
P	NS	NS	NS	NS	NS
		Oxyhemoglobin concentration (mcmol/L)			
ku	6.0	8.12	73.9	76.9	70.9
vo	20.0	23.80	84.0	94.0	74.0
ch	22.0	18.38	119.7	130.7	108.7
iv	15.0	13.58	110.4	117.9	102.9
rt	18.8	13.66	137.7	147.1	128.3
mean±SE	16.4±2.8	15.51±2.63	105.1±11.7	113.3±12.6	97.0±10.9
sh	12.0	8.00	149.9	155.9	143.9
ru	11.6	11.62	99.9	105.7	94.1
de	13.0	11.14	116.7	123.2	110.2
mean±SE	12.2±0.4	10.25±1.14	122.2±14.7	128.3±14.7	116.1±14.7
Student t	1.099	1.456	0.901	0.750	1.060
P	NS	NS	NS	NS	NS
		Cerebral blood volume (ml/100 g)			
ku	0.18	7.24	2.60	2.69	2.51
vo	0.76	22.72	3.33	3.71	2.95
ch	0.56	15.04	3.76	4.04	3.48
iv	0.24	7.32	3.38	3.50	3.26
rt	0.64	11.40	5.56	5.88	5.24
mean±SE	0.48±0.11	12.74±2.88	3.73±0.50	3.97±0.52	3.49±0.47
sh	0.56	8.02	7.06	7.34	6.78
ru	0.66	11.88	5.61	5.94	5.28
de	0.36	9.68	3.67	3.85	3.49
mean±SE	0.53±0.09	9.86±1.12	5.45±0.98	5.71±1.01	5.18±0.95
Student t	0.308	0.733	1.765	1.712	1.820
P	NS	NS	NS	NS	NS

* See table 1 for child identification: ku, vo, ch, iv, rt are children with more severe abnormalities; ru, sh, de are children with less severe abnormalities.
M = MESOR (midline-estimating statistic of rhythm), a rhythm-adjusted mean, estimated as the ordinate of the linear trend at the midpoint of the monitoring span; 2A = double amplitude, expressed in original units, a measure of the extent of predictable change within one cycle; 2A (%) is 2A expressed as a percentage of M; AM and BM are acrometron and bathymetron, calculated as AM = M + A and BM = M – A.
SE = standard error; P = P-value from test of equality of group means.

Table 7. Comparison of blood gases between infants with more or less severe neurological abnormalities*

Child ID	2A	2A (%)	M	AM	BM
			$tcpO_2$ (mm Hg)		
ch	13.88	15.62	88.90	95.84	81.96
iv	14.14	16.30	86.84	93.91	79.77
rt	13.00	16.32	79.70	86.20	73.20
mean±SE	13.67±0.34	16.08±0.23	85.15±2.79	91.99±2.95	78.31±2.63
ru	3.44	4.36	78.76	80.48	77.04
de	2.76	3.70	74.23	75.61	72.85
mean±SE	3.10±0.34	4.03±0.33	76.50±2.27	78.04±2.44	74.95±2.10
Student t	20.636	31.246	2.176	3.307	0.900
P	< 0.001	< 0.001	NS	0.046	NS
			$tcpCO_2$ (mm Hg)		
ch	1.74	4.64	37.35	38.22	36.48
iv	11.82	28.04	42.12	48.03	36.21
rt	–	–	–	–	–
mean±SE	6.78±5.04	16.34±11.70	39.74±2.39	43.13±4.91	36.35±0.13
ru	4.26	8.50	50.15	52.28	48.02
de	2.86	6.88	41.71	43.14	40.28
mean±SE	3.56±0.70	7.69±0.81	45.93±4.22	47.71±4.57	44.15±3.87
Student t	0.632	0.738	1.278	0.684	2.014
P	NS	NS	NS	NS	NS

* See Table 1 for child identification: ch, iv, rt are children with more severe abnormalities; ru, de are children with less severe abnormalities.
M = MESOR (midline-estimating statistic of rhythm), a rhythm- adjusted mean, estimated as the ordinate of the linear trend at the midpoint of the monitoring span; 2A = double amplitude, expressed in original units, a measure of the extent of predictable change within one cycle; 2A (%) is 2A expressed as a percentage of M; AM and BM are acrometron and bathymetron, calculated as AM = M + A and BM = M – A.
SE = standard error; P = P-value from test of equality of group means.

the most common serious neurological lesion encountered in preterm infants. The rational development of countermeasures should thereby be facilitated for the prevention of such lesions or at least to stop their progression. This task is the more important that hemorrhagic intracerebral involvement has been considered to be a component of a much larger lesion, basically ischemic in nature (Volpe et al. 1983).

There are precedents where alterations in the circadian dynamics of hemodynamic variables have predictive value in relation to vascular disease risk. In adult patients, an excessive circadian amplitude of blood pressure was shown to be associated with a 720% increase in the risk of ischemic stroke (Halberg and Cornelissen 1995; Otsuka et al. 1996, 1997b), a finding corroborated in an independent study using the left ventricular mass index as a surrogate outcome measure (Chen et al. 1997; see also Kumagai et al. 1992). In neonates as well, the circadian amplitude of blood pressure was found to be larger in the presence than in the absence of

familial antecedents (Halberg et al. 1990). The circadian amplitude of blood pressure was also found to be larger in neonates exposed in utero to betamimetic drugs (Halberg et al. 1990), a finding lasting into adolescence (Syutkina et al. 1995).

As informative as the assessment of circadian rhythms can be, the circadian variation is but one rhythmic component among others in a broader time structure (chronome; Halberg et al. 1991; Cornelissen and Halberg 1992; Macey 1994), consisting, in addition to the multifrequency rhythms, of chaotic elements, trends and noise. In early extrauterine life, about-weekly and half-weekly variations have been found to be more prominent than the about-daily changes, notably in the case of blood pressure and heart rate (Cornelissen et al. 1987; Halberg et al. 1994; Siegelova et al. 1996; Turti et al. 1996). Heart rate variability, assessed by the 24-hour standard deviation and by the correlation dimension, has been found to have predictive value in relation to coronary artery disease (Otsuka et al. 1997a).

In a recent study by Reynolds et al. (1997) of 106 premature and at-term newborns without major complications, the spectral power in the frequency range from 0.02 to 0.08 Hz ("low frequency") of the cerebral blood flow velocity was reduced for infants at term with birth asphyxia as compared to healthy controls, a result not found in the spectra of heart rate.

Much more work remains to be done to elucidate the precise relation between cerebral blood volume and cerebral damage, and the role of other variables such as blood pressure, heart rate, arterial oxygen saturation, pO_2 and pCO_2. The results herein illustrate the putative merits of a chronobiological approach that also accounts for the dynamic characteristics of change in all pertinent variables and their interactions.

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