Effects of sleep state and feeding on cranial blood flow of the human neonate

P M RAHILLY

Neonatal Research Unit, Department of Physiology, The London Hospital Medical College

SUMMARY Jugular venous occlusion plethysmography was performed on sleeping babies. Cranial blood flow (CBF) was calculated by correcting for noncompressible drainage pathways. Sleep state of the baby was monitored using clinical and EEG criteria. In 20 babies CBF was consistently higher in rapid eye movement (REM) sleep compared with nonREM sleep (mean difference 24.2%). In 7 babies systolic blood pressure was consistently higher in REM sleep (mean 20.2%). There was no correlation between the degree of change in blood pressure and CBF. In 11 babies in whom CBF was measured at known times after feeding, there was a consistently lower flow rate during the first hour compared with 2 hours later (mean difference 34.5%). The degree of change was unrelated to amount of feed taken, despite the method of test weighing being demonstrably accurate.

The introduction of jugular occlusion plethysmography¹⁻² with improved analysis³ has made the measurement of cranial blood flow (CBF) in the healthy neonate feasible and ethically acceptable. Preliminary studies by Milligan (D Milligan, 1979, personal communication) and Dear³⁹ have shown that jugular flow, and therefore probably CBF, are altered by sleep states and feeding. The existence of different sleep states was recognised by Galen⁴ and by the ancient Hindu philosophers.⁵ There have been various clinical and EEG classifications.⁶⁻¹¹ Confusion has been caused by ignoring species difference and placing too much emphasis on the concept of 'depth' of sleep.¹² Rapid eye movement (REM) sleep, compared with nonREM sleep, is a paradoxical state, accompanied by highly labile physiological functions;¹² it is probably present before birth,¹³ and predominates in the newborn slowly decreasing with age.^{11 14 41-42} Cerebral blood flow changes as an important component of sleep were first considered by Hill.¹⁵ Mangold *et al.*¹⁶ found a rise in CBF when subjects passed into sleep. Prinz *et al.*¹⁷ using xenon-clearance techniques, found that subjects had, compared with when awake, a higher CBF in REM sleep, but a lower one in nonREM. Milligan (D Milligan, 1979, personal communication) measuring jugular flow uncorrected for vertebral leakage, found consistently lower values in nonREM than REM sleep.

The effects of feeding on cerebral blood flow were first considered by Bayliss and Hill¹⁸ who postulated in-balance between splanchnic and cranial flow. Changes in the general circulation in the adult have been investigated extensively.¹⁹⁻²² There have also been studies in the newborn.²³⁻²⁴ The results of these various studies were contradictory but tended to indicate a rise in cardiac output after feeds with a fall in peripheral flow. Rowe *et al.*²⁵ found no change in the CBF of adults after a meal. In neonates however, studies using a zero-gradient ear thermometer²⁶⁻²⁷ and vertex thermography²⁸ indicated a rise in cranial temperature after feeds (possibly caused by a fall in the cooling arterial flow). Recently, Dear³⁹ demonstrated a consistently lower jugular flow during the first 30 minutes after a feed. His study did not take full account of sleep states, and as 'food soothes the nervous system of a child'²⁹ and lulls a child into sleep, it must be considered incomplete.

Studies of the effects of sleep (D Milligan, 1979, personal communication) and feeds³⁹ on jugular flow, as well as studies on the effects of CO₂ and 100% O₂⁴⁰ indicate that the neonate has a highly labile CBF. For this reason the work presented here includes blood pressure studies during different sleep states in an attempt to test the autonomy of the CBF.

Method

The technique and analysis used were as previously described.²⁻³ A mercury-in-Silastic strain gauge was placed round the head of a sleeping infant. This was

Department of Medicine, Royal Alexandra Hospital for Children, Camperdown, New South Wales, Australia
P M RAHILLY, neonatologist

connected via a Wheatstone bridge to a Hewlett-Packard recording system which traced the changes in head circumference caused by heart beat and jugular occlusion. To analyse the compressions, exponentials were fitted by computer program (BMDP3R).³⁰ Jugular flow was derived by calculating the differential at time zero on the inflow curve. 'Vertebral' flow (that is, flow down the noncompressible pathways) was calculated by comparing the rate constants of the inflow and outflow curves. The mathematics of this correction factor was based on a mathematical model which compared the head to an electrical capacitor.

The final formula is:

$$F_c = A Li \frac{Lo}{Lo - Li}$$

Where F_c = cranial blood flow A = height of plateau on inflow curve Li = rate constant for inflow curve Lo = rate constant for outflow curve.

Each result was obtained from a set of 10 compressions, the values being $\pm$ SE and mean.

Sleep state was monitored clinically and by EEG using biparietal discs (D Milligan, 1979, personal communication). The classification divides sleep into four states:

(1) REM, (2) transitional, (3) nonREM, (4) nonREM with trace alternans.

In the results sections stage 2 is excluded, and stages 3 and 4 are combined.

Blood pressure was monitored using a standard neonatal cuff, systolic end-point being detected with a Parks Doppler (model 801-B), the probe being placed on the brachial artery. All the babies were born in the maternity wards of The London Hospital

(Whitechapel) and were term and healthy. The mothers were chosen by the nursing staff and the purpose of the trials was fully explained to each of them. In all cases mothers were present for the studies and many of them became closely connected with the work.

Sleep study. 20 babies (mean age 98.3 hours, range 38–180; mean weight 3047.5 g, range 2000–3800) had their CBF measured in stage 1 (REM) and in stages 3–4 (nonREM) sleep. For each baby, these measurements were taken at one session (within 3 hours of each other at the most) with the baby under the same conditions (including posture) and at least 30 minutes after the last feed. Seven of these 20 babies had each set of compressions bracketed by blood pressure readings before and afterwards.

Feeding study. A series of CBF measurements was made on 25 babies. Each measurement was taken at a known time after the last feed, and while the baby was in a recognisable sleep state. Each series was performed at the same session, usually taking 3–4 hours. It was not possible to take these measurements at fixed postprandial times as during a 4-hour session the sleep states would vary greatly. Of these 25 babies only 13 produced a series of readings taken in comparable sleep states (mean age 103.8 hours, range 38–342; mean weight 3397 g, range 2850–4006).

11 of these 13 babies were breast fed. In 9 of these it was possible to 'test weigh' the babies before and after the feed. In addition, 17 bottle-fed babies (most of whom were not in the CBF trial) were 'test

Table 1 *Effects of sleep stages (cranial blood flow ml/min per 100 g)*

Case	Sleep stage 1 (REM)				Sleep stages 3–4 (nonREM)			
	Total	Jugular	Vertebral	% vertebral	Total	Jugular	Vertebral	% vertebral
9	36.2 $\pm$ 3.1	27.1 $\pm$ 1.4	9.1	25.0	23.4 $\pm$ 2.7	18.8 $\pm$ 1.0	4.6	19.6
22	37.8 $\pm$ 2.9	26.0 $\pm$ 2.1	11.8	31.2	33.4 $\pm$ 2.4	24.1 $\pm$ 1.2	9.3	28.0
33	31.0 $\pm$ 4.0	25.5 $\pm$ 2.0	5.5	17.7	28.0 $\pm$ 3.0	19.6 $\pm$ 2.1	8.4	30.0
39	38.4 $\pm$ 3.0	32.5 $\pm$ 2.6	5.9	15.3	34.0 $\pm$ 2.0	28.4 $\pm$ 1.7	5.6	16.5
40	30.0 $\pm$ 2.0	27.2 $\pm$ 1.1	2.8	9.3	27.0 $\pm$ 1.4	24.2 $\pm$ 1.1	2.8	10.3
42	53.0 $\pm$ 2.0	35.3 $\pm$ 1.1	17.5	33.0	51.0 $\pm$ 1.8	31.8 $\pm$ 2.0	19.2	37.6
45	52.0 $\pm$ 3.0	41.7 $\pm$ 1.1	10.3	19.8	47.0 $\pm$ 2.8	38.3 $\pm$ 2.1	8.7	18.5
46	24.0 $\pm$ 2.0	20.7 $\pm$ 1.3	3.3	13.8	22.0 $\pm$ 2.0	17.8 $\pm$ 1.4	4.2	19.1
50	118.0 $\pm$ 4.1	87.6 $\pm$ 3.8	30.4	25.8	102.0 $\pm$ 3.7	76.1 $\pm$ 6.4	25.9	25.5
51	40.8 $\pm$ 2.0	32.0 $\pm$ 1.9	8.8	21.5	30.0 $\pm$ 2.4	24.5 $\pm$ 2.5	5.5	18.3
56	21.0 $\pm$ 0.9	17.4 $\pm$ 0.8	3.6	17.1	19.1 $\pm$ 0.6	16.6 $\pm$ 1.0	2.5	13.1
57	30.1 $\pm$ 2.0	24.2 $\pm$ 1.4	5.9	19.6	23.4 $\pm$ 2.0	19.75 $\pm$ 1.1	3.65	15.6
67	63.1 $\pm$ 3.0	47.1 $\pm$ 2.4	16.0	25.4	40.8 $\pm$ 3.0	33.4 $\pm$ 2.1	7.4	18.1
90	22.2 $\pm$ 1.0	21.0 $\pm$ 1.0	1.2	5.4	17.6 $\pm$ 1.0	16.5 $\pm$ 1.0	1.1	6.2
91	31.8 $\pm$ 3.0	24.2 $\pm$ 2.0	7.6	23.8	28.3 $\pm$ 3.0	19.2 $\pm$ 1.4	9.1	32.1
92	21.7 $\pm$ 1.0	19.5 $\pm$ 1.4	2.2	10.1	18.2 $\pm$ 1.4	16.6 $\pm$ 1.1	2.2	12.0
93	29.3 $\pm$ 1.0	24.5 $\pm$ 1.0	4.8	16.4	20.9 $\pm$ 1.0	18.8 $\pm$ 1.2	2.1	10.0
94	47.2 $\pm$ 2.4	34.6 $\pm$ 2.0	12.6	26.7	27.8 $\pm$ 1.2	23.7 $\pm$ 1.4	4.1	14.7
97	28.25 $\pm$ 1.6	23.2 $\pm$ 1.0	5.05	17.9	20.4 $\pm$ 0.9	17.9 $\pm$ 0.7	2.5	12.3
98	44.9 $\pm$ 1.2	37.3 $\pm$ 1.1	7.6	17.0	30.7 $\pm$ 1.3	24.4 $\pm$ 0.7	6.3	20.0
Mean	40.0 $\pm$ 4.8	31.4 $\pm$ 3.4	8.5 $\pm$ 1.5	19.6 $\pm$ 1.6	32.2 $\pm$ 4.2	25.5 $\pm$ 3.0	6.8 $\pm$ 1.3	18.9 $\pm$ 1.8

Table 2 Effects of sleep state on cranial blood flow comparing stage 1 (REM) with stages 3-4 (nonREM) sleep in 20 babies

	Total	Jugular	Vertebral	% vertebral
Mean rise (ml/min per 100 g)	7.8	5.9	1.7	0.7
Mean rise (%)	24.2	23.0	25.0	3.6
Range rise (%)	69.8 to 9.5	50 to 14.2	97.8 to -34	81 to -41
Paired <i>t</i>	5.813	6.484	2.716	0.796
P	<0.001	<0.001	<0.025	NS

Fig. 1 Changes in cranial flow of 20 babies in different sleep states (bars show SE). Points are staggered for clarity of presentation. Range of change 19.5-69.8% (mean 24.2%, $P < 0.001$).

weighed' and the volume of feed taken from the bottle noted by an independent observer. The babies were kept fully clothed so that faeces and urine collected in the nappy were not lost from total weight.

Results

Sleep studies. The results from 20 babies are shown in Table 1 and summarised in Table 2. CBF was consistently higher in REM than in nonREM sleep (Fig. 1). The mean difference was 24.2% which is significant ($P < 0.001$). With the increased total flow in REM there was also an increase in the vertebral percentage. Although this rise was in absolute terms insignificant, the rise in vertebral percentage had a significant correlation with the rise in total CBF ($r = 0.734$, $P < 0.01$). In other words, when the total flow rises by more than about 20% the extra drainage is mostly provided by the vertebral system.

The direction of sleep state change did not affect the degree of changes in CBF. In 9 babies passing from REM to nonREM the mean percentage difference was 22.2% (SE = 5.6). When the change was the other way round the mean percentage change was 29.3% (SE = 7.1).

The results of the blood pressure study are shown in Table 3.

Systolic blood pressure was consistently higher in REM than in nonREM sleep (mean difference 20.2%, $P < 0.001$ by paired Student's *t* test). There was, however, no correlation between blood pressure and CBF in the individual babies in REM or nonREM. Nor was there any correlation between the degree of the change in CBF and changes in BP brought about by alterations in sleep state in the individual babies.

Feeding studies. The results from the 'test weighing' assessment are shown in Fig. 2. There is an extremely close correlation showing that when performed with care this is an accurate measurement of the amount of feed taken by a baby.

Table 3 Cranial blood flow (ml/min per 100 g), sleep states, and systolic blood pressure (BP)

Case	Sleep stage 1 (REM)				Sleep stages 3-4 (nonREM)			
	1st BP	2nd BP	Mean BP	Cranial flow	1st BP	2nd BP	Mean BP	Cranial flow
90	70	72	71	22.20 ± 1	56	57	56.5	17.60 ± 1
91	81	80	80.5	31.80 ± 3	69	70	69.5	28.30 ± 3
92	85	85	85	21.70 ± 1	70	68	69	18.20 ± 9
93	86	90	88	29.30 ± 1	78	76	77	20.90 ± 1
94	81	83	82	47.20 ± 2.4	68	68	68	27.80 ± 1.2
95*	98	100	99	8.00 ± 0.6	84	84	84	3.77 ± 1
97	106	110	108	28.25 ± 1.6	?	92	92	20.40 ± 0.9
98	92	94	93	44.90 ± 1.1	78	78	78	30.70 ± 0.9
99	96	98	97	32.50 ± 1.5	—	—	—	—

*Overriding sutures. 1st BP before set of compression waves, 2nd BP after set of compression waves.

Fig. 2 Close correlation between volume of milk given from a bottle and weight of the feed as measured by test weighing 17 different babies ($r = 0.998$).

The CBF results from the 13 babies are shown in Table 4 and summarised in Table 5. There is a consistently lower CBF in the first hour after a feed (Fig. 3) than in the 'resting' period of at least 2 hours after a feed. The mean difference (34.5%) is significant ($P < 0.005$). In those 5 babies in whom readings were available for the first 30 minutes after a feed the mean difference (31.4%) is also significant ($P < 0.05$). The readings taken during the 60- to 120-minute period show a variable recovery pattern since the postprandial fall.

There was no correlation between the volume of feed given and the changes in CBF caused by the feed ($r = 0.414$ in 10 babies).

Discussion

The mean difference in CBF (24.2%) found in REM and nonREM is similar to that found in jugular flow (23%) by Milligan (D Milligan, 1979, personal communication). These differences emphasise the importance of knowing the sleep state of a baby during any CBF studies.

The absolute values of systolic blood pressure are in keeping with previous work.³¹⁻³² The lack of correlation between either absolute values or changes

in blood pressure and CBF argue against the autonomy of the CBF being poorly developed in this age group, whatever the sleep state.

The lower CBF found during the first hour after a feed agrees with the findings of Dear.³⁹ The variability of the recovery pattern emphasises the importance of taking sleep state into account. Babies were quite often in nonREM sleep for much of the first hour after a feed and in REM sleep for the second, hence the rather high exclusion rate from this study.

The possible causes of this fall have been discussed by Dear.³⁹ The concept of Yao *et al.*²³ of the low pressure, low resistance, high output circulation of the neonate, rendering it unable to compensate for a sudden increase in splanchnic flow is not supported by the blood pressure studies. Another possibility is a metabolic cause for these changes. The rise in metabolics, such as ketones,³³⁻³⁴ which are taken up by the newborn's brain³⁵ might activate some complex negative feedback system.

Fig. 3 Change in cranial blood flow of 11 babies after feeding. Mean fall after feed 34.5%, $P < 0.001$, range 8-65% (each baby was in a constant sleep state).

Table 4 Effects of feeding (cranial blood flow, ml/100 g per min + SE) pooled in hourly intervals

Case	Sleep stage	Feed (ml/kg)	After feed								
			0-60 min			60-120 min			120+ min		
			Cranial blood flow	SE	Time after feed (min)	Cranial blood flow	SE	Time after feed (min)	Cranial blood flow	SE	Time after feed (min)
29	1	Bottle 22.6	26.6	1.4	12	12.1	1.0	75	45.2	3.1	210
			19.9	2.7	47						
			23.2	2.1	Mean						
31	1	Breast 25.0	13.0	1.0	26	37.0	3.0	65	37.0	4.0	130
									58.0	4.0	160
									47.5	1.8	Mean
39	1	Breast 4.1	33.7	3.0	27				32.0	2.0	150
									38.4	3.0	210
									35.2	4.0	Mean
45	1	Breast 8.7	34.0	1.8	50	47.0	3.0	100	37.0	1.2	130
48	1	Breast 15.0	15.2	1.0	35	23.4	2.0	90	29.0	2.5	125
54	1	Breast 6.5	22.6	1.5	25	32.9	1.0	75	23.6	0.2	125
57	1	Breast 19.7	20.1	1.7	55	29.8	2.0	90	24.0	1.0	125
67	1	Breast 6.7	25.8	0.8	55				41.0	2.7	240
68	1	Breast 25.0	50.1	5.0	35				72.0	3.0	135
70	1	Breast	10.6	0.7	45				29.8	2.0	175
74	1	Breast 10.2	24.7	2.0	25				38.0	3.5	135
55	1	Breast 5.7	23.7	3.0	45	23.1	2.0	75			
64	1	Bottle 11.3	29.9	2.0	35	22.4	2.0	85			
Overall mean			25.1	3.0	37	28.3	3.0	82	38.3	4.0	158

Table 5 Effects of feeding on cranial blood flow, comparisons between the three time periods combined (each baby in constant sleep state)

	A/B	B/C	A/C
No. of babies	8	6	11
Mean fall after feed (ml/100 g per min)	3.2	10	13.2
Fall after feed (%)	11.3	26.1	34.5
Range of % fall in paired babies	64.8 to -83	73 to -43.4	8 to 65
Paired <i>t</i>	1.427	0.627	4.224
P	NS	NS	<0.005

A 0-60 min after feed, B 60-120 min after feed, C 120 min onwards.

On each occasion the later of the postprandial readings is used as the basis for comparison.

A metabolic cause would also explain the variability of the responses to feeding and the poor correlation of the degrees of change with the amounts of feed taken. The metabolic response of the newborn is known to alter with nutritional state.³⁶ These babies, most of whom were breast fed, could be expected to have a varied nutritional state, particularly as all but one were under 2 weeks old. Again, the composition of breast milk varies greatly

from mother to mother, and even in the same mother within feeds,³⁷ so that correlation between amount of feed and actual metabolic load could be expected to be poor.

The feeds taken by these babies were, on a weight basis, similar to those given to premature babies in many units (say 200 ml/kg per 24 hours in 12 2-hourly feeds). Bolus feeding regimens could therefore, be causing quite substantial fluctuations in the premature baby. These fluctuations could, in turn, be predisposing the sick, acidotic premature infants to intraventricular haemorrhage.³⁸

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Correspondence to Dr P M Rahilly, Department of Medicine, Royal Alexandra Hospital for Children, PO Box 34, Pyrmont Bridge Road, Camperdown, New South Wales 2050, Australia.

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