Original Paper

Biol Neonate 1995;68:91–99

Acute Effects of Indomethacin on Cerebral Hemodynamics and Oxygenation

Manon J.N.L. Benders
Caroline A. Dorrepaal
Margot van de Bor
Frank van Bel

Department of Pediatrics,
Division of Neonatology,
University Hospital Leiden,
The Netherlands

Key Words
Indomethacin infusion
Cerebral blood flow/
oxygenation
Preterm babies

Abstract
Although an indomethacin-induced decrease of brain perfusion in preterm infants has been well established, the acute effects of this vasoactive drug on cerebral hemodynamics and oxygenation are not well documented. Using near infrared spectroscopy we monitored in 6 very preterm infants changes in cerebral blood volume (ΔCBV) and cytochrome oxidase concentration ($\Delta Cytaa_3$), used as relative measures of changes in brain perfusion and as an indicator for cellular oxygenation of brain tissue, during and up to 1 h after indomethacin infusion. ΔCBV showed a quick blood-pressure-related increase as compared to baseline (preindomethacin values) during indomethacin infusion (averaged maximal increase 13%), followed by a sharp decrease below baseline values (averaged maximal decrease 24%). There was a sustained recovery to baseline during the registration period. $\Delta Cytaa_3$ showed a small, early increase in 4 of 6 babies, followed by a substantial decrease below baseline in 5 babies. $\Delta Cytaa_3$ showed only a partial recovery in those 5 babies during the study period. We conclude that a therapeutic dose of indomethacin may cause substantial swings in brain perfusion and a marked and rather longstanding decrease in $Cytaa_3$, suggesting a decrease in cellular oxygenation of brain tissue. Awareness of these effects may be important in sick preterm babies during periods of pulmonary and cardiac instability.

Frank van Bel, MD, PhD
University Hospital Leiden
Neonatal Unit, Building 1-J9-R
PO Box 9600
NL–2300 RC Leiden (The Netherlands)

0006–3126/95/
0682–0091$8.00/0

Introduction

Indomethacin, a prostaglandin inhibitor, has been used extensively for noninvasive closure of a hemodynamically important patent ductus arteriosus (PDA) in the preterm infant. Indomethacin has a constrictive action on the vascular beds of important organ systems in the newborn animal and human neonate [1–4]. Several studies showed an increase of the resistance of the cerebral vascular bed with a subsequent decrease in brain blood flow up to 40% for at least 1 h after administration of a therapeutic dose of indomethacin to preterm babies [2, 5].

Although immediate significant increases in arterial blood pressure have been reported during indomethacin infusion in experimental and clinical studies [6, 7], the impact of these acute hemodynamic pertubations on the preterm cerebral circulation, which has a vulnerable autoregulation [8], and on metabolism, is not well documented.

We therefore monitored cerebral perfusion and cellular oxygenation of brain tissue in 6 preterm babies, using near infrared spectroscopy (NIRS), during and up to 1 h after intravenous infusion of 0.1 mg/kg indomethacin.

Patients and Methods

The study was performed on preterm infants, who received an initial intravenous dose of 0.1 mg/kg of indomethacin for noninvasive closure of PDA. The indomethacin was infused over a 5-min period. The diagnosis of PDA was made on clinical symptoms and radiographic features, and confirmed by Doppler echocardiographic investigation. Informed parental consent was obtained in all infants. The study was approved by the scientific board of the Department of Pediatrics.

Assessment of Cerebral Hemodynamics and Oxygenation by NIRS

The head of the neonate is relatively transparent to near infrared light. Hemoglobin (Hb) and cytochrome oxidase (the terminal member of the mitochondrial respiratory chain) are natural chromophores and both have an oxygenation-dependent absorption in this wavelength region. By selection of the appropriate wavelength, algorithms have been developed to convert absorption changes into changes in concentration of oxygenated Hb (ΔHbO_2), deoxygenated Hb (ΔHbR), total Hb ($\Delta Hb_{tot} = \Delta HbO_2 + \Delta HbR$) and cytochrome oxidase ($\Delta Cytaa_3$) in mmol/l [9, 10]. Quantification of the NIRS variables into absolute concentration changes presupposes that the pathlength is known. The interoptode distances in the present study ranged from 5 to 6 cm. The optical pathlength is supposed to be considerably greater than the interoptode distance, due to significant scattering of light in brain tissue. Similar to earlier studies by others we assumed an optical pathlength of 4.4 times the interoptode distance [9]. The NIRS instrument used (Radiometer, Copenhagen, Denmark), consisted of four semiconductor laser diodes with wavelengths of 904, 845, 805 and 775 nm. The lasers were operated sequentially, and pulsed with a repetition rate of 500 Hz for 200 ns. We placed the transmitting and receiving optodes on the parietal-frontal regions on both sides of the head above the ear. Changes in optode position will cause changes in pathlength which results in absorption changes not related to changes in cerebral blood or tissue oxygenation. We therefore used a proper fixation method of the optodes as described earlier [11]. The energy emitted by each diode was well within the orders of the British Standards Institute safety limits (BS 4803).

Relative changes in cerebral blood volume (ΔCBV) were calculated using the following equation: $\Delta CBV = \Delta Hb_{tot} \times 0.89 / [Hb]$, where [Hb] is the large vessel hemoglobin concentration in g/dl [12]. Changes in ΔCBV are thus relative changes from the baseline value and expressed in ml/100 g brain tissue. Earlier studies showed a good relationship with changes in actual brain blood flow, determined with the ^{133}Xe clearance method [10, 13]. We therefore considered that ΔCBV indicated changes in brain perfusion, if changes in ΔCBV were caused predominantly by changes in ΔHbO_2. $\Delta Cytaa_3$ is supposed to indicate changes in the oxidation level of the intracerebral mitochondrial enzyme cytochrome oxidase and has been used as a relative measure of brain cell oxygenation [12, 14]. Changes in $\Delta Cytaa_3$ are thus relative changes from the baseline value and are expressed in mmol/l.

Study Design, Data Collection and Analysis

NIRS registrations started at least 30–60 min before the start of the study to exclude the possibility of system drift. Indomethacin infusion started at the mo-

ment a stable baseline was reached for at least 5–10 min. The recordings ended 1 h after the completion of the indomethacin infusion.

Changes relative to baseline in HbO_2 (ΔHbO_2), HbR (ΔHbR), Hb_{tot} and $Cytaa_3$ ($\Delta Cytaa_3$) were determined every 4 s and stored in a personal computer for off-line analysis and calculation of ΔCBV. Transcutaneous-derived arterial PO_2 and PCO_2 ($tcPO_2$ and $tcPCO_2$), and arterial blood pressure from an indwelling catheter (2 patients) were simultaneously determined every 4 s and stored in the computer. In 4 patients blood pressure was measured using an oscillometric method (Dynamap, Criterion, Tampa, Fla., USA) just before the start of indomethacin infusion and then every 2 min up to 6 min, until completion of the infusion. Further on, blood pressures in these 4 infants were measured at 10, 20, 30 40, 50, and at 60 min after the start of indomethacin infusion. Hematocrit was determined at regular intervals.

Statistical Analysis

For statistical purposes the 4-second interval values of ΔCBV, $\Delta Cytaa_3$, mean arterial blood pressure (MABP), $tcPO_2$, and $tcPCO_2$ were averaged per 2-min time interval. Because it appeared from our data (see 'results') that changes in arterial blood pressure during indomethacin infusion might play an important role in the simultaneously detected changes in ΔCBV and $\Delta Cytaa_3$, we evaluated the relation between the various variables during indomethacin infusion (0–6 min) separately from those obtained after completion of the indomethacin infusion (7–60 min).

To investigate which factor(s) was (were) responsible for the changes in ΔCBV or $\Delta Cytaa_3$ during indomethacin infusion, we selected those variables which are known to be involved in brain perfusion: MABP, $tcPO_2$ and $tcPCO_2$. We used the (averaged) values of these variables collected at baseline, and at 1–2, 3–4 and 5–6 min after the start of indomethacin infusion. A multiple linear regression model was used. The regression equation was:

$$Y = b_0 + b_{MABP} \cdot MABP + b_{TcPO_2} \cdot TcPO_2 + b_{TcPCO_2} \cdot TcPCO_2 + \Sigma a_{IV}{}^{IV} n$$

where ΔCBV or $\Delta Cytaa_3$ are the dependent variables and b_0 its mean over all the runs. The MABP, $tcPO_2$ and $tcPCO_2$ were taken as independent variables. These independent variables were either introduced or removed from the equation, based on their significance level ($p < 0.05$). To assess the interpatient variability (IV) five patient variables for the 6 patients were also introduced as independent variables. The patients were coded using the effect coding technique [15]. This coding for interindividual (patient) variability was primarily done to account for potential confounding variables that might obscure the effect of the chosen independent variables. The overall model was tested on significance by an F test and related p value. The R^2 of the regression equation gives the correlation between the predicted $\Delta CBV/\Delta Cytaa_3$, based on the independent variables of this regression model and the actual $\Delta CBV/\Delta Cytaa_3$ values. In other words: how well the model fits the data. Furthermore, each independent variables was tested whether it had a significant effect on $\Delta CBV/\Delta Cytaa_3$ by a partial F test and related p value. A more detailed explanation has been given by Glantz and Slinker [15].

To investigate a possible relation between brain perfusion (ΔCBV) or oxygenation ($\Delta Cytaa_3$), MABP and $tcPO_2$ and $tcPCO_2$ after the completion of the indomethacin infusion, we repeated the multiple linear regression model as described above. We used the (averaged) values of these values collected at 10, 20, 30, 40, 50 and 60 min after the start of the indomethacin infusion.

To further elucidate the (individual) relationship between MABP and ΔCBV (see 'results'), we used simple linear regression analysis. To test whether or not a curvilinear fit showed a better correlation as compared to linear regression, we used a polynominal regression analysis.

Differences between hemodynamic variables and extra oxygen need before indomethacin and at 5, 30 and 60 min were investigated by analysis of variance for repeated measurements followed by Scheffe's F test if statistically significant differences were obtained. To investigate whether or not intraindividual differences between pre- and 12 h postindomethacin hematocrit existed, the Student's t test for paired observations was used. p values of less than 0.05 were considered statistically significant.

Results

Nine patients were initially included in the study. In 3 of these 9 patients it was not possible to obtain reliable NIRS recordings for at least 1 h (2 patients) or reliable blood pressure measurements (1 patient). The remaining 6 patients all met the clinical signs for PDA (characteristic murmur, bounding pulses, hyperdynamic precordium) and Doppler echo-

cardiographic investigation confirmed PDA: a diastolic reverse flow in the main pulmonary artery with a predominantly left-to-right flow through the ductus arteriosus. Moreover, all infants were mechanically ventilated (Infant star, Infrasonics Inc., San Diego, Calif., USA) and none of them could be weaned from the ventilator. The patient characteristics of these 6 infants are shown in table 1. During the study period, the infants were stable and no major changes in ventilator settings were necessary. Table 2 gives PDA-related data (mean values ± SD of MABP, pulse pressure, heart rate and extra oxygen need) as a function of time. Only MABP upon completion of the indomethacin infusion was significantly higher as compared to the MABP before indomethacin administration. The other variables did not differ during the study period. $tcPO_2$ values were stable in each infant and within the normal range (mean ± SD: 61 ± 11 mm Hg), $tcPCO_2$ values were slightly elevated in 2 infants but stable in each infant (mean ± SD: 52 ± 6 mm Hg). Individual hematocrit values did not differ before indomethacin infusion as compared to values 12 h after its administration.

Individual Patterns of ΔCBV and ΔCytaa$_3$

Individual patterns of ΔCBV and ΔCytaa$_3$ are shown in figure 1. There was a biphasic response of ΔCBV after indomethacin administration: A variable but quick increase in ΔCBV in 5 of the 6 patients (patients 1–5) as compared to baseline during indomethacin-infusion with an average maximal increase of 0.4 ml/100 g brain tissue, followed by a decrease below baseline in all patients after completion of the infusion (average maximum decrease: 0.6 ml/100 g brain tissue). These changes were almost exclusively caused by

Table 1. Patient characteristics

Patient No.	GA, weeks	BW, g	Age, days
1	25.3	835	20
2	30.6	1,835	9
3	25.0	672	20
4	28.6	900	25
5	30.9	1,730	6
6	27.0	1,000	7
Mean ± 1 SD	27.9±2.3	1,162±450	14.5±7.4

Table 2. Mean values ± SD of MABP, pulse pressure, heart rate and extra oxygen need (FiO_2) as a function of time

	Before indomethacin	After indomethacin		
		5 min	30 min	60 min
MABP, mm Hg	35±3	46±6*	40±2	41±5
Pulse pressure, mm Hg	26±5	23±8	24±6	26±6
Heart rate	154±13	145±15	150±11	149±10
FiO_2	0.43±0.18	0.45±0.21	0.39±0.18	0.40±0.17

* $p < 0.01$ vs. before indomethacin.

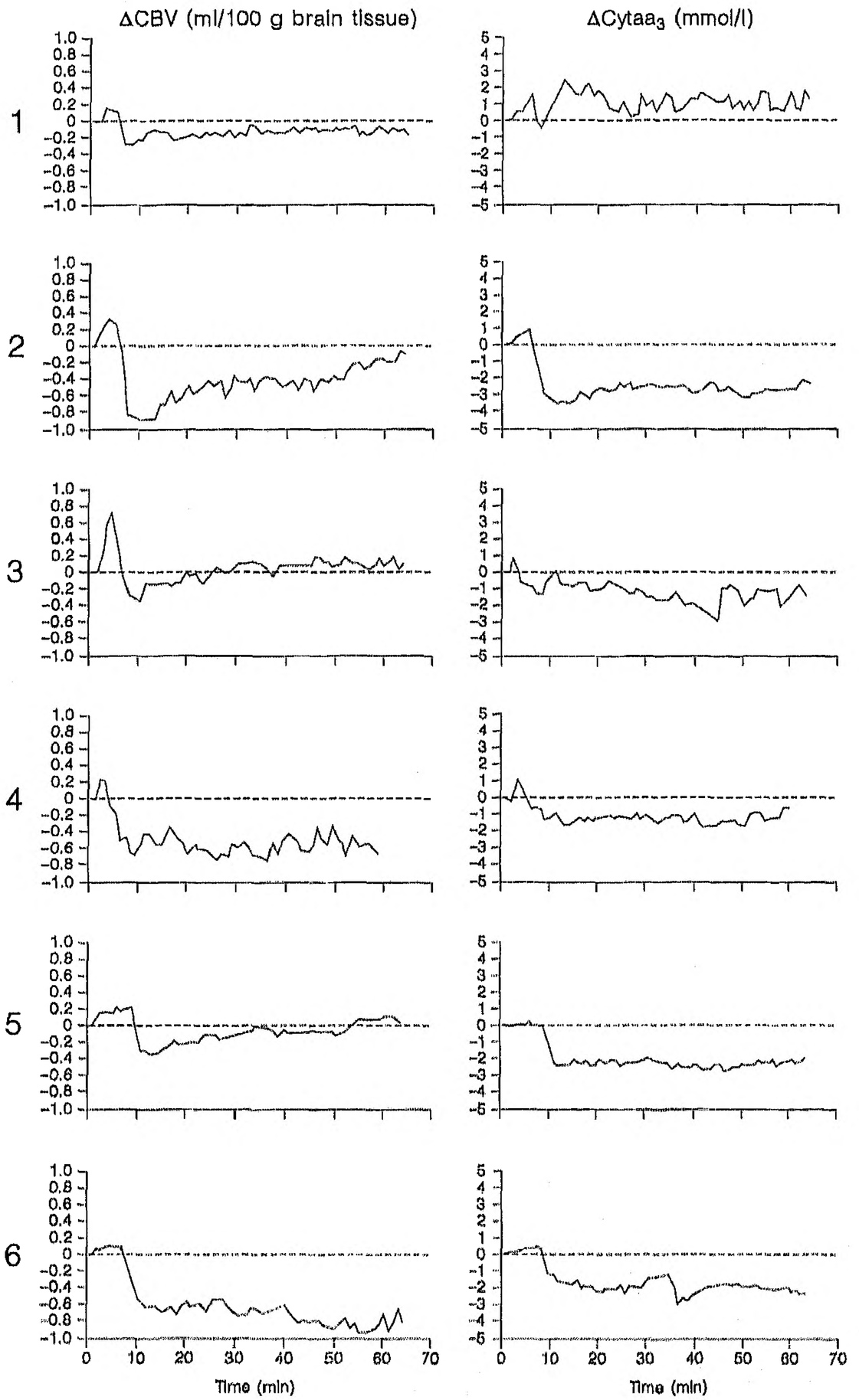
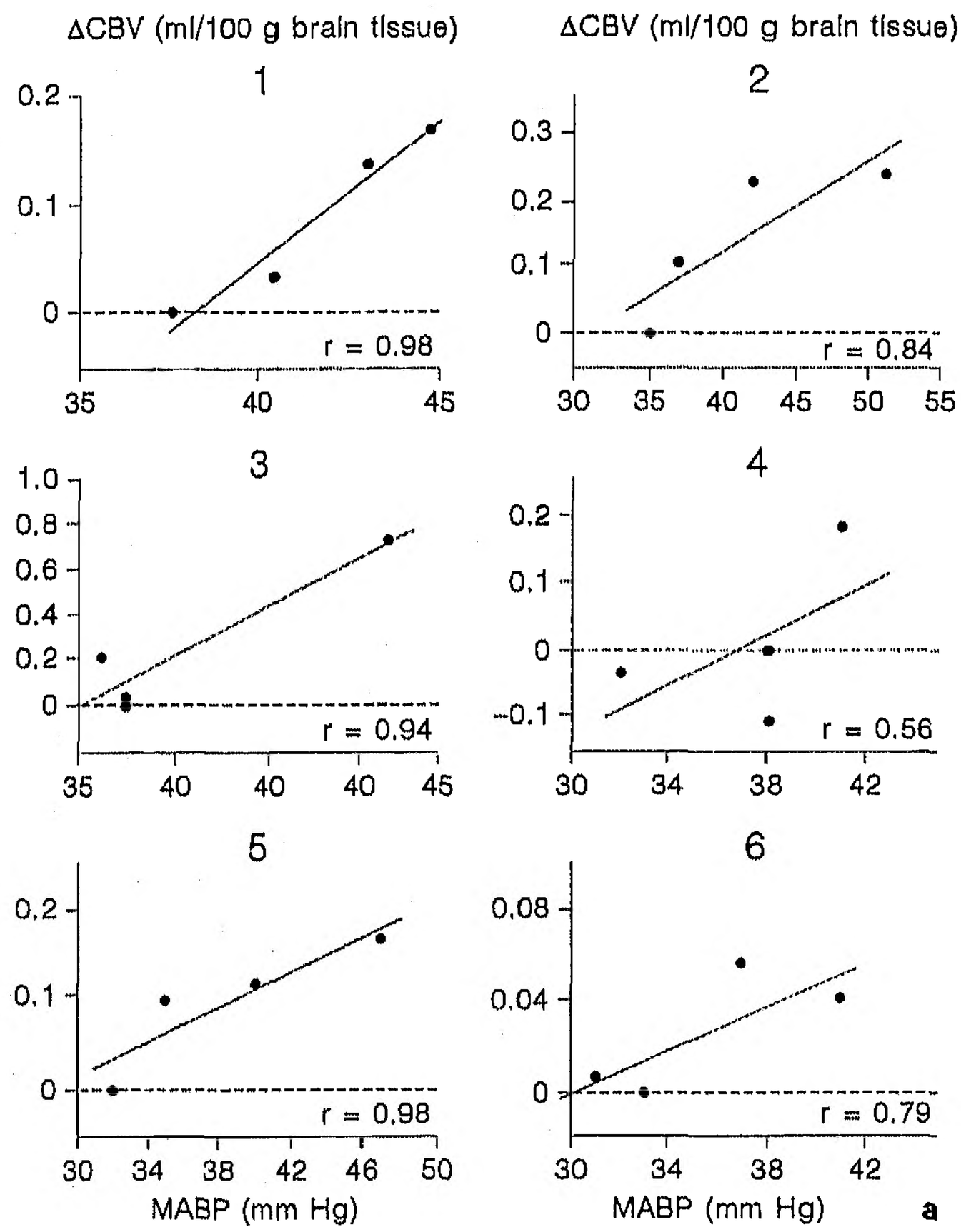


Fig. 1. Individual patterns of ΔCBV and $\Delta Cytaa_3$ as a function of time.



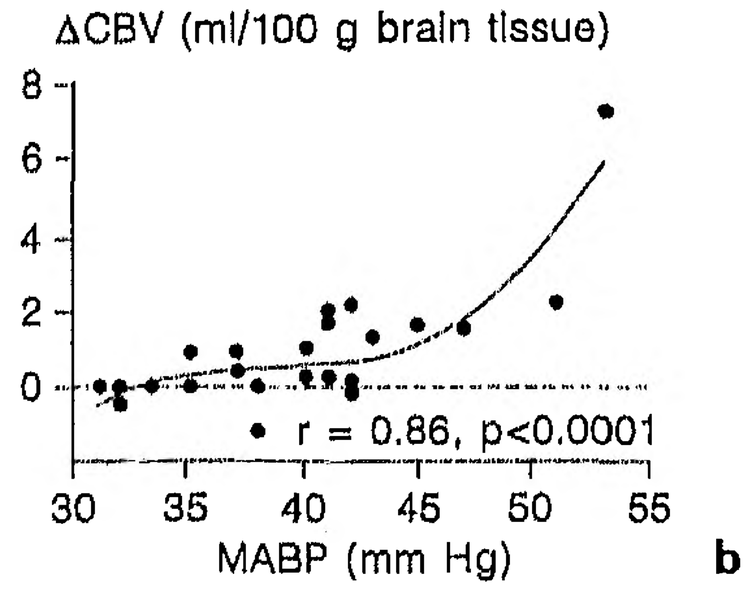


Fig. 2. a Individual relationships between MABP and ΔCBV during indomethacin infusion using linear regression analysis. **b** Overall relationship between MABP and ΔCBV during indomethacin infusion using a 3rd-order polynominal regression analysis.

changes in ΔHbO_2. Four patients showed a (mostly) sustained recovery to baseline during the recording time, but in the 2 other patients ΔCBV was well below baseline at the end of the NIRS registrations. $\Delta Cytaa_3$ showed a small early increase in 4 of the 6 babies (average maximum increase: 0.9 mmol/l) and a decrease well below baseline in 5 babies with no or an incomplete recovery to baseline at the end of the registration period (average maxi-

mum decrease: 3 mmol/l). One patient showed a second persistent increase in $\Delta Cytaa_3$ as compared to base line value from 10 min postindomethacin.

Relationship between ΔCBV or $\Delta Cytaa_3$, and MABP, $tcPO_2$, and $tcPCO_2$ during Indomethacin Infusion

We were able to construct significant regression models for both ΔCBV and $\Delta Cytaa_3$ (p values equations; <0.05 and <0.05). Only MABP appeared to be a significant predictor of ΔCBV (partial F value: 8.12, $p < 0.05$), whereas $tcPO_2$ and $tcPCO_2$ did not. There was no relation between $\Delta Cytaa_3$, and MABP, $tcPO_2$, or $tcPCO_2$. In both equations (ΔCBV and $\Delta Cytaa_3$) the interpatient variability was not significant.

Figure 2a shows the individual relationships between MABP and ΔCBV. The correlation coefficients (r) ranged from 0.56 to 0.98. The overall correlation coefficient appeared to be 0.74 ($p < 0.0001$), but increased to 0.86 ($p < 0.0001$) when a curvilinear fit was used (3rd order polynominal regression analysis). This curvilinear relationship is shown in figure 2b.

Relationship between ΔCBV or $\Delta Cytaa_3$, and MABP, $tcPO_2$, and $tcPCO_2$ after Completion of Indomethacin Infusion Onward

Also here we were able to construct significant regression models for both ΔCBV and $\Delta Cytaa_3$ (p values equations; <0.01 and <0.01). MABP, $tcPO_2$ or $tcPCO_2$ had no influence on ΔCBV or $\Delta Cytaa_3$ during the remainder of the study period. It must be mentioned, however, that MABP, $tcPO_2$ and $tcPCO_2$ were rather stable during this part of the study. The interpatient variability was significant in both equations (ΔCBV: F set 40.18, $p < 0.0001$; $\Delta Cytaa_3$: F set 10.51, $p < 0.001$).

Discussion

Although the magnitude of the individual changes were quite variable, the present study showed that intravenous infusion of indomethacin induced an arterial blood pressure-related increase of ΔCBV, whereas after the completion of the infusion ΔCBV decreased well below baseline in almost all patients. Assuming that normal CBV in these preterm babies is in the order of 2.5–3.5 ml/100 g brain tissue [12, 16], this means an approximately 13% increase and 24% decrease of CBV, respectively. As far as changes in CBV reflect changes in actual brain blood flow, the present study indicates substantial indomethacin-induced swings of brain perfusion in at least some of these preterm babies.

Although indomethacin has been shown to enhance the autoregulatory ability of the neonatal cerebral vascular bed [17], an initial, arterial blood pressure related increase in brain perfusion during indomethacin infusion, suggesting lack of cerebral autoregulation, has not yet been reported. Experimental studies report that the autoregulatory ability of the cerebral vascular bed is already operative in early fetal life, but that the autoregulatory range is narrow and resting cerebral perfusion pressure is very near its lower limit [18, 19]. Also in very preterm infants less than 32 weeks of gestation with a postnatal age between 12 and 72 h, cerebral autoregulation has been reported, again only over a narrow range (from 32 to 41 mm Hg) of mean arterial pressures [8]. Another study in preterm babies reported similar findings [20]. Although regulatory ability improves with advancing gestational and postnatal age and the range of blood pressures at which brain perfusion is constant is higher in more mature newborns [19, 21], Lou et al. [22] reported that especially in distressed (preterm) babies cerebral autoregulatory ability was often impaired. Fig-

ure 2a shows the individual best fits between ΔCBV and MABP of our study group during indomethacin infusion by linear regression analysis. It can be questioned, however, whether or not this is the appropriate manner to analyse these data for all patients: For instance, in patients 1, 3 and 4 the highest MABP values may have exceeded the upper limit at which autoregulation of the cerebral circulation was still operative, whereas in patient 5, the patient with the most advanced gestational age, the pattern of MABP-related changes suggests that the pre-indomethacin MABP was below the lower limit of autoregulatory ability of the cerebral vascular bed. In all instances a curvilinear fit rather than a linear fit might be more appropriate. This is supported by the curvilinear fit of the pooled results shown in figure 2b, which in fact show a blood-pressure-independent brain perfusion of between 35 and 42 mm Hg, surprisingly similar to earlier studies in preterm newborns with comparable gestational age [8]. However, our data must be interpreted with caution because of the small study population and heterogenicity in gestational and postnatal age.

The subsequent decrease in brain perfusion confirms earlier studies in newborn animals and preterm babies. In all these studies a decrease in brain blood flow (velocity) was reported up to 40% of pre-indomethacin values and lasting up to 2 h after indomethacin administration [2, 5, 23, 24]. Although recent studies showed a beneficial effect of early indomethacin treatment in very preterm babies with regard to periventricular-intraventricular hemorrhages [25], Leffler et al. [1] showed that cerebral oxygen consumption was decreased in hypotensive piglets that were treated with therapeutic dosages of indomethacin. As far as $\Delta Cytaa_3$ indicates changes in cellular oxygenation of brain tissue, our study provides further evidence that the indomethacin-induced drop in brain perfusion decreases brain tissue oxygenation in pulmonary and hemodynamically stable preterm newborns [26]. However, there is some concern that $\Delta Cytaa_3$ does not properly reflect changes in brain cell oxygenation. The use of wrong algorithms for calculation of changes in $\Delta Cytaa_3$ [10] and the low energy requirement of the brain cell in the preterm neonate may mask fluctuations in the oxidation-reduction level of cytochrome oxidase [27] and affect the reliability of $\Delta Cytaa_3$ as a marker of actual changes in oxidation of the enzyme cytochrome oxidase.

It is less likely that the hemodynamic changes, including the changes in ΔCBV, were related to an indomethacin-induced (transient) ductus arteriosus closure. In earlier studies in preterm infants, we found that the clinical signs of PDA subsided only 4 h after indomethacin administration [2, 3]. Moreover, in a very recent study in 20 preterm infants, in which we assessed the influence of indomethacin on cardiac and pulmonary hemodynamics, it appeared that ductal patency and pulmonary hemodynamics were not effected after indomethacin treatment until 4 h after its administration [28]. The (hemodynamic) data shown in table 2 also suggest that no important alterations occurred with respect to ductal patency during the study period.

Despite the results of the present study, indomethacin will remain an important drug for noninvasive closure of PDA. Moreover, its use for prevention of severe intraventricular hemorrhages [20] seems very promising. We propose, however, very slow infusion rates of indomethacin to avoid as far as possible blood-pressure-related acute increases in brain blood flow [26]. Furthermore, one should be aware that an indomethacin-induced decrease in brain perfusion and oxygenation in the sick preterm babies may compromize cerebral metabolism during periods of pulmonary and cardiac instability.

References

1 Leffler CW, Busija DW, Beasley DG: Effect of therapeutic dose of indomethacin on the cerebral circulation of newborn pigs. Pediatric Res 1987;21:188–192.

2 van Bel F, van de Bor M, Stijnen T, Baan J, Ruys JH: Cerebral blood flow velocity changes in preterm infants after a single dose of indomethacin: Duration of its effect. Pediatrics 1989;84:802–807.

3 van Bel F, van Zoeren D, Schipper J, Guit GL, Baan J: Effect of indomethacin on superior mesenteric artery blood flow velocity in preterm infants. J Pediatr 1990;116:965–970.

4 van Bel F, Guit GL, Schipper J, van de Bor M: Indomethacin-induced changes in renal blood flow velocity wave form in premature infants investigated with color Doppler imaging. J Pediatr 1991;118:621–626.

5 Pryds O, Greisen G, Johansen KH: Indomethacin and cerebral blood flow in preterm infants treated with patent ductus arteriosus. Eur J Pediatr 1988;147:315–316.

6 Leffler CW, Busija DW, Beasley DG, Fletcher AM, Green RS: Effects of indomethacin on cardiac output distribution in normal and asphyxiated piglets. Prostaglandins 1986;31:183–190.

7 Evans N, Iyer P: Change in blood pressure after treatment of patent ductus arteriosus with indomethacin. Arch Dis Child 1993;68:584–587.

8 Van de Bor M, Walther F: Cerebral blood flow velocity regulation in preterm infants. Biol Neonate 1991; 59:329–335.

9 Wray S, Cope M, Wyatt JS, Reynolds EOR: Characterization of the near infrared absorption spectra of cytochrome aa_3 and haemoglobin for the non-invasive monitoring of cerebral oxygenation. Biochim Biophys Acta 1988;933:184–192.

10 Pryds O, Greisen G, Skov LL, Friis-Hansen B: Carbon dioxide-related changes in cerebral blood volume and cerebral blood flow in mechanically ventilated preterm neonates: Comparison of near infrared spectroscopy and xenon-133 clearance. Pediatr Res 1990;27:445–449.

11 Liem KD, Oesenburg B, Hopman JCW: Method of the fixation of optodes in near infrared spectrophotometry. Med Biol Eng Comput 1992;30:120–121.

12 Wyatt JS, Edwards AD, Cope M, Delpy T, McCormick DC, Potter A, Reynolds EOR: Response of cerebral blood volume to changes in arterial carbon dioxide tension in preterm and term infants. Pediatr Res 1991;29:553–557.

13 Skov LL, Pryds O, Greisen G: Estimating cerebral blood flow in newborn infants: Comparison of near infrared spectroscopy and xenon-133 clearance. Pediatr Res 1991;30: 570–573.

14 Brazy JE, Lewis DV: Changes in cerebral blood volume and cytochrome aa_3 during hypertensive peaks in preterm infants. J Pediatr 1986;108:983–987.

15 Glantz S, Slinker BK: Primer of Applied Regression and Analysis of Variance. New York, McGraw-Hill, 1990, pp 777–789.

16 Brun NC, Greisen G: Cerebrovascular responses to carbon dioxide as detected by near-infrared spectrophotometry: Comparison of three different measures. Pediatr Res 1994;36:20–24.

17 Van Bel F, Klautz RJM, Steendijk P, Schipper IB, Teitel DF, Baan J: The influence of indomethacin on the autoregulatory ability of the cerebral vascular bed in the newborn lamb. Pediatr Res 1993;34:178–181.

18 Papile LA, Rudolph AM, Heymann MA: Autoregulation of cerebral blood flow in the preterm fetal lamb. Pediatr Res 1985;19:159–161.

19 Szymonowicz W, Walker AM, Yu VYH, Stewart ML, Cannata J, Cussen L: Regional cerebral blood flow after hemorrhagic hypotension in the preterm, near-term, and newborn lamb. Pediatr Res 1990;28: 361–366.

20 Greisen G, Trojaborg W: Cerebral blood flow, $PaCO_2$ changes, and visual evoked potentials in mechanically ventilated preterm infants. Acta Paediatr Scand 1987;76:394–398.

21 Altman DI: Cerebral blood flow in premature infants: Regulation, measurement, and pathophysiology of intraventricular hemorrhage; in Polin, Fox (eds): Fetal and Neonatal Physiology. Philadelphia, Saunders, 1992, vol II, pp 1587–1597.

22 Lou HC, Lassen NA, Friis-Hansen B: Impaired autoregulation of cerebral blood flow in the distressed newborn infant. J Pediatr 1979;94: 118–121.

23 Leffler CW, Busija DW, Fletcher AM, Beasly DG, Hessler JR, Green RS: Effects of indomethacin upon cerebral hemodynamics of newborn pigs. Pediatr Res 1985;19:1160–1164.

24 Ohlsson A, Bottu J, Govan J, Ryan ML, Fong K, Myhr T: Effect of indomethacin on cerebral blood flow velocities in very low birth weight neonates with a patent ductus arteriosus. Dev Pharmacol Ther 1993;20: 100–106.

25 Ment LR, Oh W, Ehrenkranz RA, Philip AGS, Vohr B, Allan W, Duncan CC, Scott DT, Taylor KJW, Katz KH, Schneider KC, Makuch RW: Low-dose indomethacin and prevention of intraventricular hemorrhage: A multicenter randomized trial. Pediatrics 1994;83:543–550.

26 Edwards AD, Wyatt JS Richardson C, Potter A, Cope M, Delpy DT, Reynolds EOR: Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet 1990;335:1491–1495.

27 Astrup J: Energy-requiring cell functions in the ischaemic brain. J Neurosurg 1982;56:482–497.

28 Benders MJNI, Van de Bor M, Van Bel F: Early effect of indomethacin on cardiac and pulmonary hemodynamics. Pediatr Res 1994;35:30A.