Estimating Cerebral Blood Flow in Newborn Infants: Comparison of Near Infrared Spectroscopy and ^{133}Xe Clearance

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ABSTRACT. A new method of measuring cerebral blood flow (CBF) in newborn infants by means of near infrared spectroscopy (CBFnirs) was compared with the i.v. ^{133}Xe clearance technique (CBFxe). Forty CBFnirs measurements were obtained during 19 ^{133}Xe measurements in 16 infants; 79 other CBFnirs data sets were discarded because the assumptions for their use were not fulfilled. The test-retest variation of repeated near infrared-measurements during each ^{133}Xe clearance was 17.5%. CBFnirs was closely related to CBFxe ($r^2 = 0.84$, $p < 0.0001$), with a slope of 0.75 (SEM = 0.064) and a intercept of 1.58 mL/100 g/min (SEM = 0.51). The difference between the measurements obtained by the two methods (CBFnirs − CBFxe) was negative in the high range of CBF, whereas the difference was close to zero in the low range. We conclude that CBF measured with near infrared spectroscopy was in good agreement with the CBF measured with the ^{133}Xe method. The near infrared spectroscopy method has the advantage of being noninvasive, and it does not involve ionizing radiation. Because of methodologic constraints, however, it may underestimate CBF in the high range of flow, and it may have limitations of application in clinical research. (*Pediatr Res* 30: 570–573, 1991)

Abbreviations

CBF, cerebral blood flow

CBFxe, cerebral blood flow measured with the ^{133}Xe technique

CBFnirs, cerebral blood flow measured with near infrared spectroscopy

NIRS, near infrared spectroscopy

SaO$_2$, arterial blood oxygen saturation

Abnormalities of CBF may play a crucial role in the pathogenesis of cerebral ischemia and hemorrhage, the commonest causes of neurodevelopment disability in children needing intensive care neonatally. When studying cerebral circulation, it is important to consider the safety, practical applicability, and quantitative accuracy before selecting an experimental method. Estimation of CBF in newborn children with i.v. ^{133}Xe clearance has been used for several years (1–3). Recently, a new method of quantifying CBF using NIRS was described (4). The present study compares these two methods for measuring CBF in sick, newborn infants.

PATIENTS AND METHODS

Cerebral blood flow was measured simultaneously by ^{133}Xe clearance and by NIRS in 29 newborn infants. In 13 infants, all of the 38 attempts of NIRS measurements were rejected because of insufficient quality, whereas none of the Xe measurements were rejected. In the remaining 16 infants, with a total of 19 Xe measurements, 41 out of 81 NIRS curves were rejected, leaving 40 measurements for analysis.

A total of 79 CBFnirs curves did not meet the quality criteria (see below): In five measurements SaO$_2$ increased insufficiently; in 20 measurements baseline SaO$_2$ was unstable; in 10 measurements changes in cerebral oxygenation index were delayed more than 8 s in proportion to changes in SaO$_2$; in 12 measurements cerebral oxygenation index did not increase markedly; and in 27 measurements cerebral blood volume changed significantly. The curve quality was not related to the magnitude of CBFxe, the inspiratory fraction of oxygen, or patient characteristics. The mean gestational age of the 16 infants was 30.7 wk (range 26–39 wk), and the mean birth weight was 1753 g (range 860–2485 g). The mean postnatal age at CBF investigation was 28 h (range 9–74 h) and the inspiratory oxygen fraction averaged 45% (range 30–60%). Eleven infants were mechanically ventilated because of respiratory distress and the remaining infants, because of severe birth asphyxia.

Method. NIRS depends on the relative transparency of the neonate's head to near infrared light, which is attenuated by scattering and absorption in the tissues (5). Our NIRS instrument (Radiometer, Copenhagen, Denmark) uses four semiconductor laser diodes with wavelengths of 775, 805, 845, and 904 nm. The lasers were operated sequentially and pulsed for 200 ns with a repetition rate of 500 Hz. Optical fiber bundles are used to transmit and receive the light. For calculation of the cerebral oxyhemoglobin concentration, the optical path length must be known and the algorithm for determining changes in cerebral Hb density must be quantitatively correct (5). In this study, we have used the assumption that the optical path length is 4.39 times the interoptode distance (6).

CBFnirs theory. The method is based on the Fick principle, according to which the amount of a substance taken up by an organ per unit of time is equal to the arterial concentration of the substance minus the venous concentration times the blood flow.

$$Q(t) = F \times \int_0^t (Ca - Cv) \, dt \qquad (1)$$

where Q(t) is the amount of the tracer in tissue, F is flow, and Ca and Cv are the concentrations of the tracer in arterial and venous blood, respectively. When the time, t, is less than the transit time through the organ, the tracer will not have reached the venous side. The flow (F) can then be measured as the ratio between the amount of tracer accumulated in the brain and the amount of tracer introduced during the period 0–t. With NIRS it is possible to measure changes in oxygenated and deoxygenated

Hb concentration ([HbO$_2$] and [HB]) as well as changes in total cerebral Hb concentration (7). Sao$_2$ is measured by a pulse oximeter placed on the right hand of the infant.

After a sudden increase in the concentration of inspired oxygen, the increase in cerebral oxyhemoglobin represents the accumulation of tracer. The product of the integral of change in Sao$_2$ with respect to time and the arterial Hb concentration (aHb) is the arterial tracer concentration and, therefore,

$$CBF = OI/aHb \times \int_0^t (Sao_2) \, dt \qquad (2)$$

where OI [HbO$_2$ − HB)/2] is expressed in mmol/100 g brain wt, aHb in mmol/mL tetraheme, and $\int_0^t$ (Sao$_2$) dt in min.

Methodologic requirements. The delay time (the difference between the lung-to-brain and the lung-to-hand circulation times) must be known. This delay must be the same for different parts of the brain. The integration period, t, used (equation 2) must be less than the minimal cerebral transit time. Before measuring CBF, [HbO$_2$ − HB] and Sao$_2$ should be stable for a period longer than the maximal cerebral transit time. During the measurement, CBF, cerebral blood volume, and cerebral oxygen extraction must also be constant.

CBFxe. ^{133}Xe (0.5 to 1.0 mCi/kg) was injected in a peripheral vein, and the clearance was recorded by scintillators placed over one frontoparietal region and the thorax, respectively. A record-

ing time of 15 min was used, and CBF was calculated from the time the activity of Xe in the lung had decreased to 15% of its peak activity (8).

Measurements. The NIRS measurements were performed during the ^{133}Xe-clearance. NIRS signals were sampled every 0.5 s. Sao$_2$ was measured by a pulse oximeter (Datex, Helsinki, Finland) in the beat-to-beat mode placed on the right hand of the infant.

After a 1-min period with constant values of oxyhemoglobin and saturation, a transient increment of 5–10% in Sao$_2$ was induced by briefly increasing the concentration of inspired oxygen to 100%. Sao$_2$ was maintained in the range of 80–98%. The analysis of the NIRS curves including quality check of the raw data and rejection of the measurement or calculation of CBF from 7.5 s integration time (CBFnirs$_{7.5}$) were made off-line by a custom-made computer program (Appendix). During the measurement of CBF, arterial blood was sampled for analysis of arterial O$_2$ and CO$_2$ tensions. Mean arterial blood pressure was recorded from an indwelling umbilical catheter if *in situ*; otherwise, it was estimated by oscillometry (Dinamap; Critikon, Tampa, FL).

Statistics. The CBF values were positively skewed and were transformed logarithmically to obtain homogeneity of variance. Linear regression and one-way analysis of variance were used to compare the data and for estimation of test-retest variability.

Table 1. *Summarized data of 16 infants**

Infant no.	GA (wk)	Birth wt (g)	Age (h)	Pco$_2$ (kPa)	CBFxe (mL/100 g/min)	CBFNIRS7.5 (mL/100 g/min)	Mean CBFNIRS (mL/100 g/min)	CBFNIRS6 (mL/100 g/min)
1	28	1405	40	4.9	7.80	5.86	5.86	9.47
2	39	3485	10	3.4	20.00	17.39	17.40	21.40
3	30	1807	12	3.8	7.20	5.04	6.21	4.74
3				3.8		6.00		7.60
3				3.8		7.52		9.52
4	27	1075	74	5.5	8.00	6.62	7.24	8.52
4				5.5		8.83		10.03
4				5.5		6.28		6.98
5	27	880	11	4.4	8.50	7.59	7.38	9.59
5				4.4		7.11		8.31
6	38	2750	12	4.3	5.10	7.11	7.04	2.71
6				4.3		6.97		13.07
7	30	1100	46	4.3	8.60	7.04	8.63	5.84
7				4.3		7.87		8.37
7				4.3		10.90		11.40
8	29	1200	24	5.3	15.60	7.59	7.59	10.69
9	27	960	9	3.6	19.20	19.32	16.30	20.72
9				3.6		13.18		15.68
9				5.1	28.00	17.60	21.00	26.40
9				5.1		24.56		35.26
10	29	1255	13	4.5	11.00	8.28	8.28	7.98
10				3.2	8.60	7.38	7.38	7.98
11	26	910	36	5.1	9.80	10.00	8.76	10.20
11				5.1		8.97		9.47
11				5.1		8.83		9.03
11				5.1		7.80		9.00
11				5.1		8.14		7.94
12	38	3300	34	4.7	21.90	14.56	12.60	15.36
12				4.7		10.56		10.26
12				4.7		12.35		13.45
12				4.7		12.97		14.57
12				4.8	20.10	14.15	16.60	19.55
12				4.8		19.11		23.61
13	26	860	36	4.8	26.00	15.73	15.70	16.73
14	37	2470	18	4.7	18.20	18.91	17.50	29.41
14				4.7		16.01		14.41
15	33	3420	50	2.6	19.00	12.01	11.50	21.61
15				2.6		10.90		13.60
16	28	1168	36	5.1	30.40	26.08	26.00	31.48
16				5.1		25.94		34.14

* GA, gestation age:postnatal age; CBFNIRS6, CBF calculated from 6 s integration; CBFNIRS7.5, CBF calculated from 7.5 s integration.

The study was approved by the Ethics Committee for Greater Copenhagen, and parental informed consent was obtained for each infant investigated.

RESULTS

The 40 measurements of CBFnirs in the 16 infants averaged 11.7 mL/100 g/min (5.0–26.1 mL/100 g/min), whereas CBFxe averaged 14.8 mL/100 g/min (5.1–30.4 mL/100 g/min) (Table 1).

The test-retest variation of the repeated NIRS measurements during each ^{133}Xe clearance was 17.5%. To improve the estimation of CBFnirs, the mean value of CBFnirs for each CBFxe was calculated. Because different numbers of investigations of CBFnirs were performed, the regression analysis was weighted by the numbers. Linear regression analysis between the mean CBFnirs and CBFxe yielded a slope of 0.75 (SE = 0.064) with an intercept of 1.58 mL/100 g/min (SE = 0.51) (r^2 = 0.84, $p <$ 0.0001) (Fig. 1).

Several sets of measurements obtained in the same infants cannot, strictly speaking, be regarded as independent observations. We therefore compared the logarithmically transformed value of the first CBFnirs and the first CBFxe in each infant. In these 16 paired data sets, the mean of the difference was −23.3 ± 6.8% ($p <$ 0.005), and the underestimation of CBFnirs was equal in the high and the low levels of CBF.

Because we do not know the true value of CBF, the mean of the results of the two measurements [½ × (CBFnirs + CBFxe)] was therefore used as the best estimate (9). The difference of the values between the two methods (CBFnirs − CBFxe) revealed lower values of the CBFnirs compared with the CBFxe in the high range of CBF, whereas the difference was close to zero in the low range (Fig. 2).

To examine the effect of a shorter integration period, we also calculated CBF from a 6-s integration time ($CBFnirs_{6.0}$). Higher CBFnirs values were obtained with a 6.0-s integration time, and they were closer to the values of CBFxe (Fig. 3). The difference between $CBFnirs_{6.0}$ and $CBFnirs_{7.5}$ was greater at high values of CBF ($p <$ 0.0003). The test-retest variation of $CBFnirs_{6.0}$, however, was as high as 40% (analysis of variance).

DISCUSSION

NIRS allows a noninvasive estimate of cerebral hemodynamics at the cotside. The method does not expose the infant to ionizing radiation, and it can be repeated as often as necessary without disturbing the infant. To quantify the NIRS signals in terms of mL/100 g/min, an algorithm obtained from *in vitro* experiments
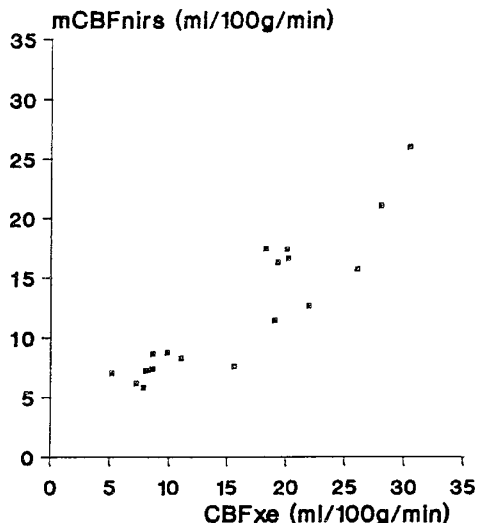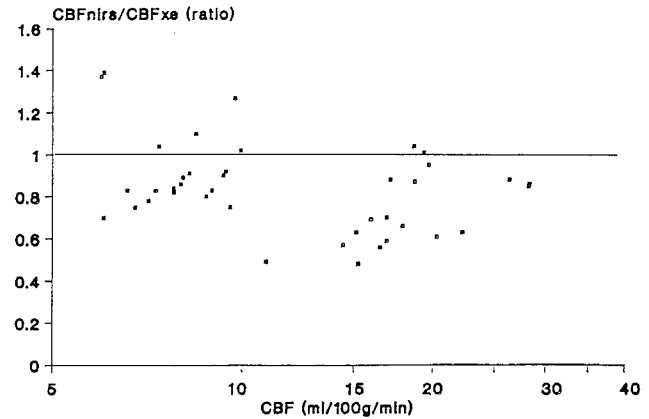
Fig. 1. CBFxe plotted against mean of CBFnirs.

Fig. 2. CBF calculated as the geometrical mean of CBFnir and CBFxe against their difference, expressed as the ratio CBFnir/CBFxe. Consistently negative differences are seen in the high range of CBF. (The geometrical mean and the ratio were used to obtain constant variance over the range of CBF, for the purpose of significance testing.)
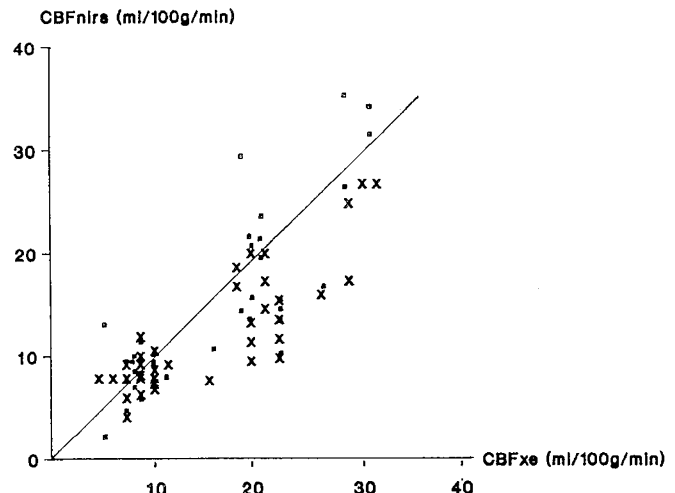
Fig. 3. $CBFnirs_{7.5}$ (×) and $CBFnirs_{6.0}$ (■) against CBFxe. Line of identity is shown. The higher values of $CBFnirs_{6.0}$ are seen, in particular in the high range of CBF. The greater variability of the $CBFnirs_{6.0}$ is also seen.

(5, 10) and a path length factor obtained by measurements of time of flight of photons in infants' brains *post-mortem* (7) was used. Despite the potential errors introduced hereby, the agreement between CBF values obtained by NIRS and ^{133}Xe was acceptable. Furthermore, the correlation between the two methods was quite good in the wide range of values of CBF obtained in different clinical situations of preterm infants with respiratory distress and in asphyxiated full-term infants.

In the present study, we have compared two indirect methods of measuring CBF, an established technique and a new technique. Although ^{133}Xe clearance has been firmly established for measurement of CBF in adults (11) and has proved to be a useful method for measuring CBF in the newborn, it has some problems. The test-retest variation for CBFxe is not less than 10–15% (2, 12). Furthermore, Xe can diffuse from vein to artery during washout. This will result in undetected recirculation and a slower clearance and, therefore, in an underestimation of the flow rate, which will be greater at low levels of flow (13). We found, however, the best agreement between the two methods in the low range of CBF.

The greatest problems in measuring CBF with an intraarterial tracer is that the transit time is very short (seconds) and the time resolution of NIRS as well as pulse oximetry has to be very good. In this study we have used an integration time of 7.5 s. This

integration time is similar to the transit time of 8 s reported by Arnot *et al.* (14) in 1970, using red blood cells labeled with carbon-11 monoxide. When using a shorter integration time for analysis (6 s instead of 7.5 s), we obtained higher values of CBFnirs, resulting in values closer to the CBF-Xe. This was predictable: assuming cerebral blood volume to be 3 mL/100 g (15), CBF of 30 mL/100 g/min corresponds to a mean transit time of 6 s only. Unfortunately, at the shorter integration period of 6 s, the test-retest variation was as high as 40%.

Estimates of CBF using ^{133}Xe clearance are based on a 15-min recording period (the period 1-5 min after ^{133}Xe injection carrying the most weight in computation of CBF). During this period, however, there can be some cyclical variation of CBF as recently reported on CBF velocity using on-line Doppler technique (16, 17). Such cyclical variation may contribute to the relatively high test-retest variation in CBFnirs, each measurement lasting only a few seconds. A test-retest variation of 17% at 7.5 s of integration may, however, call for an average of two to three measurements regardless of the cause.

Another consideration is which parts of the brain are represented by the two methods. By placing the optodes and scintillators close together, we attempted to make the fields of view similar: a 100- to 200-mL volume of both hemispheres.

Two thirds of the NIRS measurements were unsuccessful because the recordings were not of the required quality. Twenty-seven of the measurements were rejected because of significant changes in cerebral blood volume. It is still unclear whether hyperoxia changes central or cerebral hemodynamics within a few seconds. Studies in animals and adult human subjects have shown that CBF and oxygen extraction are stable with change of arterial oxygen tension between 6 and 13 kPa (18, 19). Even a change in cerebral blood volume of only a few percent, however, will result in a proportional but relatively larger error in CBFnirs and thereby affect the CBFnirs estimation (20).

Another important problem appears for the use of NIRS as a CBF method in clinical research. It may be impossible to induce a sufficient rise (or fall) in SaO$_2$ in infants with normal lung function and in infants with congenital heart disease, persistent fetal circulation, or severe respiratory distress syndrome.

We conclude that measurements of CBF with NIRS were in good agreement with results obtained by the ^{133}Xe method. The NIRS method has some advantages, although CBF may be underestimated in the high range of CBF because of methodologic constraints. The variation of 17% could demand an average of two to three measurements, thereby losing some of the advantage of the quick measurements. In addition, the method is likely to find limited application in clinical research.

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APPENDIX

Analyzing program. The SaO$_2$ signal and the NIRS signals were sampled at 2 Hz. Cerebral oxyhemoglobin (HbO$_2$), deoxyhemoglobin (HB), and total Hb concentrations (tHb) were calculated as previously described (5).

Cerebral oxygenation index (OI) was calculated as (HbO$_2$ − HB)/2.

The CBFnirs algorithm consisted of the following steps:

A. Smoothing of SaO$_2$ and OI using five points (2.5 s of data):

$$S(t) = 0.1 \cdot R(t - 2) + 0.2 \cdot R(t - 1) + 0.4 \cdot R(t)$$
$$+ 0.2 \cdot R(t + 1) + 0.1 \cdot R(t + 2)$$

where S(t) is a point of smoothed data and R(t − 2) to R(t + 2) are five points of raw data.

B. 1. Detection of the time of the abrupt SaO$_2$ increase, t$_s$; and
   2. Detection of the time of the abrupt OI increase, t$_o$.

C. Quality tests:
   1. SaO$_2$ increasing more than 2% in the 10 s after t$_s$;
   2. The mean of SaO$_2$ differing less than 1% between the periods from 30-40 s and 10-0 s before t$_s$;
   3. The variation in OI in the 40 s period preceding t$_o$ being less than 0.3 times the change in OI in the 10 s after t$_o$;
   4. The change in tHb in the 10 s after t$_o$ being less than 0.3 times the change in OI in the same period; and
   5. The delay of t$_o$ relative to t$_s$ being within the range of −4 to 4 s.

If passing quality tests:

D. Fitting a 4th order polynomial to OI from t$_o$ to t$_{o + 10s}$;
E. Calculating the baseline for SaO$_2$ for the period t$_{s - 5s}$ to t$_s$, SaO$_2$ base and
F. Calculating CBFnirs(i) for i = 6 and 7.5 s.

$$CBF = k \times [OI(t_{o + i}) - OI (t_o)]/\sum_{t_s}^{t_s + i} (SaO_2(t) - SaO_2 \text{ base})$$

G. Reestimate CBFnirs(i):
   1. For ts = ts + 2 and to = to + 2; and
   2. For j = i ± 1 to evaluate conformity to model and stability of estimate.