ID: 45

TITLE: THE RELATIONSHIP BETWEEN LEFT VENTRICULAR SYSTOLIC LONGITUDINAL DEFORMATION MEASUREMENTS AND PRELOAD IN PREMATURE INFANTS

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CONTENT:

Longitudinal deformation imaging including Strain and Strain rate (SR) is gaining interest in the neonatal field. Reference ranges in extremely low birthweight infants are emerging. However, the relationship between deformation parameters and loading conditions are still being debated. Strain is thought to be influenced by loading conditions and therefore is not reflective of intrinsic contractility. Systolic SR may be less load dependent offering a better reflection of intrinsic contractility. We aimed to assess the influence of preload on left ventricular (LV) global longitudinal strain (GLS) and SR.

We recruited three groups of premature infants < 29 weeks gestation who are enrolled in the PDA RCT (ISRCTN:13281214) over two time points (Day 2 & Day 8) to reflect different preload conditions. Group 1 (RCT-OPEN, n=22) are preterm infants with a large patent ductus arteriosus (PDA) that remains open over the two time points; Group 2 (RCT-CLOSED, n=10) are infants with a large PDA on Day 2 that closed on Day 8; and Group 3 (OBSERVED, n=11) are infants with a small or no PDA on both days. PDA diameter, left atrial to aortic root ratio (LA:Ao), LV GLS and SR (measured using speckle tracking echocardiography) were assessed on Days 2 and 8. Changes in those measurements were examined overtime.

Forty three infants with a mean ± SD gestation and birthweight of 26.7 ± 1.4 weeks and 919 ± 227 grams respectively were included. LA:Ao remained high in the RCT-OPEN Group (2.0 ± 0.3 vs. 2.1 ± 0.4, p=0.24) but decreased in the RCT-CLOSED Group (2.0 ± 0.4 vs. 1.6 ± 0.4, p=0.05) and remained low in the OBSERVED Group (1.7 ± 0.5 vs. 1.6 ± 0.6, p=0.3) over the study period (Figure). LV GLS remained high in the RCT-OPEN group, decreased in the RCT-CLOSED group, and remained low in the OBSERVED group (Figure). There were no differences in SR between the groups or over time (Figure).

Longitudinal strain is highly influenced by preload and mirrors changes in LV preload overtime. Therefore, it is not reflective of intrinsic contractility. There was no relationship between changes in preload in this cohort and longitudinal strain rate suggesting a lack of influence of preload. Strain rate is more likely to reflect intrinsic contractility in extremely premature infants.

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Figure: PDA diameter, LA:Ao, Strain and Strain Rate in the cohort over the 2 days. Values are presenting as means and Standard Error. *=p<0.05 within that time point.

COI: None Declared
ID: 46

TITLE: CIRCUMFERENTIAL AND RADIAL DEFORMATION ASSESSMENT IN PREMATURE INFANTS: READY FOR PRIMETIME?

AUTHORS: Neidin Bussmann1; Aisling Smith1; Alessia Cappelleri1; Naomi McCallion1,2; Orla Franklin3; Afif EL-Khuffash1,2.

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CONTENT:

The utility of longitudinal deformation measurements (longitudinal strain and strain rate) in premature infants is becoming well established. However, more studies are needed to demonstrate feasibility and reproducibility of left ventricular (LV) circumferential (circ) and radial strain and strain rate (SR) in this population. We aimed to assess feasibility and reproducibility of circ and radial deformation measurements in preterm infants < 29 weeks gestation, and study the impact of a haemodynamically significant patent ductus arteriosus (hsPDA) on those measurements.

We recruited premature infants < 29 weeks gestation who are enrolled in the PDA RCT (ISRCTN:13281214) over two time points (Day 2 & Day 8). The cohort was divided on the basis of the presence of a hsPDA on Day 8 (defined using a previously published PDA risk score). Circ and radial strain, systolic strain rate (SRs), early diastolic strain rate (SRe) and late diastolic strain rate (SRa) were measured on Days 2 and 8 using speckle tracking echocardiography. Intra- and inter-rater reproducibility were determined using Bland Altman analysis, intraclass correlation coefficient (ICC) and the coefficient of variation (COV). The impact of a hsPDA on all those measurements was also assessed.

40 infants with a mean ± SD gestation and birthweight of 26.9 ± 1.1 weeks and 985 ± 211 grams respectively were recruited. Imaging and offline analysis was possible in all scans. Circ parameters demonstrated excellent intra- and interrater reproducibility with minimal bias, an ICC range between 0.89 – 0.99 (all p<0.001) and a COV between 4 – 13%. Radial parameters demonstrated acceptable intra- and interrater reproducibility with minimal bias, an ICC range between 0.73 – 0.96 (all p<0.001) and a COV between 14 – 27%. Day 2 and Day 8 reference values are presented in the Table. On Day 8, infants with a hsPDA (n=21, 53%) demonstrated higher Radial strain, SRs and SRe but not SRa (Figure). There were no differences in circ parameters between those with and without hsPDA at either time point.

Measurements of circumferential and radial deformation in premature infants are feasible and reproducible. A haemodynamically significant PDA increases radial (but not circumferential) systolic strain, systolic SR and early diastolic SR. This novel information suggests that increased LV preload secondary to a hsPDA may increase intrinsic contractility in the radial but not circumferential plane.

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COI: None declared
ID: 136

TITLE: EFFECT OF FENTANYL BOLUSES ON CEREBRAL OXYGENATION AND HEMODYNAMICS IN PRETERM INFANTS

AUTHORS: Souvik Mitra1, Ege Babadagli1, Tara Hatfield1, Helen McCord1, Averie dePalma1, Walid El-Naggar1, Georg Schmölzer2, Doug McMillan1

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CONTENT:

Fentanyl, an opioid analgesic, is one of the most commonly used off-label medications for pain control and sedation in preterm infants. However, there is a growing concern with the link between fentanyl use and poor neurodevelopmental outcomes in preterm infants. Animal studies have shown that fentanyl infusion significantly reduces cerebral oxygenation in newborn piglets. Yet the effect of this medication on cerebral perfusion in preterm neonates remains unexplored.

The objective of our study was to evaluate the effect of a bolus dose of fentanyl on the regional cerebral oxygen saturation (RcSO2), cerebral fractional tissue oxygen extraction (cFTOE) and left ventricular output (LVO) as compared with pre-administration baseline in preterm infants.

A prospective observational study was conducted from October 2017-October 2018. Infants born <37 weeks of gestation receiving a bolus dose of fentanyl (1-2 microgram/kg/dose) were eligible. Infants with major congenital anomalies, medically unstable infants and those who received fentanyl bolus in the past 48 hours were excluded. Cerebral oximetry monitoring using near-infrared spectroscopy (INVOS 5100c) was started 15 minutes prior to and continued for 6 hours post fentanyl administration. Cardiac output (LVO) was measured using a non-invasive doppler ultrasound (USCOM) at 5 mins prior and at 5, 15, 30 mins and 6 h post fentanyl bolus. The primary outcome was difference between RcSO2 measured 5 mins prior to and at the above-mentioned time points after administration of fentanyl.

29 infants were enrolled during the study period [Median gestational age 28 weeks; Interquartile range (IQR) 25-30 weeks; median birth weight 1020 g (IQR 830-1275 g); median age 4 days (IQR 2.5-7.5 days)]. 28 infants received fentanyl for peripherally inserted central catheter insertion and one received fentanyl for endotracheal intubation. Mean (± standard deviation) baseline RcSO2 was 72.8% (±11.4), cFTOE was 21.9 (±11.2) and LVO was 335 (193) ml/kg/min prior to fentanyl infusion. One-way ANOVA showed no statistically significant difference between baseline and any of the post-fentanyl cerebral oxygenation or hemodynamic measures (Figures 1-3).

Administration of fentanyl bolus for procedural pain and sedation in preterm infants does not affect cerebral oxygenation, cerebral tissue oxygen extraction and cardiac output in preterm infants.

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Figure 1. Boxplot of regional cerebral oxygenation (RcSO2) values at 5 time points pre- & post fentanyl

Figure 2. Boxplot of cerebral tissue oxygen extraction (cFTOE) values at 5 time points pre- & post fentanyl

Figure 3. Boxplot of left ventricular output (LVO) values at 5 time points pre- & post fentanyl

COI: None declared
ID: 166  
TITLE: ELECTROCARDIOGRAPHIC SCREENING IN THE FIRST WEEK OF LIFE FOR DIAGNOSING HIGH-RISK CARDIOVASCULAR DISEASE  
AUTHORS: Holger Michel1, Alexander Simma2, Antonia Potapow2, Stephan Döring1, Susanne Brandstetter1, Michael Melter1, Birgit Seelbach-Göbel3, Christian Apfelbacher4, Michael Kabesch1, Stephan Gerling1, and the KUNO kids Study Group  
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CONTENT:  
Conduction abnormalities or pathological de- or repolarisation in the ECG can lead to the diagnosis of high-risk cardiac disease. With a prevalence of 1:2000 - 2500 the congenital long QT-syndrome (LQTS) is far more common than previously thought. LQTS can cause life threatening arrhythmias in infants, children and adults. It has been well documented that a prolonged QT-interval itself is associated with an increased risk of sudden infant death syndrome and an ECG screening in newborns has been proposed. Timing, QT-thresholds and methodological issues have been subject of an ongoing debate. In this study we evaluated an ECG screening in the first week of life.  
We evaluated 2251 ECGs from participants of the KUNO Kids birth cohort study, recorded between the first and the eighth day of life. A medical history regarding hereditary cardiac disease, maternal medication and pregnancy was documented. All ECGs were evaluated by pediatric cardiologists and further cardiologic examinations were carried out in case of ECG abnormalities. QT-time was manually measured and corrected for time using Bazett’s formula (QTc). If QTc was borderline or prolonged in lead II, a mean value of lead II, V5 and V6 was calculated. Newborns with a mean QTc over 450 ms received a control ECG before discharge and/or after 3-4 weeks. Participants showing a QTc time over 500 ms were admitted and monitored until improvement of the QTc time or therapy was started.  
High risk cardiac disease was found in 4 of the 2251 participants. Overall the mean QTc was 414 ms (SD 24,5 ms). In 99 (4.4%) of the participants the initial QTc was prolonged (>450 ms) and in 80 ECGs it was not measurable, leading to 8,3% of the participants receiving a second and 1,2% a third ECG. In these, the mean QTc declined from 482 ms to 426 ms. After 4 weeks only two participants showed a QTc > 450 ms. In these two, genetic analysis revealed a KCNQ1 gene mutation causing LQTS type 1. Family screening detected three more previously undiagnosed individuals. Furthermore one ECG showed a preexcitation, parents were instructed in respect to possible tachycardia. In one participant abnormal depolarization triggered echocardiography revealing a presymptomatic hypoplastic left heart syndrome. 56 participants received a second ECG recording for other reasons than QT prolongation.  
In our study cohort, ECG screening in the first week of life could detect newborns with long QT-syndrome and other high-risk cardiac conditions. Early ECG screening leads to a considerable amount of control recordings but life-threatening conditions could be diagnosed and therapy could be started before newborns were discharged. More studies concerning influencing factors, methodological and timing issues are needed.  

COI: None declared
TITLE: A MATCHED COHORT STUDY OF SURGICAL AND NON-SURGICAL TREATMENT FOR PATENT DUCTUS ARTERIOSUS IN EXTREMELY PRETERM INFANTS

AUTHORS: Karl Wilhelm Olsson 1; Sawin Yousef 1; Mattias Kjellberg 1; Renske Raaijmakers 2; Richard Sindelar 1

AFFILIATIONS: 1 Dept. of Women’s and Children’s Health, Uppsala University, Uppsala, Sweden; 2 Dept. of Pediatrics, Division of Neonatology, Sahlgrenska University, Gothenburg, Sweden

CONTENT:

Patent ductus arteriosus (PDA) continues to be a challenging problem in the care of preterm infants. PDA in extremely preterm newborn infants (<28 weeks gestational age, GA) might lead to detrimental cardiac and pulmonary complications. Due to contraindications and low efficacy of treatment with cyclooxygenase inhibitors and acetaminophen, surgical ligation is often required to close a hemodynamically significant PDA in this group. The aim of this study was to investigate the differences in peri- and postnatal factors, and outcomes, between matched surgically and non-surgically treated infants born at 22-27 weeks GA.

Between January 1st 2010 and December 31st 2016, 463 infants were born between 22-27 weeks GA at the tertiary NICU in Uppsala, Sweden. Forty-four infants were retrospectively identified as being surgically treated for their PDA (Ligated group) and matched with non-surgically treated infants (Control group; n=44) at the same gestational age (+/- 1 GA week) and time of birth (+/- 1 month). Birth weight, gender, prolonged premature rupture of membranes, administration of prenatal steroids, mode of delivery, Apgar-scores, days and type of ventilatory assistance, erythrocyte transfusions, inotropic treatment, postnatal steroids, echocardiographic variables, details of pharmacological PDA treatment, morbidity such as NEC, BPD, IVH/PVL, ROP, sepsis and mortality were compared between the groups.

There were no differences in GA or birth weight between the Ligated and the Control groups (mean ± SD; 24+4 ± 1+3 vs 24+3 ± 1+3 weeks; 683 ± 167 vs 704 ± 166 g; NS). No other major differences in perinatal characteristics were found between the groups. Larger ductal diameter prior to and lack of diameter decrease after pharmacological treatment were seen in the Ligated group (p=0.022 and p=0.048, respectively). Transfusions, postnatal steroids and longer duration of invasive respiratory support were more common in the Ligated group (p<0.01). Mortality was the same in both groups (n=5 vs n=5; NS). A higher incidence of severe BPD in the Ligated group was the only difference in long-term outcomes between the groups (p=0.025).

Early large ductal diameter and lack of decrease in ductal diameter during pharmacological treatment indicate future need for surgical ligation. Infants surgically treated for PDA required more invasive respiratory support and postnatal steroid treatment, and had a more severe BPD than infants without surgery.

COI: None declared
ID: 236

**TITLE:** THE CURRENT TREND TOWARDS CONSERVATIVE TREATMENT FOR PATENT DUCTUS ARTERIOSUS IN PREMATURITY – HOW EVIDENCE BASED IS IT?

**AUTHORS:** Tim Hundscheid 1, Esther J.S. Jansen 2, Willem P. de Boode 1

**AFFILIATIONS:** 1 Radboud university medical centre, Radboud Institute for Health Sciences, Amalia Children's Hospital, Department of Paediatrics, Division of Neonatology, Nijmegen, The Netherlands
2 Isala Women’s and Children’s Hospital, Department of Paediatrics, Division of Neonatology, Zwolle, The Netherlands

**CONTENT:**
A patent ductus arteriosus (PDA) is common in preterm and very low birth weight infants (VLBWIs). PDA is associated with mortality and neonatal morbidity, such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and intraventricular haemorrhage (IVH). Although both pharmacological and surgical treatment show a significant effect on ductus arteriosus closure rate, overall clinical outcome is not improved. Together with growing evidence of high rates of spontaneous closure in untreated patients, this has led to an increase in a conservative approach towards a PDA in which preterm infants are withheld from possible adverse effects of pharmacological treatment.

We performed a systematic literature review from 2000 till 2018 in PubMed, EMBASE and CENTRAL with the following search terms preterm infant, VLBWI, PDA, conservative treatment and placebo. We included both randomised controlled trials (RCTs) and cohort studies if they compared a conservative approach with at least one intervention group. Since many studies have high open label treatment rates we only included studies with an open label treatment rate <25%. Outcome measurements of a conservative approach for a PDA in preterm (gestational age <32 weeks) and/or VLBWI compared to both pharmacological and/or surgical treatment were extracted, analysed in Review Manager Software for meta-analysis with random effects model and presented as risk ratios (RR) with 95% confidence interval (95%-CI).

Our search revealed 401 unique articles, of which 15 could be included. Three articles were RCTs. From the included cohort studies 11/12 were retrospective. There was a heterogeneity in diagnostic approach and criteria for (haemodynamic significant) PDA. Conservative treatment ranged from watchful waiting to fluid restriction, diuretics and/or ventilator adjustments.

Conservative treatment was associated with a significant increased RR for mortality, but a significant reduced RR for BPD, IVH and ROP (Table). Since most studies were retrospective there is a high risk of treatment/selection bias, since patients were treated conservatively due to contraindications for either pharmacological and/or surgical treatment or due to a benign phenotype. This might explain the current finding of an increased risk of mortality on the one hand and a decreased risk of morbidity on the other hand.

The current trend towards a conservative approach is based on scarce, mainly retrospective and very heterogeneous cohort studies. In an attempt to answer the question whether we should treat a PDA in preterm infants or not we cannot rely on this retrospective data. Currently recruiting RCTs like the BeNeDuctus trial will form a less heterogeneous group and will give more insight whether the current conservative treatment trend remains valid.

**IMAGES:**
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Conservative treatment versus any (pharmacological and/or surgical) treatment
BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; 95%-CI, 95% confidence interval

**COI:** None declared
ID: 266
TITLE: VARIATION IN DIAGNOSTIC CRITERIA FOR HEMODYNAMICALLY SIGNIFICANT PDA IN RANDOMIZED CLINICAL TRIALS: A SYSTEMATIC REVIEW
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CONTENT:

Management of the hemodynamically significant PDA (hs-PDA) has been extensively explored through randomized clinical trials (RCTs). Meta-analyses of such trials often show substantial statistical heterogeneity thus leading to low certainty of evidence. Different diagnostic criteria have been used to diagnose hs-PDA in randomized trials. However, none of the large systematic reviews including Cochrane Neonatal reviews on PDA management have ever explored variability in PDA diagnosis as a potential source of heterogeneity.

Objective: To describe the variability in diagnostic criteria for hs-PDA in randomized clinical trials.

A systematic review of randomized control trials (RCTs) on the management of hs-PDA in preterm infants was conducted. MEDLINE (on OVID platform), EMBASE (on OVID platform), and CENTRAL (Cochrane Central Register of Controlled Trials) were searched up to April 2019. Two reviewers independently screened the search results and applied the inclusion criteria. The included studies were then evaluated for the variation in diagnosis of hs-PDA. Diagnostic criteria were categorized into clinical and echocardiographic. Data was extracted and checked in duplicate.

77 RCTs were included in our review. hs-PDA was predominantly diagnosed by echocardiography only in 43 (55.8%) studies, followed by combined clinical and echocardiographic criteria in 31 (40.3%) studies (Table 1a.). Of the echocardiographic criteria, PDA size and left atrial to aortic root ratio (LA:Ao) were most commonly used. Cut-offs for PDA size ranged from 1.3mm to 1.8mm while cut-offs for LA:Ao ratio ranged from 1.15 to 1.7 (Table 1b.). Only 16 (20.8%) studies used additional measures of PDA shunt volume beyond PDA size and LA:Ao ratio, diastolic disturbance in left pulmonary artery being the most commonly used measure. Only 2 studies graded the PDA as mild, moderate or severe based on echocardiographic criteria.

Wide variation in diagnostic criteria for hs-PDA exists in randomized trials of PDA management. Variation in diagnosis of hs-PDA could be an important contributing factor to heterogeneity obtained in meta-analysis of RCTs on PDA management. Future randomized trials and systematic reviews should use subgroup analyses based on the degree of hemodynamic significance to tease out the effects of this diagnostic variability.

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Characteristics of PDA diagnostic criteria in randomized clinical trials

COI: None declared
ID: 282

TITLE: EARLY CHANGES IN BLOOD PRESSURE PREDICT THE NEED FOR SURGICAL INTERVENTION OF A PATENT DUCTUS ARTERIOSUS IN VERY LOW BIRTH WEIGHT INFANTS

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AFFILIATIONS: Children’s Hospital, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland

CONTENT:

Very low birthweight infants are at an increased risk of developing a patent ductus arteriosus (PDA). Early recognition of infants likely to develop a hemodynamically significant PDA would allow immediate preventive measures, such as reduced fluid intake. Here we aim to find the infants with an increased risk for a PDA by using a data-driven method to analyse blood pressure changes during the first 24 hours after birth.

Our study material consisted of very low birthweight infants (birthweight < 1500 g) treated at the NICU at the Helsinki University Hospital between years 2004-2013. For this study, we included the 885 subjects for whom we had reliable continuous arterial blood pressure measurement from 4 to 24 hours after birth. Figure 1A displays average systolic (blue), mean (red) and diastolic (yellow) arterial blood pressure from 4 to 24 hours after birth for all 885 subjects. We used k-means clustering to divide the infants into two groups with distinct temporal blood pressure changes (Figure 1B). We used these groups to predict the probability of needing either a primary surgical PDA intervention or surgical intervention after unsuccessful pharmacological treatment.

During the first 24 hours of life, the majority of infants (Group 1, 514 subjects, Figure 1C) displayed an upward trend in systolic (blue), mean (red) and diastolic (yellow) blood pressure. On the contrary, in a minority of infants (Group 2, 371 subjects, Figure 1D), the systolic (blue), mean (red) and diastolic (yellow) blood pressure trends waned throughout the first 24 hours after birth. Compared to infants with rising blood pressure (Group 1), infants with waning blood pressure (Group 2) were twice as likely to need either a primary surgical PDA intervention or surgical intervention after unsuccessful pharmacological treatment (Figure 1E, p < 0.01).

In very low birthweight infants, waning blood pressure during the first 24 hours after birth predict the need for surgical intervention of a patent ductus arteriosus.

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COI: None declared
ID: 399
TITLE: REFERENCE VALUES FOR REGIONAL INTESTINAL OXYGEN SATURATION IN THE FIRST WEEK OF LIFE FOR PRETERM INFANTS
AUTHORS: B.M. Dotinga 1*, M. van der Heide 1*, R.E. Stewart 2, J.B.F. Hulscher 3, S.A. Reijneveld 2, A.F. Bos 1, E.M.W. Kooi
AFFILIATIONS: * Authors contributed equally to this work
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CONTENT:

Near-infrared spectroscopy is a non-invasive, bedside tool to measure regional tissue oxygen saturation (rSO2). Research suggests a potential clinical use of intestinal rSO2 (rintSO2) monitoring for nutritional management and for early identification of infants at risk of gastrointestinal complications, such as necrotizing enterocolitis. However, its value in clinical care is currently limited, due to a lack of reference values derived from studies with a large sample size. Therefore, we aimed to establish group and personalized reference values for rintSO2 in the first week of life for preterm infants.

In infants born at gestational age (GA) <32 weeks and/or birth weight (BW) <1.2 kg, we continuously monitored rintSO2 in the first week of life. We used INVOS 5100c near-infrared spectrometers with infraumbilical placement of neonatal SomaSensors. Infants were excluded in case of chromosomal and congenital abnormalities, necrotizing enterocolitis, sepsis, and death. We calculated mean rintSO2 from 2-hour periods per day. We assessed associations of sex, GA, postnatal age (PNA), patent ductus arteriosus, hemoglobin, nutrition, and z-scores of BW and birth head circumference (according to Niklasson) with longitudinal rintSO2 per infant in multilevel models. Missing values were imputed using predictive mean matching. Analyses were performed with IBM SPSS version 25.0.

We included 220 infants with a mean GA of 29.4 weeks (SD=2.0) and a mean BW of 1.3 kg (SD=0.4). Reference values for rintSO2 are presented in Figure 1. Higher GA was associated with higher rintSO2 (B=1.58 [95%CI 0.74 to 2.43], P<0.001). Higher BW was associated with higher rintSO2 (B=1.28 [95%CI 0.15 to 2.41], P<0.001). Higher PNA was associated with lower rintSO2 (B=-2.31 [95%CI -2.92 to -1.71], P=0.027). Together, these variables form an equation that can be used to calculate personalized reference values: rintSO2= 4.65 + 1.58*GA + 1.28*BWz-score − 2.31*PNA (R21=0.04, R22=0.16), in which PNA represents postnatal age in days, with day 0 being the first day of life. Residual diagnostics were checked and showed approximate normality.

We established reference values for rintSO2 in the first week of life for preterm infants. Higher GA and higher BW were associated with higher rintSO2, whereas higher PNA was associated with lower rintSO2. We generated an equation with GA, BW, and PNA for personalized reference values for rintSO2. Future research is needed to validate the equation presented and to elaborate on different methodological strategies (e.g. non-linear models).

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Figure 1. Reference values for rintSO2 in the first week of life for preterm infants. Day 0 represents the first day of life. We determined mean rintSO2 (dashed line) with 95% confidence interval (dotted line) using only postnatal age as an explanatory variable in a non-linear model.
COI: None declared
REFERENCE VALUES OF NEAR INFRARED SPECTROSCOPY (NIRS): DIVERSITY BETWEEN DIFFERENT DEVICES.

AUTHORS: S.J. Roerdink 1, J. Hillen 2, W.E. Kappers 3, P.R. Matthijsse 4, K.D. Liem 5

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CONTENT:

Near infrared spectroscopy (NIRS) is a non-invasive method to measure the regional oxygen saturation (rSO2) in tissue continuously. Especially in the neonatology, it is a promising tool to monitor rSO2 in brain tissue and skeletal muscle tissue. Currently, there are multiple kind of NIRS devices on the market. There are indications that the reference values are different between these NIRS devices. The aim of this study is to compare the reference values of rSO2 in muscle tissue and cerebral tissue between INVOS 4100 and NIRO 200NX.

A prospective, observational clinical study with healthy neonates (34-42 weeks) born after an uncomplicated delivery in the Radboud UMC Nijmegen was performed. In the first period the cerebral rSO2 (crSO2) and muscle rSO2 (mrSO2) were determined by the INVOS 4100 Cerebral Oximeter. During the second period the NIRO 200NX monitor was used. The sensors were placed on the forehead and the thigh. Measurements were done in the first 36h post partum for at least 30 min. The mean crSO2 and mrSO2 during the most stable 15 min of the individual neonate in the population of each device were calculated. Then the p2.5 and p97.5 of both the rSO2 from each population were calculated which are considered as reference values for the population of each device and were compared using an independent t-test.

A total of 159 neonates were included, 89 neonates in the INVOS group and 70 neonates in the NIRO group. There were no significant differences in baseline characteristics between both groups (table 1). The means ± SD (p2.5 – p97.5) of crSO2 and mrSO2 in the INVOS group were 84% ± 6 (72% - 95%) and 92% ± 5 (76% - 95%), and in the NIRO group were 70% ± 7 (58% - 85%) and 78% ± 6 (67% - 92%). This difference between the reference values in both the cerebral and the muscle tissue oxygenation between the groups was significantly different (p<0.001).

The reference values of regional tissue oxygen saturation in cerebral and muscle tissue of healthy neonates differ significantly between the INVOS 4100 Cerebral Oximeter and the NIRO 200NX near infrared oxygenation monitor. Therefore it is important to determine their own reference values for each NIRS device.

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Table 1. Baseline characteristics of the study population

COI: none declared
ID: 418
TITLE: FETAL CEREBRAL T2* AFTER MATERNAL HYPEROXYGENATION IN FETUSES WITH AND WITHOUT HEART DEFECTS
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CONTENT:

Children with major congenital heart defects risk impaired cerebral growth, delayed cerebral maturation, and neurodevelopmental disorders. The magnetic resonance imaging modality T2* is low in areas with high concentrations of deoxyhemoglobin. We have previously shown that the fetal cerebral tissue oxygenation estimated by T2* is lower in fetuses with heart defects compared to fetuses without heart defects and that T2* in the fetal brain decreases with increasing gestational age. In the present study we aimed to evaluate the fetal cerebral T2* after a short trial of maternal hyperoxygenation.

Recruitment of women expecting fetuses with and without heart defects took place at Aarhus University Hospital between 2014 and 2016. Twice during pregnancy, at mean (range) gestational age (GA) of 32 (30–34) weeks (early) and 37 (35–39) weeks (late), we compared the fetal cerebral T2* after 20 minutes of maternal hyper-oxygenation with 70% oxygen on a facemask in 22 fetuses without heart defects to that of 11 fetuses with major heart defects: transposition of the great arteries (n=3), coarctation of the aorta/hypoplastic aortic arch (n=5), tetralogy of Fallot (n=1), hypoplastic right heart (n=1), common arterial trunk (n=1). T2* was measured using a breath-hold multi-echo gradient-echo sequence with 5-16 echoes ranging from 1.42 to 120 milliseconds (ms) on a 1.5T Philips scanner.

Multilevel mixed-effects linear regression that accounted for repeated measurements within each fetus was used to estimate the relationship between GA and the fetal cerebral T2* value. Among fetuses without heart defects, the mean cerebral T2*-value after maternal hyper-oxygenation was 161 milliseconds (ms) (95% confidence interval (CI) 152 to 171) early and 127 ms (CI 120 to 134) late. These figures were not significantly different among fetuses with heart defects: transposition of the great arteries (n=3), coarctation of the aorta/hypoplastic aortic arch (n=5), tetralogy of Fallot (n=1), hypoplastic right heart (n=1), common arterial trunk (n=1). T2* was measured using a breath-hold multi-echo gradient-echo sequence with 5-16 echoes ranging from 1.42 to 120 milliseconds (ms) on a 1.5T Philips scanner.

The difference in fetal cerebral T2* between fetuses with and without heart defects, previously reported, are no longer present after a short trial of maternal hyper-oxygenation. This may indicate an effect on the fetal brain of maternal hyperoxygenation. Analyses are ongoing. However, the possible benefits of oxygen therapy may be outweighed by several disadvantages such as free radical and altered fetal blood. Further studies are needed.

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Fetal cerebral T2* after maternal hyperoxygenation (ms; y axis) by gestational age (weeks; x axis); Blue dots: fetuses without heart defect. Red dots: fetuses with heart defects. Thick blue and thick red line: regression line of the fetuses with and
without heart defects respectively. Thinner blue line: 95% prediction interval for the fetuses without heart defects. A very thin dashed line connects the results from 2 scans of the same fetus. MRI: Magnetic resonance imaging; ms: milliseconds.

COI: There are no conflicts of interest
ID: 476
TITLE: PERIPHERAL MUSCLE OXYGENATION MEASURED WITH NEAR-INFRARED SPECTROSCOPY IN PRETERM NEONATES ON THE FIRST DAY AFTER BIRTH
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CONTENT:

Near-infrared-spectroscopy (NIRS) measurements combined with venous occlusions enable to assess peripheral muscle oxygenation and perfusion. Changes over time (first minutes after birth and over several days/weeks after birth) have been described in term and preterm neonates. However, behaviour of peripheral muscle oxygenation and perfusion measured with NIRS on the first day after birth is unknown. The aim of the present study was to evaluate peripheral oxygenation and perfusion within the first 24 hours after birth in cardio-circulatory stable preterm neonates.

Secondary outcome parameters of prospective studies were analysed. Preterm neonates were included, in whom peripheral muscle NIRS measurements (NIRO 200, Hamamatsu Photonics) combined with venous occlusion were performed within the first day after birth. Heart-rate and arterial oxygen saturation were measured by pulse oximetry. Neonates had to be without any circulatory support and without signs of infection/inflammation. Measurements of neonates were divided into four ”6-hour-periods”. For each period total haemoglobin (HbT), oxygen delivery (DO2), oxygen consumption (VO2), fractional oxygen extraction (FOE), tissue oxygenation index (TOI) and mixed venous oxygenation (SvO2) were calculated. Values of the first ”6-hour-period” were compared to values of the following time periods.

133 preterm neonates (median gestational age: 33.7 weeks (32.6-34.7 weeks); median birth weight: 2070g (1745-2380g)) were included in the present study. Median age of neonates when NIRS measurements were performed was 12 hours. HbT showed a significant increase from the first to the third period (p=0.006). As well, DO2 showed a significant increase from the first to the third period (p=0.009). VO2 did not change significantly. FOE showed a significant decrease from the first to the second (p=0.012) and third (p<0.001) time period. TOI showed a non-significant increase comparing the first time period with the third period (p=0.108). SvO2 showed a significant increase from the first to the second (p=0.012) and third (p=0.001) time period. (Table1)

In preterm neonates HbT, DO2, SvO2 increased, FOE decreased and TOI showed a trend towards increase on the first day after birth, whereas VO2 did not change. The present observed changes show different behaviour when compared to measurements during the first days/weeks after birth. Therefore, the present findings have to be taken into account when preterm neonates are measured especially on the first day after birth.

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COI: None declared.
ID: 500
TITLE: DOES PATENT DUCTUS ARTERIOSUS AFFECT SPLANCHNIC OXYGENATION RESPONSE TO THE FIRST ENTERAL FEED?
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CONTENT:
Patent ductus arteriosus (PDA) is common in preterm neonates. Due to the fear of possible gastrointestinal (GI) complications, the presence of a haemodynamically significant PDA may delay the introduction of enteral nutrition in this delicate population. Near Infrared Reflected Spectroscopy (NIRS) provides a non-invasive, continuous monitoring of tissue oxygenation and an indirect estimation of regional perfusion. Current data on the influence of PDA on splanchnic oxygenation (SrSO2), however, are scarce. We aimed to evaluate whether SrSO2 patterns in response to the first feed and the subsequent rates of gastrointestinal (GI) complications differ in very preterm infants with different PDA status.

Preterm infants <32 weeks’ gestation were enrolled before enteral feeding introduction. At first feed administration, a 3-hour continuous NIRS monitoring of SrSO2 and cerebral oxygenation was performed, and splanchnic-cerebral oxygenation ratio (SCOR) was calculated. According to their echocardiographic features at enteral feeding introduction, the enrolled infants were allocated into the following groups: pulsatile PDA (pPDA), restrictive PDA (rPDA), no evidence of PDA (noPDA). SrSO2 and SCOR patterns were analysed and compared between the groups. The occurrence of GI complications (i.e., necrotizing enterocolitis, intestinal perforation, feeding intolerance) was also evaluated and compared among the study groups.

Fifty infants (pPDA group, n=11; rPDA, n=11; noPDA, n=28) were enrolled. No significant difference in SrSO2 and SCOR patterns in response to first feed administration was observed between the study groups (Figure 1). The incidence of necrotizing enterocolitis, intestinal perforation and feeding intolerance was also similar in the 3 groups.

The presence of PDA, either with restrictive or hemodynamically significant features, does not affect splanchnic oxygenation response to first feed administration and is not associated with an increased incidence of gut complications in very preterm infants. These findings support the timely introduction of enteral nutrition in preterm infants with evidence of PDA.

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Figure 1

COI: None declared.
ID: 587

**TITLE:** ACID BASE METABOLISM AND CEREBRAL OXYGENATION IN TERM AND PRETERM NEONATES DURING IMMEDIATE TRANSITION AFTER BIRTH - AN OBSERVATIONAL STUDY

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**CONTENT:**

Background: Associations between blood-glucose-level and cerebral oxygenation (cerebral-regional-Oxygen-Saturation (crSO2) and cerebral-Fractional-Tissue-Oxygen-Extraction (cFTOE)) have been described in neonates. Aim of the present study was to investigate potential impacts of acid-base-metabolism on crSO2 and FTOE during immediate transition after birth.

Methods: Post-hoc analyses of secondary outcome parameters of observational studies were performed. Preterm and term neonates born by caesarean-section were included, in whom cerebral near-infrared-spectroscopy (NIRS) measurements were performed during immediate transition after birth and blood gas analyses (lactate (LAC), pH-value (pH), base-excess (BE) and bicarbonate (BC)) were measured from capillary blood sample taken between 15 to 20 minutes after birth. Routine monitoring was performed with pulse-oximetry (arterial oxygen saturation (SpO2) and heart rate (HR)). Correlation analyses were performed to investigate potential associations between crSO2, FTOE measured by NIRS at 15 minutes after birth and acid-base-metabolism were analyzed from the blood sample.

Results: 43 preterm neonates (GA: 34.0 weeks (24.0-36.7), BW: 1850g (640-3006) and 117 term neonates (GA: 38.9 weeks (37.0-41.4), BW: 3240g (2090-4466)) were included. Median crSO2 values at 15 minutes after birth were in preterm neonates 82% (16-95) and in term neonates 83% (54-95). Median FTOE values at 15 minutes after birth were in preterm neonates 0.13 (0.00-0.82) and in term neonates 0.13 (0.00-0.41).

In preterm neonates an increasing LAC and decreasing pH and BE were associated significantly with decreasing crSO2 and increasing FTOE. In term neonates no significant correlations were observed.

Discussion: In the present study we observed associations between acid-base-metabolism and cerebral oxygenation immediately after birth in preterm neonates, but not in term neonates.

**IMAGES:**

[Link to image]

Basic demographic informations of the study population

**COI:** None declared
ID: 589
TITLE: THE STUDY OF TRANSITIONING HEMODYNAMIC INSTABILITY AND BRAIN INJURY CAUSED BY PRETERM BIRTH
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CONTENT:

A healthy cardiopulmonary system is defined by its ability to adequately deliver sufficient oxygen to the tissue to meet metabolic demands. In the care of high risk neonates, ensuring a hemodynamic stability to provide sufficient oxygen to the brain, and so as not to cause any brain injury, is our ultimate goal. Yet, maintenance of neonatal circulatory homeostasis remains a real challenge, not only due to the complex physiology during postnatal transition and the inherent immaturity of the organs, but also due to the lack of reliable hemodynamic monitor to guide our management. Low blood pressure has been used to define shock. Yet with the flow distribution by diving reflex and the impact of local vasoactive molecules, cardiac output and blood pressure hardly address the real picture of end-organ perfusion, let alone oxygen metabolism. Our aim of this study was to apply currently available hemodynamic monitors, namely blood pressure, cardiac output, cerebral blood flow by color doppler measurement, brain tissue oxygen saturation, pulseoxymetry (for SpO2), and transcutaneous CO2 monitor to investigate the influences of systemic and cerebral circulatory changes on brain injury after preterm birth.

Cardiac output was measured by electrical cardiometry AESCULON™ and compared with measurements from echocardiogram. ACA blood flow was measured by color Doppler. The transcutaneous PCO2 (tcPCO2) was measured using SenTec OxiVenTTM system. Brain tissue oxygenation (CrSO2) was monitored using near-infrared spectroscopy (NIRS) INVOSTM 5100C. The CrSO2 was recorded every five or six seconds. The cerebral fractional oxygen extraction (cFTOE) was calculated as formula: cFTOE=(SaO2 – rStO2)/SaO2. They were monitored continuously for 72 hours starting within three hours after birth. Transitional cardiovascular performance were also monitored daily for the first 3 days and continued until PDA closure or for a maximum duration of 7 days postnatally. Study period was from 2017/12 to 2018/4.

We found that CrSO2 has weak positive correlation with blood pressure SBP (r=0.255, p=0.004), DBP (r=0.267, p=0.002) and MABP (r=0.259, p=0.004). There was a strong negative correlation between CrSO2 and cFTOE (r=-0.798, p<0.001). cFTOE has a weak positive correlation to FiO2 (r=0.23, P=0.002). The tcPCO2 has a weak positive correlation to cETOE (r=0.181, p=0.015) and negative correlations to CrSO2 (r=-0.183, p=0.01).Infants with IVH had lower mean CrSO2 than infants without IVH (median 66.95, IQR (62.69, 72.27) vs. median 75.35, IQR (72.27, 81.97); p=0.001). VLBW infants who had lower mean CrSO2 within first 72 hours of life and developed PDA later was prone to failure of pharmacologic treatment of PDA (median 75.36, IQR (72.28, 82.36) vs. median 69.85, IQR (65.5, 76.8; p=0.113).

In our study, the correlations between CrSO2 and blood pressures are weak indicating systemic blood pressure does not represent organ perfusion. Infants with lower postnatal 72 hours CrSO2 were more likely to develop IVH and hsPDA, and also had higher risk of medical treatment failure for closure of PDA. Continuous cerebral NIRS monitor may help guide better management to ensure better outcome in VLBW preterm infants.

COI: None declared.
ID: 637
TITLE: ENDOTHELIAL MICROPARTICLES (EMPs) AND ENDOTHELIAL PROGENITOR CELLS (EPCs) AS EARLY BIOMARKERS OF CARDIOVASCULAR RISK IN PREPUBERTAL CHILDREN BORN PREMATURELY
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CONTENT:

Endothelial microparticles (EMPs) and endothelial progenitor cells (EPCs) are reliable, early biomarkers of endothelial dysfunction. It has been suggested that preterm birth is significantly associated with cardiovascular risk factors and endothelial dysfunction. EMPs and EPCs have not been studied, so far, in prepubertal children born prematurely. The aim of this study was to determine EMPs and EPCs in prepubertal children born prematurely and to assess possible correlations with cardiovascular risk factors.

The study population consisted of 112 children, 8-13 years old (54 preterm and 58 fullterm, as controls). Anthropometric measurements (body mass index-BMI, waist/hip circumference-WHR), arterial blood pressure and blood biochemistry (glucose, insulin, and lipid levels) were assessed. Moreover, ultrasonographic measurements of interventricular septum thickness (IVSd), left ventricular internal dimension (LVIDd), mass (LVM) and mass index (LVMI), common carotid (cIMT) and abdominal aorta (aIMT) intima-media thickness, were performed. Circulating EMPs [CD62e(+) and CD144(+)] and EPCs [CD34(+)/VEGFR2(+) and CD34(+)/VEGFR2(+)/CD45(-)] were quantified by flow cytometry. For statistical analysis, Student’s t-test, Mann-Whitney U-test, and correlation/multiple regression analysis were applied.

In comparison with controls, children born prematurely presented with higher BMI (p=0.01), WHR (p=0.04), systolic (p<0.001) and diastolic (p=0.04) blood pressure, IVSd (p=0.006), cIMT (p<0.001) and aIMT (p=0.03). Circulating CD62e(+) and CD144(+) EMPs, CD34(+)/VEGFR2(+) and CD34(+)/VEGFR2(+)/CD45(-) EPCs were significantly higher in preterm compared to fullterm (p=0.01, p=0.005, p=0.02 and p=0.04, respectively). Circulating CD62e(+) EMPs correlated significantly with total cholesterol levels (rs=0.26, p=0.03), cIMT (rs=-0.3, p=0.02), aIMT (rs=-0.2, p=0.03) and LVMI (rs=-0.27, p=0.02). Furthermore, CD34(+)/VEGFR2(+) EPCs were positively correlated with systolic (rs=0.41, p=0.001) and diastolic (rs=0.4, p=0.003) blood pressure, insulin levels (rs=0.28, p=0.01), IVSd (rs=0.31, p=0.01), LVIDd (rs=0.27, p=0.03), LVM (rs=0.38, p=0.004), cIMT (rs=0.34, p=0.005) and aIMT (rs=0.32, p=0.01).

Prepubertal children born prematurely demonstrate increased expression of endothelial microparticles (EMPs) and endothelial progenitor cells (EPCs), indicative of endothelial dysfunction and/or vascular damage, in comparison with fullterm born children. Significant correlations between EMPs and EPCs expressions and cardiovascular risk factors reflect possible endothelial injury and/or activation of vascular repair and remodeling.

COI: None declared
ID: 802

TITLE: COMPARATIVE EVALUATION OF APPROACH TO CARDIOVASCULAR CARE IN ASPHYXIATED INFANTS WITH HEMODYNAMIC INSTABILITY BETWEEN A LARGE CANADIAN VS HUNGARIAN REFERRAL CENTER

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CONTENT:

Patients with hypoxic-ischemic encephalopathy (HIE) may present with hemodynamic instability. Therapeutic hypothermia (TH) improves neurodevelopmental outcome in asphyxiated newborns, but may worsen hemodynamic instability. Our primary aim was to compare the approach to management of hemodynamic instability and short term outcomes in asphyxiated infants at two high volume centers.

In this retrospective cohort study, we studied 176 term infants with HIE, who were admitted to the NICU of the Hospital for Sick Children, Toronto, Canada (Center A, n=86) or the 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary (Center B, n=90) for TH between 2015 and 2017, and developed systemic hypotension (mean arterial pressure less than gestational age). Baseline neonatal demographics, indices of hemodynamic stability and details of hemodynamic interventions were compared. Short term outcome was evaluated based on MRI examinations. Adverse outcome was defined as perinatal death or brain injury in the basal ganglia and/or in the watershed area.

Baseline illness severity and HIE staging were comparable between groups. The average lowest systolic and diastolic blood pressure were similar (table). Interestingly 49% of the patients in Center A did not receive any cardiovascular support during TH, whereas only 3% remained untreated in Center B (p<0.001). The first line cardiovascular therapy was dobutamine (66%) in Center A vs dopamine in Center B (94%). The rate of hypertension after the initiation of cardiovascular support was 47% in Center A, while 69% in Center B (p=0.003). Other clinical outcomes (diuresis, convulsions, length of antibiotic treatment and invasive ventilation) were comparable. Adverse outcome was similar in the two centers (48% in Center A and 53% in Center B; p=0.45); however, the pattern of brain injury differed between centers and there was a trend towards increased injury in center A (table).

A more aggressive approach to cardiovascular care did not lead to better MRI outcomes, but was associated with increased rate of hypertension. Use of early comprehensive echocardiography may provide enhanced diagnostic precision enabling investigation of the relationship of heart function and systemic hemodynamics to brain injury.

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Lowest blood pressure values and MRI outcome of the study population

COI: None declared.
ID: 868

TITLE: RENAL OUTCOME IN FORMER ELBW CHILDREN AT 11 YEARS: A POOLED ANALYSIS IN SEARCH OF COVARIATES

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CONTENT:

A great number of studies examine the association between being born as extreme low birth weight (ELBW) infant, and subsequent kidney size and function later in life. However, the number of cases versus control (term equivalent age) in published cohort studies is low and multicenter cooperation to pool data together to obtain more accurate results is crucial.

We performed a subject level meta-analysis to pool data from Cracow (64 cases/34 controls) and Leuven (93 cases/87 controls). We assessed and analyzed cystatin C estimated glomerular filtration rate (eGFR), ultrasound kidney length and blood pressure (BP) in 11-years-old children born with extremely low birth weight (ELBW, birth weight < 1000 grams) compared with controls born at term. The prevalence of hypertension (HT) and prehypertension (preHT) in both groups was also analyzed.

The study group comprised 157 former ELBW children (gestational age 23-33 weeks and birth weight 430-1000 g) and 123 born at term. Former ELBW children had lower mean eGFR (100.62±16.53 ml/min/1.73m2, vs. 111.89±15.26 ml/min/1.73 m2; p<0.001), smaller absolute kidney length (8.56±0.78 cm vs. 9.008±0.73 cm; <0.001) and higher systolic (111.8±9.8 vs. 107.2±9.07 mmHg; p=0.01) and diastolic (68.6±6.8 vs. 66.3±7.7 mmHg; p=0.03) blood pressure. Lower renal size in former ELBW children was positively associated with lower birth weight, shorter gestational age, and with the severity of perinatal complications (intraventricular hemorrhage, length of stay, mechanical ventilation and oxygen therapy, postnatal steroids).

ELBW is associated with lower eGFR and a higher systolic and diastolic blood pressure. Within ELBW cases, birth weight, gestational age and perinatal complications were associated with lower renal size.

COI: the leuven study has been supported by the Safepedrug initiative (IWT-SBO)