Effect of fetal brainsparing on the early neonatal cerebral circulation

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Abstract

The effect of antenatal brainsparing on subsequent neonatal cerebral blood flow velocity (CBFV) was studied in very preterm infants. CBFV was determined, using a pulsed Doppler technique, both in the fetal and neonatal period. Neonatally, blood pressure and transcutaneous carbon dioxide tension (TcPCO₂) was monitored simultaneously; daily cranial ultrasound examinations were performed.

In infants with evidence of brainsparing a higher mean value of CBFV and a different pattern of changes of CBFV during the first week of life was demonstrated compared with infants with normal fetal cerebral haemodynamics. No differences were found in blood pressure and TcPCO₂. The incidence of intracranial haemorrhages and of ischaemic echodense lesions was also the same for both groups.

In a multivariate statistical model gestational age, antepartum brainsparing, and TcPCO₂ all contributed significantly in explanation of variation in CBFV. It is speculated that a different setting of cerebral autoregulation related to differences in gestational age or to brainsparing might explain the difference in changes found in neonatal CBFV.

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Following the report of Bada *et al* in 1979¹ considerable interest in the study of neonatal cerebral haemodynamics using Doppler ultrasound has arisen. The use of this technique in neonatology has been reported in a wide variety of pathological conditions including ductal patency, pneumothorax, and hydrocephalus. The association between intracranial haemorrhage (ICH)² or neonatal asphyxia³ and blood flow velocity waveforms has also been widely investigated. More recently, Wladimiroff *et al*⁴ and Arduini *et al*⁵ showed the feasibility of the pulsed Doppler technique, in combination with real time ultrasound in examining the fetal cerebral circulation. The phenomenon of fetal blood flow redistribution occurring in severe intrauterine growth retardation, well known from animal studies,⁶ could also be demonstrated in human pregnancy.⁷ During normal pregnancy the lowest vascular resistance is at the level of the placenta. However, during severe fetal growth retardation the region with the lowest vascular resistance is no longer the placental vascular bed, but will be at the level of cerebral vessels. In severe fetal growth retardation this will

result in a decrease of end diastolic velocities in the umbilical artery, while an increase in end diastolic velocities in cerebral vessels can be found. This centralisation of the fetal circulation is known as the 'brainsparing' effect. The ratio of umbilical pulsatility index (PI)/cerebral PI (U/C ratio) has been used as an index of the brainsparing effect.⁴ In fetal growth retardation a significant increase in U/C ratio was found.⁷ Consequences of antenatal brainsparing on cerebral haemodynamics in the preterm infant after birth are unknown. Therefore we studied the relation between antenatal haemodynamic adaptation as defined by a raised U/C ratio and cerebral haemodynamics in the neonatal period.

Patients and methods

A cohort of 117 pregnant women consecutively admitted to our department between February 1989 and December 1989 was studied. One pregnancy resulting in the birth of an infant with Down's syndrome was excluded. Two patients refused to take part in the study. In 11 cases intrauterine fetal death occurred. The data of 103 pregnancies resulting in the birth of 128 liveborn infants, with a gestational age at delivery between 25 and 33 weeks are reported. Reasons for hospital admission were imminent preterm labour (n=83), severe growth retardation (n=4), second/third trimester haemorrhage (n=2), abruptio placentae (n=2), and pregnancy induced hypertension (n=12). There were 81 singletons, 19 twin pregnancies resulting in the birth of 38 infants, and nine infants from triplet pregnancies.

FETAL BLOOD FLOW VELOCITY STUDIES

Antenatally, flow velocity waveforms were recorded from the umbilical artery and the middle cerebral artery. Recordings of signals from the middle cerebral artery were made at the level of the bifurcation of the internal carotid artery into the anterior and middle cerebral artery. Vessels were identified by real time ultrasound with a 3.5 MHz sector scanner (DRF400, Dasonics). Flow velocity waveforms were obtained with a 2 MHz pulsed Doppler probe (SD50 VingMed) attached to the imaging probe at a fixed angle of insonation of 30 degrees.⁸ Sample volume was 3 mm and the high pass filter was set at the lowest possible level of 100 Hz. Back scattered Doppler signals were displayed visually as a sonogram and the audiosignals were stored on audiotape. Recordings were made directly after maternal

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admission and thereafter at weekly intervals. The last measurement before birth was used for analysis. By replaying the stored audiosignal, spectral analysis was performed off-line using fast Fourier transformation. Calculations were performed on the maximum frequency envelope of the Doppler shift, which was automatically recognised by the Vingmed SD50. PI: $(V_{\text{sys}} - V_{\text{dias}})/V_{\text{mean}}$ ⁹ was calculated over at least five sequential cardiac cycles. Then the ratio of umbilical PI/cerebral PI (U/C ratio) was calculated.

We found in an earlier study that the one sided tolerance limit of the U/C ratio, calculated for normal pregnancies with a gestational age ranging from 25 to 33 weeks was 0.72.¹⁰ This limit delineates the lowest 95% confidence interval of a 5% chance for normal pregnancies to have a U/C ratio above this limit. A U/C ratio above the tolerance limit was considered to be indicative of the brainsparing effect. Infants were grouped according to the presence of signs of brainsparing.

NEONATAL CEREBRAL BLOOD FLOW VELOCITY (CBFV) STUDIES

In the immediate neonatal period, flow velocity waveforms from the middle cerebral artery were recorded in the transcranial plane. The same Doppler equipment was used. The Doppler transducer was placed on the temporal bone at 0.5–1 cm in front of the ear.¹¹ The angle between the Doppler beam and the axis of the vessel is near zero and permits determination of absolute flow velocities in this artery. The initial depth setting was 2.0 cm and by ranging the depth, the localisation of the sample volume was adjusted to obtain the maximal signal. The maximum frequency shift and thus the highest possible velocities were obtained by listening to the audio signal and observing the sonogram in real time. The complete audio spectrum was used to calculate the time averaged mean velocity (V_{mean}).¹² By replaying the audiotapes V_{mean} was calculated off-line automatically by the integrated computer system (SD50 VingMed) over at least five sequential cardiac cycles. Doppler studies in the neonate were performed at 1, 2, 4, 8, 12, 24, 48, 72, 120, and 168 hours after birth. Doppler studies were performed by one investigator (SAS). The results of the Doppler studies were not available to the attending clinicians.

OTHER MEASUREMENTS

Simultaneously with the neonatal Doppler recordings mean arterial blood pressure (MAP) (Dinamap 1846 SX) and transcutaneous carbon dioxide tension ($TcPCO_2$) (Hewlett Packard, type 78834A) were measured.

Neurosonography was performed at fixed intervals during the first week of life and stored on videotape. Neurosonographic findings were categorised by one observer (SAS) who was unaware of patient characteristics. The most severe ultrasound diagnosis at the end of the first week of life was used for classification. ICH was classified as proposed by Volpe.¹³ For

Table 1 Combined neurosonographic classification

Ultrasound classification	Criteria
Normal	No intracranial haemorrhage or a subependymal haemorrhage. Echodensities less bright than the choroid plexus
Suspect	Intraventricular haemorrhage (<50% of lumen filled). Any echodensity brighter than the choroid plexus, lasting less than three days
Abnormal	Intraventricular haemorrhage (>50% of lumen filled) and any intraparenchymal haemorrhage. Any echodensity brighter than the choroid plexus and lasting for more than three days.

the classification of ischaemic lesions known as echodensities the description of Pidcock *et al* was used.¹⁴ Any intraventricular haemorrhage or intraparenchymal haemorrhage was classified as a severe haemorrhage. Echodensities brighter than the choroid plexus and lasting for more than three days were considered severe forms of echodensities. The infants were subdivided according to evidence of severe ICH and/or severe echodensities on cranial ultrasound. For further analysis a classification based on the combination of haemorrhages as well as ischaemic lesions was used (table 1).

Infants were regarded as small for dates if their birth weight was below the 10th centile for gestational age, taking maternal parity and sex into account.¹⁵ All clinical decisions were made according to department standards. The study was approved by the ethics committee of the hospital.

STATISTICS

Mann-Whitney U test, Fisher's exact probability test, and analysis of variance for repeated measurements were used when appropriate, using the BMDP statistical program package. CBFV as the dependent variable was analysed using repeated measurements analysis. U/C ratio and gestational age were used as explaining variables; the time changing variables MAP and $TcPCO_2$ were used as covariables. The within subject covariance matrix was specified as having the compound symmetry structure. The coefficient of determination (R^2) was used to estimate the proportion of explained variance in neonatal CBFV.¹⁶ To select variables contributing significantly to the model a stepwise backward selection procedure based on the likelihood ratio test was done. This procedure means that first all variables are included in the model. Each variable not contributing significantly to the model were then successively excluded. Because data of the infants who died in the very early neonatal period could influence the result of the total group the data were analysed with and without these infants. A p value of less than 0.05 was assumed to denote a significant difference.

Results

In 117 of the 128 infants enrolled in the study, signals from the middle cerebral artery were recorded antenatally (91%). In the other 11 cases (singletons) we were unable to record the signals because of a short time lag between

Table 2 U/C ratio and obstetrical outcome

	U/C ratio	
	Normal (n=74)	Raised (n=43)
Range (median) gestational age (days)	179–230 (207)	188–230 (220)*
Range (median) birth weight (g)	705–2295 (1330)	605–1940 (1125)**
Appropriate weight for dates ($\geq$ 10th centile)	1	22
Small for dates (<10th centile)	73	21

*p<0.01; **p<0.001.

admission and delivery (n=9) or because of the occipitoanterior position of the fetal head (n=2). Gestational age at birth of the infants ranged between 25 and 33 weeks (median 30 weeks). Birth weight ranged between 605 and 2295 g (median 1245 g).

The 117 infants were divided into two groups according to their antenatally determined U/C ratio. The group with a raised U/C ratio consisted of 43 (37%) infants. The remaining 74 (63%) infants had a normal U/C ratio (that is below the tolerance limit). Obstetrical outcome was different for the two groups (table 2). Five infants died within the first four days of birth because of immaturity (n=3) or respiratory insufficiency (n=2). Another five infants died later in the neonatal period. Causes of death were sepsis (n=3) and multiorgan failure (n=2).

The incidence of ICH and of ischaemic lesions was not different between the two U/C ratio groups (table 3). Using the combined classification of neurosonographic findings as given in table 1 the relations between the U/C ratio, being small for dates, and brain damage were further explored. These results are given in table 4.

TIME PATTERN OF V_{mean} IN RELATION TO U/C RATIO

The pattern of changes of V_{mean} in the middle cerebral artery during the first week of life for infants with a normal or with a raised U/C ratio is shown in the figure. For both groups a profound decrease in V_{mean} was seen after the

Table 3 Neurosonographic findings; figures are number (%)

U/C ratio	Neurosonography			
	No ICH	Severe ICH	No echodensities	Severe echodensities
Normal	62 (84)	12 (16)	61 (83)	13 (17)
Raised	39 (91)	4 (9)	39 (91)	4 (9)

In five infants a severe ICH was found in combination with a severe echodensity. For the classification of no v severe ICH or echodensities see text.

Table 4 Relation between U/C ratio, being small for date, and brain damage

U/C ratio	Small for dates	Cranial ultrasound		
		Normal	Suspect	Abnormal
Normal	No (n=73)	52	9	12
	Yes (n=1)	1	–	–
Raised	No (n=21)	17	2	2
	Yes (n=22)	19	3	–

For the classification of normal, suspect, or an abnormal cranial ultrasound see table 1.

Time averaged mean (SEM) velocity (V_{mean}) of the middle cerebral artery (MCA) during the first week of life for infants with a normal or raised U/C ratio.

first measurement directly after birth. Thereafter a gradual increase was found. Analysis of variance showed that infants with a raised U/C ratio appeared to have, compared with infants with a normal U/C ratio, not only higher V_{mean} values during the first week of life ($p=0.017$), but also a significantly different pattern of change of V_{mean} in the middle cerebral artery during the first week of life ($p=0.005$). Even after exclusion of infants who died in the very early neonatal period (n=5) the relation between U/C ratio and V_{mean} (both mean values and pattern of change) remained ($p<0.01$). After excluding infants with a severe ICH (intraventricular and/or intraparenchymal haemorrhage) (n=16) the difference in neonatal CBFV (mean and change of V_{mean}) between the two groups remained significant ($p<0.02$). Exclusion of infants with severe echodensities on cranial ultrasound did not influence the results of the analysis.

TIME PATTERN OF TcPCO_2 AND MEAN ARTERIAL BLOOD PRESSURE

Directly after birth high TcPCO_2 values were found. Infants with a normal U/C ratio had a mean (SD) TcPCO_2 of 7.2 (3.68) kPa (54.1 (27.7) mm Hg) as measured one hour after birth, whereas infants with a raised U/C ratio had a mean TcPCO_2 value of 5.89 (1.33) kPa (44.2 (9.9) mm Hg). For both groups a gradual decrease took place in the 24 hours after birth. After 24 hours an increase was seen until day 7. TcPCO_2 raised to 6.21 (1.20) kPa (46.6 (9.0) mm Hg) and 5.60 (0.95) kPa (42.0 (7.2) mm Hg) in the normal and raised U/C ratio group, respectively.

MAP increased gradually both in infants with a normal as well as in infants with a raised U/C ratio. At one hour after birth the MAP for infants with a normal U/C ratio was 37.8 (6.7) mm Hg; for infants with a raised U/C ratio the MAP was 37.2 (5.4) mm Hg. At seven days postpartum MAP reached to 48.1 (7.7) mm Hg and 47.5 (8.2) mm Hg, respectively.

Statistical analysis did not show a significant difference in mean level of TcPCO_2 and MAP for infants with a normal U/C ratio compared with infants with a raised U/C ratio. We also could not show any difference in the average pattern of change in TcPCO_2 and MAP between the two U/C ratio groups.

Table 5 Relation between neonatal CBFV and some variables

Variable (X)	R	p Value	Regression line
TcPCO ₂	0.19	0.047	$y = 11.9 + 0.07 \times X$
Gestational age	0.40	<0.001	$y = 14.8 + 0.10 \times X$
U/C ratio	0.28	0.002	$y = 10.6 + 1.10 \times X$

ANALYSIS OF VARIANCE WITH REPEATED MEASUREMENTS

After the backward selection procedure the variables TcPCO₂ and either gestational age or U/C ratio were significantly associated with the level and time pattern of neonatal CBFV. Because gestational age and U/C ratio are highly correlated it is not possible to assess their independent effects on CBFV properly. The multivariate model which included the significantly correlating variables TcPCO₂ and either gestational age or U/C ratio could explain 30% of the variation of CBFV in the neonatal period. When TcPCO₂ was included in the model, analysis of variance for repeated measurements did not reveal any independent effect of MAP on neonatal CBFV changes.

The effect of TcPCO₂, gestational age, or U/C ratio on the level of CBFV is shown in table 5. The correlation coefficient (R) between the individual mean of these variables and the individual mean CBFV quantifies these effects; p values and the regression lines are shown.

Discussion

Brainsparing is defined as a circulatory adaptation of the fetus resulting in a preferential perfusion of the central nervous system. A raised U/C ratio is a sensitive indicator of the brainsparing effect and it is indicative of fetal growth retardation.¹⁷ In our population only one infant with a normal U/C ratio appeared to be small for dates (table 2). In the group with a high U/C ratio 50% of the infants were above the 10th centile of the growth curve. As a flattening of intrauterine growth might still be compatible with a birth weight above the 10th centile, infants in the high U/C ratio group classified as normally grown, according to the classical definition, might still have been growth retarded.

Using the combined classification the incidence of abnormal ultrasound findings was higher in the infants without fetal brainsparing compared with infants with a normal U/C ratio (table 4). This finding was contrary to our expectation as we hypothesised that antenatal brainsparing might be associated with an increase in fetal and neonatal brain damage. Also the incidence of suspect ultrasound findings was not higher for infants with signs of brainsparing, compared with infants without. Interestingly, the incidence of suspect findings on cranial ultrasound were equally distributed among small for date infants and normally grown infants, although both groups exhibited antenatal signs of brainsparing.

Flow velocity data of the middle cerebral artery are important, as this vessel contributes to about 80% of fetal and neonatal

hemispheric blood flow.¹⁸ Severe fetal growth retardation is clinically suspected especially at a more advanced gestational age. At early gestational age (for example, 25–26 weeks) pregnant women are seldom referred because of growth retardation. This makes it understandable that high U/C ratios were found especially at 30–33 weeks of pregnancy. It also explains the finding that high U/C ratios were so closely correlated with gestational age, making the assessment of the individual contribution of these variables on CBFV changes impossible.

Trend analysis of absolute changes of V_{mean} of the middle cerebral artery contains information on actual changes of cerebral blood flow.^{19 20} The profound decrease in V_{mean} immediately after birth is in agreement with other reports.^{21 22} Animal studies showed the fetal cerebral blood flow rate to be twice as high compared with adult animals. The rapid decrease in V_{mean} is most probably a reflection of the transition from fetal to neonatal cerebral blood flow. This occurs within the first hours after birth.²³ Absent end diastolic velocities, which are in our experience common on the first day, result in low V_{mean} values on the first day. After the initial decrease in CBFV there is a gradual increase. Gray *et al* have argued that the initial decrease cannot be explained by ductal patency alone.²⁴ On the second day after birth 50% of preterm infants still have a patent ductus arteriosus.²⁵ The fact that minor changes were seen in CBFV after day 2, suggests that the impressive changes on day 1 are not related to closure of the ductus arteriosus. The gradual increase in CBFV found after the first eight hours of life is shown in many other studies.^{21 22 26}

Carbon dioxide tension²⁷ and also blood pressure¹² were found to be important regulators of cerebral blood flow especially in the distressed newborn. Therefore, changes in CBFV might be related to changes in blood gases and/or changes in blood pressure. High CBFV immediately postpartum reflects the relatively hypercarbic state during fetal life and delivery. The decrease in CBFV in the first hours after birth may be explained by the sudden fall in carbon dioxide tension due to the initiation of respiration. TcPCO₂ values in our study are high immediately after birth and decrease significantly in the first 24 hours after birth. Although statistically the effect of TcPCO₂ may be small, changes of TcPCO₂ are profound especially on day 1, and this will effect especially the early changes in CBFV. Because of the profound changes in TcPCO₂, the effects of gestational age or of U/C ratio on CBFV were less during the early period of haemodynamic transition. They were shown to have their effect especially at the end of the investigative period. Vasoactivity of major cranial vessels causing vasoconstriction of vessels that were dilated at birth was shown by Drayton and Skidmore.²⁸ Carbon dioxide is the most important regulator of CBFV²⁹ and it explained in animal experiments 55%–90% of the reduction of CBFV at birth.²³ The relatively high CBFV in utero and directly after

birth might also be a reflection of a low fetal oxygen tension; the decrease in CBFV being the result of the increase in neonatal arterial oxygen tension. We did not show a significant influence of changes in TcPO₂ on changes in neonatal CBFV. From our data it seems unlikely that changes in CBFV occurred due to an increase of MAP. This does not exclude, however, that changes in MAP may have affected CBFV in some infants. This may particularly be the case at high TcPCO₂ values resulting in a disturbed cerebral flow autoregulation.

As infants with a raised or normal U/C ratio did not differ significantly in their patterns of change in TcPCO₂ and MAP, we could not attribute the difference found between the two groups in neonatal pattern of CBFV to these variables. As the two groups had the same prevalence of both severe intracranial haemorrhages and of severe echodensities, a vasoconstrictive effect due to ICH or because of ischaemic lesions on CBFV is also unlikely. Because the analysis yielded the same results after exclusion of the infants with an abnormal cranial ultrasound, the observed differences in CBFV cannot be attributed to intracranial pathology.

The actual mechanism by which the brainsparing effect during fetal life exerts its influence on neonatal CBFV cannot be determined from our data. In the model either gestational age or the U/C ratio were significantly associated with changes in CBFV. The high CBFV for infants with a raised U/C ratio could be a continuation of the fetal situation where a growth retarded infant (as a result of chronic hypercarbia or chronic hypoxia) has a vasodilated cerebral circulation, resulting in a higher CBFV.³⁰ Our findings are compatible with the findings of Yoshida *et al* that infants small for gestational age have a higher CBFV during systole. Intrauterine stress might, in analogy with the acceleration of lung maturation, induce a physiological alteration, leading to a different setting of the autoregulation of the cerebral circulation. A higher gestational age could have a maturational effect on cerebral autoregulation. This could also explain the association between gestational age and CBFV.

In conclusion: the level and time changes in CBFV were significantly related to TcPCO₂, whereas gestational age or U/C ratio both had a significant influence. No independent effect of changes of MAP on neonatal CBFV changes could be demonstrated when TcPCO₂, gestational age, and U/C ratio were included in the model.

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