0031-3998/87/2203-0302$02.00/0
PEDIATRIC RESEARCH

Vol. 22, No. 3, 1987
*Printed in U.S.A.*

# Brain Oxidative Phosphorylation following Alteration in Head Position in Preterm and Term Neonates

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**ABSTRACT. An alteration in head position, which effects cerebral blood flow, may increase the risk for intraventricular hemorrhage in the critically ill infant. The purpose of this study was to evaluate *in vivo* cerebral oxidative metabolism as an index of tissue oxygen delivery reflecting brain blood flow, in healthy preterm and term infants following a change in head position. Cerebral phosphoenergetics using 31 phosphorus nuclear magnetic resonance spectroscopy were measured in 10 preterm and eight term infants following three different head positions: neutral, prone, and supine. All infants were clinically stable at the time of study. The phosphocreatine to inorganic phosphate ratio, an indicator of bioenergetic reserve, was determined. The mean ± SD for phosphocreatine to inorganic phosphate ratio in the neutral position in preterm and term infants was 1.08 ± 0.15 and 1.12 ± 0.21, respectively, and did not change significantly following head turning. These data suggest that any alteration in cerebral blood flow as a result of a change in head position in the healthy neonate may be compensated by physiological and biochemical regulations so that no changes in brain oxidative phosphorylation are measurable. (*Pediatr Res* 22: 302–305, 1987)**

### Abbreviations

**ICP, intracranial pressure**
**$^{31}$P MRS, phosphorus nuclear magnetic resonance spectroscopy**
**CBF, cerebral blood flow**
**PCr, phosphocreatine**
**PD, phosphodiesters**
**Pi, inorganic phosphate**
**PME, phosphomonoester**
**PDE, phosphodiester**

The therapeutic management of anoxic brain insult and blunt head trauma in adults and older children takes head position into consideration (1, 2). However, optimal head position for critically ill infants at risk for fluctuations in cerebral perfusion and intracranial hemorrhage is controversial. Venographic studies in children indicate that a 90° head rotation results in obstruction of the ipsilateral internal jugular vein (3). This maneuver impedes outflow from the brain, resulting in increased internal jugular vein pressure and ICP when elastance is high. Anterior fontanel tonometry measurements in asphyxiated infants shown a rise in ICP following head rotation 90° from midline (4). A previous investigation (5), using continuous wave Doppler technique to measure superior sagittal sinus blood velocity in healthy term newborns, showed that turning the head effectively occluded the ipsilateral jugular vein and had profound effects on blood flow velocity.

In order to evaluate the *in vivo* cellular metabolic response to head position change, the present study used $^{31}$P MRS, in stable growing preterm and healthy term neonates. Since the relationship of low-to-no CBF to changes in MRS spectroscopy has been documented (6, 7), an optimal head position that would minimize changes in cerebral oxidative metabolism was sought.

## MATERIALS AND METHODS

*Fundamentals of MRS.* Atomic nuclei, including $^{1}$H, $^{13}$C, and $^{31}$P, with an odd number of nucleons have an intrinsic magnetism. When an external magnetic field is applied to tissues containing any of these nuclei, the nuclear dipoles align themselves parallel or antiparallel to the field. A second magnetic field can then be applied which, if it is at precisely the right frequency, will cause the alignment of the nuclei to "flip." The nuclei absorb the radiofrequency energy and resonate. The resonant frequency of a given nucleus depends on its chemical environment such that, for example, the $^{31}$P nuclei in different phosphorous containing compounds resonate at slightly different frequencies. Therefore, the individual peaks in a magnetic resonance spectrum represent the absorption of radio waves by different compounds, including the three phosphorous atoms in ATP, PCr, PD, Pi, and PME. The relative amounts of each of these compounds is reflected in the areas under each peak. In turn, the metabolic activity of a tissue can be surmised by calculating the ratios between these metabolites.

In mitochondria, ADP is converted to ATP by drawing on the phosphorous from PCr, another high energy compound. When cells are deprived of an external source of energy, ATP is maintained by the reservoir of PCr. Only when PCr is exhausted does ATP fall, leaving ADP and Pi. The PCr/Pi and PCr/ATP ratios are related to the phosphate potential (ATP/ADP × Pi and PCr/Pi × Cr) and are thus an index of the energy status of the tissue.

*Patients.* Details of the *in vivo* $^{31}$P MRS technique in neonates were reported previously (8). Eighteen infants were studied in the magnetic resonance spectroscopy laboratory located within the neonatal intensive care nursery of the Hospital of the University of Pennsylvania. All study infants were inborn and were appropriate for gestational age. The term infants, following an uneventful labor and delivery, were studied between days 1 and 3 of life. Preterm infants were studied when stable in room air without evidence of chronic lung disease, ultrasonographic evi-

Received February 23, 1987; accepted April 9, 1987.
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dence of intracranial bleed, clinical seizures, or patent ductus arteriosus. No infants received medications at the time of the study.

$^{31}$P MRS studies were done ½ to 1 h after a feeding. For each study, the infant was placed in a specially designed spectroscopy isolette (Phospho Energetics). A 4-cm radiofrequency surface coil, located in a stationary position in the supine aspect of the carriage, was placed on the temporoparietal surface of the head directly above the pinna of the ear. The isolette was then inserted into the bore of a 17.5-cm superconducting magnet (Phospho Energetics). Skin temperature, heart rate, respiratory rate, and transcutaneous blood oxygen saturation were continuously monitored. A total of four positions in which the patient was placed were: lying on the right and/or left side with head in neutral position to the body; lying supine with head turned 90° to the right; lying prone (sleeping position) with head turned to the left. Each study was started by obtaining the left and right neutral position first; prone and supine positions were randomized. Repeat measurement of the left neutral position was performed at the end of the testing to evaluate consistency of the studies and possible relationship of time from last feeding. All studies were performed with the infant lying in a horizontal position.

$^{31}$P MRS examinations were performed at 1.5 Tesla ($^{1}$H frequency 60.1 MHz; $^{31}$P frequency 24.3 MHz). Spectra were collected using a Phospho Energetics MRS spectrometer. Before collection of spectra, field homogeneity was adjusted with the $^{1}$H MRS signal from tissue water for an interval of 5 min for maximal spectral resolution of approximately 0.4 ppm. Data were acquired using the following parameters: pulse delay 4 s; pulse width 50 $\mu$s; sweep width 3000 Hz. A total of 240 free induction decays were signal averaged giving a total study time in each position of 16 min. Sampling of phosphorus compounds by the surface coil involves approximately a hemispheric volume with a 2-cm radius (9). Although part of the MRS signal could be derived from scalp muscles, these are very thin in the neonate and therefore contribute minimally to the $^{31}$P MRS signal. Fourier transformation, curve fitting, and peak measurements were done with the aid of a spectral analysis program (10). Measures of areas under the curves for the $\alpha$, $\beta$, and $\gamma$ components of ATP, PCr, Pi, PD, and PME were accumulated and displayed in the form of graphic output as well as final quantitative data. The PCr/Pi ratio was used in the analysis as it is related to the phosphate potential and thus a measure of bioenergetic reserve (11).

If an infant became agitated and cried, small amounts of glucose water were given. If an infant was not easy to console, the study was terminated and the infant returned to the nursery. A typical study lasted 1½ h, with a neonatologist present at all times. While potential hazards associated with MRS imaging and spectroscopy include body exposure to: static (DC) magnetic fields, time-varying magnetic field (dB/dT) which can induce electrical currents, and absorption of energy from radio frequency electromagnetic fields which can produce heating, no adverse effects have to date been reported, particularly at the frequency range in which our studies were conducted. The study protocol was reviewed and accepted by the University of Pennsylvania Committee on Research Involving Human Subjects and signed parental consent was obtained in all cases.

*Statistics.* Values are expressed as the mean ± 1 SD of the mean. Statistical analysis was performed by one-way analysis of variance with repeated measurements. Differences between means were determined by paired *t* test with Bonferroni correc-

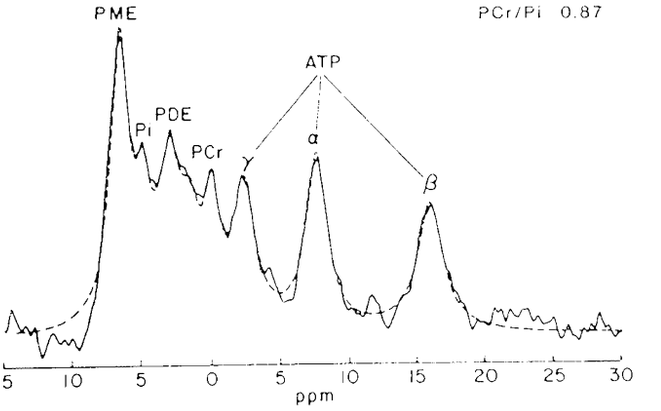


Fig. 1. $^{31}$P spectrum of brain in a 6-day-old healthy growing premature infant of 34 wk posteonceptional age using the 1.5 Tesla Phospho Energetics spectrometer. Spectral data were obtained for 16 min using a 4-s pulse delay which causes partial saturation of the PME peak. Chemical shifts of resonances (x axis) are: PME, Pi, PDE, PCr, $\alpha$, $\beta$, and $\gamma$ phosphates of ATP. Y axis is signal intensity. The PCr/Pi ratio is calculated from signal areas, which are proportional to concentration.

Table 1. *Clinical data in preterm and term infants studied with $^{31}$P MRS*

| Patient | Birth wt (g) | Gestational age (wk) | Sex | Age at study (days) | Apgar score (1 min/5 min) |
|---|---|---|---|---|---|
| 1 | 3060 | 40 | F | 2 | 8/9 |
| 2 | 3760 | 40 | M | 3 | 9/9 |
| 3 | 2880 | 40 | F | 1 | 8/9 |
| 4 | 3260 | 40 | F | 3 | 8/9 |
| 5 | 2860 | 40 | M | 1 and 2 | 9/9 |
| 6 | 2980 | 40 | F | 2 | 8/9 |
| 7 | 3320 | 40 | M | 2 | 7/9 |
| 8 | 2950 | 40 | M | 1 | 8/9 |
| 9 | 2590 | 36 | M | 7 | 8/9 |
| 10 | 1660 | 31 | F | 6 and 14 | 7/9 |
| 11 | 1820 | 34 | F | 17 and 21 | 9/9 |
| 12 | 2130 | 34 | F | 18 | 8/8 |
| 13 | 1840 | 32 | M | 4 | 9/9 |
| 14 | 1280 | 32 | F | 18 and 26 | 7/8 |
| 15 | 1946 | 32 | F | 1 | 8/8 |
| 16 | 1460 | 32 | M | 13 | 8/9 |
| 17 | 1520 | 33 | F | 6 | 7/7 |
| 18 | 1970 | 35 | M | 14 | 5/7 |

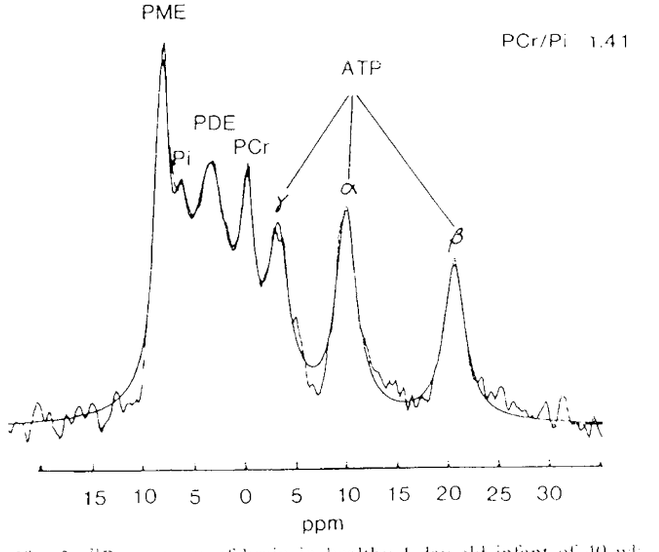


Fig. 2. $^{31}$P spectrum of brain in healthy 1-day-old infant of 40 wk postconceptional age. The chemical shifts are as depicted in Figure 1 and PCr/Pi ratio is calculated similarly.

Table 2. *PCr/Pi ratio in preterm and term infants following alteration of head position (mean ± SD)*

| Group | Head position | | | |
|---|---|---|---|---|
| | Right neutral | Left neutral | Supine | Prone |
| Preterm | 1.08 ± 0.09 (range 0.94–1.23) | 1.11 ± 0.19 (range 0.85–1.46) | 1.08 ± 0.15 (range 0.87–1.33) | 1.05 ± 0.28 (range 0.77–1.60) |
| Term | 1.13 ± 0.17 (range 0.93–1.37) | 1.00 ± 0.23 (range 0.71–1.36) | 1.09 ± 0.18 (range 0.89–1.47) | 1.05 ± 0.25 (range 0.79–1.48) |

tion when necessary. All differences were considered significant when $p < 0.05$.

## RESULTS

A total of 18 infants, 10 preterm and eight term, were studied (Table 1). All infants were healthy and clinically had a normal neurological examination for age. An example of a $^{31}P$ MRS from a preterm and term infant are shown in Figures 1 and 2, respectively. The seven labeled peaks are evident in both sets of patients. The $\alpha$, $\beta$, and $\gamma$ components of ATP magnesium complemented ATP probably include contributions from other nuclei triphosphate. The peak labeled PDE is attributable to PD and membrane phospholipids (12). The PCr/Pi ratio, an indicator of bioenergetic activity, was calculated in each position.

Control spectra for each infant were considered the spectra obtained with the head in neutral position. After these were obtained from the left and right hemispheres, the baby was placed either prone or supine so that the head was turned 90°. The spectra obtained in these positions also showed the characteristic resonance peaks.

The mean value ± SD for PCr/Pi in preterm infants was: left neutral 1.11 ± 0.19 and right neutral 1.08 ± 0.09 (Table 2). No significant difference was seen in the PCr/Pi values for term infants with the head in the supine and prone positions. The term infants had a mean ± SD for PCr/Pi ratio of: left neutral 1.00 ± 0.23 and right neutral 1.13 ± 0.17 (Table 2). Statistical analysis showed no significant change in PCr/Pi ratio with head position changes between or within groups (Fig. 3).

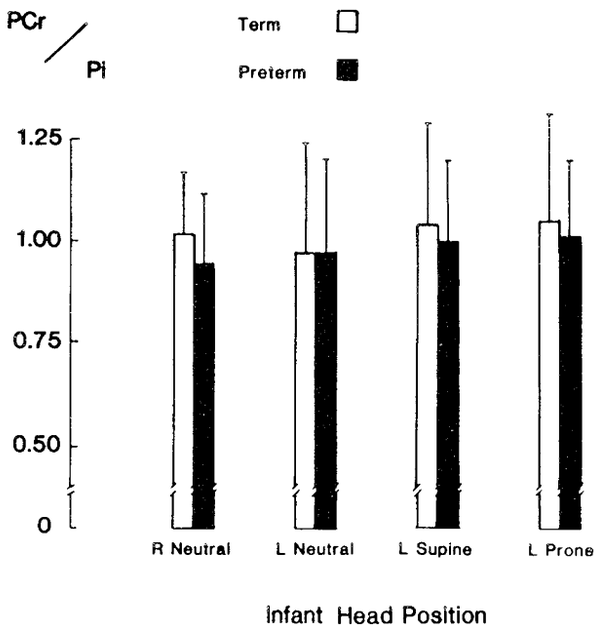


Fig. 3. Effect of varying head position on PCr/Pi ratio in healthy preterm and term infants. PCr/Pi ratio is the mean value derived from the 10 preterm and eight term infants in each head position. *Error bars* represents 1 SD. Differences between and within groups are not significant.

## DISCUSSION

Previous studies demonstrated increased intracranial pressure following head position changes in healthy and particularly in birth asphyxiated infants, with the exaggerated response in asphyxiated infants most likely due to a decrease in cerebral autoregulation (13–15). This has led to speculation as to an optimal head position whereby fluctuations in cerebral blood flow could be minimized to decrease the risk of intracranial and or intraventricular hemorrhage in the critically ill neonate. While $^{31}P$ MRS has been used to assess cerebral metabolism in infants, previous studies were obtained in neonates suffering from hypoxic ischemic episodes, such as asphyxia neonatorum. In the investigation by Hope *et al.* (16), six normal term and preterm infants were studied for comparison with the asphyxiated newborn subjects. The present study represents one of the largest series of healthy infants measured with $^{31}P$ MRS and provides insight into the basic characteristic peaks of control $^{31}P$ spectra. The $^{31}P$ spectra obtained in our normal term and preterm subjects identifies 7 peaks and are similarly to previous investigations.

Unlike the previous study by Cady *et al.* (17), we noted a lower PCr/Pi ratio in the healthy newborn infant. Part of this difference could be attributed to a saturation factor (18) that was instilled into the computation, because at a 2.25-s pulse interval, full relaxation of the atoms was not allowed but could be corrected for by a factor. In our studies we used a 4-s pulse interval and although we may have been saturating some of the larger peaks, such as PME and Pi, we used a correction factor of 1.05 which was within our significance level and could make the PCr/Pi higher. Thus all data can be corrected for saturation.

Further, it is possible to calculate from the range of the data on Table 2 that an average change of ±0.25 in PCr/Pi ratio could have occurred following alteration of head position. From this we can calculate based on Michaelis-Menten kinetics (19): $\dot{V}/\dot{V}_{max} = 1/(1 + K_1/ADP + K_2/Pi + K_3/S)$ where $\dot{V}$ = rate of oxidative metabolism, $\dot{V}_{max}$ = maximum rate of oxidative metabolism, S = substrate, and K = rate constant, what the change of tissue $PO_2$ would be, given this difference. If a reasonable assumption about the parsimony of oxygen delivery to the neonate brain can be made, a change of tissue $PO_2$ of a factor slightly greater than 2 could have occurred within the error limits observed. Since PCr/Pi is an oxygen indicator itself, we can calculate from the range of our data what would be the possible change of tissue oxygen that could have occurred within our SD as a factor of 2. This calculation emphasizes that while no detectable effects on the PCr/Pi ratio were found in the present study, it is possible that small perturbations could have been appreciated if the SE were smaller.

As the process of energy metabolism must take place in an aerobic environment, $^{31}P$ MRS is a quantitative measure of aerobic metabolism and oxygen delivery to tissues (20). During periods of anaerobic metabolism, as in asphyxia, and in low flow states as intraventricular hemorrhage (7, 16), the ability to regenerate ATP and PCr is lowered. Recent studies, in our institutions as well as in others, have shown a correlation of PCr/Pi to

asphyxial episodes (8, 16). Other studies have shown $^{31}$P MRS to be a good indicator of recovery of brain function during experimental asphyxial episodes when correlated to electroencephalography and regional CBF (7).

The findings in the present study are consistent with the Monroe-Kellie hypothesis that the brain, spinal fluid, blood, and other intracranial contents are constant, so that an initial change in volume of one compartment is offset by volume shifts in the other compartments, resulting in minimal change in intracranial pressure (21). Based on previous studies that showed that significant perturbations in ICP and blood flow velocity occurred after a change in head position even in the normal term and healthy preterm infant, these alterations may be compensated by physiological and biochemical regulations so that no change in brain oxidative phosphorylation as measured by $^{31}$P MRS in a healthy neonate is detectable.

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