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Simultaneous Influence of Blood Pressure, P_{CO_2}, and P_{O_2} on Cerebral Blood Flow Velocity in Preterm Infants of Less than 33 Weeks' Gestation

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ABSTRACT. In extremely preterm infants, the protective capacity for cerebral blood flow (CBF) autoregulation may be impaired or absent, which increases the risk for developing cerebral lesions. The purpose of this study was to quantify the simultaneous influence of several vital parameters, such as mean arterial blood pressure (MABP), P_{CO_2}, and P_{O_2}, on cerebral blood flow velocity (CBFv), which is used as a measure for CBF. In 16 mechanically ventilated infants of <33 wk gestation, the CBFv in the internal carotid artery was measured every minute for 1 h by a computer-controlled pulsed Doppler device. MABP and transcutaneous P_{CO_2} and P_{O_2} were recorded as well. A multiple linear regression analysis was performed in each patient to determine the individual MABP, P_{CO_2}, and P_{O_2} reactivities as a measure for CBF autoregulation. The medians (and ranges) of the whole group were an MABP reactivity of 7.5% (−12.5 to 20.1%) rise in CBFv/1 kPa rise in MABP, a P_{CO_2} reactivity of 32.7% (−8.1 to 79.5%) rise in CBFv/1 kPa rise in P_{CO_2}, and a P_{O_2} reactivity of −3.1% (−14.2 to 7.9%) fall in CBFv/1 kPa rise in P_{O_2}. In preterm infants, the individual's capacity for MABP-, P_{CO_2}-, and P_{O_2}-dependent CBF autoregulation can be estimated by means of the present method, even if the vital parameters change simultaneously. (*Pediatr Res* 34: 173–177, 1993)

Abbreviations

CBF, cerebral blood flow
CBFv, CBF velocity (cm/s)
MABP, mean arterial blood pressure (kPa)
MLRA, multiple linear regression analysis
t.c., transcutaneous
VLBWI, very-low-birth-weight infant

About 10 to 20% of long-term surviving VLBWI will suffer from cerebral lesions originating during the first few days of life (1). Important prerequisites are the vulnerability of the immature brain structures and a disturbed or immature autoregulation of CBF (2, 3). CBF is influenced by rapid changes in, for example, MABP (4, 5), P_{CO_2} (4, 6–8), and P_{O_2} (8, 9), and also by variables such as hematocrit (10) and hypoglycemia (11). Autoregulation of CBF, mediated by diameter changes of the cerebral resistance vessels, is the adaptive mechanism. [Autoregulation is used to describe the autonomous blood flow regulation of the brain in general. Therefore, the term "autoregulation" is not limited to the MABP-CBF autoregulation relationship, and the regulative result is not necessarily the constancy of CBF (see Discussion)]. For example, in healthy preterm infants, CBF is kept nearly constant despite changing MABP (MABP-CBF autoregulation), whereas CBF rises during acute hypercarbia or hypoxia (P_{CO_2}-CBF or P_{O_2}-CBF autoregulation) (6, 8). Each of these autoregulation relationships can be quantified by a "CBF-reactivity", which gives the percentage change of CBF per unit change in the corresponding parameter. In clinical circumstances, MABP, P_{CO_2}, and P_{O_2} may change simultaneously and interfere with their effects on CBF. Such interactions complicate the investigation of isolated "partial" relationships between CBF and one of these vital parameters. Our purpose was to establish a method for measuring the individual's capacity for CBF autoregulation in VLBWI by monitoring the vital parameters and CBFv, which may be used as a measure for CBF (12), and determining the different CBF reactivities by MLRA.

PATIENTS AND METHODS

Patients. Sixteen mechanically ventilated infants of <33 (range 25–32) wk gestation were studied at 2 to 8 d of age (Table 1). The infants were clinically stable with closed ducts. Ethical approval and informed parental consent had been obtained.

Methods. Every minute, a set of CBFv, MABP, P_{CO_2}, and P_{O_2} values was obtained during a 1-h observation period. Analysis was based solely on spontaneous changes in the observed parameters.

CBFv was measured by a computer-controlled dual-mode range gated Doppler system (HP 77020 A/AC/AR, Hewlett-Packard, Andover, MA) (13) with a Doppler probe fixed to the neonate's head by a holding device (patent pending DBP no. P4003603.0), as described previously (14, 15). The fixation device allowed monitoring for up to 2 h without readjustment. By B-scan, the sample volume (diameter, 4 mm) was adjusted to one of the internal carotid arteries beside the sella turcica, where the vessel is directed towards the anterior fontanelle (16), the cosine of the angle of insonation approximating 1. To minimize energy load on brain (17), the Doppler system was activated by the computer for 6 s/min. The average flow velocity of this sample period was used as CBFv. The SEM of the captured pulse cycles was determined as 0.24 (SD 0.9) cm/s in the last nine patients, which was <2% of the mean CBFv.

Transcutaneous P_{CO_2} and P_{O_2} were recorded every minute. P_{CO_2} was measured by a TCM 20 TC carbon dioxide monitor (Radiometer, Copenhagen, Denmark). At the start and end of each study, the instrument was calibrated against a capillary

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Table 1. *Clinical data of preterm infants studied (n = 16)**

Patient	Gestational age (wk)	Birth wt (g)	Postnatal age (d)	RDS	PVH
1	30	1980	8	n	1°
2	29	650	2	3°	1°
3	30	2015	2	3°	n
4	31	890	6	n	n
5	30	1560	4	2°	4°
6	30	920	4	2°	n
7	30	1540	5	2°	n
8	29	1370	5	n	n
9	27	870	5	n	2°
10	32	1935	4	n	n
11	30	1580	4	n	2°
12	28	865	6	n	n
13	30	545	6	n	n
14	28	1600	4	n	n
15	25	905	8	4°	n
16	28	1325	5	n	n

* RDS, respiratory distress syndrome; PVH, periventricular hemorrhage; n, normal.

blood gas analysis (AVL Gas Check 940, Graz, Austria). P_{O_2} was measured by a TCM 2 TC oxygen monitor (Radiometer).

MABP was measured oscillometrically (Dinamap, Criticon, Tampa, FL) in intervals of 3 to 5 min on the right or left upper arm. By linear interpolation, one value per minute was generated.

Statistics. In each patient, an MLRA was carried out to determine capacity for CBF autoregulation. The terms (MABP − MABP-mean), (P_{CO_2} − P_{CO_2}-mean), and (P_{O_2} − P_{O_2}-mean) were used as independent variables. The individual means were subtracted from the data to avoid a constant term in the multiple regression equation. (CBFv − CBFv-mean) was used as a dependent variable. Additionally, this term was divided by CBFv-mean to estimate the multiple regression coefficients MABP reactivity, P_{CO_2} reactivity, and P_{O_2} reactivity, not as absolute, but as relative change in CBFv/1 kPa change in the corresponding vital parameter. The reactivities, their standard errors, the partial coefficients of determination, and the multiple correlation coefficient were calculated by standard software (Statgraphics 2.6, STSC, Inc., Rockville, MD).

Some restrictions, however, are inherent in the method. The influence of MABP, P_{CO_2} and P_{O_2} on CBFv could be analyzed only if there was a significant change in the vital parameter. Readings of P_{CO_2} and P_{O_2} were in units of 1 mm Hg, approximately 2% of the absolute values. Therefore, a minimal coefficient of variation of at least 2% was defined for inclusion of P_{CO_2} and P_{O_2} in the analysis. The minimal coefficient of variation for MABP was defined as 5% because of the measurement error of about 3 to 5% (18) and the use of linear interpolation between the MABP samples.

Another inherent problem in the MLRA was colinearity between the vital parameters. From computer simulations, 0.7 was found to be the borderline correlation coefficient between the vital parameters, above which the estimated CBF reactivities become numerically unstable. If the correlation coefficient for P_{CO_2}-P_{O_2} and MABP-P_{O_2} exceeded 0.9, the influence of P_{O_2} on CBFv was neglected. If the correlation coefficient for MABP-P_{CO_2} exceeded 0.9, the estimated CBF reactivities were regarded as unreliable. Comparable considerations apply to negative correlation coefficients.

To detect the relative influences of the vital parameters on CBFv, partial correlation coefficients were calculated. Their squares, which are the partial "coefficients of determination" (19), measure the degree by which a change in the vital parameters determines changes in CBFv.

In infants with significant variation in MABP, the partial MABP-CBFv relationship was estimated from the data, assuming P_{CO_2} and P_{O_2} to be constant throughout the measurement. This was done by correcting the CBFv data for the influence of P_{CO_2} and P_{O_2}, using the multiple regression equation and the individual P_{CO_2} and P_{O_2} reactivities. The same was done for the individual partial P_{CO_2}-CBFv and P_{O_2}-CBFv relationships.

MLRA, *t* test, and Spearman rank correlation analysis were used as appropriate.

RESULTS

In the 16 infants studied, the values for CBFv, MABP, P_{CO_2}, and P_{O_2} and their variations were within the physiologic range of this age group (Table 2). In four patients, oxygen saturation was measured instead of P_{O_2}. In some cases, one or more vital parameters were too stable to determine the corresponding CBF reactivities (Table 2, highlighted). The t.c. P_{CO_2} and P_{O_2} corresponded with the blood gas samples at the end of each study.

Table 3 shows the correlations between the individual vital parameters. We observed low correlations between MABP and P_{CO_2}, except in patient 10 ($r = -0.90$). The strongest correlation between P_{CO_2} and P_{O_2} was found in patient 4 ($r = 0.96$). Regarding the whole group, there were no significant correlations between the vital parameters (MABP-P_{CO_2}, $p = 0.59$; MABP-P_{CO_2}, $p = 0.24$; P_{CO_2}-P_{O_2}, $p = 0.08$).

Table 4 summarizes the results of the individual MLRA. The medians (and ranges) of the whole group were an MABP reactivity of 7.5% (−12.5 to 20.1%) rise in CBFv/1 kPa rise in MABP, a P_{CO_2} reactivity of 32.7% (−8.1 to 79.5%) rise in CBFv/1 kPa rise in P_{CO_2}, and a P_{O_2} reactivity of −3.1% (−14.2 to 7.9%) fall in CBFv/1 kPa rise in P_{O_2}. The highest MABP reactivity was found in patient 5, who developed severe periventricular leukomalacia after a 4° hemorrhage during the neonatal period. All P_{CO_2} reactivities exceeded 27%/kPa except in patient 10, where the estimated MABP and P_{CO_2} reactivities were unreliable because of colinearity between MABP and P_{CO_2}. Except for patient 5, all P_{O_2} reactivities were negative. Comparing P_{CO_2} and P_{O_2} reactivities in units of kPa, the direct effect of P_{O_2} on CBFv was about 10 times less than that of P_{CO_2}.

Table 4 gives the partial coefficients of determination (r^2) of the vital parameters. In general, P_{CO_2} had the strongest influence on CBFv, followed by MABP and P_{O_2}. In some cases, however, MABP predominated over P_{CO_2}.

The multiple correlation coefficient (Table 4) was significant in patient 7 ($p < 0.05$) and highly significant in the other patients ($p < 0.01$), indicating a strong correlation between CBFv and

Table 2. *Mean (and SD) of CBFv and vital parameters**

Patient	CBFv (cm/s)	MABP (kPa)	P_{CO_2} (kPa)	P_{O_2} (kPa)
1	9.7 (2.8)	5.13 (0.29)	5.99 (0.55)	
2	8.7 (1.5)	4.67 (0.27)	6.23 (0.20)	11.04 (0.27)
3	8.8 (0.7)	6.87 (0.37)	4.87 (0.11)	8.27 (0.68)
4	13.4 (3.2)	4.09 (0.24)	5.82 (0.32)	8.05 (0.66)
5	12.1 (2.9)	5.06 (0.68)	5.25 (0.18)	8.32 (0.63)
6	10.1 (1.6)	4.79 (0.64)	5.47 (0.33)	7.37 (1.14)
7	9.4 (1.5)	5.57 (0.71)	**5.26 (0.10)**	
8	10.3 (1.9)	4.40 (0.26)	**4.80 (0.07)**	6.83 (0.42)
9	14.3 (3.8)	8.01 (1.53)	4.36 (0.46)	
10	11.1 (0.8)	5.81 (0.75)	5.50 (0.20)	
11	10.5 (2.9)	5.66 (0.37)	3.98 (0.47)	9.66 (1.26)
12	17.5 (1.3)	**5.74 (0.25)**	**6.95 (0.09)**	8.04 (0.25)
13	17.4 (1.7)	4.71 (0.25)	**5.66 (0.08)**	**7.13 (0.07)**
14	22.8 (1.7)	5.40 (0.39)	4.87 (0.12)	11.16 (0.74)
15	9.8 (1.3)	6.06 (1.16)	**4.95 (0.05)**	7.03 (0.35)
16	14.2 (1.8)	4.62 (0.44)	4.44 (0.39)	10.66 (0.73)

* In each patient, 60 sets of simultaneous values were obtained (one per minute). Nearly constant vital parameters, stated by small coefficients of variation (<5% for MABP, <2% for P_{CO_2} respective to P_{O_2}) are in bold. The corresponding CBF reactivities cannot be determined, as explained in Patients and Methods. Absence of data indicates that oxygen saturation was measured instead of P_{O_2}.

Table 3. *Correlation between the individual vital parameters**

Patient	Correlation		
	MABP-P_{CO_2}	P_{CO_2}-P_{O_2}	P_{O_2}-MABP
1	−0.51		
2	−0.22	0.58	−0.12
3	0.05	0.44	−0.03
4	−0.30	**0.96**	−0.34
5	−0.27	**0.72**	0.31
6	−0.19	−0.30	−0.40
7	ND		
8	ND	ND	−0.09
9	0.45		
10	**−0.90**		
11	0.01	**0.83**	−0.07
12	ND	ND	ND
13	ND	ND	ND
14	0.12	0.50	0.17
15	ND	ND	**0.71**
16	0.05	0.40	−0.43

* Correlation coefficients >0.70 or <−0.70 are in bold and indicate colinearity. In the MLRA, the corresponding CBF reactivities are not reliably calculable. Absence of data indicates that oxygen saturation was measured instead of P_{O_2}. ND, correlation coefficient was not determined because one or both vital parameters were nearly constant (see Table 2).

Table 4. *Individual MLRA**

Patient	Reactivity†			Partial r^2 (%)			Multiple r
	MABP	P_{CO_2}	P_{O_2}	MABP	P_{CO_2}	P_{O_2}	
1	−1.0 (5.3)	41.3 (3.0)		1	86		0.94
2	7.5 (3.2)	79.5 (5.2)	−3.5 (3.8)	8	80	1	0.92
3	6.1 (1.8)	26.8 (7.0)	−3.1 (1.1)	18	22	14	0.50
4	12.7 (9.1)	56.4 (6.9)	ND‡	3	55		0.74
5	20.1 (3.4)	54.9 (17.9)	7.9 (5.2)	41	16	4	0.87
6	11.9 (1.3)	32.7 (2.5)	−2.7 (0.8)	58	75	17	0.92
7	6.3 (2.7)	NS§		9			0.30
8	14.3 (6.9)	NS§	−14.2 (4.3)	5		13	0.42
9	9.8 (0.7)	31.4 (2.2)		79	78		0.96
10	6.5 (0.9)	−8.1 (3.2)		38	6		0.92
11	−4.5 (6.3)	67.6 (8.9)	−13.4 (3.4)	1	51	22	0.75
12	NS§	NS§					
13	−12.5 (3.6)	NS§	NS§	17			0.42
14	0.2 (2.0)	28.9 (7.1)	−1.5 (1.2)	0	23	3	0.47
15	10.5 (1.3)	NS§	−13.7 (4.2)	58		17	0.78
16	7.7 (1.3)	27.9 (1.4)	−1.5 (0.8)	27	79	3	0.92

* In each patient, 60 sets of parameters were obtained (one per minute).

† CBF reactivities of the vital parameters with standard errors in parentheses.

‡ ND, not determined. P_{O_2} reactivity in patient 4 was not determined because of strong colinearity between P_{CO_2} and P_{O_2} ($r = 0.96$; see Table 3).

§ Variation of vital parameter was not significant enough to determine the corresponding CBF reactivity.

the combined influence of the vital parameters. In patients with borderline changes in the vital parameters, the multiple correlation coefficient was relatively low (*e.g.* patient 7). In these cases, the undirected measurement errors of the instruments had a relatively strong influence on the statistical analysis. Large changes in the vital parameters were associated with high multiple correlation coefficients of up to 0.96 (patient 9), indicating that the combination of the vital parameters was sufficient to explain the course of CBFv.

The partial relationships between MABP, P_{CO_2}, and P_{O_2}, and CBFv are shown in Figure 1. In the whole study group, there were highly significant relationships between MABP or P_{CO_2} and CBFv (Fig. 1*A* and *B*, both $p < 0.01$). However, there were

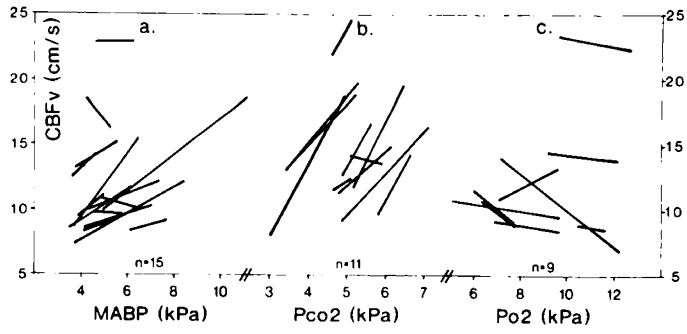

Fig. 1. *a*, Individual partial MABP-CBFv relationships of all patients with significant variation in MABP ($n = 15$). Each *line* shows the effect of the observed MABP fluctuations (MABP, mean ± 2 SD) on CBFv and corresponds to a regression line of a simple regression analysis. Its slope is equivalent to the individual MABP reactivity. *b* and *c*, Individual partial P_{CO_2}-CBFv and P_{O_2}-CBFv relationships.

individual differences. Figure 1*C* shows a slight rise of CBFv in all but one instance when P_{O_2} decreases ($p < 0.05$).

The results of the MLRA also make objective the interpretation of complex CBFv curves, when the vital parameters change simultaneously. This is demonstrated in patient 6, where the observed CBFv (Fig. 2*B*) is not obviously related to the curves of the vital parameters (Fig. 2*A*). At first, it seems that the CBFv is inversely related to P_{O_2}, with no relation to MABP or P_{CO_2}, but this subjective interpretation is refuted by the partial coefficients of determination (Table 4). The high multiple correlation coefficient of 0.92 indicates a strong relation between CBFv and the vital parameters. In Figure 2*B*, this is depicted by the similarity between the CBFv estimates, derived from the MLRA, and the observed course of CBFv. In the first 25 min, there were only slight changes in CBFv and the vital parameters. From 25 to 35 min, there was a peak rise in MABP of about 3 kPa, contributing to a rise of about 36% (3 kPa × MABP reactivity) in CBFv. After the MABP peak, the CBFv did not decrease due to a P_{CO_2} peak of about 1 kPa, contributing to a rise of about 33% (1 kPa × P_{CO_2} reactivity) in CBFv. This simultaneous influence of MABP and P_{CO_2} on CBFv was only slightly superimposed by the additional effect of P_{O_2}, contributing to an additional rise of up to 8% (−3 kPa × P_{O_2} reactivity) in CBFv. At the end of the measurement, the vital parameters and CBFv had nearly returned to their initial values.

DISCUSSION

In extremely preterm infants, CBF autoregulation may be impaired or absent, increasing the risk of cerebral lesions. Therefore, it is important to have a method for measuring the capacity for CBF autoregulation. In clinical circumstances, simultaneous changes in MABP, P_{CO_2}, and P_{O_2} on CBF make the investigation of partial autoregulation relationships difficult, as in patient 6 (Fig. 2). MLRA is a solution to this problem, requiring many sets of values, obtainable by continuous monitoring and capturing spontaneous changes in the parameters. Methods for t.c. P_{CO_2} and P_{O_2} and oscillometric MABP measurement are well established, as are Doppler methods for monitoring CBFv.

CBF and CBFv. The CBFv in one of the internal carotid arteries was used as a semiquantitative measure of CBF (12). About 40% of the brain blood flow passes through each internal carotid artery and can represent total CBF. The MABP, P_{CO_2}, and P_{O_2} reactivities measure relative changes in CBFv, as do i.v. xenon CBF studies. For the same reason, the angle of insonation need not be exactly zero, but must remain constant, as was achieved by the fixation device.

From animal studies, cerebral arteries >200 μm in diameter show resistance changes due to variations in MABP, P_{CO_2}, etc. (20). Yet one can only speculate how much of these resistance changes is contributed by the carotid artery compared with the

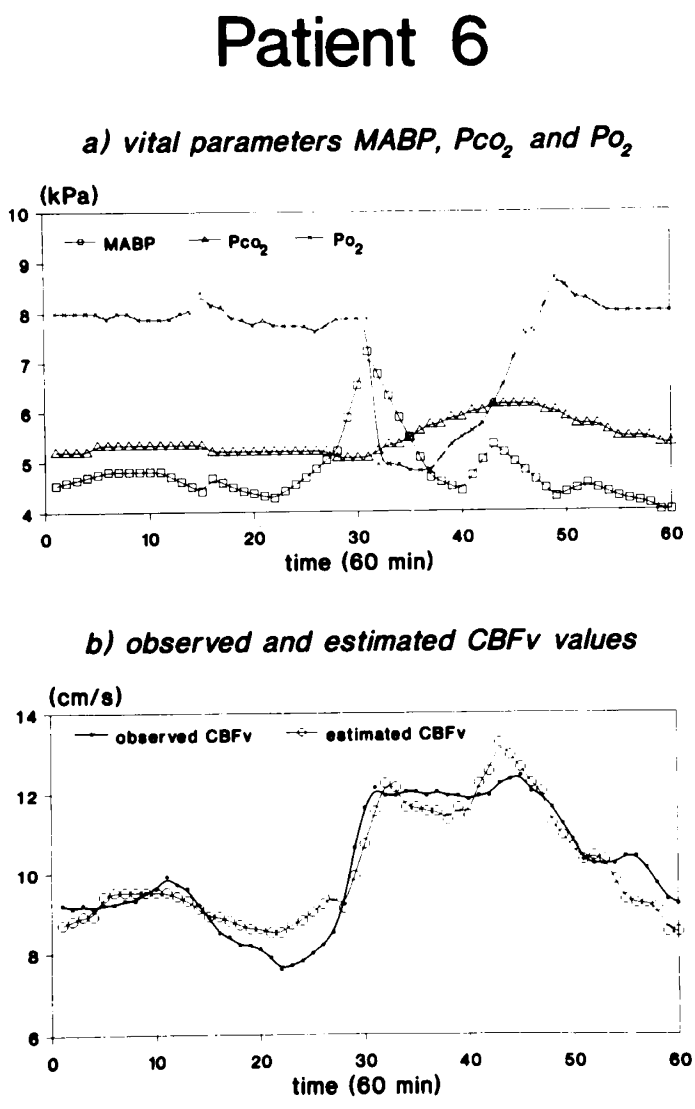

Fig. 2. Patient 6 (30 gestational wk, birth weight 920 g, 4th d). *a*, Course of vital parameters MABP, P_{CO_2}, and P_{O_2}; *b*, courses of observed CBFv (*bold line*) and estimated CBFv (*circles*), which correspond to the regression line of the MLRA.

smaller arteries. If the internal carotid artery of preterm infants is important in CBF autoregulation, mediated by diameter changes of the vessel, the proportionality between CBF and CBFv could be affected, and the effects of P_{CO_2}, P_{O_2}, and MABP on CBF would be underestimated. However, our results are comparable with results of xenon CBF studies (4, 21, 22), and so we assume proportionality between CBF and CBFv with only a small error.

The often complex course of CBFv can be interpreted by the MLRA, as in patient 6 (Fig. 2). By MLRA, the relationships between CBF and MABP, and P_{CO_2} and P_{O_2} can be "extracted" from the data.

CBFv and MABP. In healthy adults, the CBF is kept constant within a physiologic MABP range ("range of autoregulation"). This can be impaired in preterm infants, exposing their brains to the effects of hyper- and hypoperfusion (2). If MABP is within the individual's physiologic range, an MABP reactivity near zero indicates perfect MABP-CBF autoregulation, whereas a high MABP reactivity indicates impaired or absent MABP-CBF autoregulation (21). We observed MABP reactivities comparable to those in previous reports of 6 ± 5%/kPa (mean ± SD) (4) and 16.6 ± 15%/kPa (5) in preterm infants.

Patient 5, with the highest MABP reactivity, developed severe periventricular leukomalacia in the neonatal period, which suggests that impaired MABP-CBF autoregulation may be associated with intracranial bleeding (4, 21). However, impaired MABP-CBF autoregulation alters CBF only in combination with fluctuations in MABP. So it seems essential to maintain the MABP at physiologic levels, especially in case of an impaired MABP-CBF autoregulation. It remains uncertain whether impaired MABP-CBF autoregulation is a result of, or prerequisite for, cerebral lesions or whether there is a vicious circle. Further studies are needed to investigate the individual's capacity for MABP-CBF autoregulation from birth onward.

CBFv and P_{CO_2}. The healthy adult brain regulates an acute rise in P_{CO_2} by increasing CBF according to metabolic demand (12, 23). The normal adult P_{CO_2} reactivity is an approximate 30% rise in CBF/1 kPa rise in P_{CO_2} (7, 23). A P_{CO_2} reactivity close to zero indicates absent P_{CO_2}-CBF autoregulation (21) with constant CBF in spite of acute P_{CO_2} changes and was found in preterm infants with severe intracranial hemorrhage (4). Thus, in contrast to MABP-CBF autoregulation, "constancy of CBF" is not always synonymous with "healthy regulation of CBF." Acute changes in P_{CO_2} should be avoided because they may trigger brain lesions by inducing hyper- or hypoperfusion (8), especially with normal P_{CO_2}-CBF autoregulation.

Except for the nonestimable parameter in patient 10, all P_{CO_2} reactivities in our patients exceeded 27%/kPa, indicating healthy P_{CO_2}-CBF autoregulation when related to the adult normal value. The median P_{CO_2} reactivity of 32.7%/kPa was comparable to P_{CO_2} reactivities of 33 ± 6 (mean ± SD) and 29 ± 7%/kPa found in healthy preterm infants (4, 22). Other authors reported higher P_{CO_2} reactivities, varying between 52 ± 16 (mean ± SD) and 67 ± 33%/kPa (median 53%/kPa) (6, 7). These different findings suggest that there might be no normal value in preterm infants. Thus, not an absolute value but the individual's course of P_{CO_2} reactivity should better be judged.

In general, our patients were normocapnic, raising their CBFv during acute hypercarbia when correcting CBFv for the influences of MABF and P_{O_2}. Sustained hypercarbia, however, may be associated with normal CBFv. This could be explained by the well-known hypothesis that cerebral resistance vessels react more to extracellular pH than blood P_{CO_2} (24). According to the Henderson-Hasselbalch equation, this makes no difference to the effect of acute P_{CO_2} changes on CBFv, because acute P_{CO_2} changes are associated with acute pH changes. However, sustained hypercarbia with respiratory acidosis can be compensated by metabolic alkalosis with even normal pH and therefore normal CBFv.

CBFv and P_{O_2}. There is evidence that the brain reacts to P_{O_2} changes by inverse CBFv changes (8, 9), which is described by a negative P_{O_2} reactivity. Previous studies in preterm infants reported a mean P_{O_2} reactivity of −6.2%/kPa with no significant relation to CBF (22), and a significant median CBFv reduction of 0.06 cm/s/kPa rise in P_{O_2}, which was approximately −0.8%/kPa (9). We found a significant correlation between P_{O_2} and CBFv with a median fall of −3.1% in CBFv/1 kPa rise in P_{O_2}, and, except in one patient, all calculated P_{O_2} reactivities were negative.

The direct effect of P_{O_2} on CBFv was about 10 times less than the effect of P_{CO_2}, suggesting that the influence of P_{O_2} on CBF is negligible. However, from animal studies, an important but indirect effect of P_{O_2} on CBF is that prolonged hypoxia, often occurring in the unstable preterm infant, can impair CBF autoregulation (25). In our patients, there was no prolonged hypoxia during the measurement periods.

In summary, it was shown that, in clinical conditions, the capacity for CBF autoregulation can be estimated even if the influencing vital parameters change simultaneously, interfering in their effect on CBF. The MABP and P_{CO_2} reactivities in our patients were comparable to previous reports; a significant inverse relation between P_{O_2} and CBFv was found. In additional long-term studies, the noninvasive method presented here could be used to quantify the changing capacity for CBF autoregulation

in the VLBWI during the first days of life. Risk factors such as prolonged hypoxia could be quantified in their effect on CBF autoregulation. The method could help for stabilization of the cerebral circulation with the aim to prevent neurologic damage and improve prognosis.

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