

1732 **STUDIES OF OXIDATIVE METABOLITES USING 31-P NMR SPECTROSCOPY IN NEWBORN NEUROLOGIC DISORDERS.** Donald P. Younkin,* Maria Delivoria-Papadopoulos, Richard Kelly,* Robert Clancy,* John S. Leigh, Jr.,* Britton Chance.* Univ. of PA., Depts. of Neurology, Pediatrics, Physiology, Biophysics, and Biochemistry, Phila., PA. 19104

We have previously reported that cerebral spectra from newborn babies have high phosphomonoester (PME) concentration (~7 m mole/kg), low phosphocreatine (PCr) concentration (~1 m mole/kg), low PCr/Pi (inorganic phosphate) ratio (~2), and intracellular pH ~ 7.1. We present 31-P NMR results in: maple syrup urine disease, congenital lactic acidosis, gluconeogenic disorder, fetal alcohol syndrome, focal seizures and stroke, severe neurogenic arthrogryposis, lobar holoprosencephaly, and Group B strep meningitis. Spectroscopy was performed after recovery from acute metabolic or infectious abnormalities on the hypothesis that there are persistent changes in oxidative metabolites. Thus, during the study, babies were not stressed or given metabolic challenges. As a group, these babies had a phosphate potential (PCr/Pi ~ 1.0) which is characteristic of lactic acidosis. In the child with focal seizures and stroke, PCr/Pi was ~ 0.8 in the injured hemisphere vs ~ 1.8 in the normal hemisphere. In the baby with severe neurogenic arthrogryposis, PCr/Pi in resting muscle was ~ 0.3 vs > 7.0 for normal resting muscle. While there were individual differences, the mean concentration of PCr and PME and mean pH did not differ significantly from control infants. These data suggest that a wide variety of neonatal neurologic syndromes may cause persistent changes in oxidative metabolites and that 31-P NMR spectroscopy may yield significant information on the minimal value of PCr/Pi that is consistent with aerobic metabolism. (NIH T35-HD-07217-IOA1 and NIH-HD-15973-01)

PULMONOLOGY

1733 **EFFECT OF THEOPHYLLINE ON VENTILATORY RESPONSES OF GROWING PRETERM NEONATES TO COMBINED INSPIRATORY AND EXPIRATORY LOADS.** S. Abbasi, E. Sivieri, V.K. Bhutani, M.R. Wolfson, T.H. Shaffer, W.W. Fox, Univ. Pa. Sch. Med., PA Hosp, Dept. Pediatr, Temple Univ. Med. Sch. Dept of Physiol, Phila, Pa. To evaluate the effect of theophylline (TH) on ventilatory response of growing preterm infants to a combined inspiratory (I) and expiratory (E) resistive load, 6 babies were studied before (Gr. I) and during (Gr. II) TH therapy (mean ± SEM TH level = 8.0 ± 1.1 mg%). Mean ± SEM values were: birthweight = 1256 ± 138 gm; gestational age = 30.2 ± 0.8 wks; study age = 48 ± 4.4 days and study weight = 1868 ± 245 gm. Control data including tidal volume (TV), minute ventilation (MV), peak inspiratory flow (V_I), peak expiratory flow (V_E), inspiratory time/total respiratory time (T_I/T_{tot}), respiratory frequency (f) and esophageal pressure (P_{es}) were obtained before and after application of I & E loads (R₁ = 50 R₂ = 100 cm H₂O/L/sec) for 60 sec. Mean ± SEM values in Gr. II were: TV = 7.4 ± 0.8 ml/kg, MV = 172.3 ± 77.0 ml/min/kg, V_I = 3.45 ± .70 L/min, V_E = 3.12 ± .65 L/min, T_I/T_{tot} = 0.46, f = 72 ± 5 breaths/min, P_{es} 8.7 ± 2.7 cm H₂O. Application of R₁ and R₂ was associated with a significant decrease (p < .05) in both V_T (Gr. I: 25%) and MV (Gr. I: 44%, Gr. II: 29%). In addition, in Gr. I, 4 of 6 neonates did not tolerate R₁ and R₂ and had irregular respirations and pauses. P_{es} increased significantly (p < .05) only in Gr. II during both R₁ and R₂. During the loads, in Gr. II no changes in transcutaneous O₂ and CO₂ tensions were observed. These data demonstrate that TH therapy is associated with increased capability to generate higher P_{es} and improved load tolerance.

1734 **ADAPTATION OF FETAL PULMONARY BLOOD FLOW TO PHARMACOLOGIC VASODILATORS.** Frank J. Accurso, Robert Truog, Randall B. Wilkening, and Giacomo Meschia (Spon. by Frederick C. Battaglia), Depts. of Pediatrics, Physiology and OB/GYN, University of Colorado School of Medicine, Denver 80262. The normally high resistance of the fetal pulmonary circulation decreases acutely in response to some pharmacologic agents and to increases in fetal PO₂. We have previously observed adaptation of fetal pulmonary blood flow to small increases in fetal PO₂. To determine if adaptation also occurs to pharmacologic stimuli, we infused three known fetal pulmonary vasodilators, acetylcholine (A) and histamine (H) in 5 and bradykinin (B) in 3, chronically prepared fetal sheep. A cuff electromagnetic flow probe measured blood flow to the left lung (QL). Catheters in the main pulmonary artery (PA) and aorta (AO) measured pressure. A catheter was also placed in the left pulmonary artery (LPA) for direct infusion into the left lung thereby minimizing systemic effects. After a 1 hour control period, we infused A or H (0.5 µg·min⁻¹·kg⁻¹) or B (15 ng·min⁻¹·kg⁻¹) through the LPA catheter for 2 hours. After an initial increase, QL (x̄ ± SEM ml·min⁻¹) decreased toward baseline during the remaining infusion period. AO and PA pressures did not change.

	QL(control)	QL(10 minutes)	QL(2 hours)	QL(post-infusion)
A	67 ± 9	123 ± 21*	77 ± 13*	60 ± 8
H	77 ± 13	184 ± 22*	123 ± 12*	61 ± 9
B	62 ± 5	130 ± 6	77 ± 3	57 ± 7

*p < 0.05

We conclude that an adaptive response, as seen previously with small increases in PO₂, is observed in the fetal pulmonary circulation with local infusion of three pharmacologic vasodilators.

1735 **MECHANISMS OF ESTROGEN MEDIATED LUNG MATURATION.** Jahangir Ayromloo, Suchitra Bandyopadhyay and Dipak K. Das (Spon. by Philip Lipsitz). Health Sciences Center, SUNY at Stony Brook, Long Island Jewish-Hillside Medical Center, Departments of Obstetrics & Gynecology and Medicine, New Hyde Park, New York.

To investigate the mechanism of estrogen enhancement of the β-adrenergic system in fetal lung maturation, the following studies were performed. Pregnant New Zealand white rabbits of 26 days gestation were treated with 17β-estradiol (20 ug/kg) with or without actinomycin D and cycloheximide (100 ug/kg) and 24 hours thereafter the fetuses were delivered by Cesarean Section. The newborns were divided into a group receiving lung lavage and another group was killed immediately by decapitation and the lungs removed and processed for the estimation of β-adrenergic receptors, cAMP and adenylate cyclase activities. Estrogen stimulated the lecithin-sphingomyelin ratio, phosphatidyl choline contents in lung lavage, and the β-adrenergic receptors, cAMP and adenylate cyclase activities in lung tissue. These activities in lung lavage and lung tissue were inhibited by actinomycin D and cycloheximide. These studies suggest that estrogen stimulates lung maturation by synthesizing mRNA for β-adrenergic receptors, and the regulation occurs at the cellular level controlled by the cAMP system.

1736 **DIAPHRAGMATIC FATIGUE IN THE NEONATAL PIGLET.** Richard J. Badura, Jon F. Watchko, William A. LaFramboise, David E. Woodrum, Dept. of Pediatrics, Univ. of Washington, Seattle, WA.

We studied neural input to and force output of the diaphragm in 7 anesthetized neonatal piglets (wt. 2.45-3.06 kg, age 13-21 days) spontaneously breathing against a respiratory load (13x normal pulmonary resistance). Costal diaphragmatic EMG, trans-diaphragmatic pressure (Pdi), V_E, T_I, and Te were measured at baseline (BL) and during one hour of inspiratory loading. V_E (cc/min) fell significantly below BL by 5'(BL: 523±187, 5':250 ±110 p<.001) and did not change thereafter (60':288±139). Concomitantly, Pdi(cmH₂O) increased by 5'(BL: 7.8±3.2, 5':35.9 ±20 p<.001) and remained unchanged at 60'(41±12). Despite the constancy of V_E and Pdi after 5', peak EMG activity, rate of EMG activity (EMG/T_I), and slope moving average EMG progressively increased throughout the loading period.

	Peak EMG	Rate EMG	Slope EMG
5' (%BL)	170	110	165
60' (%BL)	388*	242*	280*

This failure to increase diaphragmatic force output in the presence of increasing neural drive suggested peripheral fatigue. This was confirmed by generating force-frequency curves of the diaphragm via phrenic stimulation at BL and 60' on load in 3 piglets. We found marked decreases in force output (Pdi) on load compared to BL throughout the range of frequencies tested (10-100Hz, p<.05). We conclude that diaphragmatic muscle fatigue is responsible for the decrease in diaphragm efficiency noted during resistive loading in the neonatal piglet. (*p<.02, 5'vs 60')

1737 **PNEUMOCARDIOGRAM (PCG) AND NEONATAL APNEA: ONE YEAR EXPERIENCE.** Raul C. Banagale and William E. Howatt. Sections of Newborn Services and Pulmonary Diseases, Dept. of Pediatrics, University of Michigan, Ann Arbor, MI. Twelve hour PCG was performed on 372 high risk infants (inf) [Resp Care 28:1569, 1983] from 7/1/82 - 6/30/83. Gestational age (mean±SD) was 33.6±3.8 wks and birth wt. was 2262±843.3 gms. 208 inf (Table) have normal PCGs and 144 have abnormal PCGs. PCG was normal at 38.7±3.0 wks among inf on theophylline (T) compared to inf (41.1±6.5 wks) who were not on T (p<0.01). Inf with abnormal 1st PCGs, 37.5% were treated with T, 11.1% were on home apnea monitors (Mon), 21.5% treated with T and on Mon and 29.9% received no treatment. Repeat tests at 41.0± 7.4 wks on those inf whose 1st PCG was abnormal, 61.8% were normal and 21.5% remained abnormal. Inf whose 2nd PCG was abnormal had a normal PCG when retested later, as did 16.7% inf tested elsewhere. Two of the 372 inf who died of SIDS had abnormal PCG. One was a SIB SID who was not treated with T or placed on Mon. The other was on T and on Mon but was unattached to Mon at time of death. PCG provides an objective quantification of inf ventilation and cardiac rhythm abnormalities. T is effective in regularizing the abnormality in inf breathing patterns. However, we were unable to ascertain the effectiveness of T or Mon in preventing SIDS.