0031-3998/88/2404-0461$02.00/0
PEDIATRIC RESEARCH

Vol. 24, No. 4, 1988
Printed in U.S.A.

Comparison of Electrical Impedance and ^{133}Xenon Clearance for the Assessment of Cerebral Blood Flow in the Newborn Infant

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ABSTRACT. The peak amplitude of pulsatile cerebral electrical impedance (ΔZ_p) was compared with simultaneous ^{133}xenon clearance estimations of cerebral blood flow (CBF_∞) on 28 occasions in nine infants receiving assisted ventilation who had changes in $PaCO_2$ and thereby presumably in cerebral blood flow. Percentage changes from one measurement to the next in each infant were compared. Using linear regression the relationship was $\Delta Z_p = 0.5\ CBF_\infty - 1.5$ with $r = 0.67$. The 95% confidence interval for the regression coefficient was 0.2–0.8 and the mean residual was 28%. Changes in cerebral blood flow in these clinical conditions were similarly detected by the two methods but ΔZ_p underestimated the magnitude of the change in comparison with CBF_∞ and its accuracy was insufficient to allow conclusions about the magnitude of small changes in cerebral blood flow in individual infants. (*Pediatr Res* 24: 461–464, 1988)

Abbreviations

ΔZ_p, peak amplitude of pulsatile cerebral electrical impedance
CBF_∞, cerebral blood flow estimated from ^{133}xenon clearance curve extrapolated to infinity
$TcPCO_2$, partial pressure of skin carbon dioxide
$TcPO_2$, partial pressure of skin oxygen

Cerebral blood flow is assumed to be a vital determinant of neurologic outcome in the sick newborn infant. Information on brain blood flow has been hampered by lack of suitable measurement techniques. ^{133}Xenon clearance is a standard for accurate, quantitative measurement of cerebral blood flow but is limited by the time-averaged nature of the result (because it is necessary to calculate this from the clearance curve that must be collected over some time), the inability to make rapid serial measurements and the total number of studies being determined by the safe limits of ionising radiation exposure. The cerebral electrical impedance technique provides continuous information noninvasively, but the biophysical basis of the technique remains incompletely understood. It relies on the fact that the brain and blood offer a very different resistance to the passage of electric current. As blood volume increases in the head after cardiac systole, impedance falls. The cardiac-synchronous component of cerebral impedance is determined predominantly by the instantaneous intracranial blood volume (1). Attempts to correlate cerebral electrical impedance with cerebral blood flow have been made in dogs (1) and in adults (2, 3) with variable results. Modeling the thorax or limb as a cylinder allows reasonably accurate estimates of flow to be made (4–6), but extrapolation of the cylindrical model to the brain is inappropriate because of the complexity of cerebral blood flow. In the human newborn the technique of cerebral electrical impedance has been used to show a reduction in the impedance during tension pneumothorax when cerebral blood flow would be expected to have fallen and an increase in impedance after feeding when cerebral blood flow would be expected to have risen (7). It has also been compared with strain gauge plethysmographic assessment of cerebral blood flow and in 11 of 12 cases when either 2% CO_2 or 100% O_2 were inspired the two techniques suggested changes of cerebral blood flow in the same direction (8). To our knowledge the relationship of cerebral electrical impedance to cerebral blood flow as measured by a reliable quantitative technique has not been studied in the newborn.

The aim of our study was to determine the relationship of cerebral electrical impedance and cerebral blood flow measured using the ^{133}xenon clearance method.

MATERIALS AND METHODS

^{133}Xenon clearance technique. This technique has been used in neonates at the Rigshospitalet, Copenhagen since 1977. A modification used in this study allowing the xenon to be injected into a peripheral venous cannula has recently been described in detail (9) and validated by comparison with the arterial injection method (10). In summary, 0.5-1 mCi/kg ^{133}xenon dissolved in 1-2 ml normal saline was injected over approximately a 15-s period into a vein in the hand or foot while the infant was undisturbed in the incubator at a time when blood pressure, $TcPO_2$ and $TcPCO_2$ were stable. This amount of ^{133}xenon results in a total body radiation dose of 0.2 mGy (20 mRad). Activity was recorded from one frontoparietal region using a NaI crystal detector with a 20-mm long cylindrical collimator, 17 mm in diameter. Care was taken to avoid the detector pointing caudally and including counts from the airways. The activity over the chest was detected using a similar crystal with a 40-mm long cylindrical collimator, 12 mm in diameter. The spectral window was set at 55–105 KeV. Detectors were shielded with 2 mm lead over their whole length. Activity was registered for 15 min after the injection. Background activity was measured before each study and taken into account during calculation of cerebral blood flow. The scintillation equipment was manufactured by Novo Diagnostic Systems (Bagsvaerd, Denmark). The mean flow to gray and white matter, CBF_∞, was calculated using variable metric approximation assuming a two-compartment model (11) and a blood-brain partition coefficient for xenon of 0.8 ml/g at

Received January 28, 1988; accepted June 2, 1988.
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The Dagmar Marshall Foundation and the Gangsted Rasmussen Foundation gave financial support for the ^{133}xenon clearance equipment. P. C. was supported by grants from the University of Sydney Medical Foundation, Wellcome Trust and British Council.
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a blood Hb of 8.8 mmol/liter adjusted by −0.03 ml/g/mmol/liter higher blood Hb (9). Inasmuch as the neonate's head is small and the scintillation collimation geometry allows counts from a volume of about 100–200 ml, CBF_∞ was considered to represent global cerebral blood flow.

Cerebral electrical impedance. The instrumentation and software were developed (12) at the Biomedical Engineering Centre, Oxford, U.K. An analogue circuit based on one previously described (13) provided a constant current source of 1 mA at a frequency of 60 kHz. A voltage detection circuit distinguished cardiac-synchronous pulsatile impedance changes from basal tissue impedance. The pulsatile impedance signal was digitized and 16 cardiac-synchronous waveforms averaged by a dedicated microprocessor using the R wave of the electrocardiogram as a trigger. Averaging was necessary to minimize the effects of respiratory-synchronous impedance changes and of artefact that occurred when the infant moved. Electrodes were 1 cm diameter silver-silver chloride cup electrodes. The current electrodes were attached to the scalp anteriorly in the midline at the hairline and posteriorly about 1 cm superior to the occipital protuberance. Voltage electrodes were attached approximately 2 cm lateral to these, which resulted in a basal tissue impedance (Z_o) of 35–50 ohm. Electrodes were filled with electrode contact gel and then fixed in place with adhesive tape (Micropore, 3M, St. Paul MN) and stabilized with a loose circumferential band of elasticized material (Coban no. 1582 3M). The averages of ΔZ were plotted on a chart recorder and the mean ΔZ_p estimated for the same 15 min over which CBF_∞ was collected. The mean ΔZ_p data were estimated without knowledge of the xenon CBF_∞ results.

Either two or three measurements were made in each infant. All measurements in each infant were made within a 4-h period. During the 15 min required to collect the xenon data, $TcPO_2$ and $TcPCO_2$ (TCM2, Radiometer, Copenhagen, Denmark) was measured continuously and arterial blood pressure measured either continuously via indwelling umbilical or peripheral arterial catheter or intermittently by oscillometry (Dinamap 847, Critikon, Tampa, FL). During a period when observations were stable, arterial blood was taken for blood gas analysis (ABL 3, Radiometer). For alterations in cerebral blood flow to occur, spontaneous changes in $PaCO_2$ were anticipated or the ventilator rate adjusted with the aim of optimizing blood gases.

Comparison of ΔZ_p between patients cannot be made because of dependence on an unknown relationship with basal tissue impedance. Therefore to compare data between patients, and to allow pooling of the data, percentage change of ΔZ_p and CBF_∞ was calculated between the first and second estimations and where available, the second and third. Linear regression was calculated using the least squares method. Multiple linear regression was used to establish a regression coefficient for $PACO_2$.

The study was approved by the Ethics Committee of Greater Copenhagen and parental consent obtained.

Patient population. Nine neonates admitted to the Department of Neonatology, Rigshospitalet were studied. All were receiving assisted ventilation for a variety of reasons (Table 1). Mean birth weight was 1725 g, gestational age 32.3 wk, and postnatal age 5 days. No attempt was made to study an homogeneous population in order to avoid possible biases that either of the techniques might have in a particular clinical state.

Table 1. *Patient details*

Study no.	Birth wt (g)	Gestational age (wk)	Postnatal age (days)	Diagnosis
1	2880	36	1	Volvulus
2	1870	33	6	Meconium ileus
3	885	26	13	Preterm
4	1275	29	1	Preterm
5	2300	37	15	Nephrostomy
6	1160	28	1	Preterm
7	Same patient as 6		2	
8	970	33	1	Asphyxia
9	Same patient as 8		2	
10	2990	40	2	Convulsions
11	1195	29	1	Preterm

RESULTS

Two of the nine neonates were studied twice, a day apart. One infant was so active that the first two measurements had to be abandoned because movement artefact made the impedance recording technically unsatisfactory. A total of 28 simultaneous estimations of CBF_∞ and ΔZ_p was made. Results are shown in Table 2 and in graphical form in Figure 1. The 17 percentage change values that resulted are shown in Figure 2. The regression equation for the percentage change values was $\Delta Z_p = 0.5\ CBF_\infty - 1.5$ with $r = 0.67$ and 95% confidence intervals for the slope being 0.20–0.80 and 95% confidence intervals for prediction of a change in ΔZ_p from CBF_∞ being ± 60%. For instance if during a recording in a ventilated infant CBF_∞ increased by 30%, ΔZ_p can be predicted to have changed from between −30 and +90%.

To investigate the factors that significantly influenced impedance and to determine if pooling the data may have masked important differences in responses related to gestational age or birth weight, these two parameters as well as blood pressure, $PaCO_2$ and PaO_2 were entered into a multiple linear regression. $PaCO_2$ but not blood pressure was significantly associated with both CBF_∞ and ΔZ_p ($p = 0.01$). The percentage change of CBF_∞ and ΔZ_p/kPa $PaCO_2$ change was similar: 26 and 21%, respectively, with 95% confidence limits of ± 8% in both cases.

DISCUSSION

Interpretation of the results is made difficult by the fact that there is no single method of measuring cerebral blood flow which provides a standard for comparison of other techniques. Cerebral blood flow may be nutritive or nonnutritive through shunts and occurs through vessels of widely differing diameter to two compartments (white matter and gray matter) which may have different responses to perturbations. Different techniques are

Table 2. *Results of ΔZ_p and CBF_∞*

Study no.	ΔZ_p (mOhm)	CBF_∞ (ml/100 g/min)
1	14.5	11
	17.5	22
	16	9.7
2	12	24.1
	6	6.5
3	29	14.1
	14	9.7
4	25	10.9
	28	9.2
5	35	6.3
	45	10.6
	35	10.7
6	17	13.8
	23	13.3
	18	16.1
7	15	14
	10	9.7
	14	12.4
8	43	28.9
	77	47.7
	62	39.3
9	58	11.5
	42	11.1
10	28	15.1
	22	9.4
	26	7.5
11	17	10.1
	16	9.6

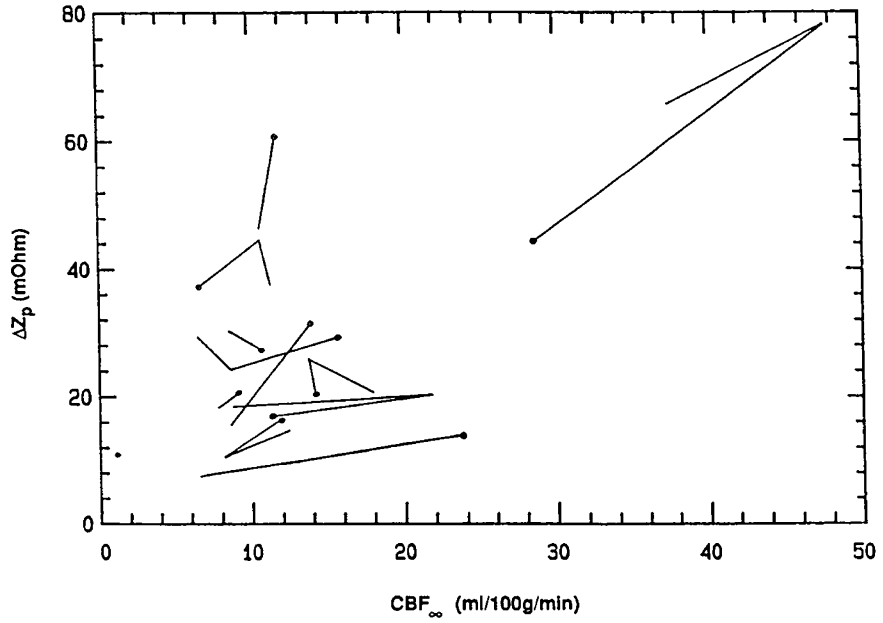

Fig. 1. CBF_∞ and ΔZ_p. The *closed circles* designate the first measurement in each study and subsequent measurements in the same patient are joined by a line. Some values are shown approximated to avoid overlap of points or lines. The original data are given in Table 2.

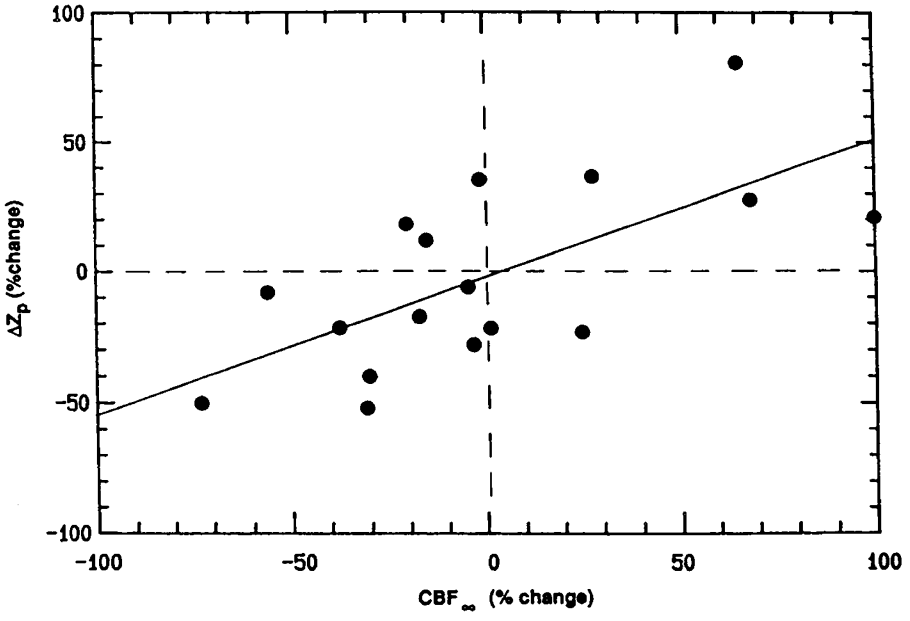

Fig. 2. Percentage change of CBF_∞ and of ΔZ_p (pooled data) with regression line.

likely to have different sensitivities to these various components. For example because white matter has a lower electrical impedance than gray matter (14), current density in white matter will be higher and cerebral electrical impedance is likely to be influenced more by white matter flow. However, because gray matter flow is much higher than white matter flow there will be an unknown and variable effect of flow in these two compartments on cerebral electrical impedance. ^{133}Xenon clearance is more sensitive to high flow regions (gray matter) in the early part of the clearance curve and to blood flow to white matter later in the clearance curve (15).

In the one previous report comparing impedance to cerebral blood flow as measured using the venous strain gauge plethysmography technique in the newborn (8), there was a linear relationship with the impedance change being approximately twice the observed percentage change in plethysmographically determined cerebral blood flow. However, the venous occlusion technique has never been validated against a reliable technique for measurement of cerebral blood flow and not only are its results critically dependent on the mathematical model used and differences in skull compliance but use of the technique may itself alter cerebral blood flow (16). In our study the relationship while apparently linear was not one to one. The slope of the regression equation was 0.50: a change of 100% in CBF_∞ was associated with only a 50% change in ΔZ_p. This may be in part because the error of the xenon measurement, assumed to be approximated by the reproducibility coefficient, previously estimated to be about 15% (17), has the effect of reducing the slope (18). More importantly, the pulsatile impedance signal is determined mainly by the cardiac-synchronous intracranial blood volume change. With high cerebral blood flow rates induced by raised $PaCO_2$, there is a larger increase in the diastolic (*i.e.* nonpulsatile) component of flow than there is in the systolic (*i.e.* pulsatile) component of blood flow (19). Inasmuch as changes induced in cerebral blood flow by other mechanisms such as blood pressure changes, may have different effects on the relative

changes in pulsatile and nonpulsatile components of blood flow, our results may not be reproduced if changes in cerebral blood flow were induced by other stimuli. An additional factor that may reduce the slope to less than one is our assumption of a linear relationship between ΔZ_p and CBF_∞, an assumption that seems valid from experimental observations (1). However, we have insufficient data from each baby to validate this assumption and the pooled data may mask a nonlinear relationship. A further limitation on interpretation of these data is that the maximum time over which the data were collected in each patient was 4 h. Beyond this time there is no certainty that the same results would be obtained because factors that influence impedance such as hematocrit and brain-blood temperature fluxes may vary considerably over longer periods.

Large changes in CBF_∞ were observed over a wide range of flow rates which are similar to those reported using other techniques (20). All large changes gave concordant results for the two techniques. All but one of the discordant results occurred with changes of less than 23%, probably within the measurement error.

Large residuals around the regression line make the quantitative estimation of changes in cerebral blood flow using the impedance technique inaccurate. Nonetheless, the impedance technique provides continuous information noninvasively and with minimal disturbance to the baby, and may provide information on such events as changes with vasoactive drugs, pressure-flow autoregulation, and carbon dioxide reactivity. The use of appropriate models, perhaps using features other than peak amplitude of the cardiac-synchronous pulsatile impedance waveform, might lead to results that correlate better with other techniques of measurement of cerebral blood flow.

Acknowledgments. Dr. D. Murphy, Professor P. Rolfe, and Mr. P. Burton developed and built the impedance equipment and kindly made it available for use in Copenhagen. Professor B. Friis-Hansen's support enabled the study to be performed in Copenhagen.

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