

day (P) 7). Both groups received iNO (5 ppm) or air from E21 to P7. Animals were evaluated at P3, P10 and P21 using immunohistochemistry, cognitive functions and mass spectrometry imaging.

iNO significantly attenuated the severity of hyperoxia-induced WMD induced in neonatal rats. Specifically, iNO decreased white matter inflammation, cell death, and enhanced the density of developing oligodendrocytes and oligodendroglial maturation. Furthermore, iNO triggered an early upregulation of P27kip1 and brain-derived growth factor (BDNF). Whereas hyperoxia disrupted early associative abilities, iNO treatment maintained learning scores to a level similar to that of control pups. In contrast to its marked neuroprotective effects, iNO induced only small and transient improvements of CLD.

These findings suggest that iNO exposure at low doses is specifically neuroprotective in an animal model combining simultaneously injuries of the developing lung and brain that mimicked CLD and WMD in preterm infants.

09 THE SIGMA-1 RECEPTOR AGONIST PRE-084 ATTENUATES INFLAMMATION-SENSITIZED NMDAR-MEDIATED EXCITOTOXIC BRAIN INJURY IN NEWBORN MICE

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Excitotoxicity and inflammation play crucial roles in the etiopathogenesis of perinatal brain injury. We have shown that the sigma-1 receptor agonist 2-(4-morpholinethyl) 1-phenylcyclohexanecarboxylate (PRE-084) protects against N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxic brain injury. In models of adult central nervous system pathology, PRE-084 has demonstrated potent anti-inflammatory properties, which makes it a promising candidate for countering inflammation-enhanced perinatal brain injury.

In the present study we evaluated the effect of PRE-084 in a neonatal mouse model of inflammation-sensitized excitotoxic brain injury.

From postnatal days 1 to 4, pups were pre-sensitized by intraperitoneal injections of IL-1 β (10ng). Two hours after the last IL-1 β dose, pups received an intracranial ibotenate injection, 1 hour after the insult they were randomly treated with i) 0.1 μ g/g bodyweight PRE-084 or ii) vehicle.

Administration of PRE-084 resulted in a significant decrease in cortical grey (mean length of the lesion: vehicle 780.00 μ m \pm 495.35 vs. PRE-084 433.33 μ m \pm 116.51; n=8-9; p<0.05) and adjacent white matter damage (mean length of the lesion: vehicle 767.50 μ m \pm 489.07 vs. PRE-084 391.11 μ m \pm 126.14; n=8-9; p<0.05). No sex-specific differences in lesion size were detected (n=3-6, p>0.05). PRE-084 treatment significantly reduced the number of isolectin B4-positive activated microglial cells in perilesional white matter (mean number of isolectin B4-positive activated microglia vehicle 36.40 \pm 6.96 vs. PRE-084 19.93 \pm 11.99; n=5; p<0.05).

We are the first to report that PRE-084 reduces inflammation-sensitized NMDAR-mediated excitotoxic perinatal brain damage. Since sigma-1 receptor agonists are investigated in clinical trials in adult neurological diseases, they might be considered a promising therapeutic option also in perinatal brain injury.

10 mTOR ACTIVATES HYPOXIA-INDUCIBLE FACTOR-1 α AND INHIBITS NEURONAL APOPTOSIS IN THE DEVELOPING RAT BRAIN DURING THE EARLY PHASE AFTER HYPOXIA-ISCHEMIA

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The mammalian target of rapamycin (mTOR) exerts neuroprotective effects under hypoxic or ischemic conditions. To explore whether mTOR participates in neuroprotective signaling through regulation of hypoxia-inducible factor-1 α (HIF-1 α), vascular endothelial growth factor (VEGF) and neuronal apoptosis in developing rat brain with hypoxia-ischemia (HI), we operated on postnatal day 10 rats by ligating the common carotid artery followed by exposure to systemic hypoxia. Brains were collected at various intervals to detect the expression of mTOR, phosphorylated mTOR (p-mTOR), HIF-1 α , VEGF and cleaved caspase 3 (CC3), using immunohistochemistry and Western blot analysis. We also used terminal deoxynucleotidyl transferase-mediated dUTP-nick end labeling (TUNEL) to detect neuronal apoptosis. The p-mTOR protein expression increased at 2 h after HI, peaked at 8 h, lasted 24 h, and then dropped to the basal level. Also, the expression of HIF-1 α and VEGF was significantly enhanced and peaked at 8 h after HI. Up-regulated expression of CC3 was observed at 2 h, peaked at 24 h, and lasted 72 h after HI. Increased neuronal apoptosis is associated with reduced HIF-1 α and VEGF expression. Furthermore, pretreatment with rapamycin, a mTOR specific inhibitor, significantly inhibited HIF-1 α and VEGF protein after HI. The expression of CC3 and the number of TUNEL-positive cells were up-regulated at 8 h and down-regulated at 24 h after HI in the rapamycin-treated group. Our findings suggest that mTOR may participate in the regulation of HIF-1 α , VEGF and neuronal apoptosis, serving neuroprotective functions after HI in developing rat brain.

11 FLUID THERAPY SHOULD BE GUIDED BY FLUID RESPONSIVENESS

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Background To predict fluid response is very Important because a little or excessive expansion may alter the prognosis of the child in shock.

Methods We review experimental and clinical articles in adult and children about parameters that could predict fluid responsiveness in shock. We also analyze our experimental data in pediatric experimental model of hemorrhagic shock.

Results The most used parameters to try to predict hemodynamic response to fluids are: static pressure parameters as central venous pressure (CVP); volume as global end diastolic ventricular index (GEDVI) or stroke volume index (SVI); dynamic parameters, as pulse pressure variation (PPV) and systolic volume variation (SVV), and the response to a maneuver that increases blood volume without expanding the patient (leg raises). Several studies in adults suggest that hemodynamic volume parameters (SVI or GEDVI) predict better the response to fluids than pressure parameters (PVC); that dynamic parameters (PPV and SVV) predict better the response to fluids than static parameters; and that maneuver leg raises maneuver is the best predictive parameter. However, the results of other studies are contradictory. In children there are few studies and there is no evidence that dynamic parameters are better predictors than static volume parameters. Our experimental studies confirm these findings. Preliminary data suggest that leg raise maneuver has not good predictive power in children.

Conclusion at this time fluid therapy in children with shock should be guided by fluid responsiveness. Macrohemodynamic, microhemodynamic and tissue parameters should be used to control the response to fluid therapy.

12 COMPARISON OF NORMAL SALINE, HYPERTONIC ALBUMIN AND HYPERTONIC ALBUMIN PLUS TERLIPRESSIN RESUSCITATION IN AN INFANT ANIMAL MODEL OF HYPOVOLEMIC SHOCK

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Background and aims To determine if in an infant animal model of hemorrhagic shock, hypertonic albumin plus single bolus of terlipressin, as opposed to isotonic crystalloid, would improve global hemodynamic and perfusion parameters. No previous experience in children or infant animal models has been reported.

Methods Prospective, randomized study in 30 two month-old piglets (9.9±2kg). Following mechanical ventilation, hypovolemia was induced by controlled 30 ml/kg bleed. After 30' pigs randomly received: Normal Saline (NS) 30 ml/kg, n=10, Albumin 5% plus Hypertonic 3% Saline (AHS) 15 ml/kg, n=10, or single bolus of terlipressin 20 µg/Kg iv plus AHS (TAHS) 15 ml/kg, n=10, over 30 min. Heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), brain tissue oxygenation by near infrared spectroscopy (bTOI), internal carotid artery flow (ICAF), arterial lactate and intramucosal gastric pH (pHi) were compared by ANOVA.

Results 30' after bleeding as well as 30', 60' and 90' after infusion no significant differences between groups were observed. However, 90' after infusion the TAHS group presented trends towards higher MAP (NS: 71±8, AHS: 74±7, TAHS: 82±7 mmHg); CI (NS: 3.2±0.3, AHS: 3.8±0.3, TAHS: 4.2±0.3 L/min/m²); lactate (NS: 1.7±1.7, AHS: 0.8±1.4, TASH: 3.6±1.4 mmol/L); bTOI (NS: 42±5, AHS: 45±4, TASH: 48±6%); and ICAF (NS: 41±4, AHS: 42±4, TASH: 48±3 mL/min); with no differences in HR (NS: 166±11, AHS: 145±10, TAHS: 159±9 bpm); and pHi (NS: 7.1±0.1, AHS: 7.2±0.1, TASH: 7.2±0.1).

Conclusion All fluids achieved similar hemodynamic and perfusion endpoints without a significant improvement secondary to the use of terlipressin.

13 VALIDATION OF EXTRAVASCULAR LUNGWATER MEASUREMENT BY TRANSPULMONARY THERMODILUTION IN SEVERE PULMONARY EDEMA IN A NEWBORN ANIMAL MODEL

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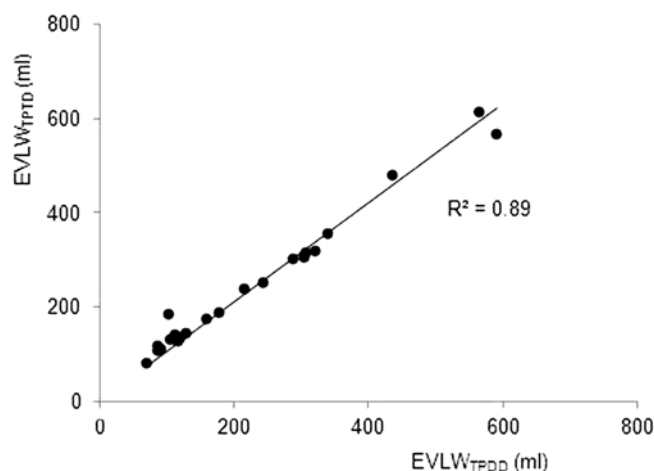
Introduction Extravascular lungwater (EVLW) can be measured at the bedside using the transpulmonary thermodilution method (TPTD), which quantifies the amount of pulmonary edema. This technique has never been validated in conditions of high indexed EVLW levels measured in infants and young children. We compared EVLW_{TPTD} measurements with the transpulmonary double indicator dilution method (TPDD; ice-cold indocyanin green) and post mortem gravimetry.

Methods In eleven newborn lambs pulmonary edema was induced using a surfactant wash-out lavage ALI model. Serial EVLW measurements by TPTD and TPDD were performed at various levels of lung water and the final EVLW values were compared with the post mortem gravimetry results. Data were analyzed using correlation statistics (Spearman's coefficient of rank correlation (rho)).

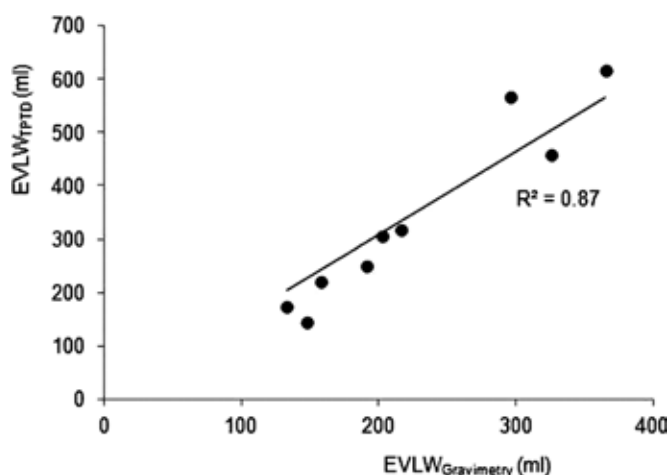
Results A total of 25 simultaneous TPTD and TPDD measurements from ten lambs were analyzed with a median EVLW_{TPDD} of 24.0 (IQR 20.7) ml/kg. One lamb died before the measurements

were performed. Correlation between EVLW_{TPTD} and EVLW_{TPDD} was r=0.94 (figure1; p<0.0001, 95%CI 0.87–0.97). Median EVLW_{Gravimetry} was 23.9 (IQR9.4) ml/kg. The correlation between the final EVLW_{TPTD} and the EVLW_{Gravimetry} was r=0.93 (figure2; p<0.0002, 95%CI 0.71–0.99).

Conclusions EVLW measurements by TPTD in severe pulmonary edema correlate well with the gold standards.



Abstract 13 Figure 1 Correlation EVLW-TPTD and EVLW-TPDD



Abstract 13 Figure 2 Correlation EVLW-TPTD and EVLW-gravimetry

14 PREDICTION OF FLUID RESPONSIVENESS IN MECHANICALLY VENTILATED CHILDREN USING TRANSOESOPHAGEAL DOPPLER (TOD) AND TRANSTHORACIC ECHOCARDIOGRAPHY (TTE) IN ALGERIAN'S PICU

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Background and aims Circulatory failure treatment needs to assess blood volume status, in order to detect a hypovolemia requiring blood volume expansion. In this way, new dynamic echocardiographic and TOD parameters have recently been proposed in mechanically ventilated children, using the heart lung interactions, such as respiratory changes of aortic blood flow velocity, and inferior vena cava diameter.