## †1547 THE EFFECTS OF APNEA AND BRADYCARDIA ON CEREBRAL BLOOD FLOW VELOCITY (CBFV) IN THE PRETERM INFANT.

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Although apnea is a common neonatal problem, its impact on the cerebral circulation is unknown. CBFV was measured with the transcutaneous Doppler technique at the anterior fontanel. Determination of area under the velocity curve (A.U.V.C.) was utilized to quantitate CBFV. The objective of this study was to examine the effects of apnea on CBFV. Ten infants <1500 gm were studied at rest and during apnea. Apnea was defined as cessation of respiration for >15 sec. In each patient, the effects were similar. Initially, a decrease in diastolic flow velocity (DFV) occurred as the heart rate decreased. With marked bradycardia (heart rate <80), a decrease in systolic flow velocity (SFV) developed and a further decrease in DFV was noted. SFV and DFV returned to baseline within sec. following the onset of spontaneous respiration, but with a delay in those requiring resuscitation. Simultaneous intra-arterial blood pressure (BP) recordings in 4 patients demonstrated similar changes in systolic and diastolic BP. Mean changes for 61 episodes is shown.

| | AUVC | Heart Rate | |
|---|---|---|---|
| Rest | 32.6 ± 9.3* | 155 ± 7 | *P<.001 |
| Apnea | 21.9 ± 5.4* | 77 ± 7.2 | |

The data show that apnea with bradycardia results in a progressive decrease in CBFV, most severe with heart rate <80. It seems possible that such repeated decreases in CBFV could cause or exacerbate cerebral hypoxic-ischemic injury.

## ●1548 ELIMINATING FLUCTUATING CEREBRAL BLOOD FLOW VELOCITY (FLUC. CBFV) IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME (RDS) SIGNIFICANTLY REDUCES THE INCIDENCE OF INTRAVENTRICULAR HEMORRHAGE (IVH).

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Utilizing the transcutaneous Doppler technique at the anterior fontanel, we have demonstrated previously the nearly constant association of fluc. CBFV and the subsequent development of IVH in preterm infants with RDS (New Engl. J. Med. 309:204, 1983). Paralysis with pancuronium was shown to convert the fluc. CBFV to a stable CBFV pattern. The objectives of this prospective, randomized study in intubated preterm infants with RDS and fluc. CBFV was to examine the effects of pancuronium on the occurrence of IVH. Seventeen infants <1500 gm have been studied; 9 infants were paralyzed within 24 h of birth and 8 were not paralyzed (controls). Paralysis was maintained for approximately 48 h. All 8 control infants developed large IVH within 48 h, consistent with our previous observations. In contrast, none of the 9 paralyzed infants developed IVH while on pancuronium. However, 4 infants developed small IVH from 1-9 days after cessation of paralysis. Even if the latter 4 infants are included in the statistical analysis, the difference in incidence of IVH in the two patient groups remains significant ($p < 0.05$).

Thus, this study of muscle paralysis in ventilated infants with fluc. CBFV, who are at extreme risk for development of IVH, demonstrates a significant reduction in incidence (as well as severity) of the IVH in the paralyzed patients.

## ●1549 REGULATION OF FETAL BREATHING MOVEMENTS (FBM) IN SHEEP BY PROSTAGLANDIN (PG) $E_2$.

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In sheep, FBM occur intermittently, and only during low voltage, fast electrocortical activity; at birth, when $PGE_2$ concentrations ($[PGE_2]$) fall, breathing becomes continuous. Meclofenamate (Mec), a PG synthetase inhibitor, decreases $[PGE_2]$ and stimulates FBM to occur almost continuously, even during high voltage, slow electrocortical activity (HVSA). To investigate the role of $PGE_2$ in regulating FBM, we studied 6 fetal sheep at 127-134d gestation. We infused Mec for 34 hr; after 12 hr we added incremental doses of $PGE_2$, each for 2-3 hr. These caused no changes in pH, $Pco_2$, $Po_2$, or blood pressure. Mec decreased $[PGE_2]$ to neonatal levels and increased the incidence of FBM, especially during HVSA. Effects of $PGE_2$ on FBM during Mec are:

| | | Meclofenamate (0.45-1.5 mg/kg/hr) | | | | |
|---|---|---|---|---|---|---|
| | | $PGE_2$ (ng/kg/min) | | | | |
| Incidence of FBM | Prior to Infusions | 0 | 9 | 18 | 36 | 90 |
| % of time | 29 | 67 | 52 | 42 | 34 | 16 |
| % of time in HVSA | 2 | 57 | 30 | 17 | 7 | 2 |

The relationship between $PGE_2$ dose and FBM can be described by a curvilinear equation ($r = 0.77$, $p < 0.001$). At a dose of 36 ng/kg/min, $PGE_2$ closely reproduced the pattern of FBM seen during control periods. These data support the hypotheses: a) endogenous $PGE_2$ inhibits FBM during HVSA, and b) at birth, the fall in circulating $[PGE_2]$ contributes to the onset of continuous breathing. (Supported by USPHS HL 27356 Pulmonary SCOR and ALA Fellowship Grant.)

## ●1550 TOLAZOLINE (T) DOSE ADJUSTMENTS BASED UPON NEONATAL PHARMACOKINETICS.

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T doses in current clinical use were derived without pharmacokinetic studies in infants. We developed a chemically-specific assay for T and measured its pharmacokinetics following pulse and infusion doses (n=12) and its concentration changes during infusion doses in 8 infants. T half-life correlated with urine output from 0.40-2.35 ml/kg/hr (R=0.77). The overall T beta (β) averaged 0.0033±0.0023 (±SD, n=12) with distribution volume of 1495±630 ml/kg in 6 infants who received single pulse doses. T infusions between 1.0 and 5.8 mg/kg/hr for 10.8-101.5 hrs produced progressive accumulation of T in all patients. The highest infant T concentration (16.4 µg/ml) approached lethal, cardiotoxic levels in animals (21.8 µg/ml). Current T infusion doses exceed neonatal clearance of T, even with normal urine output. Using the infants' average β and $Vd_\beta$, the T infusion dose to maintain a constant plasma T concentration can be estimated as 0.2 mg/kg/hr for each 1.0 mg/kg loading dose. Current infusion doses of T are much higher than those predicted by neonatal T pharmacokinetics, may account for accumulation of T in neonates, and may lead to adverse effects. Oliguria during T infusion may require further decreases in dose. Intermittent pulse doses of T may be safer than continuous infusions.

## 1551 TYPE II CELLS ISOLATED FROM NEWBORN RATS EXPOSED TO 100% OXYGEN HAVE DECREASED SECRETION OF SURFACTANT PHOSPHOLIPIDS.

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Type II cells isolated from 6 day old rats and cultured for 24 hours in 95% air, 5% $CO_2$ actively secreted phospholipids into the medium. The ratio of disaturated phosphatylcholine (DSPC) to the phosphatylcholine in the media of cells obtained from room air controls was 81%. A similar ratio of DSPC to PC was found in the cells themselves. PC accounted for 59% of total phospholipid in both the cells and in the medium. PG concentration was approximately 10% in the cells and 11% in the medium. The ratio of phospholipids in cells cultured in $O_2$ for 24 hours was reduced by 30%. The ratio of PC to total extracted phospholipid secreted into the medium by oxygen exposed cells was also decreased by 30%. Type II cells were also isolated from newborn rats exposed to 100% oxygen for 6 days. Yields of cells from oxygen treated animals was about 75% of room air controls (approximately $6.6 \times 10^6$ cells per rat versus $8.6 \times 10^6$ cells per rat). These studies indicate that functional type II cells can be isolated from oxygen exposed newborn rats and that surfactant synthesis is decreased by 24 hours of oxygen exposure. Supported by USPHS Grant HD 17785.

## 1552 RANDOMIZED CONTROLLED TRIAL OF THE PREVENTION OF APNEA OF PREMATURITY BY OSCILLATING AIR MATTRESS (OAM).

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Pre-term infants <72 hrs old, of birth-weight 750-1499g, who were not being ventilated, were assigned randomly to be nursed on OAM or conventional mattress (C). To demonstrate a reduction from 50% to 25% in the proportion of infants with ≥ 1 day of >5 episodes of apnea and bradycardia (AB) required a minimum sample size of 50 per group ($\alpha$-.05, $\beta$-0.2). Entry was stratified in 250g birth-weight groups and each study concluded after 14 days or at GA=34 weeks. Theophylline was given only if ABs exceeded 10 per day. Episodes of AB (apnea >15 secs, ± heart-rate <80 or requiring stimulation) were recorded by nurses and three 6-hour cardio-respirograph recordings were made. Growth and neurobehavioural development were measured. Birth-weight, gestational age and severity of initial RDS were similar in each group. The average number of ABs per day in each of 3 initial 5-day epochs was similar, as were the proportions requiring theophylline (OAM=17/50, C=17/63) or IPPV(OAM=3, C=1), or having a single day with >5 ABs (OAM=53%, C=56%). There was no difference in the incidence of NEC or IVH and no infant died. Oscillating air mattresses do not prevent apnea.

| N | Birth Wt. | B.Wt. <1000g | Gest.Age | Av.ABs/Day 1-5d | 6-10d | 11-15d | No.with >1 day with >5 ABs |
|---|---|---|---|---|---|---|---|
| OAM 59 | 1294±266 | 11 | 30.7±2.9 | 3.06 | 3.12 | 3.08 | 31 |
| C 63 | 1298±241 | 9 | 31.2±2.6 | 3.10 | 3.68 | 2.69 | 35 |