Multivariate autoregressive modelling combined with transcephalic electrical impedance: method to relate neonatal systemic circulation and respiration to cerebral circulation

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Abstract—*We studied the pulsatile component of cerebral circulation with transcephalic electrical impedance (ΔZ) in six preterm newborns, three of whom had severe cerebral bleeding, peri-intraventricular haemorrhage (PIVH). The transcephalic electrical impedance ΔZ signal, ECG, arterial blood pressure, (aBP) and respirogram were recorded on analogue magnetic tape for 30 min. Artefact-free stationary segments (lasting for 2 min) of the four signals were digitised. A digital multivariate autoregressive (MAR) model was used to study frequency-specific variability in the signals and to quantify interrelations between the variabilities of ΔZ, HR, aBP and respiratory signals. MAR modelling describes a system where all the signals simultaneously explain each other. The inherent variability of ΔZ was lower and the influences of respiration and aBP on ΔZ significantly greater in infants with severe PIVH than in controls. These changes were observed at high frequencies corresponding to respiration and heart rate. This may be interpreted as a marker of pressure passivism in the cerebral circulation following PIVH. We conclude that in preterm babies the applicaiton of MAR modelling, together with transcephalic impedance, may be a new, helpful and quantitative method for the study of simultaneous interrelations between variables of cerebral and systemic circulations and respiration.*

Keywords—*Cerebrovascular circulation, Multivariate autoregressive modelling, Newborn infant, Peri-intraventricular haemorrhage*

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1 Introduction

PERI-INTRAVENTRICULAR HAEMORRHAGE is a common brain condition that occurs in 25–30% of prematurely born neonates with gestational age less than 35 weeks (VOLPE, 1989). The structural background to this disorder is the immature developmental stage of the cerebral periventricular vascular bed of these infants (HAMBLETON and WIGGLESWORTH, 1976), but the triggering mechanism of the bleeding is still unknown. Development and research on cerebral ultrasonography have greatly enhanced the fast non-invasive diagnosis and grading of the severity of PIVH during the last decade (BADA *et al.*, 1979; DE VRIES *et al.*, 1985; LEVENE, 1990; PAPE *et al.*, 1983). Isotope techniques and, in particular, positron emission tomography have made it possible to show that PIVH is often associated with global cerebral circulatory problems (LOU *et al.*, 1979; VOLPE *et al.*, 1983). However, at present, our knowledge of the circulatory and metabolic events before and even after the PIVH still remains rather scarce.

The selection of techniques for long-term monitoring of circulatory and metabolic variables of neonates is rather limited and is still at the developmental stage. Changes of blood flow velocity in a single (middle) cerebral artery can be monitored by means of Doppler ultrasound technique (FENTON *et al.*, 1990). Patterns of oxygenated and nonoxygenated haemoglobin and cytochrome may be followed using infra-red

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spectroscopy (EDWARDS *et al.*, 1992; LIVERA *et al.*, 1992), but this method has been successfully applied only in a small number of cases and it needs considerable further development. An old rheographic principle was applied, making use of modern digital engineering techniques by Tarassenko *et al.* (TARASSENKO, *et al.*, 1984), Weindling (WEINDLING *et al.*, 1982) and Murphy (MURPHY, 1987). When used to monitor instantaneous changes of intracranial blood volume, it is called transcephalic electrical impedance plethysmography, and it may be used for the non-invasive monitoring of sick neonates for periods of hours or days. This method was used by Colditz *et al.* (COLDITZ *et al.*, 1990) who were unable to show, during the first 48 h after birth, any clearcut step changes in the impedance signal in babies who developed PIVH. This group used an averaged transcephalic electrical impedance signal which was not computationally compared to other circulatory signals, such as heart rate or arterial blood pressure.

In order to study interactive phenomena, it would be helpful to relate a signal of cerebral circulation on a beat-by-beat basis to signals of systemic circulation and respiration, which represent the principal driving and interfering forces of cerebral blood flow. One potential method to allow this is multivariate autoregressive (MAR) modelling, describing simultaneously interrelations between all the signals studied (KALLI *et al.* 1988). Our aim was to investigate the feasibility of MAR modelling in relating respiratory and systemic circulatory signals to cerebral circulation assessed by transcephalic electrical impedance in preterm infants with serious PIVH in the brain.

2 Subjects and methods

2.1 *Material and signal acquisition*

Three babies with severe grade III PIVH detected by ultrasonography were studied, together with three babies with normal brain structure (controls). All the babies had respiratory distress syndrome (RDS), a condition caused by the immaturity of the lungs, and therefore they were receiving ventilatory therapy at the time of the data acquisition (ventilator frequencies 25–60/min). All the babies were between two and five days of age when studied, and they were in quiet sleep during the recording (Table 1). The recordings were repeated in two of the newborns with PIVH on the following day. None of the infants had evidence of hypoxia or hypercarbia at the time of recording. No sedatives or inotropic drugs were administered, and their systemic circulation were clinically stable at the time of recording.

The gestational age of the control babies was 27–32 weeks, and that of the babies with PIVH was 24–26 weeks. The respective 1 min Apgar scores were 2–5 and 2–3 and the birth weights were 695–1470 g and 765–975 g. These clinical parameters did not differ significantly between the groups (Table 1).

The precordial ECG, respirogram (transthoracic electrical impedance) and arterial blood pressure signal (aBP) via an umbilical catheter were recorded with a neonatal monitor.* The transcephalic electrical impedance signal (ΔZ) was recorded with a special-purpose impedance monitor (MURPHY, 1987). All the signals were recorded on an analogue tape (Racall 4 DS, South., England) for 30 min, visually verifying an appropriate signal quality.

A four-electrode impedance system was used to assess the cerebral circulation. Two pairs of Ag–AgCl electrodes (diameter 0·8 cm) were attached with collodion at the occipitofrontal circumference, one frontally and the other occipitally, so that the electrode-to-electrode distance in each pair was 2·5 cm. A 1 mA 60 kHz current was applied to the outer electrode in each pair, and the respective voltage was measured from the inner electrodes.

Impedance to the passage of an electrical current is an inherent property of biological material, and it can be calculated using Ohm's law $Z = V/I$, where Z is electrical impedance, V is voltage and I is current. Electrical impedance consists of reactive and resistive components. The reactive component results from the inductive and capacitive properties of tissue which are negligible at the frequencies of 10–100 kHz used (JAFFRIN and VANHOUTTE 1979; NICHOLSON 1965). The pulsatile component of the transcephalic impedance is related to the instantaneous change in the resistive component, mainly consisting of intracranial blood volume, as follows:

$$\Delta V = \Delta Z^* p^* (L/Z_0)^2$$

where ΔV is the pulsatile change in the intracranial blood volume, ΔZ is the pulsatile component of impedance, Z_0 is the basal impedance, p is the resistivity of blood and L is the distance between the voltage electrodes.

2.2 *Signal analysis*

Noise-free segments (2 min long) of the ΔZ, aBP and respiratory signals were visually selected and then digitised at a sampling frequency of 16·7 Hz using a minicomputer with a graphic terminal (Nova 3, Data General, Southboro, Mi, USA). The recording period of 2 min was an empirical compromise to obtain a sufficient amount of data and appropriate signal stationarity. Antialiasing low-pass filtering was done at 3 Hz (3 dB point, roll-off rate 24 dB/octave). From the respective ECG segments, the R-waves were detected with an adjustable

* Hewlett Packard

Table 1 Clinical data of source subjects

	birth weight, g	gestational age, weeks	timing of PIVH, days	postnatal recording age, days	1 min Apgar score	5 min Apgar score	ventilator frequency, min^{-1}
control 1	1470	29	—	3	5	8	60
control 2	1344	32	—	2	5	8	30
control 3	695	27	—	4	2	8	30
PIVH 1	765	26	1	3	3	6	25
PIVH 2	975	25	2	4 and 5	2	6	25
PIVH 3	798	24	1	2 and 3	3	9	25

control = neonatal patient in the control group
PIVH = neonatal patient in the PIVH group

threshold trigger and the R–R intervals were measured using an interval counter (1 kHz). The resulting heart-rate signal was synchronised with the other signals. All the signals were then sampled at a sampling frequency of 8 Hz for the final anlaysis using an IBM-compatible PC-486. Thirty-eight 2 min data segments were classified for the control group, and 49 for the PIVH group.

2.3 *Multivariate autoregressive model*

The multivariate autoregressive (MAR) model describes each signal as a linear combination of its own past values and the past values of the other signals, plus a predictive modelling term, assuming that all the signals are related to each other (KALLI *et al.*, 1988). We wanted to make use of the MAR model to be able to quantify interrelations of the four signals simultaneously. The multivariate autoregressive stochastic process $x(k) = [x_1(k), x_2(k), \ldots, x_m(k)]^T$ of m variables, i.e. four signals in our case (HR, aBP, respiration and ΔZ) is described by the equation

$$x(k) = \sum_{i=1}^{M} a(i)x(k-1) + e(k)$$

where

$$a(i) = \begin{cases} a_{11}(i) & a_{12}(i) & \cdots & a_{1m}(i) \\ a_{21}(i) & a_{22}(i) & \cdots & a_{2m}(i) \\ \vdots & \vdots & & \vdots \\ a_{m1}(i) & a_{m2}(i) & \cdots & a_{mm}(i) \end{cases} \quad \text{for } i = 1, 2, \ldots, M$$

are the MAR coefficient matrices, M is the model order and $e(k)$ is a white noise vector process $e = [e_1(k), e_2(k), \ldots, e_m(k)]^T$.

According to the equation, the process $x(k)$ depends only on the past value of the variables. The model order M denotes the number of the past values that are used to generate a new value for the process. The definition of the model order M was based on the Akaike information criterion and was computed separately for each 2 min segment (AKAIKE 1979). The model order 30 was found best to suite all the segments.

The frequency-specific analysis of the signal variability was performed by means of spectral density estimates of the MAR model. Cross-spectral analysis between two signals at a time was also applied to reveal frequency-specific joint-variability. The actual intersignal relations were computed as signal source contribution ratios using transfer functions between the signals. The inherent variability of the signal was called autocontribution, and the simultaneous intersignal influences were studied as cross-contributions. A detailed description of the MAR signal analysis has been published earlier (KALLI *et al.*, 1988).

The auto- and cross-spectral densities and contributions were analysed over five frequency bands: 0·02–0·07 Hz (F1, corresponding to peripheral sympathetic vasomotor thermoregulation), 0·07–0·18 Hz (F2, frequency around the natural oscillation of baroreflex), 0·18–0·30 Hz (F3), 0·30–1·50 Hz (F4, area corresponding to neonatal spontaneous breathing and artificial ventilator rates (25–60/min), 1·50–3·00 Hz (F5, frequency corresponding to heart rate, 122–174min) (AKSELROD *et al.*, 1981; HYNDMAN *et al.*, 1971; KITNEY *et al.*, 1982; SAYERS, 1973). For the frequency-specific intergroup comparisons, the spectral density and signal source contribution were band-integrated over frequency.

Table 2 Autospectral density in control and PIVH groups (arbitrary units ± SEM for each variable); no significant intergroup differences were observed

		control	PIVH
HR	0·02–0·07 Hz	2·7 ± 0·1	2·0 ± 0·2
	0·07–0·18 Hz	1·3 ± 0·2	0·8 ± 0·1
	0·18–0·30 Hz	0·2 ± 0·0	0·2 ± 0·0
	0·30–1·50 Hz	0·0 ± 0·1	2·0 ± 0·2
	1·50–3·00 Hz	0·1 ± 0·0	0·1 ± 0·0
aBP	0·02–0·07 Hz	0·2 ± 0·1	0·3 ± 0·1
	0·07–0·18 Hz	0·1 ± 0·0	0·8 ± 0·2
	0·18–0·30 Hz	0·1 ± 0·0	0·4 ± 0·1
	0·30–1·50 Hz	0·5 ± 0·1	1·1 ± 0·2
	1·50–3·00 Hz	7·1 ± 0·3	5·5 ± 0·6
ΔZ	0·02–0·07 Hz	0·5 ± 0·1	0·2 ± 0·0
	0·07–0·18 Hz	2·3 ± 0·3	1·1 ± 0·2
	0·18–0·30 Hz	1·0 ± 0·1	0·5 ± 0·1
	0·30–1·50 Hz	3·3 ± 0·3	2·6 ± 0·3
	1·50–3·00 Hz	0·7 ± 0·1	2·8 ± 0·4
respiration	0·02–0·07 Hz	0·1 ± 0·0	0·1 ± 0·0
	0·07–0·18 Hz	0·5 ± 0·1	0·2 ± 0·1
	0·18–0·30 Hz	0·6 ± 0·1	0·2 ± 0·1
	0·30–1·50 Hz	6·7 ± 0·5	4·6 ± 0·2
	1·50–3·00 Hz	0·3 ± 0·1	0·2 ± 0·1

2.4 *Statistical analysis*

The statistical analysis was performed using the nested analysis of variance (BMDP 3V). The fixed factor whose effect was of interest was the state (control versus PIVH) and the newborn itself acted as a random factor nested to its group (DIXON, 1985). The between-group analysis for birth weight, gestational age and Apgar scores was performed with the Kruskall–Wallis nonparameteric test (BMDP 3S).

3 Results

3.1 *Spectral estimates of signal variability*

The autospectral densities for HR, aBP, ΔZ and respiration were found to be statistically equal in the groups of controls and PIVH at all frequency bands analysed (Table 2). However, ΔZ spectral density seemed to be slightly higher in the infants of the PIVH group than in the controls at the highest frequency band. It was also noted that the spectral density of HR in both groups was concentrated mainly in the lower frequency band (0·02–0·07 Hz) corresponding to variabilities caused by thermoregulation, whereas the spectral density of aBP coincided with the highest frequency band (1·50–3·00 Hz) corresponding to the heart rate level. The spectral density of respiration clustered mainly to the frequency band of the ventilator frequencies (0·30–1·50 Hz). The two infants with repeated recordings on successive days showed similar results on both occasions in all the signals analysed.

The cross-spectral density between the aBP and ΔZ signals was significantly greater in the high-frequency region, F5 (1·50–3·00 Hz) in the infants with PIVH, 1·8 arbitrary units, than in the controls, 0·7 arbitrary units ($p = 0·040$) (Fig. 1). The computation of cross-spectra between the signals did not reveal any other intergroup differences.

3.2 *Signal source contribution*

The autocontributions and cross-contributions of HR, aBP or respiration signals did not show any significant differences between the groups.

The autocontribution of the ΔZ signal was lower in the PIVH group than in the controls, as follows: F3: 77·0% in the PIVH-group, 83·1% in the controls ($p = 0·039$); F4: 73·3%,

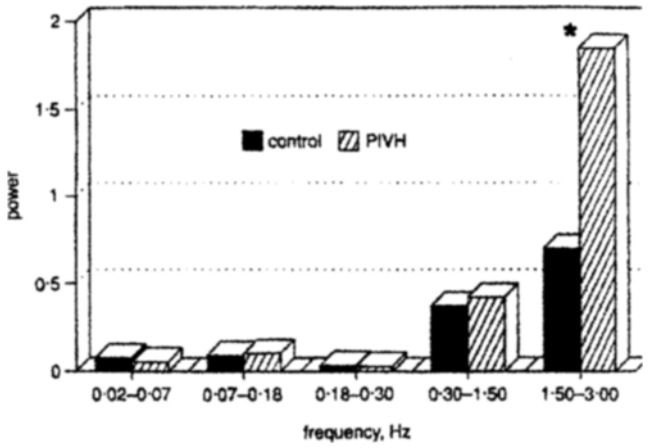

Fig. 1 *Average cross-spectral densities of periodic variability between aBP and ΔZ in five frequency regions: F1 (0·02–0·07 Hz), F2 (0·07–0·18 Hz), F3 (0·18–0·30 Hz), F4 (0·30–1·50 Hz) and F5 (1·50–3·00 Hz); high-frequency cross-spectral variability (F5) was greater in infants with PIVH (p = 0·040)*

82·6% ($p = 0·002$); and F5: 63·9%, 77·8% ($p < 0·001$), respectively. The cross-contribution of the respiration to the ΔZ signal was higher in the infants with PIVH than in the controls, as follows. F4: 11·4% in the PIVH group, 5·7% in the controls ($p < 0·001$); and F5: 13·0%, 7·2% ($p < 0·001$, respectively. The cross-contribution of aBP to ΔZ was also higher in the PIVH group than in the control group in the high-frequency region F5: 12·1% in the PIVH group, 7·8% in the controls ($p = 0·016$) (Fig. 2).

4 Discussion

In the MAR model the high-frequency (F5, heart rate frequency) influence of aBP on ΔZ was significantly greater in the infants with PIVH than in the controls. Moreover, the cross-spectral joint-variability of aBP and ΔZ at the respective frequencies was greater in the infants with PIVH than in the controls. Thus, it seems that pulsations of arterial blood pressure at every heart beat are mediated to cerebral circulation more prominently in the preterm infants with PIVH than in the preterm babies without PIVH. There was also a higher ΔZ variability in this frequency range in the PIVH than in the control babies, although the difference was not statistically significant. Our results probably agree with those of Lou and coworkers, which showed a loss of autoregulation of cerebral circulation in distressed newborn infants due to an abnormal 'luxury perfusion' in the damaged brain (LASSEN, 1966; LOU *et al.*, 1979). This pressure passivism makes the cerebral circulation vulnerable to abrupt changes in the systemic circulation.

The autocontribution of ΔZ (inherent variability) was smaller and the cross-contribution (influences) of respiration to ΔZ was greater in the infants with PIVH than in the controls at frequencies over 0·30 Hz, representing both mechanical ventilation and spontaneous breathing. This may suggest that respiratory mechanics affected the high-frequency variability of cerebral circulation to a greater extent in the infants with the PIVH than in the controls. This is in accordance with the findings of Perlman *et al.* (PERLMAN *et al.*, 1983) about prominent respiratory changes in cerebral circulation prior to PIVH. It could be speculated that this effect is a motion artefact but this is unlikely because the babies with severe PIVH were seriously ill and thus calmer than the healthy babies. It appears that high-frequency changes in systemic circulation (aBP) and in respiration are more intensively mediated to the cerebral circulation of a newborn with verified PIVH. This could be explained by the concept of a pressure passive cerebral circulation suggested by Lou *et al.* 1979.

We may speculate on whether the higher ventilator frequencies in the control infants may cause some bias. This is unlikely because the variabilities of respiratory activity were fairly similar in the controls and in the babies with PIVH. In fact, the spectral densities of respiration and ΔZ corresponding to the respiratory rate were slightly lower in the infants with PIVH than in the controls, and yet the respective cross-contribution of respiration to ΔZ was higher in the infants with PIVH than in the controls.

The maturity of the subjects in our two groups differed slightly. We believe that this did not cause a major problem, because neither the structure of the cerebral vascular bed nor the incidence of PIVH changed very much from the gestational age of 24–32 weeks.

Spectral anlaysis makes it possible to quantify signal variabilities in the frequency domain. The classical method for the estimation of joint variability between two signals is to compute their cross-spectral density (GRÖNLUND *et al.*, 1989;

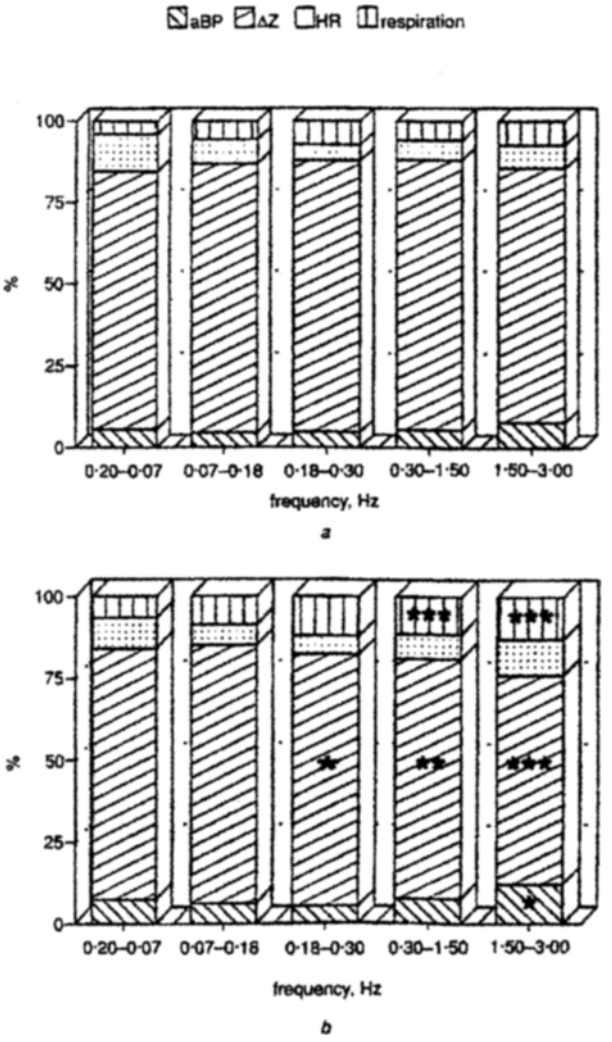

Fig. 2 *Frequency-specific signal source contributions of ΔZ, in (a) control infants; (b) infants with PIVH; autocontribution of ΔZ signal was dominant; auto-contribution of ΔZ was lower at frequencies > 0·18 Hz in infants with PIVH than in controls (p = 0·039 for F3, p = 0·002 for F4 and p < 0·001 for F5); cross-contribution of respiration to ΔZ was higher at frequencies F4 and F5 (p < 0·001) in infants with PIVH than in controls; cross-contribution of aBP to ΔZ was higher in PIVH group than in control group in high-frequency region F5 (p = 0·016)*

VÄLIMÄKI, *et al.*, 1990). In our study spectral anlaysis, however, displayed the linkage between the arterial blood pressure and the cerebral circulation, but left the simultaneous respiratory influence undetected. Nor does the cross-spectrum identify the effector of influence; it describes inter-relations only between two signals at a time. In the MAR model we can utilise internal signal sources and transfer functions between the signals to provide measures of the signal source contribution, and hence display directly the magnitude and the origin of the interaction between the signals. The direction of the influence can thus be examined, provided that there is a physiological explanation. All this can be done simultaneously for several signals (KALLI *et al.*, 1988).

In the present study, we used the transcephalic electrical impedance plethysmography. It is non-invasive, can be used continuously and does not interfere with the nursing of the baby. Namon *et al.* (NAMON *et al.*, 1967) used dogs with the circulation connected to a pulse-oxygenator system. As the pulsatile component of the flow was reduced, the height of the pulsatile transcephalic impedance fell. The amplitude of the pulsatile signal varied, depending on the respective changes in the pCO_2 which is a powerful regulator of brain vascularity. An important point to remember is that the impedance technique does not estimate total cerebral blood flow, only the pulsatile component and beat-by-beat changes in the blood volume of the brain. A positive and meaningful correlation has been found between the strain gauge plethysmography and impedance techniques in the study of human neonatal cerebral circulation (COSTELOE *et al.*, 1984). Also, a positive correlation between the pulsatile component of transcephalic impedance and blood flow velocity, as well as the pulsatility index in the anterior cerebral artery of the premature neonate, has been established (FRENZEL *et al.*, 1989). Colditz *et al.* (COLDITZ *et al.*, 1988) found a positive correlation between the peak amplitude of ΔZ and the Xenon-clearance method in the estimation of changes in the cerebral blood flow of human neonates, but the impedance technique tended to underestimate these changes. Only weak correlations were found between the peak amplitude of ΔZ and radiolabelled microspheres and laser Doppler spectroscopy (COLDITZ *et al.*, 1993). Concerning the latter, this is understandable because the laser Doppler spectroscopy focuses on the cortical circulation, whereas the impedance method deals with the global cephalic tissue, and a major portion of cerebral circulation is directed to the central structures rather than the cortex at the gestational age of below 32 weeks. The greatest problem of the transcephalic impedance technique is that it is extremely vulnerable to movement artefacts. In part this can be eliminated by recording during quiet sleep, signal averaging and template matching (Murphy 1987), but an averaged signal cannot be utilised for the MAR modelling. Moreover, the scalp blood flow may induce a bias. However, it has been experimentally investigated and theoretically calculated that scalp blood flow contributes less than 20% to the ΔZ signal (MURRAY, 1981; NAMON *et al.*, 1967; WEINDLING *et al.*, 1982). At present, the pulsatile component of transcephalic electrical impedance is believed to reflect instantaneous changes in total cerebral blood volume, and thus the pulsatile component of cerebral blood flow.

Several other techniques have been used to study the cerebral circulation in newborns. Decreased cerebro-vascular resistance (BADA *et al.*, 1979) and a fluctuating pattern of cerebral blood flow (PERLMAN and VOLPE, 1982; PERLMAN *et al.*, 1983) have been found in infants with PIVH by measuring cerebral blood flow with the Doppler technique. A new Doppler method still under development is continuous monitoring of flow velocity in the mean cerebral artery (FENTON *et al.*, 1990). A disadvantage of Doppler monitoring is that it displays changes of flow velocity, not flow, in a single artery. ^{133}Xe clearance has been used to quantify neonatal cerebral circulation since 1977 (LOU *et al.*, 1977). This technique has been considered accurate, except for low flow rates. A disadvantage is the radiation of the isotope, and thus it is not a suitable method for repeated measurements, only momentary ones. Venous occlusion plethysmography (CROSS *et al.*, 1976) can be used in scientific experiments in healthy full-term infants, but not in ill preterm babies during intensive care, because it may be hazardous owing to venous congestion. Near-infrared spectroscopy is a promising new cot-side technique under vigorous development, but it has many similar problems to ΔZ (BRAZY *et al.*, 1985; LIVERA *et al.*, 1992; ROLFE *et al.*, 1992).

In the present technical study we investigated six babies, three of whom had a severe grade III PIVH at the beginning of the study. Thus, the results must be interpreted with caution because of the small number of babies. The length of the sample is also an important limiting factor to the relevance of the low-frequency variability; it is thought that at least three cycles of the slowest periodic oscillation must be included in the sample. Therefore, only frequencies above 0·025 Hz can be reliably studied in 2 min samples. The lowest frequency studied was 0·02 Hz in our system. On the other hand, the sample length had to be limited because a stationary, movement-artefact free segment is essential for the reliability of the analysis.

The identification of infants with disturbed control of cerebral circulation may be possible with methods allowing the study of simultaneous interrelations between cerebral and systemic circulation and respiration. In the present study, we were able to detect differences between preterm infants with and without PIVH in the impact of systemic circulation and respiration on cerebral circulation. On the basis of our observations, we conclude that cerebral circulation, continuously assessed with the pulsatile component of transcephalic electrical impedance, studied together with systemic circulation and respiration and analysed with MAR modelling yields information about simultaneous interactions between the cerebral circulatory and cardiorespiratory systems in preterm babies. The applicability of this cot-side technique warrants further studies immediately after birth.

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