Comparison between Near Infrared Spectroscopy and ^{133}Xe Clearance for Estimation of Cerebral Blood Flow in Critically Ill Preterm Infants

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ABSTRACT. Estimations of cerebral blood flow were performed by both near infrared spectroscopy and ^{133}Xe clearance on 12 occasions in nine critically ill premature infants (26–29 gestational wk) who required mechanical ventilation and supplemental oxygen. For each study, one determination of cerebral blood flow by ^{133}Xe was compared with the mean of two to five measurements by near infrared done within 1–19 (median 5) h. ^{133}Xe measurements ranged from 9.6–16.9 mL/100 g/min, and mean near infrared measurements ranged from 8.6–25.0 mL/100 g/min. There was a significant correlation between the two sets of measurements ($r = 0.80$, $p < 0.001$). The mean difference between the methods was 1.6 mL/100 g/min, and the 95% limits of agreement were -0.5 – 3.8 mL/100 g/min. This study showed that cerebral blood flow can be measured noninvasively in critically ill premature infants at the bedside by near infrared spectroscopy and by the ^{133}Xe clearance technique. The methods give comparable results. (*Pediatr Res* 33: 56–60, 1993)

Abbreviations

CBF, cerebral blood flow
 FiO_2 , fraction of inspired oxygen
deoxy-Hb, deoxyhemoglobin
 HbO_2 , oxyhemoglobin
NIRS, near infrared spectroscopy
 SaO_2 , arterial oxygen saturation
 XeC , ^{133}Xe clearance technique

of this study was to compare the values obtained by NIRS with those obtained by XeC in critically ill premature infants. In contrast to a similar comparison done by Skov *et al.* (3), we used for NIRS a commercially available instrument with six wavelengths instead of four, and for XeC we used equipment with nine detectors instead of two. Different methods were used for analyzing the data obtained by both techniques.

MATERIALS AND METHODS

Principle of Quantifying CBF by NIRS. Theory 1: NIRS. Spectral analysis of transmitted light in the visible spectrum (400–700 nm) has long been established as a method for measuring the oxygenation of whole blood *in vitro*. However, visible light is highly absorbed by tissue, and thus can penetrate only a few mm. Near infrared light, in the special range 700–1000 nm, is absorbed much less and can penetrate much further, up to 8 cm of tissue. These optical properties allow transmission spectroscopy to be performed *in vivo* (4).

In a nonscattering medium, the attenuation of light due to absorption is a measure of the concentration of chromophore present. The relation between absorption and the concentration of the chromophore is described by the Lambert-Beer law. However, attenuation of light in a scattering medium such as biologic tissue is a complex function of both the scattering and absorption coefficients of the tissue, as well as the geometry of the tissue and measurement optics. The Lambert-Beer law therefore has to be modified to take these variables into account (5). For linear transillumination of tissue, the modified Lambert-Beer law can be expressed as:

$$\text{OD} = (a[c]LP) + G \quad (1)$$

where:

- OD = the attenuation of light in optical densities
- a = the extinction coefficient of the chromophore ($\text{mM}^{-1} \text{cm}^{-1}$)
- $[c]$ = the concentration of chromophore (mM)
- L = the distance between points of light entry and exit (cm)
- P = a “pathlength factor,” which takes account of the increased optical path due to the scattering of light in the tissue
- G = a factor related to tissue and optode geometry.

The attenuation due to scattering and the geometric factor (G) are usually not known, and thus $[c]$ cannot be quantified absolutely. However, in a given tissue with fixed optical geometry it is likely to remain constant; thus, changes in attenuation can be attributed solely to changes in the concentration of chromophore:

Hypoxic-ischemic brain injury is a major cause of long-term neurodevelopmental disability in newborn infants—especially in very immature ones—who survive after intensive care. Impaired CBF may be an important factor in the pathogenesis of this type of cerebral injury. However, the exact mechanism is still unknown. Noninvasive quantitative techniques are therefore required to investigate the role of CBF in the pathogenesis of this condition.

There are several methods that could be used to quantify CBF in the neonate: venous occlusion plethysmography (1), positron emission tomography (2), XeC , and NIRS. XeC and NIRS can both be applied at the bedside with minimal interference with care and were selected for comparison in this study. The purpose

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$$\Delta[c] = \frac{OD}{aLP} \quad (2)$$

Scattering causes the distance traveled by the light to be greater than L by a factor P , and the distance traveled is given by the product of L and P . Provided these factors and the extinction coefficients of the chromophores present are known, changes in chromophore concentration can be quantified using equation 2. If the technique is applied to the neonatal brain, the chromophores that absorb light in the spectral range 700–1000 nm and whose concentrations change over the short term are HbO_2 , deoxy-Hb, and cytochrome aa_3 . Experiments *in vitro* have defined the extinction coefficients of HbO_2 and deoxy-Hb, and the extinction coefficient of oxidized-reduced cytochrome aa_3 has been deduced from measurements from the brains of Hb-free rats whose blood had been exchanged with a fluorocarbon blood substitute (6). HbO_2 and deoxy-Hb can be differentiated because of differences in their absorption spectra. The optical path length factor P has been calculated from measurements of the time taken for picosecond pulses of light to traverse the tissue to be 4.2 ± 0.2 (7). Knowing this factor, it is possible to calculate quantitative changes in the concentration of HbO_2 and deoxy-Hb from observed changes in the attenuation of light at several wavelengths.

Theory 2: Measurement of blood flow using NIRS (8). The Fick principle states that the rate of accumulation of a tracer substance in an organ (Q) is equal to the difference between the rate of arrival and the rate of departure of that substance. If a tracer is suddenly introduced into the arterial blood, a measurement of the amount accumulated in the organ can be made at the time (t) later. When t is less than the minimum transit time of blood through the organ, the tracer will not appear in the venous efflux, and flow (f) can be measured as the ratio of tracer accumulated to the quantity of tracer introduced over the time period (t). The quantity of tracer introduced by time t is equal to the integral of the change in the arterial concentration of tracer at time t [$Pa(t)$] with respect to time. Thus:

$$f = \frac{Q(t)}{\int_0^t Pa(t)dt} \quad (3)$$

If a small, sudden change occurs in arterial oxygen saturation, then, provided certain conditions are met, the resulting increase in arterial HbO_2 concentration can be considered as an intravascular tracer. HbO_2 can be observed by NIRS; this provides a measure of the increase in tissue HbO_2 concentration ($\Delta[HbO_2]$) and quantifies the amount of tracer accumulation. Because changes in dissolved organ oxygen can be disregarded, the quantity of tracer introduced is given by the integral of ΔSaO_2 with respect to time. SaO_2 can be measured continuously and noninvasively by pulse oximetry. Blood flow (F) may then be derived by consideration of the Hb concentration in whole blood (tHb), which is determined from a blood sample. Thus:

$$F = \frac{\Delta[HbO_2] \cdot k}{tHb \cdot \int_0^t (\Delta SaO_2)dt} \text{ mL/100 g/min} \quad (4)$$

where k is a constant reflecting the molecular weight of Hb (64 500), tissue density (1.05) (9), and decimal conversions.

To improve the signal to noise ratio of NIRS data, equation 4 was modified slightly. Because tissue Hb concentration could be shown to be constant during the observation, changes in HbO_2 and deoxy-Hb concentration could be assumed to be equal and opposite. Thus, the NIRS signal representing the difference between the change in HbO_2 and deoxy-Hb was twice the amplitude of the corresponding signal representing the change in HbO_2 . This signal will have a higher signal-to-noise ratio than either HbO_2 or deoxy-Hb alone. Substituting in equation 4:

$$F = \frac{\Delta[HbO_2] - \Delta[Hb]}{tHb[2 \cdot \int_0^t (\Delta SaO_2)dt]} \text{ mL/L/min} \quad (5)$$

Principle of XeC. The theory of XeC for measuring CBF in neonates has been described extensively before (10, 11). In brief, ^{133}Xe , a diffusible tracer, is injected i.v. Disappearance of the tracer from the head is recorded by eight detectors that register the gamma radiation over a period of 15 min. An additional detector, placed over the right lung, is used to correct for arterial recirculation (12).

Subjects. Newborn infants requiring mechanical ventilation and 25–55% oxygen in the inspired air were chosen for the study when blood pressure, heart rate, and respirator settings had been stable for at least 2 h. Clinical details are given in Table 1.

The study protocol was approved by the ethical committee of the Children's Hospital of Zurich, and informed consent was given by the parents of each infant.

Study procedure. For measuring the ^{133}Xe clearance, eight small cadmium-telluride detectors were placed over the head and one over the right lung. When the baby was stable, 0.5–1.0 mCi/kg body weight diluted in 1 mL saline was injected into a peripheral vein. The sharp increase and slow decrease of gamma radiation was recorded during the 15 min after injection.

For the NIRS measurements, light from six laser diodes was carried to the infant's head by light-fiber cable that was applied at the temporal region. Light transmitted across the skull was collected by a similar cable on the opposite temporal region and returned to the spectrophotometer (NIR-1000 Hamamatsu). SaO_2 was monitored with a pulse oximeter (Nellcor N-200, Hayward, CA) using a neonatal sensor fixed at the angle of the mouth or at an ear lobe. NIRS and SaO_2 measurements were made every 2 s. When the infant was stable, the concentration of inspired oxygen was suddenly increased to produce a step increase of SaO_2 by 3 to 5% within a range of 85 to 98%. The changes in HbO_2 , deoxy-Hb, and SaO_2 were observed for 8 s. After a restabilization period of at least 5 min, this maneuver was repeated up to eight times.

During both measurements, transcutaneous carbon dioxide tension and heart rate were recorded continuously. Blood pressure was monitored via an arterial catheter (Statham transducer, Hellige, Freiburg, France) or by oscillometry on the right arm (Dinamap, Critikon, Norderstedt, Germany).

Data analysis. The xenon clearance curves were analyzed by A. E. L. in Zurich, and the NIRS studies were analyzed by A. D. E. in London, neither being aware of the results of the other. The infrared data were checked before analysis and rejected if baseline saturation was not stable (variation >2%) at least 10 s before the increase and if a clear change of at least 4% was not achieved within 6 s. The results of the two techniques were first compared by least-square regression analysis and then by plotting the difference between a pair of values against their mean as proposed by Bland and Altman (13). A possible influence on the difference between the two methods was looked for by including carbon dioxide tension, mean arterial pressure, and time gap between measurements in a stepwise linear regression model with the difference between a pair of values as dependent variable.

RESULTS

Twelve comparisons were performed in nine critically ill infants (Table 2). Two additional infants with severe pulmonary interstitial emphysema had to be excluded from the analysis, as ^{133}Xe measurements were technically inadequate. Forty-three of 61 NIRS measurements did not fulfill the quality criteria and were rejected, but at least two could be analyzed in every infant.

There was a significant correlation between the two techniques ($r = 0.80$, $p < 0.001$) (Fig. 1). The slope of the regression line was 1.83 (SD 0.43) and the intercept -8.8 (SD 5.46). The mean

Table 1. Clinical information on patients*

Patient no.	Sex	Birth wt (g)	Gestational age at birth (wk)	Postnatal age (d)	Main disorder	Brain scan	Outcome at 18 mo
1	M	1180	26	3 and 8	RDS	SEH	MDI 111, PDI 100
2	M	880	27	4	RDS	IVH	MDI 91, PDI 72
3	F	1300	29	1 and 3	RDS	SEH	MDI 88, PDI 88
4	F	1010	26	1 and 5	Sepsis	SEH	Dead, d 41
5	F	790	29	2	RDS	IVH	Dead, d 5
6	M	1470	29	3	RDS	LM	Dead, d 4
7	M	1250	28	4	RDS	IPH	Dead, d 5
8	M	1070	28	1	RDS	SEH	MDI 122, PDI 108
9	M	800	27	5	Sepsis	IVH	Dead, d 19

* SEH, subependymal hemorrhage; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; MDI, Bayley Mental Developmental Index (normal 84–133); IPH, intraparenchymal hemorrhage; PDI, Bayley Physical Development Index (normal 70–132); LM, cystic leukomalacia.

Table 2. Comparison of near infrared and xenon data

Near infrared							Xenon			
Patient no.	CBF* (mL/100 g/min)	n	FiO ₂ (%)	PaCO ₂ (kPa)	MAP (mm Hg)	Age (h)	CBF (mL/100 g/min)	PaCO ₂ (kPa)	MAP (mm Hg)	Age (h)
1	17.7 (14.3, 21.1)	4	32	5.6	35	58	13.5	6.8	35	55
1	25.0 (24.6, 25.4)	2	25	5.6	40	181	16.9	5.5	37	180
2	16.4 (15.3, 17.6)	2	25	5.4	40	74	13.1	5.4	40	73
3	10.6 (7.8, 13.3)	5	31	5.5	34	19	13.2	5.1	34	24
3	13.1 (9.7, 16.5)	4	38	4.8	33	67	12.7	5.4	33	71
4	10.9 (3.6, 18.2)	4	50	4.3	30	20	10.0	4.7	37	18
4	8.6 (5.6, 11.7)	4	49	4.4	32	116	9.6	6.0	36	109
5	20.4 (14.1, 26.8)	2	55	7.4	26	28	13.2	8.1	27	34
6	9.6 (4.7, 14.4)	4	30	6.5	47	60	9.8	5.1	47	52
7	11.3 (7.4, 15.2)	3	32	4.7	32	85	12.9	5.3	33	90
8	14.8 (13.0, 16.7)	5	30	4.5	31	16	15.0	5.6	34	21
9	12.5 (9.9, 15.1)	4	31	4.7	43	100	11.6	4.9	49	81

* Mean (95% confidence interval). When $n = 2$, both values are given. MAP, mean arterial pressure; PaCO₂, arterial PCO₂.

Fig. 1. Plot of CBF results, in critically ill prematurely born infants, obtained by NIRS vs those obtained by XeC. $r = 0.80$; $p < 0.001$; slope of the regression line 1.83 (SD 0.43); intercept -8.8 (SD 5.46).

Fig. 2. Plot of the differences between NIRS and XeC CBF values vs the means of both values for each comparison. The mean difference is -1.6 mL/100 g/min (95% confidence limits $-0.54, 3.78$).

difference between the methods was 1.6 mL/100 g/mL, and the 95% limits of agreement were -0.54 – 3.78 mL/100 g/min (Fig. 2).

No significant correlation between the difference of the two techniques and carbon dioxide tension, mean arterial blood pressure, and interval between measurements was found.

DISCUSSION

This study demonstrates reasonable agreement between two noninvasive methods for measuring CBF that differ both in theory and in execution. Both methods are based on a modifi-

cation of the Fick principle, but XeC uses a gas that freely crosses the blood tissue barrier as a diffusible tracer, whereas NIRS uses an increase in HbO₂ as a nondiffusible tracer. Both methods rest on several assumptions.

Assumptions of NIRS method for measuring CBF. 1) The tracer is not consumed by the organ; 2) the flow to the organ remains constant; 3) the total volume of Hb in the organ remains constant; and 4) the measurement is made over a time period less than the minimum transit time of the tracer through the organ. These will be addressed in turn.

1) The Fick principle is invalid if tracer is consumed, so it is essential that there is no change in oxygen consumption with

increased oxygen saturation. Oxygen consumption in tissue is a function of the metabolic rate. In the physiologic range, if metabolic requirements are being met, an increase in oxygen delivery is not associated with increased oxygen extraction (14).

2) Animal experiments have shown that CBF is closely linked to metabolic needs, and this, as well as the phenomenon of autoregulation, keeps resting blood flow constant (14).

3) If there is a significant fluctuation in the total amount of Hb in the tissue during an NIRS measurement, this will alter the apparent change in HbO₂ and invalidate the measurement. Fortunately, NIRS allows the continuous monitoring of total Hb concentration; by observation of the sum of the HbO₂ and deoxy-Hb signals, it can be determined that this remains constant.

4) The Fick principle requires quantification of the total amount of tracer accumulated, and thus either a measurement is needed of any tracer leaving the organ or, as in the NIRS method, measurement must be made before any tracer leaves the organ. Consequently, measurements must be completed in less than minimum transit time of blood through the organ. Although minimum transit time was not measured in our subjects, an estimate of the mean transit time from measurements with labeled erythrocytes gave a value of 8 s (15).

Assumptions of XeC. Assumptions 1 and 2 also apply to XeC. Xenon is an inert gas with a physical half-life of 5.2 d and therefore leaves the brain only and completely by the veins. As xenon is highly diffusible, equilibration between brain concentration and venous concentration can be assumed. The blood-brain partition coefficient has been shown to be the same for the white and the gray matter in newborn infants and is assumed to be 0.8 for an Hb concentration of 15 mg/100 mL (16).

The XeC is based on monitoring the washout of radioactivity over 15 min by detectors placed around the head. Three washout curves can be separated representing blood flow rates in the extracerebral tissue, the gray matter, and the white matter. Only the two latter compartments are taken into account to calculate the mean CBF (11).

Practical problems. For the NIRS method, fiberoptic cables must be fixed on the infant's head either opposite each other when the diameter is approximately <7 cm or in orthogonal position between 3 and 6 cm apart. Fixation is easy with a self-adhesive bandage. A double-adhesive ring between skin and the optic coupling reduces movement artifacts. Contamination by stray light can be considerably diminished by carefully wrapping a light-tight sheet around the head and the light emitting and receiving fiberoptic bundles. A sudden increase in SaO₂ by at least 3–5% can be achieved by a change in FiO₂ of at least 10%. This maneuver is not possible in infants with oxygen saturation >95% breathing room air. However, Elwell *et al.* (17) overcame this drawback in healthy adults by giving them an oxygen-air mixture with FiO₂ of 0.15 to breathe and then switching to an FiO₂ of 0.21.

In infants requiring a high FiO₂ above 0.8 to achieve baseline oxygen saturation around 90%, a sudden transient decrease in oxygen saturation may be used to calculate CBF.

The XeC requires injection of the tracer into a peripheral vein. The syringe must be carefully shielded from the detectors during the whole procedure. Another source of error is the escape of xenon beside the intratracheal tube. The xenon then has to be collected by a mask and suctioned continuously. The radiation dose has been calculated to be 4 mrad for the whole body and 25 mrad for the lungs, which is comparable to the doses obtained from standard x-ray examination of the chest.

Errors and reproducibility. The test-retest variability in the same subject has been reported to be 15–20% for both techniques (18, 19). Accuracy is increased by repeating measurements. This is easier with the NIRS technique, as it is quicker and not radioactive. Large right to left shunts are a problem with both techniques. In those cases, the increase in arterial oxygenation might not be sharp or large enough for the NIRS technique. For the XeC, such shunts can be compensated mathematically by

assuming a five-compartment model (11). In two patients with pulmonary interstitial emphysema, xenon was trapped in the interstitial air, and therefore the lung curves used to correct for recirculation could not be analyzed.

Comparison. This study confirms the close relation between NIRS and XeC reported by Skov *et al.* (3) using different equipment and different methods for analysis.

In contrast to the results reported by Skov *et al.*, in this study the NIRS values tended to be higher than the XeC values. The difference between the two methods correlated significantly with the means of the two methods. NIRS values might be too high as a result of underestimation of the area under the curve due to smoothing of the saturation curve. However, this bias should not be correlated with the level of CBF. Therefore, we believe this tendency might be due to chance, which is supported by the finding that the mean difference for all measurements was not significantly different from zero.

Although arterial carbon dioxide varied up to 1.6 kPa between NIRS and XeC in the same patient, CBF was not adjusted for changes in carbon dioxide. This is justified by low or absent adaptation of CBF to arterial carbon dioxide due to immaturity and the severe brain damage present in most of these patients. In fact, in patients 1 and 4, CBF dropped from comparison 1 to 2, whereas carbon dioxide increased. Consequently, no association between the difference of the two techniques and arterial carbon dioxide, blood pressure, and time gap between the two measurements could be demonstrated.

Clinical implications. This study demonstrates practicability and agreement of two different methods for measuring CBF, both of which are noninvasive and can be used in critically ill premature infants at the bedside. These methods are therefore suited to detect abnormal cerebral perfusion and to explore its role in the pathogenesis of brain damage. NIRS is easier to perform, and instruments are available from several companies. In addition, NIRS can measure not only CBF but also cerebral blood volume and redox state of cytochrome aa₃. This technique therefore may be used more widely in clinical research.

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