EVOLVEMENT OF LV PUMPING DURING TRANSITION-ADAPTATION IN PDA PHYSIOLOGY AND PATHOPHYSIOLOGY

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Introduction: The model ventricular-arterial coupling (E_A/E_{ES}) describes the interaction between the left ventricle (LV) and the arterial system. The model characterizes the systolic pump function of the LV as estimated by the end-systolic pressure-stroke volume relation (effective arterial elastance, E_A) and the end-systolic pressure-volume relation (endsystolic left ventricular elastance, E_{ES}). We hypothesized that the physiologic transition-adaptation sequence would have an impact on the immature left ventricle (LV) that must pump an appropriate stroke volume (SV) while facing high systemic afterload. Aim was to apply the E_A/E_{ES}-model to the left ventricle (LV) during transition-adaptation in stable preterm infants (S-group) and in preterm infants with hemodynamically significant patent ductus arteriosus (hPDA-group).

Methods: E_A/E_{ES}, E_A, and E_{ES} of very preterm infants (23+0 until 32+6 weeks of gestation) were estimated from computerized records and were analyzed by groups: S-group, clinically stable neither catecholamine nor anti-pulmonary hypertension treatment, no hPDA; hPDA-group, PDA with a pure left-to-right shunt and an end-diastolic maximal velocity in the left pulmonary artery ≥ 0.2m/s. Subgroup analyses were performed by periods, respectively (early transition: days of life 1-3, late transition: 4-7, adaption: 8-30).

Results: 175 echocardiographic examinations of 126 preterm infants were analysed. In the S-group (n=122), E_A/E_{ES}-coupling ratios were higher than in the hPDA-group (n=53) (p=0.0876) and decreased from 0.65 in early transition to 0.45 in adaptation whereas E_{ES}, being initially low, increased. Thus LV pumping was characterized by a "matched" E_A: high E_{ES} relation in adaptation. In the hPDA group time trend analyses showed significantly lower E_A-($p<0.0001$) and E_{ES}-values (p=0.0062) and LV pumping was characterized by a lowE_A:lowE_{ES} relation throughout transition-adaptation.

Conclusions: Our analysis confirmed that the physiologic transition-adaptation sequence has an impact on the systolic pump function of the immature LV and that LV pumping becomes more energy-efficient towards adaptation. Whereas the physiologic PDA adds to LV pumping and SV, an h-PDA leads to LV volume overload and low afterload.

EFFECT OF VASOPRESSIN IN HYPOXIC PPHN

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Background: Persistent pulmonary hypertension of the newborn (PPHN) is marked by high pulmonary vascular resistance (PVR). Vasopressin, used as a pulmonary vasodilator in PPHN, systemic vasoconstrictor acting on smooth muscle V1R receptors.

Objective: To determine effects of vasopressin infusion on pulmonary and systemic hemodynamics, in an animal model of hypoxic PPHN, using 2D echocardiography.

Hypothesis: Vasopressin will acutely reduce PVR in hypoxic PPHN piglets.

Methods: Newborn piglets with PPHN (N=7, by exposure to FiO2 10% x 72 hrs) and age-matched controls (N=6) at 3 days age were anesthetized and ventilated, with central venous and arterial lines. After 15 min stabilization and baseline echo, PPHN and control piglets were randomized (crossover design) to start in

Block 1: Normoxic ventilation x 30 min, then ECHO-N; Vasopressin infusion 0.0012 units/kg/min x 30 min, then ECHO-NV; washout period without vasopressin x 45 min; or Block 2: Hypoxic ventilation x 30 min, then ECHO-H; Vasopressin infusion x 30 min, then ECHO-HV; washout x 45 min.

ECHO parameters: Pulmonary VTI [velocity time interval], RVO [right ventricular output], AT/ET [acceleration time/ejection time]; FAC [fractional area change], TAPSE [tricuspid annular plane systolic excursion], RV EDV [end-diastolic volume], TR [tricuspid regurgitation], SVC [superior vena cava] VTI, interventricular septum flattening [ISs, d] and eccentricity index [EIs, d] in systole and diastole.

Results: PPHN piglets had increased TR [p 0.014], lower pulmonary VTI (p 0.002), lower PCO (p 0.009); EId >1 [p 0.04]; flattened ISs [p 0.0005] and ISd [p 0.02], versus controls. RV EDV and SVC flow were not different in PPHN animals. Vasopressin infusion changed neither heart rate, BP, pulmonary blood flow nor resistance parameters in controls. Control hypoxic animals on vasopressin had lowered pulmonary VTI, but no other change in pulmonary hemodynamics. In PPHN piglets, vasopressin increased BP during normoxic ventilation. There was a non-significant effect of vasopressin on RVO, and no change in RV EDV or pulmonary AT/ET ratio.

Conclusions: Vasopressin in PPHN piglets has no effect on RVO, AT/ET, TR nor septal flattening, implying no direct pulmonary vasodilator effect within the timeframe of this study. We conclude that vasopressin does not acutely decrease PVR in PPHN.

EARLY DIASTOLIC DYSFUNCTION AND RESPIRATORY MORBIDITY IN PREMATURE INFANTS: AN OBSERVATIONAL STUDY

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Background: Premature infants often require respiratory support during the early neonatal period; with some requiring prolonged ventilation. The relationship between diastolic function assessed over the first 12 hours following birth and early respiratory morbidity remains unexplored. We hypothesise that diastolic dysfunction measured over the first 12 hours of age is associated with the need for ventilation in preterm infants.

Methods: This was a retrospective observational study of infants less than 32 weeks gestation. All infants in this cohort underwent a comprehensive echocardiography assessment over the first 12 hours after birth using tissue Doppler imaging to measure left ventricular (LV), septal and right ventricular (RV) s`, e`, and a` velocities. LV and RV e` wave to a` wave ratios were also assessed. Measurements were compared between invasively ventilated infants and those on continuous positive pressure ventilation (CPAP) and between infants with and without pulmonary haemorrhage (PH).

Results: One hundred and eighty-three infants with a mean gestation and birthweight of 27 ± 2 weeks and 999 ± 296 grams were included. Ninety-six infants (53%) were ventilated at the time of the echocardiogram. Ventilated infants have lower LV e` (3.4 ± 1.0 vs. 4.1 ± 1.5 cm/s, p<0.01) and lower LV ea` ratio (0.8 ± 0.2 vs. 1.0 ± 0.4, p<0.01) when compared with infant on CPAP. A higher LV e` and LV ea` remained independently associated with a lower risk for invasive ventilation when adjusting for important confounders (LV e` adjusted OR 0.62, 95% CI 0.45 – 0.87, p<0.01; LV ea` adjusted OR 0.14, 95% CI 0.03 – 0.68, p=0.01). Infants with PH (n=11) had a lower LV e` (2.9 ± 1.2 vs. 3.8 ± 1.3 cm, p=0.04) and a lower LV ea` (0.68 ± 0.10 vs. 0.93 ± 0.32, <0.01) when compared to infants without PH. This association remained significant when adjusting for confounders (LV e` adjusted OR 0.64, 95% CI 0.46 – 0.90, p<0.001; LV ea` adjusted OR 0.11, 95% CI 0.02 – 0.58, p < 0.01).

Conclusion: Left ventricular diastolic function in premature infants may play an important role in the evolution of respiratory morbidity as manifest by the need for invasive ventilation and pulmonary haemorrhage.

Table 4: Tissue Doppler Velocities in in the two groups.

	CPAP (n=87)	Invasive ventilation (n=96)	p
Left Ventricle free wall			
s` (cm/s)	3.1 ± 0.8	3.0 ± 0.9	0.80
e` (cm/s)	4.1 ± 1.5	3.4 ± 1.0	<0.01
a` (cm/s)	4.5 ± 1.8	4.5 ± 1.7	0.92
ea`	1.0 ± 0.4	0.8 ± 0.2	<0.01
Septum			
s` (cm/s)	2.6 ± 1.0	2.5 ± 0.7	0.26
e` (cm/s)	2.9 ± 1.0	2.9 ± 0.9	0.73
a` (cm/s)	4.1 ± 1.4	4.0 ± 1.3	0.44
ea`	0.8 ± 0.2	8.0 ± 0.2	0.61
Right Ventricle free wall			
s` (cm/s)	4.0 ± 1.0	3.8 ± 1.1	0.14
e` (cm/s)	4.4 ± 1.4	4.1 ± 1.4	0.22
a` (cm/s)	7.4 ± 1.9	6.8 ± 2.1	0.04
ea`	0.6 ± 0.2	0.7 ± 0.2	0.69

Data is presented as means ± SD.
CPAP, continuous positive airway pressure

ASSOCIATION OF TRANSITIONAL HEMOGLOBIN AND SPONTANEOUS CLOSURE OF THE DUCTUS ARTERIOSUS IN VERY LOW BIRTH WEIGHT INFANTS

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Background: Closure of the ductus arteriosus (DA) is a complex process which includes vessel constriction with clot formation leading to fibrosis. Reports of association between platelet level (PLT) and closure are published, but the influence of plasma hemoglobin (Hb) has not been studied. Our primary aim was to investigate the relationship of Hb after birth with presumed spontaneous DA closure (psDAc).

Methods: A retrospective study of preterm infants born (2013-2016) between 24 and 29 weeks of gestational age (GA) was conducted at the largest level 3 perinatal center in Switzerland. We collected Hb and PLT levels at birth and days 3 and 10 in patients treated for a PDA (medical and/or surgical) and patients with psDAc. The latter was defined by a closed DA on echocardiography or lack of receipt of treatment during the hospitalization. We hypothesized a priori that higher Hb after birth was associated with psDAc. Antenatal and postnatal demographic data and details of relevant neonatal morbidity were collected. Univariate analysis was performed to compare characteristics of both groups. Variables with a $p<0.1$ were entered in a multiple logistic regression to investigate factors associated with psDAc.

Results: We screened 184 premature infants of which 146 (79.3%) satisfied eligibility criteria. Of these 68 (46.6%) received PDA treatment [indomethacin alone, n=34 (50%); acetaminophen alone or combined with indomethacin, n=18 (20.7%); surgery, n=18 (20.7%)]. Neonates with psDAc had lower rate of chorioamnionitis, higher rate of antenatal corticosteroids, less surfactant and lower CRIB score (**Table 1**). Infants in the psDAc group were noted to have higher levels of Hb on postnatal days 3 and 10 day and higher PLT count at 10 DOL. Multiple logistic regression analysis revealed that maternal chorioamnionitis, gestational age, receipt of surfactant, Hb and PLT level remained significant (**Table 2**).

Conclusions: This is the first study to highlight an association between hemoglobin during the transitional period and psDAc. The biological nature of this observation requires prospective clarification but may relate to higher blood viscosity and the influence of Poiseulle's law.

Table 1: Neonatal characteristics of infants demonstrating presumed spontaneous ductal closure as compared to those requiring medical or surgical therapy for the ductus arteriosus.

	psDAC (n=78)	PDAT (n=68)	p
DEMOGRAPHIC INFORMATION			
GA (weeks)	27.7 (0.9)	26.7 (1.3)	<0.001
BW (grams)	947 (220)	868 (230)	0.04
Chorioamnionitis (n, %)	44 (56.4)	28 (41.2)	0.07
Full course of steroids (n, %)	71 (91.0)	54 (79.4)	0.04
Surfactant (n, %)	33 (42.3)	58 (85.3)	<0.001
ILLNESS SEVERITY			
CRIB score (P50 (P25/P75))	2 [1, 6]	5 [2, 8]	<0.001
iNO d3 (n, %)	2 (2.6)	2 (3.0)	ns
HEMATOLOGIC PARAMTERS			
HEMOGLOBIN			
At birth (mean (g/l), SD)	156 (22)	151 (20)	ns
Postnatal day 3 (mean (g/l), SD)	152 (19)	144 (15)	0.005
PLATELETS			
At birth (mean (G/l), SD)	238 (86)	227 (82)	ns
Postnatal day 3 (P50 (P25/P75), G/l)	204 [148/263]	185 [134/227]	ns
NEONATAL SHORT-TERM OUTCOMES			
Death (n, %)	2 (2.6)	10 (14.7)	0.008
Death or BPD (n, %)	30 (38.5)	52 (76.5)	<0.001
Severe IVH (Grade III-IV) (n, %)	5 (6.4)	14 (20.6)	0.01

BPD: Broncho-pulmonary dysplasia; BW: birth weight; CRIB, Clinical Risk Index for Babies; IVH : Intraventricular hemorrhage ; iNOd3 : Inhaled nitrite oxide during the 3 first day of life; GA : gestational age ; PDAT: Patent ductus arteriosus treated; psDAc: Presumed spontaneous ductus arteriosus closure

Table 2: Logistic regression analysis predict the relationship between factors with a $p<0.1$ on univariate analysis and the likelihood of spontaneous ductal closure.

Variable	Model
Gestational age (OR, 95%CI)	2.45 (1.56, 3.84), p<0.001
Surfactant administration (OR, 95%CI)	0.23 (0.09, 0.60), p = 0.003
Chorioamnionitis (OR, 95%CI)	0.211 (0.08, 0.56), p = 0.002
CRIB score (OR, 95%CI)	1.07 (0.92, 1.23), p = ns
Complete antenatal steroid course (OR, 95%CI)	1.54 (0.41, 5.73), p = ns
Hemoglobin postnatal day 3 (OR, 95%CI)	1.03 (1.0, 1.05), p = 0.04

CI: Confidence interval; CRIB: Clinical Risk Index for Babies; OR: Odds Ratio;