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CEREBRAL CIRCULATION IN THE NEONATE:
ASSESSMENT USING TRANSCEREPHALIC IMPEDANCE AND DOPPLER ULTRASOUND
Colditz PB, Valimaki IAT, Murphy DF, Rolfe P, Wilkinson AR

Biomedical Engineering Centre and Department of Paediatrics,
University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

It has been suggested that fluctuations in arterial blood pressure and cerebral arterial flow velocity (CAV) alter brain perfusion and lead to intraventricular haemorrhage (Perlman et al, New Eng J Med 309: 209, 1983). Although intermittent measurements of CAVF can be obtained by Doppler ultrasound, a major problem is the inability to monitor cerebral circulation continuously.

Experimental design: A microprocessor based technique of transcranial electrical impedance (dZ_c) was used to monitor the cerebral circulation continuously (Murphy et al, in "Electronics in Medicine and Biology", IERE, London 1986). Average dZ_c , arterial blood pressure and heart rate were continuously displayed and stored. Measurements of avg dZ_c amplitude were compared with intermittent values of CAVF (Angioscan III) obtained from the anterior cerebral artery. Neonates with birth weight <1500g were studied for the first 48 hours. Those who received either indomethacin or aminophylline were studied before and for one hour after the dose.

Results and comments: In the 48-hour studies ($n=3$) the r values for the intra-individual correlation between avg dZ_c and mean CAVF were 0.40, 0.70 and 0.74 (all $p<0.05$). In the 1-hour studies ($n=5$) indomethacin caused a decrease of 25-30% in both signals. CAVF is an estimate of blood flow in the anterior cerebral artery whereas dZ_c reflects global changes in instantaneous intracerebral pulsatile blood volume. Our preliminary results suggest a relationship between these signals.

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VISCOSITY REDUCTION OF RED BLOOD CELLS FROM PRETERM AND FULL-TERM NEONATES AND ADULTS IN NARROW TUBES
Linderkamp O, McKay CB
(Dept. Pediatr., Univ. Heidelberg, FRG)

In blood vessels as well as in artificial tubes with diameters of less than 500- μ m, the blood viscosity decreases with decreasing diameter (Fahraeus-Lindqvist effect). The present study was designed to measure viscosity of red blood cells (RBC) from ten preterm infants, ten term neonates and ten adults by means of a capillary viscometer. RBC were suspended in buffer solution at hematocrits of 0.20, 0.40 and 0.60 l/l. Tubes with diameters of 50, 100 and 500- μ m were perfused with these suspensions. At a given hematocrit viscosity in the 500- μ m tubes was not significantly different among the preterm infants, term neonates and adults. Viscosity decreased significantly, at each of the adjusted hematocrits, in the three groups when going from a 500- μ m tube to a 50- μ m tube. The viscosity reductions increased with increasing hematocrit. At a hematocrit of 0.60 l/l, the viscosity reduction averaged 48 $\pm$ 7% in the preterm infants, 42 $\pm$ 8% in the term neonates and 35 $\pm$ 5% in the adults, whereas the viscosity reductions at a hematocrit of 0.20 l/l were only 32 $\pm$ 6%, 27 $\pm$ 4%, and 24 $\pm$ 6% respectively. For the combined data, there were significant linear relations of the viscosity reduction in 50- μ m tubes at a hematocrit of 0.60 l/l to the MCV ($r=0.67$), to the variation coefficient of MCV ($r=0.56$) and to the hemoglobin F ($r=0.48$). The enhanced viscosity reduction of neonatal RBC in narrow tubes may contribute to the low vascular resistance in neonates. Moreover, the present data suggest that a high hematocrit does not impede blood flow in neonates as much as in adults, unless the neonatal RBC are exchanged for adult RBC.

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Calcium channel blockers in the prevention of perinatal ischemic brain damage.
H.C. LOU (John F. Kennedy Institute, Glostrup, Denmark)

Ischemia plays a crucial role in the pathogenesis of perinatal brain damage; the sites of predilection are the watershed regions between different arterial supply systems, notably in periventricular leukomalacia. Cerebral blood flow (CBF) studies in the immediate postnatal period have shown a strong correlation between low neonatal CBF and subsequent neurologic and intellectual development. Furthermore, ischemia seems to be the major determinant of subsequent periventricular hemorrhage which in turn may induce secondary regional perihemorrhagic ischemia.

Counteracting perinatal cerebral ischemia may, therefore, be a reasonable approach in the prevention of perinatal brain damage. In experiments with newborn sheep, it has been shown that administration of Nimodipine, a dihydropyridine channel blocker, increased CBF markedly in all brain regions in normo- and hypotension. We have found that calcium blockers, in particular Nimodipine, effectively blocks potassium induced vasoconstriction which presumably is of major importance in the development of perihemorrhagic ischemia. By decreasing calcium influx in neural cells calcium blockers may also limit hypoxic cell damage. We therefore suggest that controlled trials of Nimodipine on the effect of CBF and outcome should be carried out in carefully selected patient groups.

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Calcium and vascular smooth muscle contraction.
G. PFITZER (Dept. Pediatrics, Div. Neonatology,
Univ. of Heidelberg, Heidelberg, W-Germany)

Vascular smooth muscle contraction is triggered by a rise in the intracellular free Ca^{2+} concentration, the amplitude of the contractile activity being dependent on the magnitude of the calcium signal. The change in the Ca^{2+} concentration can be due to an increased influx of Ca^{2+} from the extracellular space or to a release of Ca^{2+} from intracellular stores. The influx of Ca^{2+} occurs via two separate pathways, i.e. through voltage dependent Ca^{2+} channels which are opened by depolarization of the cell membrane, and receptor-operated calcium channels which are opened by the interaction of agonists with their receptors. In contrast to striated muscles activation of smooth muscle involves the reversible phosphorylation of myosin by a specific kinase, the myosin light chain kinase which is activated by Ca^{2+} via the intracellular calcium receptor calmodulin. Although Ca^{2+} is the major determinant of the contractile activity, the response of the contractile apparatus to Ca^{2+} can be modulated over a wide range. Modulators are H^+ -ions and inorganic phosphate, which may accumulate during hypoxia, and the cyclic nucleotide cAMP and cGMP which play an important role in vasodilation. The relationship between Ca^{2+} and contraction may also be modulated by certain drugs (e.g. calcium antagonists).

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OXYGEN RADICALS STIMULATE PROSTAGLANDIN SYNTHESIS IN THE RAT SMALL INTESTINE

Foulsen, J.P., Bjørro, K., Kreyberg, S., Saugstad, O.D.
The National Hospital, Oslo, Norway.

We studied the effects of oxygen radicals produced by Hypoxanthine (Hx) and Xanthine Oxidase (XO) on the rat small intestine to see whether this model could mimic the intestinal damage seen in infants with Necrotizing Enterocolitis (NEC). In anesthetized rats the ileum was divided with a silk suture preserving the blood supply into eight 5cm long segments. Each loop was injected with 0.5ml of Ringer acetate or Hx 1mM/l dissolved in Ringer plus 0.1, 2 or 5 units of XO. After 2 hours the animals were sacrificed, the loops of the intestine taken out, and the following parameters measured: Fluid volume (ml), electrolytes (mmol/l) and prostaglandins (pg/0.1ml) in the intestinal fluid. Results:

XO	Volume	Na	K	Cl	PGF _{2a}	6-keto PGF _{1a}
1	0.28	205	13	22	358	110
2	0.34	196	11	34	453	194
5	0.92	162	11	58	818	568
p $\leq$	0.001	0.05	NS	0.05	0.05	NS

The intestines were also studied by light microscopy. In rats given 5u of XO there was haemorrhage into mucosa and muscularis propria with necrosis of villi. Several of the rats showed pronounced oedema. These findings were considerably less marked with smaller concentrations of XO ($p\leq 0.05$). The present model demonstrates that the Hx/XO system potentially affects biochemical functions of the small intestine. With high concentrations of XO the mucosa, the muscularis propria and the villi are damaged, and we speculate whether this might represent the pathogenesis of NEC. Further, these experiments suggest that oxygen radicals can stimulate prostaglandin synthesis in the small intestine.

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BLOOD VOLUME OF PRETERM NEONATES DURING FLUID RESTRICTION

Versmold H, Arleth S, Leifels-Fischer B, Linderkamp O,
Div. Neonatology, Frauenklinik, Univ. of Munich, FRG

Fluid restriction in neonates reduces the incidence of patent ductus arteriosus and intracranial hemorrhage, enhances the elimination of excess lung water, but may cause hypovolemia with impaired renal and cerebral blood flow. We studied changes in blood volume (BV) during a loss of 10% of body weight in 10 AGA infants of 750-1500g after birth, at the time of minimal weight (3.2 $\pm$ 1.3d) and when birth weight was regained (11 $\pm$ 3d). Plasma volume (PV) was measured by the Evans Blue dilution technique, BV and RBC mass were calculated from PV and venous HCT. Results (mean $\pm$ SD; * $p<0.05$) are given in the table:

	After birth	Min. Weight	Re Birth Weight
Weight (g)	1235 $\pm$ 231	1112 $\pm$ 182	1257 $\pm$ 196
Fluids (ml/kg.d)	69.6 $\pm$ 9.6	117.6 $\pm$ 21.6	141.6 $\pm$ 21.6
BV (ml/kg)	82.4 $\pm$ 4.7	76.3 $\pm$ 5.3	83.4 $\pm$ 3.7
PV (ml/kg)	43.7 $\pm$ 4.3	45.4 $\pm$ 4.3	51.3 $\pm$ 4.5
RBC mass (ml/kg)	38.7 $\pm$ 5.7	30.9 $\pm$ 2.5	32.1 $\pm$ 4.0
O2 capacity (ml/dl)	23.1 $\pm$ 2.3	20.6 $\pm$ 1.2	19.0 $\pm$ 2.3
Systol. BP (mmHg)	49.4 $\pm$ 4.6	51.4 $\pm$ 4.9	50.4 $\pm$ 5.0
Urine (ml/kg.h)	1.5 $\pm$ 0.9	4.7 $\pm$ 0.8	4.0 $\pm$ 1.0

When weight decreased by 10%, BV decreased by 7.5%. This reduction of BV was not associated with hypotension or oliguria. It may not increase the risk of hypoxic ischemic encephalopathy. A marked fall in RBC mass and O2 capacity, despite substitution of sampled RBC's, may be of clinical relevance. To maintain RBC mass, additional RBC transfusion appears necessary.