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A SIMPLE TIME DOMAIN ESTIMATE FOR DETERMINING THE BARORECEPTOR REFLEX MEDIATED HEART RATE RESPONSE IN NEWBORNS

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Introduction: The baroreceptor reflex mediated heart rate response is generally estimated by complex cross-spectral analysis (transfer function gain) between R-R interval and systolic blood pressure (SBP) fluctuations in the low frequency (LF, 0.04–0.15 Hz) band: the baroreceptor reflex sensitivity (BRS, ms/mmHg) (Andriessen, P. et al. Pediatr Res 2003;53:89–97).

Aim: To evaluate the BRS with a simple time domain (t-BRS) estimate rather than a complex frequency domain (f-BRS) estimate.

Methods: Forty-two infants (postconceptional age, range: 28–42 wk) were studied in the first days after birth whose intensive care management required an arterial catheter. Data analysis was performed on 192-s-long stationary segments during the quiet sleep state. f-BRS was estimated using transfer function analysis (LF transfer gain) based on cross-spectral analysis of R-R interval and SBP density curves, using 5 half-overlapping fast Fourier transform 64-s segments, at coherence values > 0.5 indicating statistical reliability. t-BRS was estimated by the ratio of SD of (R-R)i intervals (square root of variance or root-mean-square for the mean) divided by the SD of SBP beat-to-beat values in the 192-s-long segments.

Statistics: linear regression analysis and difference of mean as function of mean of both methods with its 95% limits of agreement (Bland-Altman).

Results: Time domain assessment of BRS (t-BRS) correlated significantly with LF cross-spectral analysis (f-BRS): r2 = 0.85; t-BRS = f-BRS + 1; $p<0.01$. The mean difference of both methods (f-BRS - t-BRS) was -1 mmHg/ms. The 95% limits of agreement were between -5 and +3 mmHg/ms.

Conclusions: The baroreceptor reflex mediated heart rate response can reliable estimated by this simple time domain estimate and may be useful to determine in critical ill patients with signs or symptoms of cardiovascular instability. Low BRS implicates poor short-term regulation of BP fluctuations. Intensive care management should aim at reducing interventions causing blood pressure changes in these patients.

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REDUCTION OF URINARY PGE2 INDUCED BY IBUPROFEN TREATMENT IN PRETERM INFANTS WITH PATENT DUCTUS ARTERIOSUS.

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Background: Patent ductus arteriosus (PDA) is a common finding among preterm infants. Hemodynamically significant PDA requires medical treatment with cyclooxygenase inhibitors such as indomethacin or ibuprofen (IBU). IBU has been shown to be as effective as indomethacin in ductal closure, with fewer adverse effects.

Aim: To investigate urinary excretion changes of PGE2 induced by IBU treatment in preterm infants with PDA.

Methods: Twenty preterm infants (gestational age, 24 to 32 weeks; birth weight, 640 to 1820 g) with a significant PDA at 48–72 hours of age were enrolled. Two serial urine samples were noninvasively collected in each patient, by a cotton wool ball method, just before and 12–24 hours after a conventional course of IBU treatment, respectively. Urinary PGE2 concentrations were measured by a sensitive and accurate enzyme immunoassay (EIA) method (Cayman Chem, Ann Arbor, MI, USA). Furthermore, serum creatinine and other renal function parameters were assessed before and after IBU treatment.

Results: Mean urinary PGE2 concentrations decreased significantly after IBU treatment (from baseline values of 66.95+/-16.78 to 27.15+/-17.92 pg/mL, $P<0.001$). Post-treatment urinary levels of PGE2 particularly low (<5 pg/mL) were found in two patients, who developed clinically relevant manifestations (intraventricular hemorrhage, acute renal failure, and intestinal perforation). Serum creatinine concentration increased from baseline value in 7 of 20 patients, 4 of them having an increase of >20%, after IBU treatment.

Conclusions: The adverse effects of cyclooxygenase inhibitors may involve different organs of newborn, but particularly the kidney, which is considered prostaglandin-dependent. Although IBU represents the most safe drug in ductal closure, it induced a significant reduction of urinary PGE2 concentrations in our study population. In newborns with relevant side effects this reduction was dramatic. Further studies are needed to confirm these data and to determine whether urinary PGE2 may represent an index of toxicity in clinical settings.

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RENAL PGE2 IN PRETERM INFANTS: A POSSIBLE ROLE IN THE ADAPTATION TO EXTRAUTERINE LIFE

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Background: Prostanoids contribute to important changes during transition from fetal to newborn life. In particular, PGE2 play a crucial role in protecting the immature kidney from high levels of angiotensin II.

Aim: To measure urinary PGE2 excretion in preterm neonates of different G.A. at birth, since there is evidence that PGE2 concentrations in urine reflect predominantly their renal generation and then could be correlated with kidney maturation or renal problems.

Methods: Thirty-eight preterm infants admitted to the neonatal intensive care unit at the University of Cagliari, Italy, were divided in three groups according to their G.A.: Group A (n=9, mean G.A. 27.6+/-1.7 wks, mean B.W. 1013+/-340 g); Group B (n=19, mean G.A. 30.8+/-0.8 wks, mean B.W. 1529+/-468 g); Group C (n=10, mean G.A. 34.4+/-1.3 wks, mean B.W. 2056+/-515 g). None of the neonates had been asphyxiated at birth and none had a specific renal abnormality or other clinical conditions influencing renal function. Spot urine samples, collected on days 2–3 of life, were analyzed for PGE2 using a commercially available kit (Cayman Chem, Ann Arbor, MI, USA).

Results: By comparing PGE2 concentrations among the three groups with ANOVA test (Group A: 65.67+/-12.97 pg/ml; Group B: 77.84+/-11.46 pg/ml; Group C: 51.90+/-11.49 pg/ml), a statistically significant difference was observed ($F=16.01$, $p<0.001$). Moreover, in neonates of groups A and B with a G.A. <33 weeks, a positive linear correlation was found between PGE2 values and G.A. ($r=0.53$, $p=0.003$).

Conclusions: From our data, the higher PGE2 values observed in neonates where nephrogenesis was not completed (G.A. <33 wks) could be due to an altered passive reabsorption of PGE2 along the nephron because of kidney immaturity or could reflect a mechanism of protection for these neonates at higher risk to develop renal problems.

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INDIVIDUALIZED FORTIFICATION OF HUMAN MILK: DOES IT MAKE THE DIFFERENCE?

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Background: Inadequate nutrition leading to growth failure is common among premature infants. Although fortified breast milk is the preferred feeding, nutrient intakes achieved with fortified breast milk fall short of meeting nutrient needs consistently. This is mainly due inadequate protein content of fortifiers and high inter- and intra-individual variation in composition of expressed breast milk.

Objective: To test a new adjustable fortification regimen designed to ensure that protein needs of premature infants are met all the time. The new regimen encompassed increasing the amount of fortifier and the addition of extra protein to breast milk. These periodic adjustments of fortification were guided by determinations of BUN. The study tested the hypothesis that the new regimen leads to higher protein intake and to improved weight gain compared to standard fortification.

Methods: In a prospective, controlled trial, preterm infants with birth weights of 600-1750 grams and gestational ages between 26–34 weeks were fed their own mother's milk, or banked donor milk, or both. Infants were randomly assigned to either the new (adjustable) fortification regimen or the standard regimen. The study period began when feeding volume reached 150 ml/kg/day and ended when infants reached 2000 g. The standard fortification regimen (STD) consisted in the addition of the recommended amount of HMF. The adjustable regimen (ADJ) consisted of standard fortification, but with addition of extra HMF and supplemental protein guided by twice-weekly BUN determinations. Primary outcome was growth, serum biochemical indicators and nutrient intakes were secondary outcomes.

Results: Thirty-two infants completed the study as planned (16 ADJ, 16 STD). Infants receiving the ADJ regimen had mean protein intakes of 2.9, 3.2, 3.4 g/kg/d, respectively, in weeks 1, 2 and 3, whereas infants receiving the STD regimen had intakes of 2.9, 2.9, 2.8 g/kg/d, respectively. Infants on the ADJ regimen showed significantly greater gain in weight (17.5 ± 3.0 g/kg/d vs 14.4 ± 3.0 g/kg/d, $p<0.01$) and greater gain in head circumference (1.4 ± 0.3 vs 1.0 ± 0.3; $p<0.05$) than infants on the STD regimen. Weight and head circumference gain were significantly correlated with average protein intake ($r=0.39$, $p<0.05$ for both). No significant correlations were found between growth parameters and intake of fat and energy. In the ADJ group BUN concentrations increased significantly ($p<0.001$) over time but were not significantly higher than in the STD group.

Conclusion: Premature infants managed with the new adjustable fortification regimen had significantly higher weight and head circumference gains than infants managed with standard fortification. Higher protein intake appears to have been primarily responsible for the improved growth with the adjustable regimen. With the new regimen protein intakes approached intrauterine accretion rates without evidence of metabolic stress. The new fortification method seems to be a promising approach to solving the problem of undernutrition among premature infants fed human milk.

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DETERMINANTS OF NOSOCOMIAL INFECTION (NI) IN SIX ITALIAN NEONATAL INTENSIVE CARE UNITS (NICUS).

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As care improves many neonates with life-threatening disorders now survive. Nonetheless Nosocomial Infections (NI) are still a major cause of morbidity and mortality in NICUs. A prospective multicentric surveillance study was conducted in six Italian NICUs to describe the epidemiologic profile and determinants of NI in NICU. 1692 neonates, consecutively admitted to the NICUs from July 2000 to October 2002 and monitored for the development of NI were enrolled into the study. The standard definition criteria for NI formulated by the Centers for Disease Control in Atlanta were used. The cumulative probability and hazard ratios (HR) for the first episode of infection were estimated by the Kaplan-Meier method and the Cox model. A total of 217 neonates had 255 episodes of NI. The incidence rate of NI was 7 per 1000 patient-days. The cumulative probability of first infection was 20% (95% CI, 7.50–23.30) and 27.6% (95 CI, 23.20–32.80) at 30 and 60 days after admission to the NICU. After adjustment for the severity of illness, the main risk factors related to NI in very-low-birth-weight neonates (VLBW) were surgical procedures (HR 2.69;95% CI 0.60–12.08), nasal ventilation (CPAP) (HR, 2.51; 95% CI, 0.93–6.76), continuous enteral feeding (HR 1.89; 95% CI, 0.20–17.50), mechanical ventilation (HR, 1.70; 95%CI, 0.72–4.00) and intravenous infusions (HR 1.46; 95% CI, 0.32–6.52). Among neonates with a birth weight over 1500 g, risk factors for NI were parenteral nutrition with lipid emulsion (HR, 12.41; 95% CI, 4.19–36.78), surgical procedures (HR 2.78; 95% CI, 0.82–9.44), and intravenous infusions (HR, 2.63; 95% CI, 0.27–25.53). Risk factors for NI were related more to the severity of illness than to healthcare procedures in VLBW babies and more to medications among neonates weighing more than 1500 g at birth.

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