**† 324** EFFECT OF CAFFEINE ON VENTILATION DURING POST-NATAL MATURATION OF BREATHING IN AWAKE LAMBS. Pierre W. Blanchard, Steven Hobbs, Aurore Côté, Daniel Dalle, Jacob V. Aranda, Michel A. Bureau.McGill University-Montreal Children's Hospital Research Institute,Montreal, CANADA.

Caffeine is an efficient respiratory stimulant during the neonatal period, but its action on respiration beyond this period remains unclear. This study was performed to evaluate the effect of caffeine on ventilation in relation to post-natal maturation. Nineteen lambs divided in 3 groups of different ages were studied;I: 7 lambs with a mean age of 1 week;II: 6 lambs, mean age of 2 1/2 months and III: 6 sheep, 6 months old. After a baseline period, saline (as a control infusion) then, 10 minutes later, caffeine 10 mg/kg I.V. were injected to the animals. Ventilation was measured using a mask adapted to the animal's facial contour and connected to a pneumotachograph; on-line values of $\dot{V}E$ (minute ventilation), Vt/Ti, (mean inspiratory flow) and Ti/Ttot (timing of respiration) were derived from the flow signal using a computerized system.No response was seen after saline;but in all three groups, $\dot{V}E$ (ml/min/kg) increased significantly after caffeine; this increase was 36% in group I; 46% in group II; and was 48% in group III. This increase in $\dot{V}E$ was due mainly to an increase in Vt/Ti (ml/sec/kg), which increased in groups I,II, III by 36,41 and 26%. Ti/Ttot did not change significantly at any time. The plasma concentrations were 9.7,8.8,10.0 mg/l in groups I,II,III. We conclude that: the magnitude of the ventilatory response and the strategy of breathing in response to the therapeutic blood concentration of caffeine persists without major difference between 1 week to 6 months of age in lambs.

**† 325** CHEMORECEPTOR MEDIATED RESPONSE OF VENTILATION TO CAFFEINE INFUSION IN LAMBS. Pierre W. Blanchard, Steven Hobbs, Aurore Côté, Patrice Foulon, Michel A. Bureau (Spon. by Jacob Aranda).McGill University-Montreal Childdren's Hospital Research Institute, Montreal, CANADA.

Caffeine is frequently used as a respiratory stimulant in the therapy of infants with apnea.The site of action of caffeine remains unclear and this present study was undertaken to evaluate the role of the chemoreceptors in the increase of ventilation following caffeine therapy. To achieve this goal we decided to study the response to caffeine after carotid body denervation (CBD). Twelve animals were studied, 6 had CBD and 6 had a sham denervation (intact) at a mean age of 13 days. The present study was carried out at a mean age of 80 days in an awake and not sedated state. The caffeine dose used was that recommended for human infants:10 mg/kg I.V. and the plasma concentration achieved was in the therapeutic range;CBD:9.0, intact:8.8 mg/l. The intact lambs responded significantly to caffeine by an increase in $\dot{V}E$ of 46% from 274±10(±SEM) to 400±21 ml/kg/min at 1 min. This response gradually faded, but at 2 hours $\dot{V}E$ was still greater than baseline being 314±21. This increase in ventilation was mainly caused by a change in Vt/Ti;from baseline 9.9 ml/kg/min it reached 14.0 at 1 min and was still increased at 120 min:11.2. In the CBD lambs no increase in $\dot{V}E$ (from baseline 263±25) and Vt/Ti was seen. No change in Ti/Ttot was seen in both groups. We concluded that: for the usual therapeutic dose of caffeine, CBD abolishes the increase in ventilation seen in intact lambs. This suggests that the carotid body receptors play an important role in the mediation of the ventilatory response to caffeine.

**● 326** BILIRUBIN DISPLACEMENT BY SULFISOXAZOLE: ENTRY OF UNBOUND BILIRUBIN INTO THE BRAIN. Dag Bratlid, William J. Cashore, Ann-Mari Brubakk, William Oh. Brown Univ., Women & Infants Hosp., Dept. of Ped., Providence,RI

This study was designed to assess the mechanism of bilirubin entry into the brain in rats when subjected to bilirubin displacement by sulfisoxazole. Hyperbilirubinemia (approximately 170μM/l or 10 mg/dl)) was established by infusion of unconjugated bilirubin at a rate of 30 mg/kg/hr for three hours. After 2 hours of bilirubin infusion, displacement of bilirubin was produced by a bolus infusion of sulfisoxazole at a dose of 50 mg/kg, resulting in a significant but transient increase in the serum concentrations of unbound bilirubin from 1.84±0.29 μg/dl at 120 mins to 3.10±0.38 μg/dl at 130 mins. (Mean ±S.E.M., p<0.001, paired t-test). After 3 hours of bilirubin infusion the rats were sacrificed and the brains perfused in situ with cold saline. Brain bilirubin was determined by chloroform extraction. The integrity of the blood-brain barrier was assessed by measurement of brain albumin as $^{125}$I albumin content. Results were (mean±S.E.M.):

| N: | Control (13) | Sulfisoxazole (10) |
|---|---|---|
| Brain bilirubin (μg/g wet wt) | 1.42±0.20 | 5.14*±0.74 |
| Brain albumin (μg/g wet wt) | 168±23 | 117±7 |

*p<0.05 when compared with control

The results indicate that unbound bilirubin displaced by sulfisoxazole can pass through an intact blood brain barrier.

**● 327** INFLUENCE OF EARLY INDOMETHACIN ON VENOUS ADMIXTURE IN INFANTS WITH HMD. Donna L. Bratton, Mats Mellander, Elizabeth D. Krueger, Mildred T. Stahlman, Robert B. Cotton, Vanderbilt University Medical Center, Department of Pediatrics, Nashville, Tennessee.

Twenty infants <1500 g with HMD known to be at high risk (75%) of developing symptomatic PDA were entered in a randomized controlled study. Mean birth weight was 1074g±158SD and gestational age 28.9w±1.5SD. Seven infants received indomethacin 0.2mg/kg IV at 24h of age prior to evidence of ductus shunting while 13 controls were observed initially without indomethacin. Both groups were comparable for birth weight, gestational age, average venous admixture (VA) and mean airway pressure prior to indomethacin administration. Although none of 7 infants given prophylactic indomethacin developed symptomatic PDA as opposed to 7 of 13 untreated controls, we observed significant higher VA in treated infants during the 24 hours following indomethacin administration (32.9%±1.2SE vs. 29.3%±1.1SE for control infants, p<.05). This increased VA was unexpected and could not be attributed to fluid retention secondary to the renal effects of indomethacin. Urine output after indomethacin was significantly reduced during the period 24-48 hours (53cc/kg±11.9SE vs. 102cc/kg±10.9SE for controls, p=.01), but fluid input was similarly decreased for indomethacin infants such that input to output ratios for treated and control infants were not significantly different (1.9±0.6SE vs. 1.4±0.3SE). These results indicate that indomethacin, possibly through its suppression of prostaglandin synthesis, might have adverse effects on ventilation-perfusion matching, pulmonary vascular resistance, or surfactant production or release.

**328** THE IN VITRO RESPONSE OF THE PULMONARY ARTERY OF NEONATAL RABBITS BORN IN HYPOBARIC HYPOXIA TO HISTAMINE AND EPINEPHERINE. Jack H.T. Chang and Joe Rutledge, Depts. Surgery and Pathology, The University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas. Sponsor: Joseph Warshaw.

Two weeks old pregnant New Zealand White rabbits were placed in a hypobaric chamber and maintained at 3657 meters (1200 feet) until delivery (30±1 days). The newborn pups were sacrificed by cervical dislocation, autopsied, and a ring of mainsten pulmonary artery removed. The right ventricle, left ventricle, and intraventricular septum were weighed. The vessel was placed in a 30ml modified Kreb's solution aerated by 95% oxygen 5% carbon dioxide, secured to a stay pin, and attached to a force transducer. Dose response curves were generated for histamine and epinepherine.

While the total heart weights of the two groups were similar, the right ventricle to left ventricle plus intraventricular septal weight ratios of the hypobaric pups (0.65±0.11) were significantly (p<0.05) increased from controls (0.60±08) indicating pulmonary hypertension. The pulmonary artery segments of hypobaric hypoxia bred pups responded in a significantly exaggerated fashion as compared to control vessels when exposed to histamine or epinepherine. Significance was found at $5x10^{-5}$M histamine and $5x10^{-8}$M epinepherine.

This model provides a means for examining the mechanism of induced pulmonary hypertension and may be useful in the assay of antihypertensive pharmacologic agents.

**329** THE DEVELOPMENTAL COURSE OF THE MORO REFLEX IN NARCOTIC-ADDICTED INFANTS. Ira J. Chasnoff and William J. Burns. (Spon. by Stan Shulman). Northwestern University Medical School, Departments of Pediatrics and Psychiatry, Chicago.

In order to evaluate the immediate and prolonged effects of neonatal addiction on the Moro reaction, a 20-point Moro Scale Score was developed. Two matched groups of term infants were evaluated: Group A (N=25) were delivered to women on low-dose methadone maintenance and Group B (N=20) delivered to drug-free women. Interexaminer reliability was .90. There was a significant difference between the two groups of infants (ANOVA) on mean Moro scores at all ages:

| Age (months) | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| A | 16.0 | 13.2 | 11.1 | 8.6 | 5.1 | 2.8 |
| B | 11.1 | 8.9 | 4.1 | 1.8 | 1.7 | 0 |

There was also a significant difference (F=30.29, p<.0001) between the two groups as to duration of the Moro reaction: 6.3 months for Group A vs. 4.2 months for Group B. For the Group A infants, there was a significant relationship between total Moro scores and small head circumference ($r_{pb}$=-.46) and between increased duration of the Moro reflex and small head circumference ($r_{pb}$=-.55). There was also a significant relationship (r=.35) between total Moro scores and poor state control on the BNBAS. Just as a developmental course of all neurologic reflexes has been shown in normal children, our findings suggest this method of serial testing of reflexes can be applied to the development course of abnormal children.