

# Proceedings of the 15<sup>th</sup> International Newborn Brain Conference: Other forms of brain monitoring, such as NIRS, fMRI, biochemical, etc.

Fota Island, Cork, Ireland, February 28<sup>th</sup> – March 2<sup>nd</sup> 2024

Ceyda Acun, Collins Akugizibwe, Hany Aly, Alexa AschAlexander Avian, Nur Aycan, Nariae Baik-Schneditz, Sean Bailey, Vera Balog, Magdolna Barra, Ellen Bartolini, Murat Basaranoglu, Priska Bauerstätter, Angel Bazan, Angelika Berger, James P Boardman, Geraldine Boylan, Marlies Bruckner, Jenny Bua, Julia Buchmayer, Martha Caprio, Sara Cherkerzian, Venkata Chirumammilla, Helen Christou, Derya Cay Demir, Eugene M Dempsey, Mohamed El-Dib, Julia Elis, Hoda El-Shibiny, Isaac Emurang, Michael J. Esser, German Figueroa, Daragh Finn, Maria Angela Franceschini, Hans Fuchs, Aisling Garvey, Vito Giordano, Katharina Goeral, Seth Goldstein, Rathinaswamy B Govindan, Ellen Grant, Kerstin Gründler, Marlene Hammer, Katie Hannon, Balazs Hauser, Chuan-Heng Hsiao, Imran Ilahi, Terrie Inder, Agnes Jermendy, Pauline De Jesus, Edith Mbabazi Kabachelor, Enoch Kainja, Serap Karaman, Sreenivas Karnati, Lukasz Karpinski, Gregor Kasprian, Miriah Kemigisha Katugi, Janine Khan, Ursula Kiechl-Kohlendorfer, Seh Hyun Kim, Melinda Kis-Tamas, Katrin Klebermass-Schrehof, Lisa Klein, Lilijana Kornhauser-Cerar, Georg Langs, Luca Laura Bogner, Rakesh Lavu, Brenda Law, Pei-yi Lin, Gianluca Lista, Wei Liu, Vicki Livingstone, Joshua Magombe, Sean Mathieson, Lukas Mileder, Khorshid Mohammad, Michael Moore, Ronald Mulondo, Chelsea Munster, Deirdre Murray, Esther Nalule, Davis Natukwatsa, Nicholas Nicoletti, Christa Nöhammer, Tatiana Nuzum, Simeo Ochieng, Mandana O'Donnell, Monika Olischar, Silvia Orlandi, John O'Toole, Anna Lucia Paltrinieri, Andrea Pardo, Andreea Pavel, Tina Perme, Daniel Pfurtscheller, Gerhard Pichler, Cara Pleau, Ana Laguna Pradas, Sandra Pusil, Subhash Puthuraya, Ajay Rajaram, Dimitrios Rallis, Braulio Ramírez, Alam Randhawa, Nicola J Robertson, Sandra Pusil, Steven Schiff, Sarah Schlatterer, Christoph Schlatzer, Georg M Schmölzer, Silvia Schönthaler, Bernhard Schwabegger, Christoph E Schwarz, Marvin Seruwu, Laila Springer, Mirjam Steiner, Iaria Stucchi, John Sunwoo, Jason Sutin, Miklos Szabo, Eniko Szakmar, Tomasz Szczapa, Julia Tatz, Starlin Tindimwebwa, Sarolta H. Trinh, Oguz Tuncer, Helen L Turner, Berndt Urlesberger, Klemens Vierlinger, Gabriel A. Vignolle, Rutvi Vyas, Moses Wabukoma, Elena Wachtel, Benjamin Warf, Michael Woglom, Christina H. Wolfsberger, Kristine Woodward, Eyyup Yurekturk

## Machine learning predicts outcomes in preterm neonates with intraventricular hemorrhage using targeted proteomics

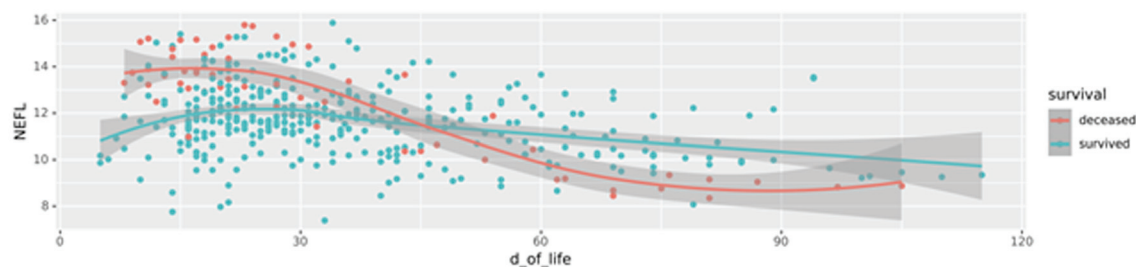
Gabriel A. Vignolle<sup>2</sup>, Priska Bauerstätter<sup>2</sup>, Silvia Schönthaler<sup>2</sup>, Christa Nöhammer<sup>2</sup>, Monika Olischar<sup>1</sup>, Angelika Berger<sup>1</sup>, Gregor Kasprian<sup>3</sup>, Georg Langs<sup>4</sup>, Klemens Vierlinger<sup>2</sup>, **Katharina Goeral<sup>1</sup>**

<sup>1</sup>Medical University of Vienna – Comprehensive Center for Pediatrics, Department of Pediatrics and Adolescent Medicine, Division of Neonatology, Intensive Care and Neuropediatrics, <sup>2</sup>Austrian Institute of Technology - Center for Health & Bioresources, Competence Unit Molecular Diagnostics, Austrian Institute of Technology, <sup>3</sup>Medical University of Vienna – Department of Radiology, Division of Neuroradiology and

*Musculoskeletal Radiology, <sup>4</sup>Medical University of Vienna – Department of Radiology, Computational Imaging Research Lab*

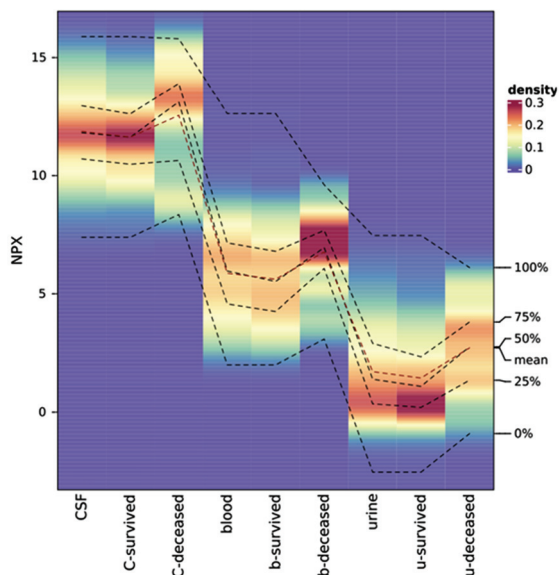
**BACKGROUND AND OBJECTIVE:** Preterm neonates with intraventricular hemorrhage (IVH) are at risk for posthemorrhagic ventricular dilatation (PHVD). In recent years targeted proteomics has developed into a powerful protein quantification tool in biomedical research, systems biology, and clinical applications. This study aims to inform therapeutic decision-making and parental counseling using proteomics in this high-risk group.

**METHODS:** In this prospective study, we investigated preterm neonates born <34 weeks of gestation between 2011 to 2023 with intraventricular hemorrhage (IVH). We performed targeted proteomics analysis on different biological matrices (blood, urine, and CSF), derived from a longitudinal neonatal cohort spanning a decade. We employed explainable machine learning (ML) algorithms



to predict PHVD development, patient survival, and identify disease-specific protein-biomarkers. The targeted approach applied in this study was a Proximity Extension Assay (PEA), which combines the specificity of dual antibody recognition with qPCR readout and enables the detection of low concentrations of proteins in biofluids as previously shown in several publications. We applied various ML methods from different domains (statistics, regularization ML, deep learning, decision trees, Bayesian) to the targeted proteomic data for biomarker detection to understand PHVD development and predict the survival of IVH patients. We trained and evaluated 600 models using cross-validation techniques.

**RESULTS:** A total of 100 patients were included in the analysis, 29 of whom did not survive. Median GA was 25.6 (24.1-27.1), and median IVH grade was 3 (3-4), with bilateral IVH (n=89) in the majority. A significant number of survivors required neurosurgical intervention for PHVD (n=45 of 71 (63%)). We identified both known (e.g. NEFL (neurofilament light chain)) and novel biomarkers that serve as key indicators for PHVD development and survival prediction. Figure 1 shows a feature plot in CSF of NEFL, while Figure 2 shows NPX values of NEFL in different biofluids between neonates who survived vs. died (distribution shown as heatmap).



**CONCLUSION:** Our study provides new insights into clinically relevant biomarkers within defined time frames. It demonstrates the robustness of our machine learning models and benefits from a unique neonatal patient cohort.

### Blood lactate levels increases prediction of clinical outcomes of neonates with hypoxic ischemic encephalopathy

Nicholas Nicoletti<sup>1</sup>, Rakesh Lavu<sup>1</sup>, Wei Liu<sup>1</sup>, Sreenivas Karnati<sup>1</sup>, Subhash Puthuraya<sup>1</sup>, Hany Aly<sup>1</sup>, **Ceyda Acun<sup>1</sup>**

<sup>1</sup>Cleveland Clinic Children's Hospital

**BACKGROUND:** Neonatal hypoxic-ischemic encephalopathy (HIE) is one of the most common causes of severe neurological deficit in children. The severity of lactic acidemia reflects the degree of fetal hypoxia-ischemia, but a single lactate measurement gives no definitive information regarding the duration of asphyxia. It is currently unknown if prolonged duration of normalization of lactate level associated with poor neurodevelopmental outcomes in infants with HIE undergoing therapeutic hypothermia.

**OBJECTIVE:** The objective of this study is to assess the association between duration of blood lactate normalization, severity of lactic acidosis, and short-term outcomes in neonates with HIE treated with therapeutic hypothermia (TH).

**METHODS:** This is a retrospective, single-center cohort study of HIE neonates, gestational age  $\geq 36$  weeks who underwent TH between January 2012 and December 2022. Neonates with lethal congenital malformations, chromosomal anomalies, or need for extracorporeal membrane oxygenation were excluded.

**RESULTS:** Overall, 151 patients were studied, with 56.3% males, 60.3% cesarean section delivery, 42.4/14.6% moderate/severe HIE, and median gestational age at 39.3 weeks. Of all neonates, 66.7% of patients' lactate levels were normalized in the first 24 hours. Only 11.3% of neonates had background EEG normalization in the first 24 hours of life. Initial lactate levels of  $>10$  mmol/L was

Table 1: Outcomes by initial lactate ≤10 mmol/L or >10 mmol/L

	Total (N=151)	≤10 mmol/L (N=54)	>10 mmol/L (N=97)	p-value
Background EEG (The first 24 hours)				<0.001 <sup>b</sup>
Normal	15 (9.9)	7 (13.0)	8 (8.2)	
Mild	42 (27.8)	21 (38.9)	21 (21.6)	
Moderate	37 (24.5)	17 (31.5)	20 (20.6)	
Severe	57 (37.7)	9 (16.7)	48 (49.5)	
Duration of normalization of EEG background (hours)				0.92 <sup>b</sup>
≤24	17 (11.3)	7 (13.0)	10 (10.3)	
24<-48	8 (5.3)	2 (3.7)	6 (6.2)	
48<-72	2 (1.3)	0 (0)	2 (2.1)	
72<-84	5 (3.3)	2 (3.7)	3 (3.1)	
>84	119 (78.8)	43 (79.6)	76 (78.4)	
Seizures	46 (30.5)	8 (14.8)	38 (39.2)	0.002 <sup>c</sup>
Clinical	9 (19.6)	1 (12.5)	8 (21.1)	
Subclinical	10 (21.7)	1 (12.5)	9 (23.7)	
Clinical and subclinical	27 (58.7)	6 (75.0)	21 (55.3)	
MRI Brain abnormality				
Normal	78 (51.7)	33 (61.1)	45 (46.4)	0.083 <sup>c</sup>
Cortical injury	21 (13.9)	4 (7.4)	17 (17.5)	0.085 <sup>c</sup>
Basal ganglia/thalamic	11 (7.3)	3 (5.6)	8 (8.2)	0.75 <sup>d</sup>
Posterior limb of internal capsule injury	4 (2.6)	0 (0)	4 (4.1)	0.30 <sup>d</sup>
Mechanical ventilation	94 (62.3)	29 (53.7)	65 (67.0)	0.11 <sup>c</sup>
Duration of mechanical ventilation (days)*	2.0 [1.0, 5.0]	1.0 [1.0, 3.0]	2.0 [1.0, 5.0]	0.31 <sup>b</sup>
Duration of non-invasive ventilation (days)*	0 [0, 1.0]	0 [0, 1.0]	0 [0, 0]	0.76 <sup>c</sup>
DOL full enteral feeds*	6.0 [5.0, 8.0]	6.0 [5.0, 7.0]	6.0 [5.0, 8.0]	0.058 <sup>b</sup>
DOL full PO feeds*	7.0 [6.0, 12.0]	7.0 [6.0, 10.0]	7.0 [6.0, 12.0]	0.70 <sup>b</sup>
Home with tube feeding*				>.99 <sup>d</sup>
No	131 (92.3)	47 (92.2)	84 (92.3)	
NG	5 (3.5)	2 (3.9)	3 (3.3)	
GT	6 (4.2)	2 (3.9)	4 (4.4)	
NICU length of stay (days)	10.0 [8.0, 16.0]	10.0 [8.0, 14.0]	11.0 [8.0, 18.0]	0.53 <sup>b</sup>
NICU mortality	6 (4.0)	0 (0)	6 (6.2)	0.089 <sup>d</sup>

associated with abnormal EEG background in the first 24 hours of life (p<0.001), and seizures (p=0.002). The duration of lactate normalization ≥48 hours were associated with higher level of background EEG abnormality in the first 24 hours of life (p=0.001) and higher likelihood of seizures (p<0.001). Besides, the duration of lactate normalization ≥48 hours were associated with higher likelihood of abnormal MRI results, mechanical ventilation support and NICU mortality, as

well as longer days ventilation support, full enteral (PO) feeds, and NICU stay (all p<0.05).

**CONCLUSION:** Duration of blood lactate normalization ≥48 hours was associated with increased seizure burden, abnormal EEG and MRI findings, prolonged mechanical ventilation, and increased mortality in infants with HIE who underwent TH.

Table 2: Outcomes by time to lactate normalization (hours of life)

Factor	<12 (N=38)	12-24 (N=60)	24-48 (N=36)	≥48 (N=13)	p-value
Background EEG (The first 24 hours)					0.001 <sup>b</sup>
Normal	5 (13.2) <sup>a</sup>	6 (10.0) <sup>a</sup>	4 (11.1) <sup>a</sup>	0 (0) <sup>1,2,3</sup>	
Mild	14 (36.8)	19 (31.7)	9 (25.0)	0 (0)	
Moderate	10 (26.3)	15 (25.0)	8 (22.2)	2 (15.4)	
Severe	9 (23.7)	20 (33.3)	15 (41.7)	11 (84.6)	
Duration of normalization of EEG background (hours)					0.34 <sup>b</sup>
≤24	6 (15.8)	6 (10.0)	5 (13.9)	0 (0)	
24<-48	3 (7.9)	5 (8.3)	0 (0)	0 (0)	
48<-72	0 (0)	2 (3.3)	0 (0)	0 (0)	
72<-84	2 (5.3)	1 (1.7)	1 (2.8)	1 (7.7)	
>84	27 (71.1)	46 (76.7)	30 (83.3)	12 (92.3)	
Seizures	5 (13.2) <sup>a</sup>	16 (26.7) <sup>a</sup>	14 (38.9)	9 (69.2) <sup>1,2</sup>	<0.001 <sup>c</sup>
Clinical	2 (40.0)	3 (18.8)	1 (7.1)	2 (22.2)	
Subclinical	1 (20.0)	4 (25.0)	5 (35.7)	0 (0)	
Clinical and subclinical	2 (40.0)	9 (56.3)	8 (57.1)	7 (77.8)	
MRI Brain abnormality					
Normal	28 (73.7) <sup>1,4</sup>	32 (53.3)	15 (41.7) <sup>1</sup>	3 (23.1) <sup>1</sup>	0.005 <sup>c</sup>
Cortical injury	2 (5.3)	7 (11.7)	9 (25.0)	3 (23.1)	0.070 <sup>c</sup>
Basal ganglia/thalamic	2 (5.3)	4 (6.7)	3 (8.3)	2 (15.4)	0.61 <sup>d</sup>
Posterior limb of internal capsule injury	0 (0)	3 (5.0)	1 (2.8)	0 (0)	0.58 <sup>d</sup>
Mechanical ventilation	27 (71.1)	34 (56.7)	18 (50.0) <sup>a</sup>	12 (92.3) <sup>2</sup>	0.025 <sup>c</sup>
Duration of mechanical ventilation (days)*	2.0 [1.0, 3.0] <sup>a</sup>	1.0 [1.0, 3.0] <sup>a</sup>	3.0 [1.0, 5.0] <sup>a</sup>	8.5 [3.5, 12.0] <sup>1,2,3</sup>	<0.001 <sup>b</sup>
Duration of non-invasive ventilation (days)*	0 [0, 0]	0 [0, 1.0]	0 [0, 1.0]	0 [0, 1.0]	0.45 <sup>b</sup>
DOL full enteral feeds*	5.0 [5.0, 7.0] <sup>a</sup>	6.0 [5.0, 7.0] <sup>a</sup>	6.0 [6.0, 8.0] <sup>a</sup>	13.0 [9.0, 16.0] <sup>1,2,3</sup>	<0.001 <sup>b</sup>
DOL full PO feeds*	6.0 [5.0, 7.0] <sup>a</sup>	7.0 [6.0, 11.0] <sup>a</sup>	7.0 [6.0, 12.0] <sup>a</sup>	19.5 [14.0, 29.5] <sup>1,2,3</sup>	<0.001 <sup>b</sup>
Home with tube feeding*					0.21 <sup>d</sup>
No	36 (94.7)	53 (89.8)	33 (97.1)	8 (80.0)	
NG	1 (2.6)	4 (6.8)	0 (0)	0 (0)	
GT	1 (2.6)	2 (3.4)	1 (2.9)	2 (20.0)	
NICU length of stay (days)	10.0 [8.0, 14.0] <sup>a</sup>	10.0 [8.0, 14.5] <sup>a</sup>	10.5 [8.0, 16.0]	30.0 [14.0, 38.0] <sup>1,2</sup>	0.026 <sup>b</sup>
NICU mortality	0 (0)	0 (0) <sup>a</sup>	1 (2.8)	3 (23.1) <sup>2</sup>	<0.001 <sup>d</sup>

## Implementation of cerebral near-infrared spectroscopy in a tertiary neonatal intensive care unit in the UK

**Helen L Turner**<sup>1,2</sup>, James P Boardman<sup>1,3</sup>, Nicola J Robertson<sup>1,4</sup>

<sup>1</sup>Centre for Clinical Brain Sciences, The University of Edinburgh, <sup>2</sup>Simpson Centre for Reproductive Health, The Royal Infirmary of Edinburgh, <sup>3</sup>Centre for Reproductive Health, The University of Edinburgh, <sup>4</sup>EGA Institute for Women's Health, University College London

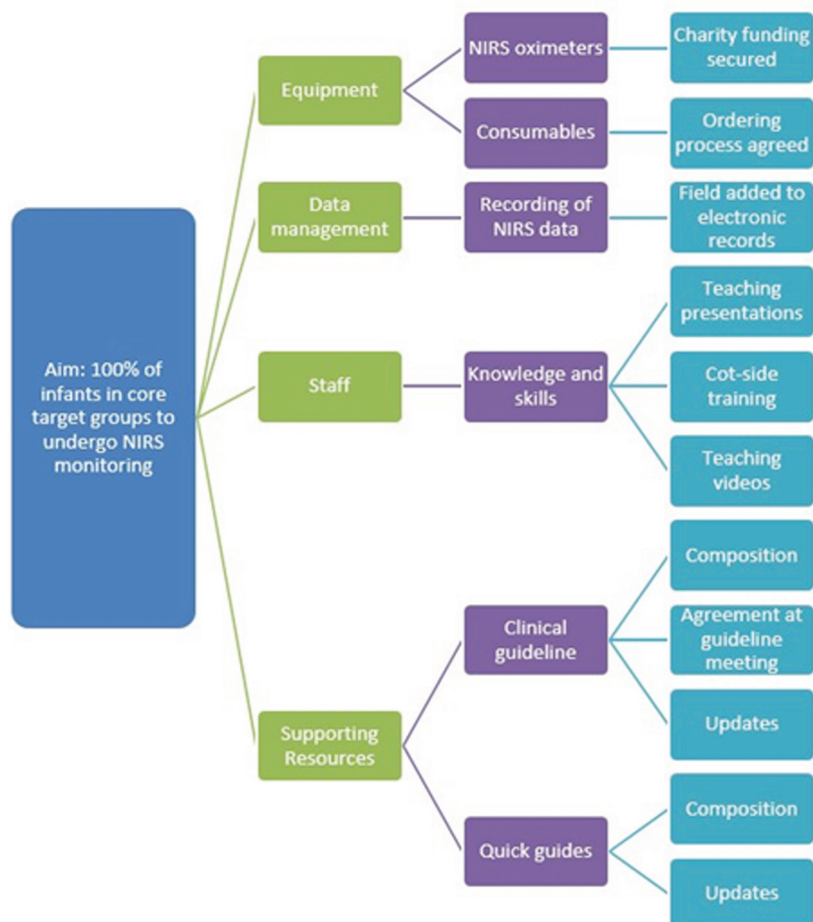
**BACKGROUND:** Monitoring cerebral oxygenation saturation using near-infrared spectroscopy (NIRS) at the cot-side may contribute to the improved neurocritical care of high-risk newborns and prevention of secondary injury. Our aims are to describe the implementation of cerebral NIRS within our NICU; to assess compliance in target groups; and to monitor for adverse events.

**METHODOLOGY:** This project was set in the Royal Infirmary of Edinburgh, the tertiary referral centre for South East Scotland, where between 45-60 infants born at <28 weeks gestational age (extremely preterm) and 12-15 term infants with moderate-severe neonatal encephalopathy (NE) receive care annually. NIRS monitoring, using O3 Regional Oximeters (Masimo, California, USA) with neonatal sensors, was introduced in December 2021.

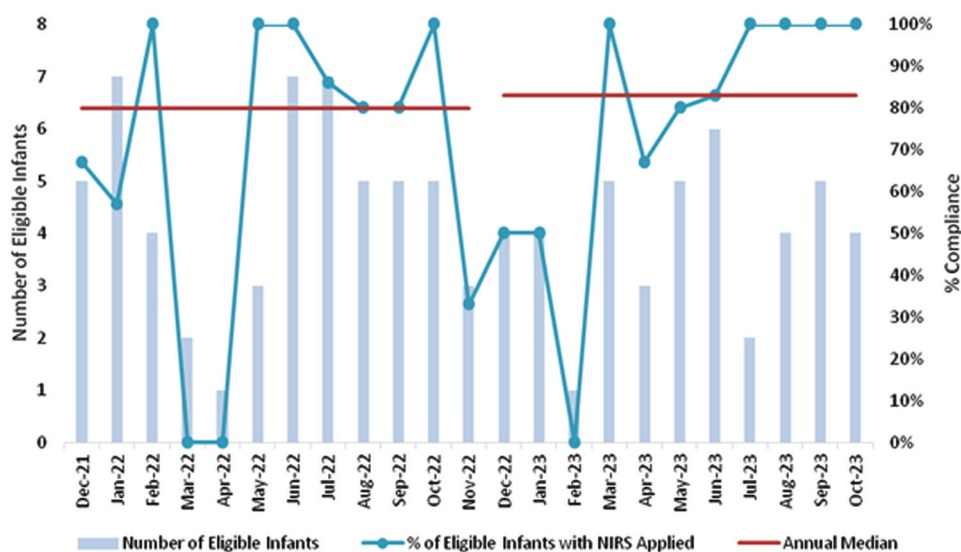
QI methodology was used to plan and assess implementation. The implementation process, including production of a clinical guideline and multi-disciplinary teaching, is illustrated in Fig 1. Compliance was used as a process measure in two key groups: extremely preterm infants for the first 72 hours after birth and infants undergoing therapeutic hypothermia for NE. The secondary outcome measure was NIRS-associated adverse events.

Eligible infants were identified through screening of electronic admission records (BadgerNet). Individual electronic records (clinical notes and observations charts) were reviewed manually and data extracted for analysis using Microsoft Excel.

**Figure 1: Process Diagram for Implementation**



**Figure 2: Eligible Infants and Monthly Compliance**



**RESULTS:** NIRS monitoring was applied to 76 (78%) of the 97 eligible infants admitted over 23 months. Sixty-one (80%) infants were extremely preterm: mean gestational age (GA) 25.74 weeks (range 23.00 – 27.84) and mean birthweight 798 grams (range 515 – 1200). Fifteen (20%) were infants with NE: mean GA 38.99 weeks (range 36.14 – 41.84) and mean birthweight 3447 grams (range 2370 – 4170).

Monthly compliance with application of NIRS monitoring is shown in Fig 2. Median compliance was 80% over the first 12 months, increasing to 86% for the next 11 months.

Reasons for non-compliance were examined. Amongst 21 cases where infants were not monitored, there were equipment issues in seven (33%) cases and concerns regarding skin fragility in five (24%) infants of 22 weeks GA. The need for further education regarding eligibility and troubleshooting equipment issues was identified and actioned. No reason was documented in eight (38%) cases. Regarding adverse events, the probe was removed early in four (5%) infants. There was bruising in one infant, who had a bleeding diathesis. In the other three, skin traction was a concern, but no skin damage was noted.

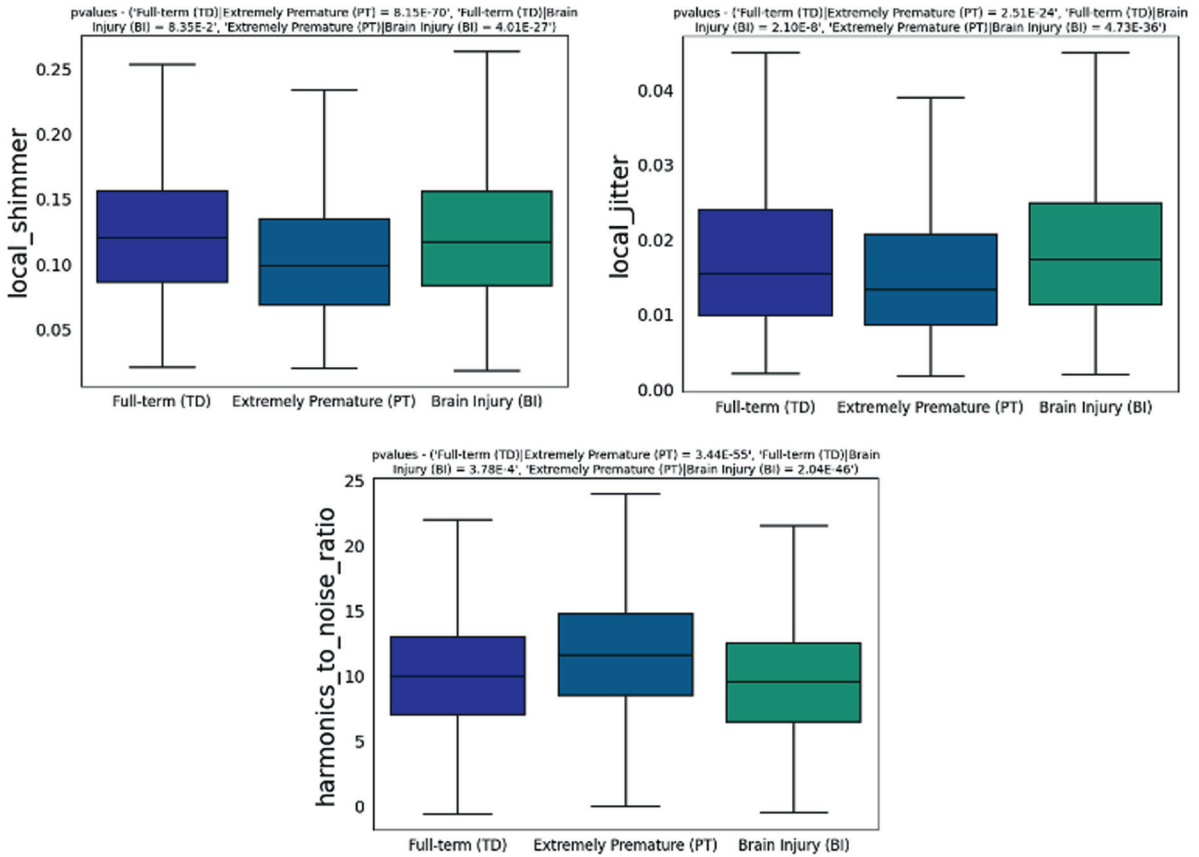
**CONCLUSION:** We have successfully implemented cerebral NIRS in our tertiary NICU, with 80% median compliance. Using QI methodology allowed us to identify and target reasons for non-compliance. Amongst our predominantly extremely preterm population, adverse events were uncommon. Using cerebral NIRS to target specific research questions is our next priority, and recruitment to prospective observational studies has begun.

### Quantitative analysis of cry acoustics and neurophysiological signals for assessing the infant health status

**Ana Laguna Pradas<sup>1</sup>**, Sandra Pusil<sup>1</sup>, Anna Lucia Paltrinnieri<sup>2</sup>, Angel Bazan<sup>1</sup>, Silvia Orlandi<sup>3</sup>

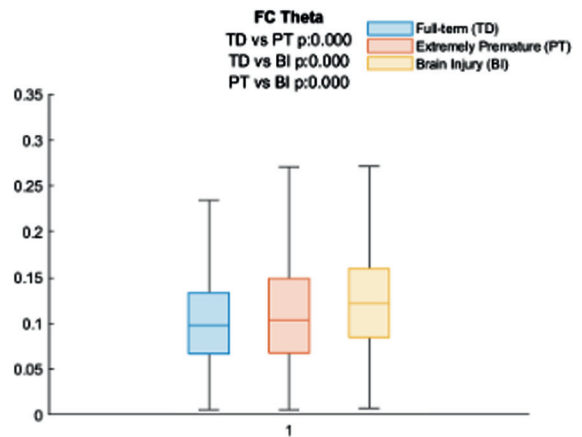
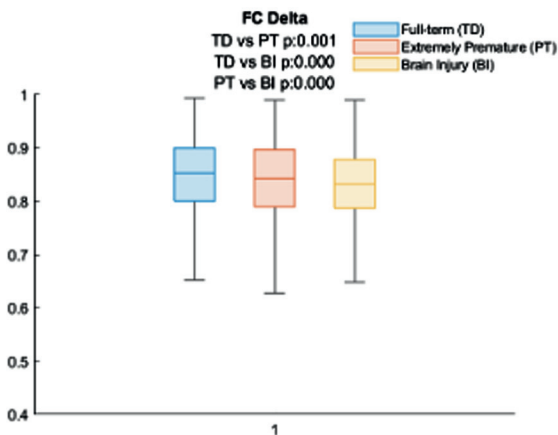
<sup>1</sup>ZOUNDREAM AG, <sup>2</sup>Neonatology Department, Barcelona Centre for Maternal-Fetal and Neonatal Medicine (BCNatal), Hospital Clínic, Universitat de Barcelona, <sup>3</sup>Department of Electrical, Electronic and Information Engineering “Guglielmo Marconi”(DEI), University of Bologna

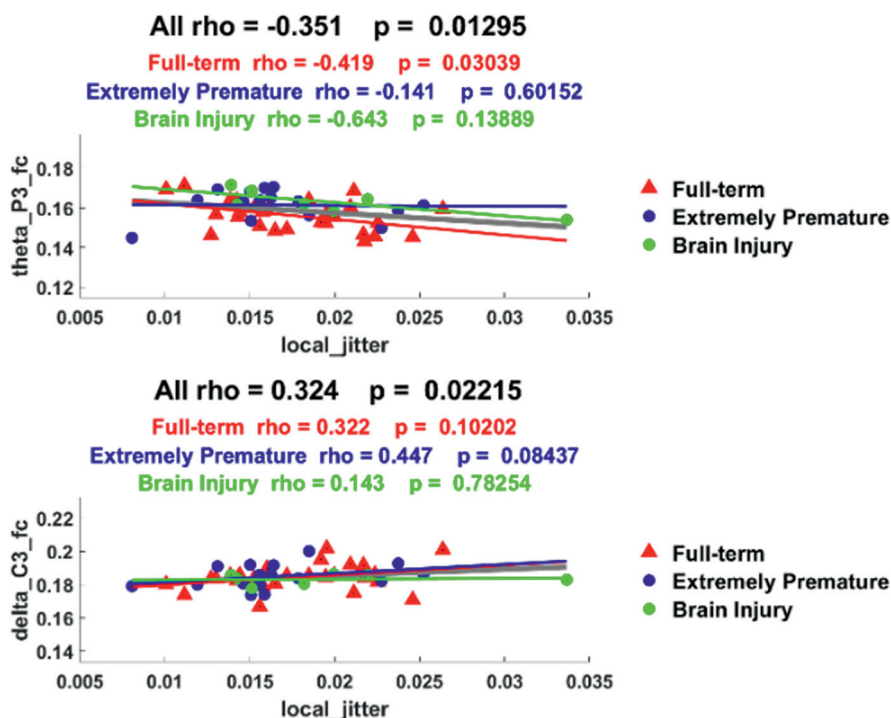
**BACKGROUND AND OBJECTIVE:** In the early stages of life, infant crying stands as the first proper attempt by which humans engage with their caregiver. Hence, cry is not solely recognized as a communicative signal, but also as a concrete indication and/or manifestation of symptoms or signs providing insights into the health status and development of the child. During cry production, the vagal system is the central factor influencing the variations in cry acoustics. Impairments in either brainstem function or higher-level brain functions can impact the regulation of crying by the vagal system, leading to irregularities in the characteristics of cry sounds. This preliminary study aimed to explore differences in the acoustic features of cries and neurophysiological patterns among three groups of infants: full-term, extremely premature, and infants with brain injuries. The purpose was to ascertain the viability of cry analysis as an objective non-invasive technique contributing to the early identification of infants vulnerable to developmental challenges improving neonatal care prognosis.



**METHODOLOGY:** A dataset comprising audio recordings of spontaneous infant cries and neurophysiological signals were collected from the three aforementioned groups of infants at Hospital Clinic (Barcelona, Spain). Acoustic features, including time, frequency, and spectral characteristics, were extracted from the cry recordings. Neurophysiological signals were processed to analyze brain activity patterns. Statistical analyses, including ANOVA and correlation tests, were conducted to assess differences and relationships among the groups and variables.

**RESULTS:** Significant statistical differences were identified among groups based on both acoustic and neurophysiological patterns. Specifically, pathological infants exhibited higher levels of jitter, shimmer, and noise ( $p < 0.001$ ). On the neurophysiological signals, infants with brain injuries exhibited a reduced delta band power ( $p < 0.001$ ), whereas theta band power demonstrated an inverse trend by increasing in affected infants ( $p < 0.001$ ). Significant correlations were also identified among different data signals ( $p < 0.05$ ). Delta and theta were significantly correlated with jitter, shimmer and harmonic noise to ratio.





**CONCLUSION:** The observed differences in cry acoustics and neurophysiological patterns suggest the potential of cry to be used as a non-invasive biomarker in the neurological assessment of the newborn. This research paves the way for the incorporation of data-driven analysis into neonatal care, potentially improving early diagnosis and intervention for at-risk infants, thereby improving their overall well-being and developmental outcome.

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**Monitoring parameters of premature neonates <32Weeks’ gestation with&without adverse outcome-A secondary analysis of the COSGOD-III-trial**

**Bernhard Schwabegger**<sup>1,2,3</sup>, Berndt Urlsberger<sup>1,2,3</sup>, Christina H. Wolfsberger<sup>1,2,3</sup>, Nariae Baik-Schneditz<sup>1,2,3</sup>, Daniel Pfurtscheller<sup>1,2,3</sup>, Katharina Goeral<sup>4</sup>, Marlene Hammerl<sup>5</sup>, Tina Perme<sup>6</sup>, Eugene M Dempsey<sup>7</sup>, Laila Springer<sup>8</sup>, Gianluca Lista<sup>9</sup>, Tomasz Szczapa<sup>10</sup>, Hans Fuchs<sup>11</sup>, Jenny Bua<sup>12</sup>,

Lukasz Karpinski<sup>10</sup>, Alexander Avian<sup>13</sup>, Brenda Law<sup>14,15</sup>, Julia Buchmayer<sup>4</sup>, Ursula Kiechl-Kohlendorfer<sup>5</sup>, Lilijana Kornhauser-Cerar<sup>6</sup>, Christoph E Schwarz<sup>7</sup>, Kerstin Gründler<sup>8</sup>, Ilaria Stucchi<sup>9</sup>, Katrin Klebermass-Schrehof<sup>4</sup>, Georg M Schmölzer<sup>14,15</sup>, Gerhard Pichler<sup>1,2,3</sup>

<sup>1</sup>Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria, <sup>2</sup>Research Unit for Microcirculation and Macrocirculation of the Newborn, Medical University of Graz, <sup>3</sup>Research Unit for Cerebral Development and Oximetry Research, Medical University of Graz, <sup>4</sup>Comprehensive Center for Pediatrics, Department of Pediatrics and Adolescent Medicine, Division of Neonatology, Intensive Care and Neuropediatrics, Medical University of Vienna, <sup>5</sup>Department of Pediatrics II, Neonatology, Medical University of Innsbruck, <sup>6</sup>NICU, Department for Perinatology, Division of Gynaecology and Obstetrics, University Medical Centre Ljubljana, <sup>7</sup>INFANT Research Centre, University College Cork, Cork University Maternity Hospital, <sup>8</sup>Department of Neonatology, University Children’s Hospital of Tübingen, <sup>9</sup>Neonatologia e Terapia Intensiva Neonatale (TIN) Ospedale dei Bambini “V Buzzi”, <sup>10</sup>II Department of Neonatology, Neonatal Biophysical Monitoring and Cardiopulmonary Therapies Research Unit, Chair

of Neonatology, Poznan University of Medical Sciences, <sup>11</sup>Division of Neonatology and Pediatric Intensive Care Medicine, Center for Pediatrics and Adolescent Medicine, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, <sup>12</sup>Neonatal Intensive Care Unit, Institute for Maternal and Child Health, “IRCCS Burlo Garofolo”, <sup>13</sup>Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, <sup>14</sup>Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital, <sup>15</sup>Department of Pediatrics, University of Alberta

**BACKGROUND:** To identify differences in demographic characteristics and monitoring parameters between premature neonates <32weeks’ gestation who died or had cerebral injury (adverse outcome) compared to those who survived without cerebral injury (favorable outcome).

**METHODOLOGY:** This ancillary study is a post-hoc analysis of secondary outcome parameters of a multicenter randomized clinical trial (COSGOD-III) in which neonates were randomized either to cerebral oxygen saturation (crSO<sub>2</sub>) monitoring by near-infrared spectroscopy (NIRS) in addition to routine monitoring within the first 15 minutes after birth to guide stabilization or a control group with standard care. In the present study all included premature neonates were assigned either to adverse outcome group (composite of mortality and cerebral injury defined as any grade of intraventricular hemorrhage or

cystic periventricular leukomalacia) or favorable outcome group (survival without cerebral injury). Group differences of demographic characteristics, and monitoring parameters (heart rate [HR], arterial oxygen saturation [SpO<sub>2</sub>] and crSO<sub>2</sub>) were assessed.

**RESULTS:** In total, 607 premature neonates were included in the COSGOD-III-Trial. In the present study 117(19%) and 490(81%) were assigned to adverse outcome group and favorable outcome group, respectively. In the adverse outcome group, premature neonates had lower median gestational age [26.7(25.5-28.9) vs. 29.3(27.3-30.7); p<.001], birth weight [900(690-1195) vs. 1150(885-1435); p<.001] and Apgar scores (p<.001) compared to the favorable outcome group. The adverse outcome group had significantly lower HR from 2 to 4min and SpO<sub>2</sub> from 2 to 8min, thereafter both parameters were similar in both groups. crSO<sub>2</sub> was similar in both groups within the first minutes and was significantly lower in the adverse outcome group from 4 to 15min after birth compared to the favorable outcome group (Table 1).

**CONCLUSION:** Beside lower gestational age, birth weight and Apgar scores, premature neonates <32weeks’ gestation with adverse outcome had lower HR, SpO<sub>2</sub> and crSO<sub>2</sub> after birth. While routine parameters (HR and SpO<sub>2</sub>) equalized between groups shortly after birth (4 and 8 minutes, respectively), crSO<sub>2</sub> values continued to be lower in the adverse outcome group until minute 15 after birth demonstrating a potential benefit of using NIRS monitoring for identifying neonates in need for medical interventions to potentially prevent adverse outcome.

MINUTES AFTER BIRTH	HEART RATE (HR)			ARTERIAL OXYGEN SATURATION (SpO <sub>2</sub> )			CEREBRAL OXYGEN SATURATION (crSO <sub>2</sub> )		
	adverse outcome	favorable outcome	p-value	adverse outcome	favorable outcome	p-value	adverse outcome	favorable outcome	p-value
2 min	104.3 (99.5-109.1)	120.5 (118.2-122.9)	<.001	53.5 (50.7-56.2)	57.1 (55.8-58.4)	0.019	30.9 (27.5-34.4)	32.5 (30.9-34.1)	0.424
3 min	115.1 (110.6-119.6)	127.0 (124.8-129.2)	<.001	58.7 (56.2-61.2)	62.6 (61.3-63.8)	0.007	37.8 (34.4-41.1)	38.8 (37.2-40.3)	0.595
4 min	123.1 (118.6-127.5)	131.8 (129.6-134.0)	0.001	64.6 (62.1-67.1)	71.3 (70.1-72.5)	<.001	42.0 (38.7-45.3)	46.6 (45.0-48.1)	0.015
5 min	128.8 (124.4-133.2)	137.5 (135.3-139.6)	0.001	72.8 (70.3-75.3)	79.4 (78.2-80.6)	<.001	50.3 (47.0-53.6)	56.8 (55.3-58.4)	0.001
6 min	136.0 (131.6-140.4)	139.6 (137.4-141.8)	0.152	78.5 (76.0-81.0)	84.4 (83.2-85.6)	<.001	55.8 (52.6-59.1)	64.4 (62.8-65.9)	<.001
7 min	139.2 (134.9-143.6)	143.6 (141.5-145.8)	0.080	81.6 (79.2-84.1)	87.6 (86.4-88.8)	<.001	59.7 (56.4-63.0)	69.7 (68.1-71.2)	<.001
8 min	141.9 (137.5-146.2)	145.0 (142.9-147.2)	0.205	84.5 (82.0-87.0)	89.5 (88.3-90.7)	<.001	63.2 (59.9-66.4)	72.4 (70.9-74.0)	<.001
9 min	147.2 (142.8-151.6)	147.4 (145.3-149.6)	0.925	87.4 (84.9-89.9)	90.0 (88.8-91.2)	0.061	65.2 (62.0-68.4)	74.2 (72.6-75.7)	<.001
10 min	147.4 (143.0-151.8)	149.7 (147.5-151.8)	0.362	87.9 (85.5-90.4)	90.7 (89.5-91.9)	0.045	66.4 (63.2-69.6)	75.5 (74.0-77.1)	<.001
11 min	151.4 (147.0-155.8)	151.1 (148.9-153.2)	0.906	88.2 (85.8-90.7)	90.9 (89.7-92.1)	0.057	67.6 (64.3-70.8)	75.9 (74.3-77.4)	<.001
12 min	153.3 (148.9-157.6)	153.0 (150.8-155.1)	0.902	89.6 (87.1-92.1)	91.0 (89.8-92.2)	0.314	69.5 (66.3-72.8)	76.9 (75.4-78.5)	<.001
13 min	154.8 (150.5-159.2)	153.9 (151.8-156.1)	0.706	90.0 (87.5-92.5)	91.1 (89.9-92.3)	0.414	71.0 (67.8-74.3)	77.0 (75.4-78.5)	0.001
14 min	154.9 (150.5-159.2)	154.8 (152.6-156.9)	0.965	90.0 (87.5-92.4)	91.1 (89.9-92.3)	0.418	71.3 (68.0-74.6)	77.3 (75.8-78.9)	0.001
15 min	156.5 (152.1-160.8)	156.8 (154.6-158.9)	0.907	90.2 (87.7-92.7)	91.6 (90.3-92.8)	0.342	71.1 (67.8-74.4)	77.8 (76.2-79.3)	<.001



**Persistent pulmonary hypertension affects cerebral oxygenation in neonates with neonatal encephalopathy**

Dimitrios Rallis<sup>1</sup>, Hoda El-Shibiny<sup>2</sup>, Eniko Szakmar<sup>3</sup>, Aisling Garvey<sup>2</sup>, Helen Christou<sup>2</sup>, **Mohamed El-Dib<sup>2</sup>**

<sup>1</sup>University of Ioannina, <sup>2</sup>Division of Newborn Medicine, Department of Pediatrics, Brigham and

Women’s Hospital, Harvard Medical School, <sup>3</sup>Division of Neonatology, 1st Department of Pediatrics, Semmelweis University

**BACKGROUND AND OBJECTIVE:** Persistent pulmonary hypertension of the newborn (PPHN) affects systemic oxygenation and may worsen brain injury in neonates with neonatal encephalopathy (NE). Our aim was to evaluate the impact of PPHN on cerebral regional oxygenation (crSO<sub>2</sub>), as measured with near-infrared

	Encephalopathy with PPHN (n=19)	Encephalopathy without PPHN (n=145)	p
Gestational age, weeks	38.5±2.1	38.6±1.7	0.643
Birthweight, g	3181±626	3094±655	0.548
Sex, male	11 (58%)	88 (61%)	0.808
Delivery mode, cesarean section	11 (58%)	65 (46%)	0.307
Inborn	14 (74%)	107 (75%)	0.914
Prolonged rupture of membranes	1 (5%)	24 (17%)	0.312
Maternal Group B <i>Streptococcus</i> colonization	1 (5%)	30 (21%)	0.128
Placenta abruption	4 (21%)	11 (8%)	0.080
Meconium-stained liquor	10 (53%)	27 (19%)	0.002
Chorioamnionitis	2 (11%)	22 (15%)	0.742
Parity single	5 (26%)	79 (56%)	0.247
Apgar 1 <sup>st</sup> minute	2 (1-4)	2 (2-4)	0.912
Apgar 5 <sup>th</sup> minute	5 (3-6)	7 (5-8)	0.012
Apgar 10 <sup>th</sup> minute	5 (4-7)	7 (7-8)	0.008
Umbilical vein pH	7.05±0.14	7.13±0.12	0.024
Umbilical vein bicarbonate	18.8±3.9	19.8±3.1	0.300
Umbilical vein base deficit	11.2±7.8	9.6±5.2	0.308
Umbilical vein lactate	10.6±4.7	7.5±2.5	0.048
Highest neonatal encephalopathy score	8 (5-12)	5 (4-8)	0.016
Intubation in the delivery room	11 (58%)	26 (18%)	<0.001
Seizures electrical	6 (32%)	5 (4%)	<0.001
Seizures clinical	5 (26%)	3 (2%)	0.001
Encephalopathy			0.013
• Mild	6 (35%)	88 (62%)	
• Moderate	9 (53%)	53 (37%)	
• Severe	2 (12%)	2 (1%)	
Respiratory insufficiency	18 (95%)	47 (33%)	<0.001
Intubation	18 (95%)	34 (24%)	<0.001
Mechanical ventilation days	6 (4-11)	1 (0-1)	<0.001
Non-invasive ventilation days	3 (0-7)	0 (0-1)	<0.001
Highest FiO <sub>2</sub> (72h)	0.79±0.26	0.23±0.07	<0.001
Highest mean airway pressure	15±3	8±2	<0.001
Highest pO <sub>2</sub>	145±80	93±37	0.019
Meconium aspiration syndrome	7 (37%)	5 (4%)	<0.001
Surfactant	11 (58%)	9 (6%)	<0.001
iNO	10 (53%)	-	<0.001
Inotropes	15 (79%)	3 (2%)	<0.001
Patent ductus arteriosus	17 (90%)	2 (1%)	<0.001
Weeks MRI score			
• Basal ganglia	0 (0-2)	0 (0-0)	0.001
• Watershed	0 (0-4)	0 (0-0)	0.004
• Posterior limb internal capsule	0 (0-1)	0 (0-0)	0.002
• Brainstem	0 (0-0)	0 (0-0)	0.005
• Deep gray matter	2 (0-8)	0 (0-0)	<0.001
• Cortex	0 (0-2)	0 (0-0)	0.013
• White matter	0 (0-2)	0 (0-0)	0.005
• White matter cortex	3 (0-10)	0 (0-1)	0.001
• Total score	7 (2-19)	1 (0-3)	<0.001
Survival	16 (84%)	142 (99%)	0.005

spectroscopy (NIRS), in neonates with NE treated with therapeutic hypothermia (TH).

**MATERIALS AND METHODOLOGY:** We retrospectively evaluated neonates with NE in our institution, between 2018-2022, comparing neonates with vs without PPHN. Overall, 164 (76%) neonates were analyzed, including 19 (12%) neonates with PPHN and 145 (88%) neonates without. crSO<sub>2</sub> was expressed as the mean of the 24-hour recording, within the first, second and third day of hypothermia, the rewarming period, and the period after rewarming. Weeke score was applied for the evaluation of the brain magnetic resonance imaging (MRI). To adjust for the severity of NE, we calculated the predicted probability based on meconium-stained amniotic fluid, Apgar score at 10 minutes, umbilical arterial pH, the initial aEEG pattern, and the highest NE score, and a propensity score matching was performed between neonates with and without PPHN, with nearest neighbor and caliper set to 0.2. Linear regression analysis was then

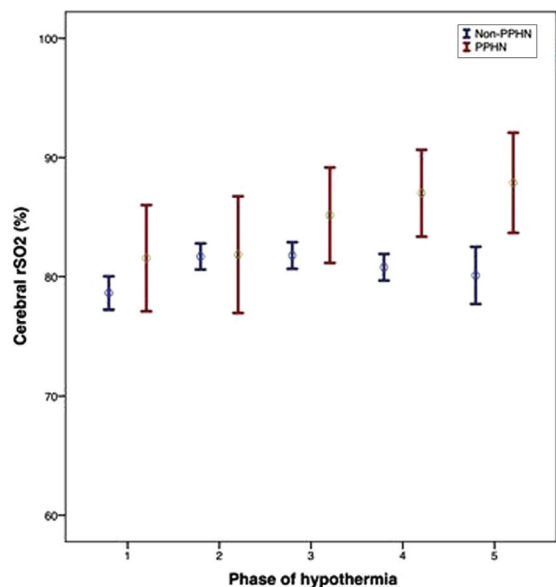
performed to evaluate the impact of PPHN on crSO<sub>2</sub> and total MRI injury score, adjusted for the predicted probability.

**RESULTS:** Neonatal characteristics and outcomes are depicted in Table 1. During the first 3 phases of hypothermia, no differences were recorded in crSO<sub>2</sub> between PPHN and non-PPHN groups; however, neonates with PPHN had significantly higher crSO<sub>2</sub> during the rewarming period, and the period after rewarming compared to the non-PPHN group (87±6 vs 80±6, p=0.001, and 87±5 vs 80±7, p=0.008, respectively), (Figure 1). Also, neonates with PPHN had a significantly higher total MRI injury score [7(2-19) vs 1(0-3), p<0.001]. After adjusting for the predicted probability, PPHN was significantly associated with higher cerebral rSO<sub>2</sub> on the rewarming period (b 6.89, 95%CI 3.10-10.68, p=0.001) and the period after rewarming (b 9.92, 95%CI 1.17-18.67, p=0.029), and the total MRI injury score (b 6.64, 95%CI 0.36-12.92, p=0.039), (Table 2).

**CONCLUSION:** PPHN was associated with higher cerebral crSO<sub>2</sub> during and after the rewarming periods, and worse brain MRI injury score, indicating a significant impact of PPHN on brain injury in neonates with NE undergoing TH.

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	<b>b</b>	<b>95% CI</b>	<b>p</b>
<b>crSO<sub>2</sub> during the rewarming period</b>			
PPHN	6.89	3.10-10.68	0.001
Predicted probability	9.00	-3.22-21.23	0.143
<b>crSO<sub>2</sub> during the period after rewarming</b>			
PPHN	9.92	1.17-18.67	0.029
Predicted probability	8.89	-17.56-35.34	0.478
<b>Weekes MRI score</b>			
PPHN	6.64	0.36-12.92	0.039
Predicted probability	6.33	-11.79-24.46	0.483

## Cerebral pulsatile NIRS: Heart rate monitoring during neonatal transition in term neonates-an observational study

**Bernhard Schwabeger**<sup>1,2,3</sup>, Christoph Schlatzer<sup>1,2,3</sup>, Marlies Bruckner<sup>1,2,3</sup>, Berndt Urlesberger<sup>1,2,3</sup>, Gerhard Pichler<sup>1,2,3</sup>, Lukas Mileder<sup>1,2,3</sup>, Nariae Baik-Schneditz<sup>1,2,3</sup>

<sup>1</sup>Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria, <sup>2</sup>Research Unit for Microcirculation and Macrocirculation of the Newborn, Medical University of Graz, <sup>3</sup>Research Unit for Cerebral Development and Oximetry Research, Medical University of Graz

**BACKGROUND:** Recent guidelines recommend continuous monitoring of heart rate (HR) and arterial oxygen saturation (SpO<sub>2</sub>) during neonatal transition using electrocardiography (ECG) and/or pulse oximetry. Recently, Hamamatsu Photonics K.K. (Japan) introduced a new pulsatile near-infrared spectroscopy mode (pNIRS), enabling the measurement of the cerebral pulse rate (cPR). The aim of the study was to evaluate the feasibility and reliability of HR monitoring using pNIRS compared to the two routine monitoring methods.

**METHODOLOGY:** HR was measured in term neonates delivered by cesarean section using ECG, pulse oximetry, and pNIRS during the first 10 minutes after birth. Analysis of variance (ANOVA) was conducted for normally distributed values or Kruskal-Wallis tests for non-normally distributed values to compare the minute-to-minute mean values of the three monitoring methods. Data analysis commenced from the third minute after birth due to missing values in minutes 1 and 2 after birth.

**RESULTS:** A total of 55 term neonates (gestational age median [IQR]: 38+5 [38+2-39+1]) were included. Cerebral pulse rate measurement using pNIRS was feasible in every newborn. Cerebral pulse rate correlated well with ECG data. Until the fifth minute after birth, the HR from pNIRS was on average higher than that from pulse oximetry. However, a significant difference among the three methods was observed only in the fourth minute (p=0.016), [Minute 4: ECG versus pulse oximetry (p=0.030), pulse oximetry versus pNIRS (p=0.036), ECG versus pNIRS (p=1.000)]. No significant differences were noted among the three monitoring methods from the fifth minute onwards.

**DISCUSSION:** Cerebral pulse rate measurement using pNIRS was feasible in every newborn. The pNIRS-derived HR was closer to ECG data than to pulse oximetry in the

first minutes after birth. The ability to measure cerebral pulse rate provides continuous information about cerebral perfusion for the first time. The significance of pNIRS in neonates with respiratory failure and hemodynamic instability needs further evaluation in consecutive studies.

## Reference ranges for cerebral oxygen saturation during neonatal transition in extremely and very preterm neonates

**Bernhard Schwabeger**<sup>1,2,3</sup>, Christina H. Wolfsberger<sup>1,2,3</sup>, Berndt Urlesberger<sup>1,2,3</sup>, Katharina Goeral<sup>4</sup>, Marlene Hammer<sup>5</sup>, Alexander Avian<sup>6</sup>, Tina Perme<sup>7</sup>, Eugene M Dempsey<sup>8</sup>, Laila Springer<sup>9</sup>, Gianluca Lista<sup>10</sup>, Tomasz Szczapa<sup>11</sup>, Hans Fuchs<sup>12</sup>, Lukasz Karpinski<sup>11</sup>, Jenny Bua<sup>13</sup>, Brenda Law<sup>14,15</sup>, Julia Buchmayer<sup>4</sup>, Ursula Kiechl-Kohlendorfer<sup>5</sup>, Lilijana Kornhauser-Cerar<sup>7</sup>, Christoph E Schwarz<sup>8</sup>, Kerstin Gründler<sup>9</sup>, Iliaria Stucchi<sup>10</sup>, Katrin Klebermass-Schrehof<sup>4</sup>, Georg M Schmölzer<sup>14,15</sup>, Gerhard Pichler<sup>1,2,3</sup>

<sup>1</sup>Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria, <sup>2</sup>Research Unit for Microcirculation and Macrocirculation of the Newborn, Medical University of Graz, <sup>3</sup>Research Unit for Cerebral Development and Oximetry Research, Medical University of Graz, <sup>4</sup>Comprehensive Center for Pediatrics, Department of Pediatrics and Adolescent Medicine, Division of Neonatology, Intensive Care and Neuropediatrics, Medical University of Vienna, <sup>5</sup>Department of Pediatrics II, Neonatology, Medical University of Innsbruck, <sup>6</sup>Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, <sup>7</sup>NICU, Department for Perinatology, Division of Gynaecology and Obstetrics, University Medical Centre Ljubljana, <sup>8</sup>INFANT Research Centre, University College Cork, Cork University Maternity Hospital, <sup>9</sup>Department of Neonatology, University Children's Hospital of Tübingen, <sup>10</sup>Neonatologia e Terapia Intensiva Neonatale (TIN) Ospedale dei Bambini "V Buzzi," Milano, Italia, <sup>11</sup>II Department of Neonatology, Neonatal Biophysical Monitoring and Cardiopulmonary Therapies Research Unit, Chair of Neonatology, Poznan University of Medical Sciences, <sup>12</sup>Division of Neonatology and Pediatric Intensive Care Medicine, Center for Pediatrics and Adolescent Medicine, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, <sup>13</sup>Neonatal

*Intensive Care Unit, Institute for Maternal and Child Health, "IRCCS Burlo Garofolo",<sup>14</sup>Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital,<sup>15</sup>Department of Pediatrics, University of Alberta*

**OBJECTIVE:** To define reference values and centile charts for arterial oxygen saturation (SpO<sub>2</sub>), heart rate (HR) and cerebral oxygen saturation (crSO<sub>2</sub>) during the first 15 minutes after birth in extremely and very low gestational age preterm neonates with favourable outcome.

**METHODOLOGY:** Preterm neonates <32 weeks of gestational age, included in the COSGOD III trial with visible NIRS measurements and with favourable outcome, defined as surviving without cerebral injuries (any intraventricular haemorrhage or cystic periventricular leucomalacia) or inflammatory morbidities (culture proven sepsis or necrotizing enterocolitis) until term age, were eligible for inclusion to define reference ranges and centile charts. Pulse oximetry was used for measurements of SpO<sub>2</sub>, and electrocardiography was used for measurements of HR. crSO<sub>2</sub> was assessed using the INVOS 5100c monitor. Measurements were performed during the first 15 minutes after birth. Reference ranges and centile charts (10th to 90th centile) were defined for each minute starting at minute two.

**RESULTS:** A total of 210 preterm neonates with a median gestational age of 29.7 (27.6-30.9) weeks and a birth weight of 1200 (900-1460) grams were eligible for analysis. The 10th centiles of SpO<sub>2</sub> were 32%, 52%, 83% and 85% at minute two, five, ten and 15, respectively. The 10th centiles of HR at minute two, five, ten and 15 were 70bpm, 109bpm, 126bpm and 134bpm, respectively. The 10th centiles of crSO<sub>2</sub> at minute two, five, ten and 15 were 15%, 27%, 59% and 63%, respectively.

**CONCLUSION:** This study provides reference ranges and centile charts for SpO<sub>2</sub>, HR and crSO<sub>2</sub> for extremely and very low gestational age preterm neonates with favourable outcome. These centile charts might help to target oxygenation during resuscitation after birth in very preterm neonates.

## Using broadband optical spectroscopy to characterize newborn hypoxic ischemic injury: A pilot study

**Imran Ilahi<sup>1</sup>**, Janine Khan<sup>1</sup>, Andrea Pardo<sup>1</sup>, Seth Goldstein<sup>1</sup>

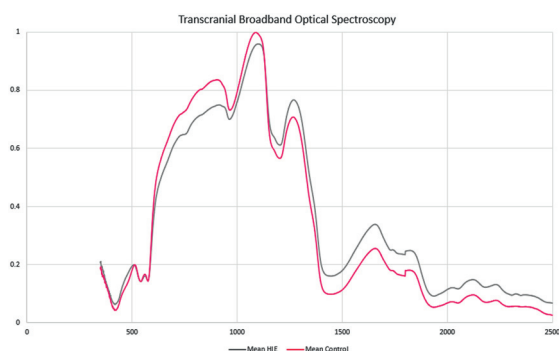
<sup>1</sup>*Ann & Robert H. Lurie Children's Hospital of Chicago*

**BACKGROUND:** Hypoxic ischemic encephalopathy (HIE) is a common cause of mortality and severe disability. HIE is diagnosed with a combination of biochemical and clinical findings (1). Neonates with moderate to severe HIE benefit from therapeutic hypothermia (TH) starting within 6 hours of life to prevent death or severe disability (2). Prompt diagnosis of HIE is key to initiating therapeutic interventions within the appropriate time window. Broadband optical spectroscopy (BOS) uses a noninvasive infrared reflectance light measurement, consisting of a handheld probe connected to a broadband halogen light source via fiberoptic cables, coupled with a spectroradiometer that detects a wide range of wavelengths (Figure 1). BOS offers 500 times greater granularity than commercially available near-infrared oximeters. BOS involves contact with the skin for less than a second and does not generate warmth or discomfort. It does not expose the infant to ultraviolet rays or ionizing radiation. BOS may improve the early diagnosis of neonates that may benefit from TH.

**METHODOLOGY:** Neonates were identified as candidates for TH on admission to the NICU, and healthy controls underwent transfontanelar BOS. Controls were age-matched neonates without critical illness or intracranial pathology. Inclusion criteria consisted of neonates  $\geq$  36 weeks gestational age (GA) with moderate to severe HIE, eligible for TH. Exclusion criteria were neonates < 36 weeks GA, birth weight <1800g, and suspected subgaleal hemorrhage.

**RESULTS:** BOS was obtained from 12 neonates within the first 24 hours of life. There were 6 neonates with HIE eligible for TH, and 6 healthy controls; the median GA was 39.4 weeks and the median weight was 3.5 kg. No safety concerns or changes to clinical care were noted. Average spectroscopy signatures are shown in Figure 2. There were differences between the near-infrared and short-wave infrared portions of the curves.

**CONCLUSION:** Our pilot study presents differences in BOS data in neonates with HIE vs. healthy controls. This safe, non-invasive diagnostic tool may help early HIE detection and monitoring of at-risk neonates in the NICU. These findings suggest that BOS could be an adjunct to current clinical practices for HIE assessment in neonates,



improving the identification of neonates eligible for TH and potentially other neuroprotective interventions.

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### Cerebral oxygenation changes in neonates under anesthesia

**Vera Balog**<sup>1</sup>, Sarolta Trinh<sup>1</sup>, Magdolna Barra<sup>2</sup>, Balazs Hauser<sup>3</sup>, Miklos Szabo<sup>1</sup>, Agnes Jermendy<sup>1</sup>

<sup>1</sup>Division of Neonatology, Pediatric Center, MTA Center of Excellence, Semmelweis University,

<sup>2</sup>Department of Nuclear Medicine, Semmelweis University, <sup>3</sup>Department of Anesthesiology and Intensive Therapy, Semmelweis University

**BACKGROUND:** Intraoperative cerebral hypoxia can increase the risk of adverse postoperative outcomes. Cerebral NIRS monitoring can provide early warning signs of impaired tissue oxygenation (rSO<sub>2</sub>), however, it is not part of the routine monitoring setup, and normal values and lower safety limits are not well-defined. We aimed to describe rSO<sub>2</sub> changes during neonatal non-cardiac surgeries and their relation to other physiological parameters.

**METHODOLOGY:** A prospective observational study was conducted in the operating room of the Pediatric Centre, Semmelweis University. Neonates under 6 kg were enrolled, who were admitted to our level III NICU due to a condition that required surgical intervention between 2020-2023. The monitoring setup included a patient monitor, an anesthesia machine (Dräger Infinity DeltaXL and Perseus A500), and a Medtronic InVivo 5100C NIRS monitor. NIRS events were categorized based on the difference from the median values of the first recorded minute. A mild decrease was defined as an 11-20% decrease from the baseline or an absolute rSO<sub>2</sub> value of 60-69. A moderate decrease was considered a 21-30% decrease or an absolute rSO<sub>2</sub> value between 50-59. Events were labeled severe decrease if more than a 30% decrease occurred or the absolute rSO<sub>2</sub> value was below 50. Event severity was described based on the lowest value. Events with severe rSO<sub>2</sub> decrease were analyzed separately, and synchronous changes in heart rate (HR), peripheral oxygen saturation (SpO<sub>2</sub>), end-tidal carbon dioxide (etCO<sub>2</sub>), and mean arterial pressure (MAP) were assessed. Wilcoxon signed-rank test was used to analyze the differences between the rSO<sub>2</sub> nadirs and HR, SpO<sub>2</sub>, MAP, and etCO<sub>2</sub> nadirs.

**RESULTS:** 95 patients were enrolled in the final analysis, with a median 36 [28; 38] weeks gestational age and 2500 [1125; 3030] grams birth weight. 55% of the patients were premature. The length of NIRS measurements was a median of 120 [79; 190] minutes with a 98 [43; 100] % ratio of data points in each patient. We observed 59 events of mild decrease in the NIRS values, that lasted for a median of 2.5 [1.5; 5.7] minutes, while moderate decrease appeared 30 times, with a median of 18 [7.0; 42.8] minutes length. Interestingly, severe decreases appeared 40 times,

but they lasted much longer: 39.2 [15; 85] minutes. During severe events, we compared the lowest HR, SpO<sub>2</sub>, MAP, and etCO<sub>2</sub> values. We found that only etCO<sub>2</sub> showed a significant decrease (median -22.5 [-60.9; 4.3] %) at the time of nadir rSO<sub>2</sub> compared to levels 5 mins before the severe rSO<sub>2</sub> events (p=0.034).

**CONCLUSION:** Undesired rSO<sub>2</sub> changes were frequent during neonatal anaesthesia. EtCO<sub>2</sub> showed association with the rSO<sub>2</sub> changes during severe events, suggesting that ventilation has a marked influence on cerebral oxygenation.

### Neurointensive monitoring during neonatal anaesthesia: Synchronous cerebral oxygenation and mean arterial pressure changes

**Ms Luca Laura Bogner**<sup>1</sup>, Dr Sarolta H. Trinh<sup>1</sup>, Dr Magdolna Barra<sup>2</sup>, Dr Vera Balog<sup>1</sup>, Prof. Dr Miklos Szabo<sup>1</sup>, Dr Melinda Kis-Tamas<sup>3</sup>, Dr Balazs Hauser<sup>3</sup>, Dr Agnes Jermendy<sup>1</sup>

<sup>1</sup>*Division of Neonatology, Paediatric Centre, Semmelweis University, Budapest, Hungary,*

<sup>2</sup>*Department of Nuclear Medicine, Medical Imaging Centre, Semmelweis University, Budapest, Hungary,*

<sup>3</sup>*Department of Anaesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary*

**BACKGROUND:** Safeguarding children's brains is of great importance during paediatric anaesthesia. Near-infrared spectroscopy (NIRS) is nowadays widely used in neonatal care, however it is seldom applied during non-cardiac surgeries of newborns. Since blood pressure does not reflect end-organ perfusion precisely, the addition of NIRS monitoring may aid hemodynamic management during neonatal anaesthesia. We aimed to describe hypotensive events and their relation to low cerebral oxygenation (crSO<sub>2</sub>) episodes during general anaesthesia of newborns in a tertiary neonatal surgical center.

**METHODOLOGY:** This was a prospective observational study, conducted between June 2021 and March 2023 in the Paediatric Centre, Semmelweis University, Budapest, Hungary. A total of 100 patients (61 preterm and 39 term neonates) were enrolled who required general anaesthesia for surgical care. Cerebral oxygenation were recorded with a NIRS monitor (Medtronic INVOS 5100C) with a 5 second frequency and non-invasive blood pressure measurement were taken with a 5 minute frequency. Low cerebral oxygenation was defined as crSO<sub>2</sub> events lasting longer than 1 minute, relative decrease of crSO<sub>2</sub> values 11 to 20% below baseline value or absolute crSO<sub>2</sub> value

below 70%. For preterm infants <7 days old mean arterial pressure (MAP) less than their gestational age in weeks was defined as hypotension, for infants >7 days old MAP was defined according to de Graaff's recommendations. Data are shown in median [IQR] and %.

**RESULTS:** Gestational age of the total population was 32[28;38] with a bodyweight of 2.7[1.9;3.4] kg. The age at the time of surgery was 26[6;68] days of life. We recorded a median of 116[75;173] minutes of anaesthesia. The length of anaesthesia was longer in term vs preterm neonates (126[104;180] vs 95[68;157] minutes, respectively, p<0.01). We found a weak correlation between MAP and crSO<sub>2</sub> values (r=0.241). In our population, the majority of patients, 79 neonates, had crSO<sub>2</sub> decrease during anaesthesia. It lasted a median 10[5;25] minutes, corresponding to 39% of the anaesthesia time in term neonates, while it was 12[2;32] minutes in preterm neonates, corresponding to a longer median period, 46% (p<0.01). Hypotension occurred in 62 patients. In the term population, hypotensive periods were shorter, 22[15;36] minutes, 38% of the recorded time. In the preterm group the length was 29[15;40] minutes, 49%. A total of 53 patients had both decreased crSO<sub>2</sub> and hypotensive events during their general anaesthesia. Synchronous decrease lasted for median 29 minutes, which corresponded to 22% of the total anaesthesia time, but only 44% of the crSO<sub>2</sub> decrease time and 51% of the hypotension time.

**CONCLUSION:** In summary, crSO<sub>2</sub> decrease occurs frequently during neonatal anaesthesia, especially among preterm neonates, but it coincides with hypotension only half of the time. NIRS could be a useful addition to the monitoring of newborns undergoing general anaesthesia and may aid therapy.

### Multi-modal monitoring of infants with hypoxic-ischaemic encephalopathy within 12-hours of birth and prediction of outcome

**Aisling Garvey**<sup>1,2,3</sup>, Brian Walsh<sup>1,2,3</sup>, Sean Mathieson<sup>1</sup>, Michael Moore<sup>4</sup>, John O'Toole<sup>1,2</sup>, Vicki Livingstone<sup>1,2</sup>, Andreea Pavel<sup>1,2</sup>, Daragh Finn<sup>1,2</sup>, Geraldine Boylan<sup>1,2</sup>, Deirdre Murray<sup>1,2</sup>, Eugene Dempsey<sup>1,2</sup>

<sup>1</sup>*Infant Research Centre, <sup>2</sup>Department of Pediatrics and Child Health, University College Cork,*

<sup>3</sup>*Department of Pediatrics, Division of Newborn Medicine, Brigham and Women's Hospital, Harvard Medical School, <sup>4</sup>Department of Radiology, Cork University Hospital*

**BACKGROUND:** Hypoxic-ischaemic encephalopathy (HIE) carries a significant risk of brain injury and adverse

		n (normal/abnormal)	Normal Outcome	Abnormal Outcome	p-value	AUC	95% CI	n (normal/abnormal)	Normal Outcome	Abnormal Outcome	p-value	AUC	95% CI
		6 hours						12 hours					
<b>Barkovich Scoring +/- Death</b>													
NIRS	cSO <sub>2</sub>	33 (21/12)	76.5 (66.5 - 85.0)	78.0 (72.3 - 81.4)	0.754	0.54	0.34-0.73	55 (38/17)	80.5 (74.5 - 88.3)	80.0 (76.0 - 85.0)	0.682	0.54	0.38-0.69
	F <sub>TOE</sub>	26 (16/10)	0.19 (0.13 - 0.30)	0.21 (0.16 - 0.28)	0.623	0.56	0.34-0.79	46 (32/14)	0.15 (0.09 - 0.25)	0.17 (0.11 - 0.24)	0.599	0.55	0.38-0.72
NICOM	CO	13 (7/6)	70.3 (64.9 - 84.4)	87.3 (71.1 - 98.8)	0.138	0.76	0.50-1.00	22 (14/8)	74.9 (66.8 - 86.6)	82.3 (60.2 - 95.9)	0.868	0.53	0.25-0.81
	HR	13 (7/6)	127 (89 - 140)	127 (116 - 133)	0.836	0.54	0.20-0.87	22 (14/8)	125 (102 - 133)	126 (108 - 141)	0.57	0.58	0.32-0.83
	SV	13 (7/6)	0.63 (0.46 - 0.85)	0.73 (0.58 - 0.77)	0.836	0.55	0.22-0.88	22 (14/8)	0.64 (0.56 - 0.72)	0.57 (0.52 - 0.79)	0.616	0.57	0.30-0.85
EEG	Spectral Power FB1	34 (22/12)	175.4 (81.3 - 279.0)	133.6 (82.9 - 334.3)	0.709	0.54	0.33-0.75	56 (38/18)	210.8 (91.4 - 282.8)	85.2 (36.4 - 263.9)	<b>0.046</b>	0.67	0.50-0.83
	Spectral Power FB2	34 (22/12)	12.0 (7.1 - 15.8)	8.8 (5.5 - 16.5)	0.606	0.56	0.35-0.77	56 (38/18)	11.4 (6.5 - 15.4)	8.5 (3.0 - 14.0)	0.065	0.65	0.49-0.81
	Spectral Power FB3	34 (22/12)	5.3 (3.7 - 8.0)	4.9 (3.6 - 8.9)	0.901	0.52	0.30-0.73	56 (38/18)	5.7 (4.4 - 7.0)	4.2 (1.8 - 6.9)	0.15	0.62	0.45-0.79
	Spectral Power FB4	34 (22/12)	3.1 (2.5 - 5.7)	3.6 (1.7 - 5.0)	0.873	0.52	0.31-0.73	56 (38/18)	3.7 (2.3 - 6.5)	2.3 (0.8 - 4.1)	<b>0.028</b>	0.68	0.53-0.84
Qualitative EEG Grade		34 (22/12)	1.0 (0.8 - 3.0)	1.0 (1.0 - 2.8)	0.817	0.53	0.32-0.73	56 (38/18)	1.0 (1.0 - 2.0)	1.5 (1.0 - 2.5)	0.062	0.64	0.48-0.81
<b>Abnormal 2 year outcome +/- Death</b>													
NIRS	cSO <sub>2</sub>	27 (20/7)	79 (68-85)	78 (71-81)	0.725	0.55	0.30-0.80	43 (34/9)	85 (76-89)	78 (65-84)	<b>0.039</b>	0.73	0.55-0.90
	F <sub>TOE</sub>	21 (16/5)	0.21 (0.14-0.29)	0.17 (0.11-0.22)	0.445	0.63	0.37-0.88	37 (30/7)	0.16 (0.09-0.23)	0.20 (0.14-0.26)	0.312	0.63	0.40-0.85
NICOM	CO	13 (9/4)	75.6 (68.8-94.7)	75.3 (65.2-91.7)	0.71	0.58	0.23-0.95	18 (14/4)	78.5 (69.5-89.5)	65.1 (58.1-85.1)	0.158	0.75	0.42-1.0
	HR	13 (9/4)	127 (109-135)	119 (94-139)	0.94	0.51	0.13-0.90	18 (14/4)	127 (120-134)	118 (90-145)	0.778	0.54	0.12-0.95
	SV	13 (9/4)	0.70 (0.57-0.78)	0.68 (0.51-0.83)	1	0.53	0.16-0.90	18 (14/4)	0.63 (0.54-0.78)	0.59 (0.47-0.71)	0.505	0.63	0.30-0.95
EEG	Spectral Power FB1	26 (20/6)	166.4 (84.7-334.3)	175.4 (108.4-279.0)	1	0.50	0.27-0.74	44 (34/10)	198.2 (86.6-269.4)	81.4 (42.1-243.6)	0.096	0.68	0.48-0.88
	Spectral Power FB2	26 (20/6)	10.6 (6.2-16.3)	12.5 (11.2-14.5)	0.457	0.61	0.39-0.83	44 (34/10)	11.2 (6.5-14.8)	8.6 (1.8-12.6)	0.206	0.64	0.42-0.85
	Spectral Power FB3	26 (20/6)	4.9 (3.6-8.1)	5.3 (4.2-5.6)	0.929	0.52	0.30-0.73	44 (34/10)	5.6 (3.7-7.1)	3.9 (1.2-5.9)	0.058	0.70	0.51-0.89
	Spectral Power FB4	26 (20/6)	3.4 (2.6-5.0)	2.8 (1.5-3.1)	0.054	0.77	0.58-0.95	44 (34/10)	3.5 (2.2-6.4)	1.7 (0.6-3.6)	<b>0.016</b>	0.75	0.57-0.93
	Relative Spectral Power FB1	26 (20/6)	0.89 (0.85-0.91)	0.89 (0.87-0.93)	0.573	0.58	0.32-0.85	44 (34/10)	0.89 (0.85-0.92)	0.90 (0.83-0.91)	0.649	0.55	0.35-0.75
	Relative Spectral Power FB2	26 (20/6)	0.053 (0.042-0.070)	0.060 (0.043-0.082)	0.533	0.59	0.32-0.86	44 (34/10)	0.059 (0.042-0.073)	0.059 (0.047-0.097)	0.553	0.57	0.36-0.77
	Relative Spectral Power FB3	26 (20/6)	0.030 (0.024-0.038)	0.028 (0.021-0.037)	0.614	0.56	0.31-0.84	44 (34/10)	0.029 (0.023-0.040)	0.026 (0.023-0.043)	0.815	0.52	0.30-0.75
	Relative Spectral Power FB4	26 (20/6)	0.018 (0.015-0.028)	0.014 (0.010-0.016)	<b>0.016</b>	0.83	0.66-0.99	44 (34/10)	0.017 (0.015-0.026)	0.018 (0.012-0.023)	0.447	0.58	0.35-0.82
	Spectral Difference FB1	26 (20/6)	0.015 (0.013-0.018)	0.013 (0.011-0.018)	0.614	0.58	0.31-0.84	44 (34/10)	0.015 (0.013-0.017)	0.014 (0.012-0.016)	0.354	0.6	0.40-0.80
	Spectral Difference FB2	26 (20/6)	0.043 (0.034-0.047)	0.041 (0.028-0.044)	0.219	0.68	0.44-0.91	44 (34/10)	0.042 (0.037-0.045)	0.038 (0.031-0.044)	0.075	0.69	0.49-0.88
	Spectral Difference FB3	26 (20/6)	0.033 (0.030-0.037)	0.028 (0.020-0.033)	<b>0.046</b>	0.78	0.55-1.00	44 (34/10)	0.033 (0.029-0.038)	0.030 (0.023-0.034)	0.08	0.69	0.48-0.89
	Spectral Difference FB4	26 (20/6)	0.016 (0.014-0.020)	0.014 (0.009-0.017)	0.123	0.72	0.46-0.97	44 (34/10)	0.016 (0.014-0.019)	0.016 (0.012-0.017)	0.481	0.58	0.37-0.79
	Qualitative EEG Grade		26 (20/6)	1 (1-2)	1 (0-3)	0.386	0.60	0.30-0.91	44 (34/10)	1 (1-2)	2 (1-3)	0.354	0.60

cSO<sub>2</sub>, cerebral oxygenation; F<sub>TOE</sub>, fractional tissue oxygen extraction; CO, cardiac output; HR, heart rate; SV, stroke volume; FB, frequency band. p-values derived from Mann-Whitney U test. Values in bold indicate p<0.05.

neurodevelopmental outcome (1, 2). Early identification of at-risk infants is critical to optimise intervention. We aimed to investigate the ability of currently available bedside monitoring techniques to predict short-term MRI and long-term neurodevelopmental outcome in infants with HIE.

**METHODOLOGY:** Prospective observational study conducted in a tertiary NICU, Ireland. Infants with all grades of HIE had continuous electroencephalography (EEG), non-invasive cardiac output monitoring (NICOM) and near-infrared spectroscopy (NIRS) commenced within the first 6 hours of admission to the NICU. One-hour epochs of time-synchronised data were selected at 6 and 12 hours. Abnormal short-term outcome was defined as an abnormal MRI (Barkovich scoring) and/or death in the first week after birth. Abnormal long-term outcome was defined as a score of <1SD below the mean in any of the developmental domains of the Bayley’s Developmental Assessment at approximately 2 years of age or death of the infant.

**RESULTS:** Fifty-seven infants with HIE were included (27 mild, 24 moderate, 6 severe). Median gestational age was 39.9 weeks (IQR 38.1–40.7) and birthweight was 3.4 kgs (IQR 3.0-3.7). Three infants died in the first week and neurodevelopmental outcome was available in 42 infants at a median age of 25 months (IQR 23-26). At 6 hours, quantitative EEG features of relative spectral power and spectral difference at the higher frequency bands were significantly associated with abnormal long-term outcome: AUC 0.83, 95%CI 0.66-0.99 and AUC 0.78, 95%CI 0.55-1.00 respectively (Table 1). At 12 hours, quantitative EEG features of spectral power significantly predicted abnormal short-term outcome (AUC 0.68, 95%CI 0.53-0.84). Quantitative EEG features of spectral power and cerebral

oxygenation (cSO<sub>2</sub>) significantly predicted long-term outcome: AUC 0.75, 95%CI 0.57-0.93 and AUC 0.73, 95%CI 0.55-0.90 respectively. Combining different modalities did not improve prediction. NICOM measurements were not helpful in identifying infants with abnormal outcome at either time point.

**CONCLUSION:** EEG remains the best individual predictor of outcome in infants with HIE. Quantitative EEG features at 6 and 12 hours successively predicted both short- and long-term outcome in infants with HIE.

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**Long-term impact of posthemorrhagic ventricular dilatation on cerebral oxygenation in preterm infants with intraventricular hemorrhage**

**Julia Elis<sup>1</sup>**, Mirjam Steiner<sup>1</sup>, Lisa Klein<sup>1</sup>, Vito Giordano<sup>1</sup>, Monika Olischar<sup>1</sup>, Angelika Berger<sup>1</sup>, Katharina Goeral<sup>1</sup>

<sup>1</sup>Medical University of Vienna

**BACKGROUND AND OBJECTIVE:** Intraventricular hemorrhage (IVH) and its complication, posthemorrhagic ventricular dilatation (PHVD), remain significant contributors to morbidity and mortality in premature infants. Despite prior research demonstrating the short-term effects of IVH on cerebral oxygenation, this study seeks to investigate the long-term consequences. Specifically, we will explore the implications of consecutive PHVD development as well as the impact of neurosurgical interventions (NSI) in patients with IVH and PHVD. Utilizing near-infrared spectroscopy, we aim to gain a better understanding of their long-term impact.

**METHODOLOGY:** In this prospective study preterm neonates with a gestational age <33 weeks born from 2013 to 2023 were investigated. Regional cerebral oxygen saturation (rScO<sub>2</sub>) was monitored repetitively starting at the time of IVH diagnosis for nearly 20 weeks of life. Further analysis involved assessing the duration of rScO<sub>2</sub> values falling outside the established normal range (<55% or >85%) as well as the computation of fractional cerebral tissue oxygen extraction (cFTOE). The median values of those parameters were analyzed by postnatal age and injury group (IVH only; IVH+PHVD without NSI; IVH+PHVD with NSI).

**RESULTS:** This study included 146 preterm infants with a median gestational age of 25.7 (24.3-27.6) weeks and the diagnosis of IVH. Among them, 52.8% (n=77) were diagnosed with PHVD, of which 72.7% (n=56) required NSI. The analysis revealed substantial disparities among these groups. Specifically, patients with IVH+PHVD requiring NSI, exhibited lower rScO<sub>2</sub> values (66.1 % vs. 55.7%, p<0.001), longer durations of rScO<sub>2</sub> outside the established normal range (4.6% vs. 46.7%, p<0.001), and higher levels of cFTOE (0.29 vs. 0.42, p<0.001) compared to IVH infants who were not affected by PHVD. Conversely, IVH+PHVD patients without the need for NSI did not show significant difference compared to IVH patients without ventricular dilatation.

**CONCLUSION:** Our findings emphasize the profound cerebral effects in neonates affected by IVH and PHVD and highlight the enduring physiologic consequences. In particular, infants who required NSI, showed a continuous decline in rScO<sub>2</sub> during the first 20 weeks of life, indicating persistent inadequate cerebral oxygenation, whereas their elevated cFTOE levels reflect increased oxygen demand.

## Oxidant and antioxidants following neonatal hypoxic ischemia

Nur Aycan<sup>1</sup>, Derya Cay Demir<sup>2</sup>, Serap Karaman<sup>1</sup>, Eyyup Yurekturk<sup>1</sup>, Murat Basaranoglu<sup>1</sup>, Oguz Tuncer<sup>1</sup>

<sup>1</sup>Van Yuzuncu Yil University Pediatrics, <sup>2</sup>Van Yuzuncu Yil University Chemistry

**BACKGROUND:** Neonatal hypoxic-ischemic encephalopathy (HIE) is a significant cause of perinatal and postnatal morbidity and mortality worldwide. No specific marker of neonatal hypoxia has been reported with good predictive effect still today. Therapeutic hypothermia is established as the standard of care to improve neurologic recovery in infants with HIE. Catalase (CAT) is the most crucial hydrogen peroxide-scavenging enzyme in the body, and catalase activity detection is used to detect levels of inflammation and oxidative stress. Lipid peroxidation levels marked after hypoxia can be detected based on the level of Malondialdehyde (MDA). In the neonatal period, glutathione (GSH) is the most critical non-enzymatic endogenous antioxidant. Magnetic resonance imaging (MRI) is a valuable tool for predicting long-term outcomes of neonates with HIE, in which hypothermia and systemic supportive care form the cornerstone of therapy. We aim to explain the pathways and relations between the oxidant and antioxidant status to detail oxidant-antioxidant balance and cellular mechanisms.

**METHODOLOGY:** After ethics committee approval and informing the families, serum levels of malondialdehyde, as an oxidative stress marker, and catalase and glutathione as antioxidant enzymes were measured in first blood samples of fifty-two neonates diagnosed with neonatal hypoxic-ischemic encephalopathy in our neonatal intensive care unit. The mean, standard error, and correlations of the oxidant and antioxidant parameters were calculated.

**RESULTS:** Older than 37 weeks of gestation and hypoxic, fifty-two neonates, 84% of whom were born vaginally delivery (28 boys, 24 girls), were included in our research. Gestation weeks were 38.03±0.13, and the birth weight of patients was 3202.34±96.202. Compared to healthy newborns (n=23), catalase was statistically significantly lower than in the healthy group (p=0.0001), while MDA serum level was significantly higher in hypoxic newborns (p=0.01). The negative correlation between GSH and MDA was statistically significant (r=-0.32, p=0.02). The evaluation of the relationship of early (at postnatal fifth day) diffusion MRI findings with oxidants and antioxidants is ongoing.

**CONCLUSION:** HIE pathophysiology involves oxidative stress, mitochondrial energy production failure, glutaminergic excitotoxicity, and apoptosis. Explaining the pathways between oxidant-antioxidant balance and cell death, which will explain the pathophysiology of HIE, is essential in order to develop life-saving treatment strategies that will minimize the effects of oxygen deprivation on other body organs, especially the brain.



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**How does neonatal hypoxia affect thyroid hormones?**

**Nur Aycan**<sup>1</sup>, Eyyup Yurekturk<sup>1</sup>, Murat Basaranoglu<sup>1</sup>, Serap Karaman<sup>1</sup>, Oguz Tuncer

<sup>1</sup>*Van Yuzuncu Yil University*

**BACKGROUND:** Thyroid hormone plays an essential role in brain development and fetal, neonatal, and adult brain function and may influence neuronal recovery after hypoxia and traumatic brain injury. We aimed to see whether there is a relationship between the effects of hypoxia at the cellular level and the stages of the disease.

**METHODOLOGY:** After ethics committee approval and informing the families, demographic characteristics, laboratory parameters, diffusion MRI images, and TSH and free T4 levels from thyroid function tests on a postnatal day five were recorded retrospectively in newborns who were hospitalized with the diagnosis of hypoxic-ischemic encephalopathy in the neonatal intensive care unit of our hospital in the last two years.

**RESULTS:** A total of 81 patients over 37 weeks of gestation were included in the study. Of the babies, 35 (43.2%) were female and 46 (56.8%) were male. Their mean gestational age was 38.26±1.87, and their mean birth weight was 3010±75.28. Sarnat staging (stage 1 n=23, stage 2 n=47, and stage 3 n=11) was performed according to the clinical status of the patient. According to Sarnat scoring, there was no statistical difference between TSH levels on postnatal day 5 (p=0.17), but free T4 level was statistically significantly higher in stage 2 than in stage 1 and stage 3 (p=0.001).

**CONCLUSION:** Thyroid hormone is known to have significant effects on energy catabolism, thermoregulation, growth, development, bone and central nervous system development. The fact that thyroid hormones can be

detected differently in different clinical conditions of hypoxia suggests whether they can be used as a parameter in the staging of hypoxia.

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**Heart rate variability during therapeutic hypothermia in neonatal encephalopathy**

**John Sunwoo**<sup>1</sup>, Seh Hyun Kim<sup>2</sup>, Katie Hannon<sup>2</sup>, Eniko Szakmar<sup>2,3</sup>, Aisling Garvey<sup>2,4</sup>, Chelsea Munster<sup>2</sup>, Sara Cherkerzian<sup>2</sup>, Hoda Elshibiny<sup>2</sup>, Helen Christou<sup>2</sup>, Terrie Inder<sup>2,5</sup>, Maria Angela Franceschini<sup>1</sup>, Mohamed El-Dib<sup>2</sup>

<sup>1</sup>*Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School,* <sup>2</sup>*Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Harvard Medical School,* <sup>3</sup>*Division of Neonatology, 1st Department of Pediatrics, Semmelweis University,* <sup>4</sup>*INFANT Research Centre, Cork, Ireland;* <sup>5</sup>*Department of Paediatrics and Child Health, University College Cork,* <sup>5</sup>*Center for Neonatal Research, Children's Hospital of Orange County, Orange; Department of Pediatrics, University of California Irvine*

**BACKGROUND:** Continuous monitoring of autonomic nervous system (ANS) responses during therapeutic hypothermia (TH) in neonates offers important markers for hypoxic-ischemic encephalopathy. Heart rate variability (HRV) indices, which reflect ANS activity, are particularly informative during TH. The high frequency component of HRV—a marker of parasympathetic tone—is known to increase with cooling[1], promoting the

**Table 1. Demographics of N=43 infants by Weeke score >3**

Variables	Total (N=43)	Normal (N=34)	Weeke >3 (N=9)	*P value
Gestational age (weeks)	38.8 ± 1.7	39.0 ± 1.6	38.0 ± 1.9	.13
Birth weight (kg)	3.14 ± .67	3.21 ± .69	2.90 ± .54	.23
Male	27 (62.8%)	22 (64.7%)	5 (55.6%)	.71
Apgar at 1 min	2.0 (1.0 - 5.0)	2.0 (1.0 - 5.0)	2.0 (2.0 - 6.0)	.13
Apgar at 5 min	7.0 (5.0 - 8.0)	7.0 (5.0 - 8.0)	8.0 (5.5 - 8.0)	.24
Weeke score	1 (0 - 3)	1 (0 - 2)	9 (4 - 16)	<.0001
Maternal Age	33.0 ± 5.7	34.0 ± 5.4	29.6 ± 5.5	.036

\* T-test was used for continuous variables that passed the normality test (otherwise Wilcoxon/Kruskal-Wallis Rank Sums test was used) and Fisher's Exact Test was used for categorical variables; Data are presented as N (Column %) for categorical variables, except when presented as mean ± SD and when presented as median (25-75<sup>th</sup>).

recovery of cerebral tissues and circulatory functions; However, only few studies have reported a comparative analysis of HRV changes throughout the entire cooling and subsequent rewarming periods, especially in the context of adverse brain injury outcomes. We hypothesized that infants with brain injury would exhibit a blunted HRV response to TH.

**METHODOLOGY:** EKG was collected from infants who underwent TH for neonatal encephalopathy at Brigham and Women's Hospital, MA. Post-TH brain injury was assessed using Weeke et al.'s MRI-based grading (PMID:29246356). A Weeke score >3 was considered 'brain injury'. The R-to-R interval was extracted and cleaned using automated algorithms and visual examinations, and analyzed across high (HF=0.2-2Hz), low (LF=0.04-0.2Hz), and very-low frequency (VLF=0.01-0.04Hz) bands using a wavelet transform technique. HF indices were combined into 1-hour medians, represented by each point in Figure 1, and further grouped into 6-hour bins for the cooling stage and 3-hour bins for the rewarming stage. A mixed model was used to account for repeated measures in each bin.

**RESULTS:** We analyzed 43 infants in this report. Absolute HF values were log<sub>10</sub>-transformed to achieve normality. In both groups, we found the anticipated increases in HF during cooling, and in heart rate during rewarming (Figure 1). In the brain injury group, we found a consistently lower log<sub>10</sub>HF (Figure 1-a), while their normalized HF was not different from the normal group (Figure 1-b). Both groups exhibited a gradual increase in Total Power, LF, and VLF during cooling, and a decrease upon rewarming (not shown). Although visually subtle, the brain injury group maintained a statistically higher heart rate throughout TH (Figure 1-c).

**CONCLUSION:** We report HRV indices and heart rate changes during therapeutic hypothermia, confirming the anticipated responses to cooling and rewarming.

Cooling-induced HF increases suggested enhanced parasympathetic activity in both brain injury and normal groups. However, the brain injury group showed consistently lower HF levels and higher heart rates, suggesting diminished parasympathetic tone and its capacity. Insignificant differences in relative HF power may be due to a proportional increase in Total Power during cooling. Future work will incorporate cerebral oxygenation, and covariates that can induce parasympathetic withdrawal, such as modes of ventilation. This work provides additional insights into HRV changes during TH and their possible association with brain injury outcomes.

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#### NIRS for prediction of adverse neurological outcomes in infants with HIE receiving therapeutic hypothermia

**Alam Randhawa**<sup>1</sup>, Pauline De Jesus<sup>1</sup>, Kristine Woodward<sup>2</sup>, Khorshid Mohammad<sup>2</sup>, Michael J. Esser<sup>2</sup>

<sup>1</sup>University of Calgary, <sup>2</sup>Alberta Children's Hospital

**BACKGROUND:** Hypoxic Ischemic Encephalopathy (HIE) in term and near-term infants can result in brain injury due to oxygen and/or blood flow deprivation (1). Despite, therapeutic hypothermia (TH) treatment, consequences of HIE still include death or life-long disability. Current tools may not accurately predict the long-term outcomes (2,3). Near-infrared spectroscopy (NIRS) measures of cerebral regional oxygenation (rSO<sub>2</sub>) is a growing area of interest for prognostication (4).

**OBJECTIVE:** To determine if changes in NIRS (rSO2) in neonates with HIE, and receiving TH, were associated with other markers of brain injury and neurodevelopmental outcomes.

**METHODOLOGY:** A retrospective cohort study of 36 term infants (>35 weeks gestation) born between March 01, 2018, and March 21, 2020, meeting HIE and TH criteria. The rSO2 values were measured via one sensor in the left frontal region, in conjunction with EEG, MRI and other clinical variables. Statistical analysis and machine learning (ML) algorithms were used to determine which variables were associated with the short-term outcome of brain injury on MRI or longer-term outcomes of neurodevelopmental impairments within 3 years of life.

**RESULTS:** The distribution of our cohort was skewed towards mild HIE. HIE severity was not associated with short-term brain injury or longer-term neurodevelopmental outcomes. The mean rSO2 was not associated with MRI results which were also not associated with neurodevelopmental outcomes. Although not statistically significant, higher mean rSO2 values, with concomitant less variability, were associated with greater likelihood of neurodevelopmental impairments within 3 years of life. Using ML techniques, rSO2, measured by NIRS was the most important predictor for neurodevelopmental outcomes in models where only EEG and MRI were included, and remained the most important predictor when other clinical variables were considered (sex, arterial pH, resuscitation etc.).

**CONCLUSION:** Infants with HIE and poor neurodevelopmental outcomes may have persistent dysregulation in cerebral oxygenation during TH. Future work should include larger sample sizes, enhancing data capture to facilitate greater utility of machine learning (ML) algorithms, expanding follow-up to school age children expanding follow-up to school age children to determine potential effect on higher cortical functioning and wider coverage of NIRS probes to better ascertain regional differences.

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**Transcranial doppler ultrasonography in assessing intervention effects in hydrocephalus infants in Uganda**

**Marvin Seruwu**<sup>2</sup>, Rutvi Vyas<sup>1</sup>, Davis Natukwatsa<sup>2</sup>, Ronald Mulondo<sup>3</sup>, Starlin Tindimwebwa<sup>2</sup>, Collins Akugizibwe<sup>2</sup>, Moses Wabukoma<sup>2</sup>, Enock Kainja<sup>2</sup>, Joshua Magombe<sup>2</sup>, Isaac Emurang<sup>2</sup>, Esther Nalule<sup>2</sup>, Michael Woglom<sup>1</sup>, Simeo Ochieng<sup>2</sup>, Chuan-Heng Hsiao<sup>1</sup>, Ajay Rajaram<sup>1</sup>, German Figueroa<sup>1</sup>, Braulio Ramirez<sup>1</sup>, Julia Tatz<sup>1</sup>, Steven Schiff<sup>3</sup>, P. Ellen Grant<sup>1</sup>, Benjamin Warf<sup>1</sup>, Miriah Kemigisha Katugi<sup>2</sup>, Edith Mbabazi Kabachelor<sup>2</sup>, Jason Sutin<sup>1</sup>, Pei-yi Lin<sup>1</sup>

<sup>1</sup>Boston Children’s Hospital, <sup>2</sup>CURE Children’s Hospital of Uganda, <sup>3</sup>Yale School of Medicine, Yale University

**BACKGROUND:** Neonatal hydrocephalus is a major global health issue, especially in low- and middle-income

**Table 1. Baseline Infant Characteristics of the Entire Exposure Group and by Intervention Subgroup**

Variable	All Patients (n=190)	ETV/CPC (n=157)	VPS (n=33)	P Value <sup>a</sup>
Girls	71 (37.37)	57 (36.31)	14 (42.42)	0.56 <sup>b</sup>
Prior VSGS	20 (10.53)	7 (4.46)	13 (39.39)	<0.001 <sup>b</sup>
Etiology				0.004 <sup>c</sup>
Aqueeductal stenosis	23 (12.11)	20 (12.74)	3 (9.09)	
HC secondary to MM	26 (13.68)	22 (14.01)	4 (12.12)	
Dandy-Walker	24 (12.63)	24 (15.29)	0 (0.00)	
PIH	85 (44.74)	61 (38.85)	24 (72.73)	
Other	32 (16.84)	30 (19.11)	2 (6.06)	
Age at admission, days	66 (31 to 110)	64 (27 to 111)	68 (42 to 91)	0.81
Age at definitive surgery, days	81 (44 to 130)	74 (41 to 130)	115 (81 to 158)	0.01

Binominal data presented as n (%); continuous as median (IQR).

Abbreviations: MM, myelomeningocele; PIH, post-infectious hydrocephalus; VSGS, ventriculosubgaleal shunt.

<sup>b</sup> P values by Fisher Exact test. <sup>c</sup> P values by Chi-square test. Otherwise, P values by Student 2-tailed, unpaired t t-test.

**Table 2. TCD Doppler Results Grouped by ETV/CPC and VPS**

Variable	ETV/CPC (N=152)	VPS (N=24)	Mean Difference	p-value
<b>Pre-operative</b>				
Systolic flow velocity (cm/s)	68.56 ± 1.62	73.37 ± 4.09	-4.81 ± 4.40	0.276
Diastolic flow velocity (cm/s)	14.61 ± 0.62	15.94 ± 1.57	-1.33 ± 1.69	0.431
Resistive index	0.77 ± 0.01	0.77 ± 0.02	-0.00 ± 0.02	0.948
Pulsatility index	1.47 ± 0.03	1.48 ± 0.07	-0.01 ± 0.08	0.858
<b>Mean Difference (Post-Pre)</b>				
Systolic flow velocity (cm/s)	10.41 ± 1.83	7.11 ± 4.66	3.30 ± 5.01	0.510
Diastolic flow velocity (cm/s)	9.34 ± 0.90	6.39 ± 2.29	2.95 ± 2.46	0.232
Resistive index	-0.08 ± 0.01	-0.05 ± 0.02	-0.03 ± 0.02	0.234
Pulsatility index	-0.28 ± 0.03	-0.22 ± 0.08	-0.06 ± 0.09	0.502

Data presented as mean ± SE.

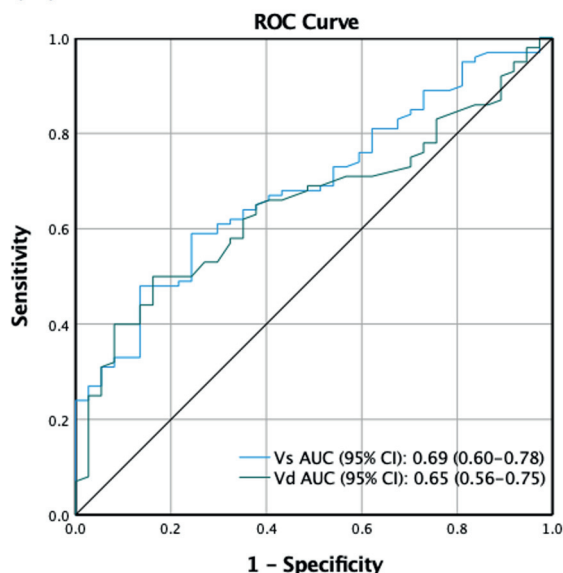
Linear mixed-effects model of TCD variables with age at intervention as covariate. P tests  $H_0: \beta=0$ .

**Table 3. Pre- and post-ETV/CPC TCD Results by ETV/CPC Outcome.**

Variable	Failure-free (N=100)	Failure (N=37)	Mean Difference	p-value
<b>Pre-operative</b>				
Systolic flow velocity (cm/s)	70.41 ± 1.99	60.56 ± 3.34	9.84 ± 3.94	<b>0.014</b>
Diastolic flow velocity (cm/s)	14.85 ± 0.73	11.87 ± 1.22	2.98 ± 1.44	<b>0.041</b>
Resistive index	0.77 ± 0.01	0.79 ± 0.02	-0.01 ± 0.02	0.440
Pulsatility index	1.46 ± 0.03	1.52 ± 0.06	-0.05 ± 0.07	0.436
<b>Post-operative</b>				
Systolic flow velocity (cm/s)	79.41 ± 2.26	76.84 ± 3.82	2.57 ± 4.51	0.570
Diastolic flow velocity (cm/s)	24.14 ± 1.12	22.36 ± 1.90	1.78 ± 2.24	0.428
Resistive index	0.69 ± 0.01	0.72 ± 0.02	-0.03 ± 0.02	0.217
Pulsatility index	1.17 ± 0.04	1.27 ± 0.06	-0.10 ± 0.08	0.210

Data presented as mean ± SE.

Linear mixed-effects model of TCD variables with age at intervention as covariate. P tests  $H_0: \beta=0$ .

**Figure 1. ROC Analysis of Systolic (Vs) and End Diastolic (Vd) Flow Velocities as Classifiers of ETV/CPC Outcome.**

countries (LMICs) where post-infectious hydrocephalus (PIH) is endemic yet access to neurosurgical care is limited. CURE Children's Hospital of Uganda (CCHU) developed endoscopic third ventriculostomy/choroid plexus cauterization (ETV/CPC) as the only implant-free treatment for infant hydrocephalus. ETV/CPC is as effective as the traditional treatment of implanting a ventriculoperitoneal shunt (VPS) (Kulkarni et al. 2017), but about a third of treatments fail within six months for reasons not well understood. Transcranial Doppler Ultrasound (TCD) is a readily available point of care tool for measuring large artery cerebral blood flow velocity that is not currently a uniform standard of care. Our objective is to investigate perioperative changes in TCD variables in infants treated with ETV/CPC and their relationship with surgical outcome.

**METHODOLOGY:** This is a subgroup analysis of a prospective, observational study of patients at risk for ETV/CPC treatment failure (NCT 03650101) (Vadset et al. 2022). Infants under six months old considered to be treated with ETV/CPC for hydrocephalus were eligible for the study. Systolic (Vs) and end diastolic (Vd) flow

velocities, resistive (RI) and pulsatility (PI) indices of the anterior cerebral artery were measured preoperatively and postoperatively by TCD within a few days of surgery. ETV/CPC treatment failure is defined as the need for any re-operation related to hydrocephalus within six months. Paired t test was used to test the intervention effect of TCD variables. Linear mixed model with age at intervention as a covariate was used to compare TCD results sub-grouped by intervention and ETV/CPC outcome. ROC analysis was used to evaluate the performance of the TCD assessment in ETV/CPC risk prediction.

**RESULTS:** Two-hundred patients were enrolled and 190 (71F/119M; median (IQR) age: 66 (31-110) days) were included in this analysis. Of those intended for ETV/CPC, 33 (17%) crossed to VPS, with crossovers more likely to have PIH, wait longer to receive their definitive surgery and 39% had a prior ventriculosubgaleal shunt (Table 1). Despite these differences in clinical characteristics, neither pre-operative TCD variables, nor their change following intervention differed significantly between patients treated with ETV/CPC or VPS. (Table 2). Patients with ETV/CPC failure are younger than patients with successful outcome (failure-free) (Mean difference: 34.2 ± 10 days, p<0.001). After ETV/CPC, Vs and Vd improved and RI and PI decreased, regardless of the treatment outcome (p<0.001, T-test). However, both pre-op Vs and Vd are higher in the failure-free group than those in failure group after controlling for age (Table 3). ROC analysis demonstrated a moderate discriminatory ability in predicting ETV/CPC treatment success (Figure 1).

**CONCLUSION:** Our results suggest TCD has potential for risk assessment and clinical decision making in the management of hydrocephalus.

## A prospective study describing splanchnic NIRS in infants receiving minimal enteral nutrition during therapeutic hypothermia

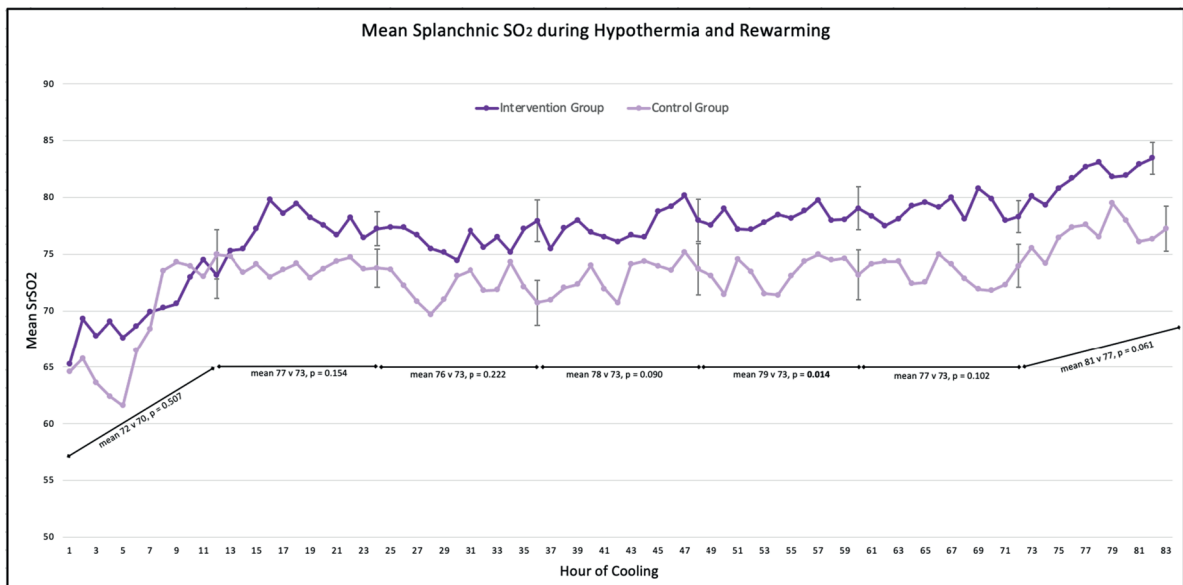
**Tatiana Nuzum**, Martha Caprio, Sean Bailey, Elena Wachtel

<sup>1</sup>Hassenfeld Children’s Hospital at NYU Langone, <sup>2</sup>NYCH+H Bellevue Hospital Center

**BACKGROUND:** Therapeutic Hypothermia (TH) is the standard of care for moderate to severe neonatal encephalopathy (NE). Historically, minimal enteral nutrition (MEN) has been withheld during TH due to concerns about splanchnic perfusion. Recent observational studies have shown that providing MEN during TH is safe and is associated with several benefits. Human milk is known to contain mesenchymal stem cells which are potentially neuroregenerative. Splanchnic perfusion measured by near-infrared spectroscopy (NIRS) has not yet been assessed in this population.

**OBJECTIVE:** To compare clinical outcomes and splanchnic regional oxygen saturation (SrSO<sub>2</sub>) levels between infants who received MEN during TH, and those who did not.

**METHODS:** Infants were prospectively enrolled after informed consent was obtained. All infants that qualified for TH based on NICHD criteria were eligible. Exclusion criteria included dopamine infusion > 10mcg/kg/min or 2 vasoactive agents simultaneously, or baseline SrSO<sub>2</sub> < 45%. Infants received 10-15 mL/kg/day of expressed or donor human milk for the duration of TH and rewarming. SrSO<sub>2</sub> was recorded hourly. A group of historic controls



Subject Demographics	Intervention Group (n = 32)	Control Group (n = 32)	p - value
Gestational Age (weeks) *	38.9 ± 1.7	39.1 ± 1.8	0.692
Birth Weight (g) *	3195 ± 454	3206 ± 602	0.934
Female sex <sup>+</sup>	10 (31%)	17 (53%)	0.128
Delivery via Cesarean Section <sup>+</sup>	25 (78%)	20 (63%)	0.387
Delivery under GA <sup>+</sup>	9 (28%)	3 (9%)	0.107
Apgar Score - 1minute <sup>†</sup>	2 [1, 2]	2 [1, 4]	0.095
Apgar Score – 5 minutes <sup>†</sup>	5 [4, 7]	5.5 [3, 7]	0.616
Apgar Score – 10 minutes <sup>†</sup>	6 [5, 7]	6.5 [4, 7]	0.886
Apgar Score – 15 minutes <sup>†</sup>	6 [5, 6]	5.5 [3, 7]	0.457
Delivery Room Resuscitation			
Intubation	16 (50%)	18 (58%)	0.802
Chest Compressions	5 (16%)	7 (22%)	0.750
Epinephrine	5 (16%)	3 (9%)	0.708
Venous Cord Gas pH*	7.12 ± 0.16	7.10 ± 0.19	0.759
Venous Cord Gas BD*	11.5 ± 7.0	10.9 ± 5.9	0.771
Arterial Cord Gas pH*	7.02 ± 0.14	7.01 ± 0.17	0.794
Arterial Cord Gas BD*	13.8 ± 7.2	13.0 ± 6.3	0.651
Postnatal Gas pH*	7.14 ± 0.12	7.14 ± 0.16	0.992
Postnatal Gas BD*	16.1 ± 5.0	15.3 ± 6.0	0.536
Postnatal lactate*	11.4 ± 3.9	10.9 ± 5.1	0.719
Sarnat Grade <sup>+</sup>			1.000
Moderate	30 (94%)	30 (94%)	
Severe	2 (6%)	2 (6%)	
Outborn Infant <sup>+</sup>	17 (53%)	28 (88%)	<b>0.005</b>
Duration of Intubation (days)*	1.9 ± 2.7	1.7 ± 1.8	0.753
Duration of Respiratory Support (days)*	6.2 ± 5.8	7.8 ± 5.8	0.278
Vasopressor Requirement <sup>+</sup>	12 (38%)	9 (28%)	0.595
Pulmonary Hypertension <sup>+</sup>	4 (13%)	6 (19%)	0.732
Ventricular Dysfunction <sup>+</sup>	2 (6%)	0 (0%)	0.492
MRI NICHD Score <sup>+</sup>			0.412
0 (Normal)	15 (47%)	14 (44%)	
1A/1B	1 (3%)	4 (13%)	
2A/2B	15 (47%)	14 (44%)	
3	1 (3%)	0 (0%)	
vEEG Abnormality <sup>+</sup>			0.831
Mild	16 (50%)	15 (47%)	
Moderate	6 (19%)	8 (25%)	
Severe	10 (31%)	9 (28%)	
Seizures <sup>+</sup>	2 (6%)	4 (13%)	0.672
Early-Onset Sepsis <sup>+</sup>	1 (3%)	0 (0%)	1.000

who were NPO during TH was also compiled after applying the same exclusion criteria. Clinical data for the infant's NICU course was collected.

**RESULTS:** Infants were prospectively enrolled after informed consent was obtained. All infants that qualified for TH based on NICHD criteria were eligible. Exclusion criteria included dopamine infusion > 10mcg/kg/min or 2 vasoactive agents simultaneously, or baseline SrSO<sub>2</sub> < 45%. Infants received 10-15 mL/kg/day of expressed or donor human milk for the duration of TH and rewarming. SrSO<sub>2</sub> was recorded hourly. A group of historic controls

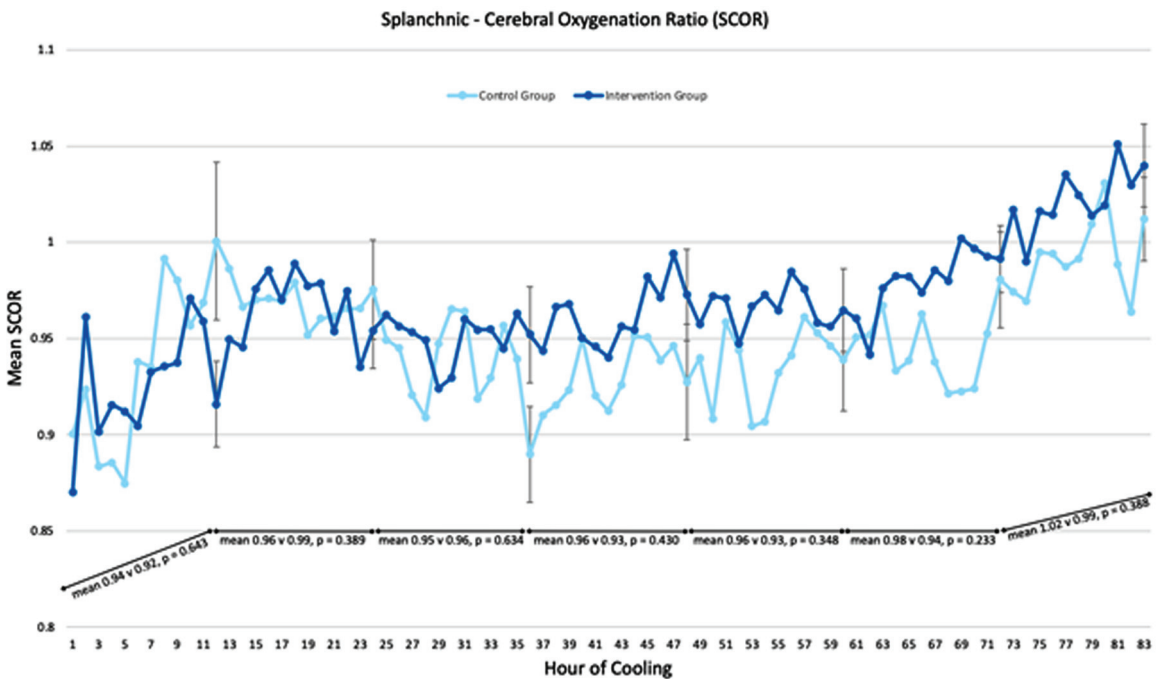
who were NPO during TH was also compiled after applying the same exclusion criteria. Clinical data for the infant's NICU course was collected.

**CONCLUSION:** SCORs were within normal ranges throughout hypothermia and rewarming and did not differ between groups. Providing MEN during TH is safe and results in several important benefits including fewer central line days, shorter hospital stays and greater human milk feeding success. Future directions will include assessing long-term neurodevelopmental outcomes.

Outcomes			
Late-Onset Sepsis <sup>†</sup>	0 (0%)	0 (0%)	N/A
Necrotizing Enterocolitis <sup>†</sup>	0 (0%)	0 (0%)	N/A
Age at start of feeds (hours)*	26.1 ± 11.8	101.1 ± 11.9	< 0.001
Time to achieve full enteral feeds (days)*	5.7 ± 1.6	7.1 ± 1.4	< 0.001
Time to achieve full oral Feeds (days)*	9.1 ± 5.9	13.1 ± 9.6	0.058
Duration of IV Fluids (days)*	5.7 ± 1.8	6.8 ± 1.3	0.006
Duration of Central Line placement (days)*	5.7 ± 1.7	6.6 ± 1.3	0.026
Feeds at Discharge <sup>†</sup>			0.002
Human Milk	11 (35%)	3 (9%)	
Formula	6 (19%)	19 (60%)	
Combination	14 (45%)	10 (31%)	
Gastrostomy Tube placement <sup>†</sup>	0 (0%)	1 (3%)	1.000
Mortality <sup>†</sup>	1 (3%)	0 (0%)	1.000
Length of Stay (days)*	12.0 ± 6.4	17.7 ± 13.0	0.031

\*= mean ± sd, <sup>†</sup> = n (%), † = median [IQR]

GA = General Anesthesia, APGAR = appearance, pulse, grimace, activity, respiration score, pH = potential of hydrogen, BD = base deficit, MRI = Magnetic Resonance Imaging, NICHD = National Institute of Child Health and Human Development, vEEG = video electroencephalogram, IV = intravenous



## Multi-modal analysis of infant cry types characterization: Acoustics, body language and brain signals

Ana Laguna Pradas<sup>1</sup>, Sandra Pusic<sup>1</sup>, Anna Lucia Paltrinieri<sup>2</sup>, Angel Bazan<sup>1</sup>, Silvia Orlandi<sup>3</sup>

<sup>1</sup>ZOUNDREAM AG, <sup>2</sup>Neonatology Department, Barcelona Centre for Maternal-Fetal and Neonatal Medicine (BCNatal), Hospital Clínic, Universitat de Barcelona, <sup>3</sup>Department of Electrical, Electronic and Information Engineering “Guglielmo Marconi” (DEI), University of Bologna

**BACKGROUND AND OBJECTIVE:** Infant crying is the first attempt babies use to communicate during their initial months of life. A misunderstanding of the cry message can compromise infant care and future neurodevelopmental process.

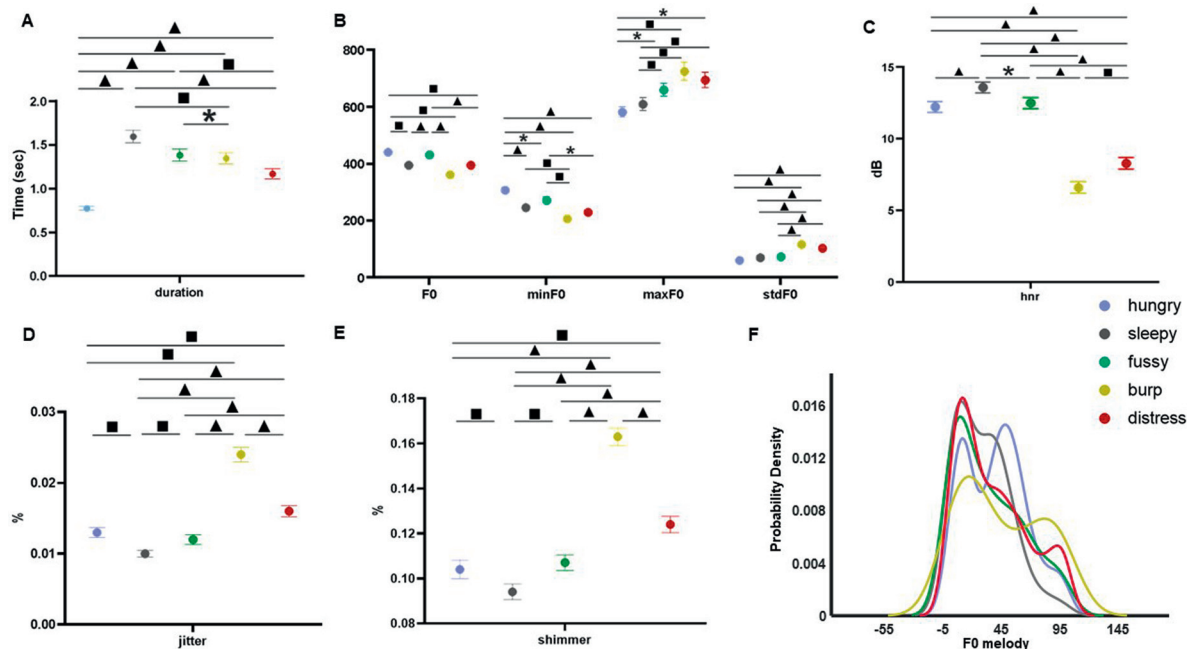
**METHODOLOGY:** An exploratory study collecting multimodal data (i.e., crying, electroencephalography (EEG), near-infrared spectroscopy (NIRS), facial expressions, and body movements) from 38 healthy full-term newborns was conducted at Hospital Clínic-Maternitat Barcelona. Cry types were defined based on different conditions (i.e., hunger, sleepiness, fussiness, need to burp, and distress). Statistical analysis, Machine Learning (ML), and Deep Learning (DL) techniques were used to identify relevant features for cry type classification and to evaluate a robust DL algorithm named Acoustic MultiStage Interpreter (AMSI).

types based on acoustics, EEG, NIRS, facial expressions, and body movements. Acoustics and body language were identified as the most relevant ML features to support the cause of crying. The DL AMSI algorithm achieved an accuracy rate of 92%.

**CONCLUSION:** This study set a precedent for cry analysis research by highlighting the complexity of newborn cry expression and strengthening the potential use of infant cry analysis as an objective, reliable, accessible, and non invasive tool for cry interpretation, improving the infant-parent relationship and ensuring family well-being.

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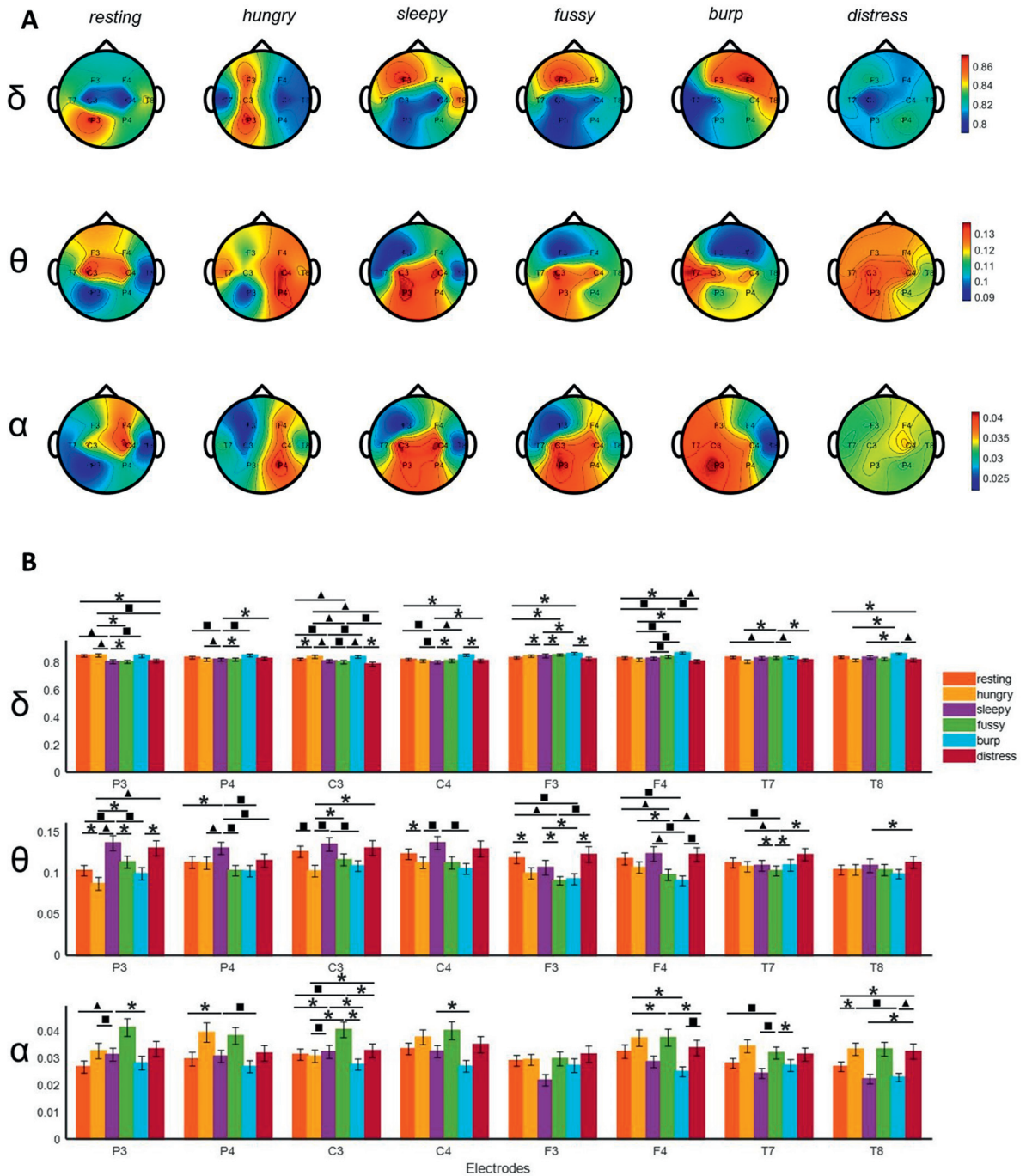


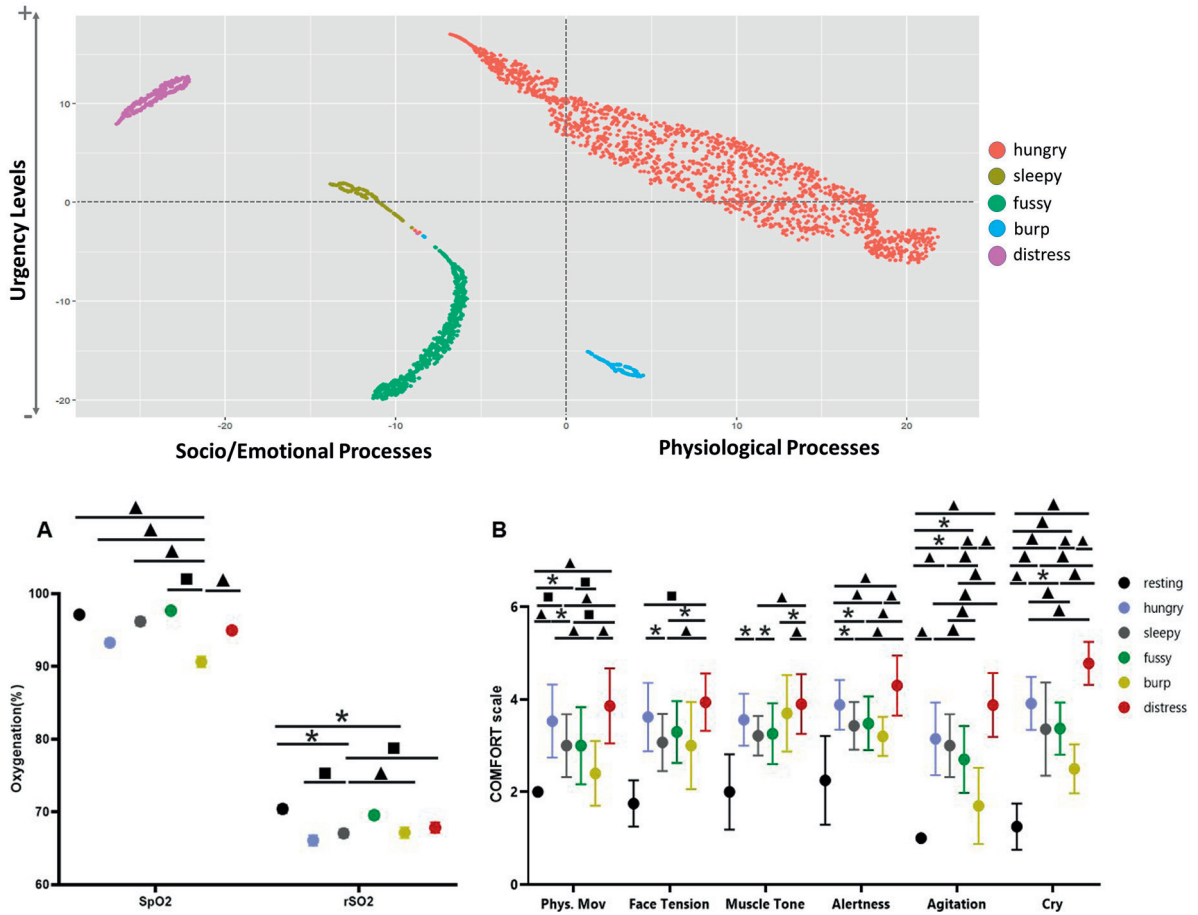
**RESULTS:** Significant differences were found across cry



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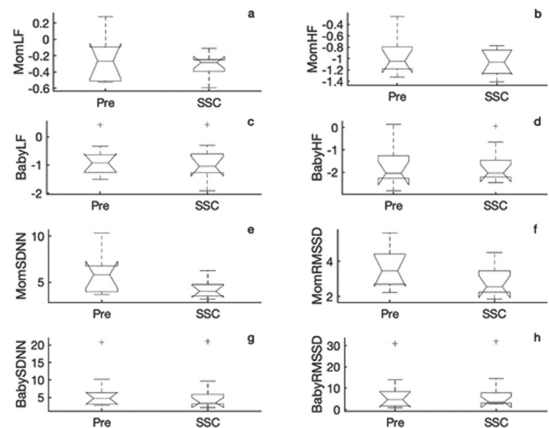
**Skin-to-skin in congenital heart disease: impact on mother and infant autonomic function and maternal anxiety**

Alexa Asch<sup>1</sup>, Rathinaswamy B Govindan<sup>1,4</sup>, Ellen Bartolini<sup>1,2</sup>, Venkata Chirumammilla<sup>1</sup>, Cara Pleau<sup>5</sup>, Mandana O'Donnell<sup>6</sup>, Sarah Schlatterer<sup>1,3,4</sup>

<sup>1</sup>Prenatal Pediatrics Institute, Children's National Hospital, <sup>2</sup> Developing Brain Institute, Children's National Hospital, <sup>3</sup> Department of Neurology, George Washington University School of Medicine and Health Sciences, <sup>4</sup>Department of Pediatrics, George Washington University School of Medicine and Health Sciences, <sup>5</sup>Division of Cardiology, Children's National Hospital, <sup>6</sup>Children's National Hospital

**BACKGROUND AND OBJECTIVE:** Skin-to-skin contact (SSC)—a holding technique in which the diapered infant is held against the mother's bare chest—has been extensively studied in the preterm population and found to have significant benefits for both mothers and preterm

infants. SSC has been understudied in the congenital heart disease (CHD) population, which consists primarily of term neonates, and is often not routinely practiced in pediatric cardiac intensive care units (CICU). In this



**Figure 1:** Heart rate variability metrics for infants with CHD and their mothers before and during skin-to-skin contact (SSC). a. Maternal Low Frequency (LF) heart rate variability (HRV). b. Maternal High Frequency (HF) HRV c. Infant LF HRV. d. Infant HF HRV. e. Maternal standard deviation of all normal RR (NN) intervals (SDNN) HRV. f. Maternal root mean square of standard deviation (RMSSD) HRV. g. Infant SDNN HRV h. Infant RMSSD HRV

single-center prospective pilot study, we aim to evaluate the impact of low-dose post-operative SSC on maternal stress and autonomic function, measured through heart rate variability (HRV), in infants with CHD in the Children’s National Hospital CICU and their mothers. We also evaluated feasibility of SSC post-operatively.

**METHODOLOGY:** Six mother-infant dyads participated in three sessions of SSC within a 10-day post-operative period. Mother and infant heart rates were simultaneously recorded using the Biopac MP-160® device for 15 minutes before SSC and for an hour minimum during SSC. We calculated HRV metrics, including high frequency (HF), low frequency (LF), standard deviation of all normal RR (NN) intervals (SDNN), and root mean square of standard deviation (RMSSD) of RR intervals, using 5-minute epochs of EKG for each mother and infant. The mothers completed the State Trait Anxiety Inventory-6 (STAI-6) at the beginning of the study period and after each SSC session.

**RESULTS:** Table 1 shows that STAI-6 scores significantly decreased after SSC. Figure 1 illustrates our HRV data. SDNN significantly decreased during SSC compared to pre-SSC in our cohort (p=0.02 in mothers, p=0.04 in infants). RMSSD significantly decreased in mothers during SSC (p=0.03) but not in infants. A reduction in SDNN has been associated with decreased stress in healthy individuals in other studies.<sup>1</sup> There was no significant

	STAI-6 Score		p-value
	Pre-SSC	After 3 <sup>rd</sup> SSC Session	
Subject 1	2.395	-3.128	<b>&lt;0.001</b>
Subject 2	0.017	-1.723	<b>0.181</b>
Subject 3	-0.005	-2.772	<b>0.010</b>
Subject 4	0.338	-2.415	<b>0.025</b>
Subject 6	-1.01	-3.128	<b>0.011</b>
Mean	0.347	-2.633	<b>0.011</b>

**Table 1:** STAI-6 scores at the beginning of the 10-day study period for each study subject vs. STAI-6 score after 3<sup>rd</sup> session of SSC. Higher scores indicate more anxiety. Paired two sample t-test was used to calculate p-values. **Bold** indicates significance. Subject 5 STAI-6 scores were excluded due to an incomplete questionnaire.

change in HF or LF metrics of HRV during SSC. Neither mothers nor CICU nurses reported any significant challenges to feasibility of SSC during our study.

**CONCLUSION:** These findings demonstrate that SDNN and RMSSD decreased after SSC, and there were significant improvements in anxiety (STAI-6 scores) after SSC. Our data suggest that SSC does impact maternal and fetal autonomic function and reduce maternal anxiety. This study is limited by a small sample size, and a larger n will be required to validate these preliminary data and further characterize the impact of SSC on HRV and maternal anxiety in the CHD population. Our data suggest that further study of SSC in CHD is warranted, and that SSC is likely beneficial to both mothers and infants.

