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# Mapping hemodynamic changes during hypoglycemia in the very preterm neonatal brain: Preliminary results

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## ABSTRACT

Critical glyceic events, such as hypo- or hyperglycemia, are extremely common during the first week post-partum in very preterm neonates. Both hypo- and hyperglycemic changes have been associated with poor neurological outcome. Continuous glucose monitoring (CGM) is a promising tool to reduce glyceic variability in the preterm population and whole-head Diffuse Optical Tomography (DOT) is a promising tool for continuous monitoring of brain hemodynamics in newborns. In this study, we performed a combined CGM-DOT acquisition in a very preterm newborn (28 weeks gestational age). The newborn was monitored for 7 days continuously. Twelve events were detected during this period: 8 mild hypoglycemic events, one severe hypoglycemic event, two mild hyperglycemic events and one event with a mild hypo- followed by a mild-hyperglycemia. DOT data were available for all the events but two. DOT data were reconstructed with a neonatal head model for the severe hypoglycemic event before the start of the hypoglycemic event and during the maximum peak of hypoglycemia. These preliminary results showed a regional specificity of the hemodynamic changes during hypoglycemia, with a predominant recruitment of the motor and parietal areas. This study highlights the importance of using whole-head DOT in this research field and the feasibility to perform combined CGM-DOT monitoring in very preterm neonates. Future clinical trials are required to investigate this clinical problem more thoroughly and shed light on the impact of tight glyceic control on the newborn brain.

**Keywords:** DOT, preterm neonates, continuous glucose monitoring, hypoglycemia

## 1. INTRODUCTION

Preterm neonates are at high risk of hypo- and/or hyperglycemic episodes during the first week post-partum. This is due to the impairment of glucose homeostasis characterizing this early age of life<sup>1</sup>. Both hypo- and hyperglycemic episodes have been associated with increased mortality and exposure to cognitive and neurological deficits, caused by damage mostly located in the occipital and parietal cortex, but with contradictory results<sup>2,3</sup>. Previous studies demonstrated a relationship between blood glucose levels and cerebral blood flow in preterm infants, and hypothesized the presence of a cerebral glucose sensing mechanism<sup>4</sup>. A recent study demonstrated an association between blood glucose concentration and cerebral oxygenation measured with near-infrared spectroscopy immediately after birth in preterm infants<sup>5</sup>. Continuous glucose monitoring (CGM) is a promising tool to reduce glyceic variability in the preterm population<sup>6</sup>, providing real-time data to continuously adjust glucose intakes and deliver prompt correction of hypoglycemia. The impact of tight glyceic control on brain development and long-term outcome is however still unknown. Diffuse Optical Tomography (DOT) is the most suitable neuroimaging technique to shed light on this question, since it can provide continuous regionally specific information on oxy-(HbO), deoxy-hemoglobin (HbR) and blood volume (HbT) changes that can be related to glyceic changes. Longitudinal and complex clinical trials are required to fully unveil the impact of CGM on brain development. Here, we describe preliminary findings from prolonged CGM and DOT monitoring of a very preterm neonate studied for 7 days to set the ground for longitudinal trials aimed to assess the effect of CGM on short term cerebral oxygenation and its impact on long-term neurodevelopmental outcome.

## 2. MATERIAL AND METHODS

### 2.1 Patient characteristic and acquisition

A neonate admitted to the NICU at the University Hospital of Padova, born at 28 weeks' gestation through cesarean section for placental abruption (birthweight: 1145g) was enrolled in the study, after parental consent. CGM-DOT acquisition was started within 48 hours from birth and was ended after 7 days. DOT acquisition was performed with a multichannel continuous wave system (NIRScout, NIRx Medical Technologies LLC, Glen Head, New York), equipped with 32 LED sources (16 emitting light at 760 nm and 16 at 850 nm) and 24 detectors. Only 8 detectors were used in this investigation, given the small size of the head, in order to cover the entire head with 105 channels (Fig. 1). The sampling frequency was set to 6.25 Hz. Further information on DOT data acquisition can be found in <sup>7</sup>. CGM data were acquired with a G4 Platinum CGM system (Dexcom, Inc, San Diego, CA) inserted in the thigh after disinfection of the site.

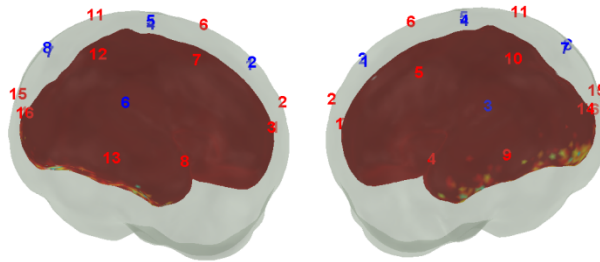


Figure 1. Probe layout displayed on the head surface of the preterm neonatal head model. Sources are displayed in red and detectors in blue. The sensitivity distribution of the array is displayed on the gray matter surface mesh. The array is sensitive to the entire cortical surface of the preterm brain.

### 2.2 Data analysis

DOT data relative to each glyceemic event (defined as hypo- or hyperglycemia) were extracted from the total acquired data and were pre-processed using some of the Homer2 functions<sup>9</sup>. Channels with intensity values beyond the device recommendations and with low SNR were pruned and excluded from further analysis. Intensity data were converted into attenuation changes. Motion artifacts were corrected by applying target PCA<sup>9</sup> followed by wavelet motion correction (iqr = 0.8)<sup>10</sup>. Data were then smoothed with a Savitzky-Golay filter (order 3, frame size 325) and baseline corrected by removing the mean activity of a small interval selected during euglycemia. DOT data were reconstructed using AtlasViewer<sup>11</sup> and a preterm neonatal head model<sup>12</sup>. The average HbT activity (HbO+HbR) before the start of the event and the average HbT activity during the time periods where glyceemic values were beyond thresholds were reconstructed using default settings (Tikhonov regularization of 0.01).

## 3. RESULTS

Twelve glyceemic events were detected during the acquisition period: 8 mild (<72 mg/dl) and one severe hypoglycemic event (<47 mg/dl), two mild hyperglycemic events (>144 mg/dl) and one event with a mild hypo- followed by a mild-hyperglycemia. DOT data were available for all but two of these events. We focused only on the severe hypoglycemic event in the following. Fig. 2 displays the reconstructed images before the decrease in hypoglycemia (top left) and during the hypoglycemic peak (bottom left) and on the right panel the glyceemic changes for this event. The reconstructed images revealed a regional specific pattern of hemodynamic changes during hypoglycemia, with predominant positive increases in HbT in motor, temporal and parietal areas, more pronounced in the right than left hemisphere. This increase in HbT is compatible with the hypothesis that, during hypoglycemia, the preterm brain recruits unperfused capillaries to maintain the transportation of glucose to neurons<sup>4</sup>. The regional variations in hemodynamic changes are in line with the hypothesis that brain areas react differently to hypoglycemia, as regionally specific neural damages have been found as a consequence of neonatal hypo- and hyperglycemia.

## 4. CONCLUSIONS

Our preliminary results indicate that continuous CGM-DOT acquisitions in very preterm newborns are feasible and that there seems to be regionally specific hemodynamic changes during hypoglycemia. Further studies are required to confirm and support these findings and to understand the impact of CGM use on brain development.

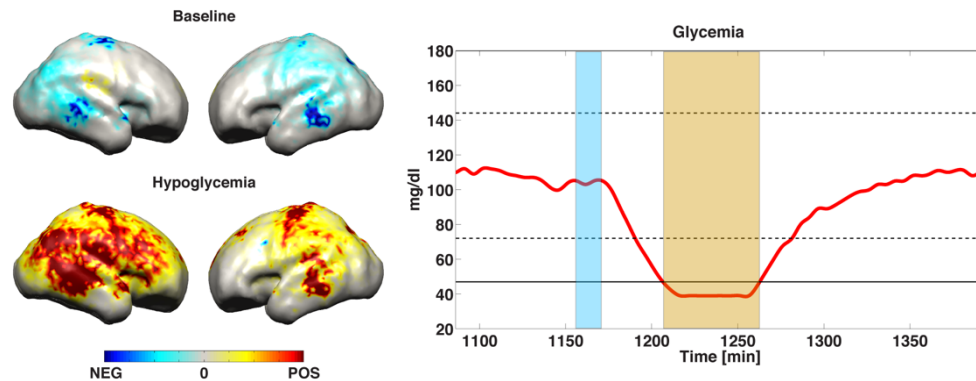


Figure 2. Reconstructed DOT images before the start of the hypoglycemic event (top left) and during the hypoglycemic event (bottom left). The right panel displays the glycemic signal where a prolonged severe hypoglycemia is appreciable. The light blue shaded area corresponds to the time periods used for the baseline reconstruction while the light red shaded area corresponds to the time period used for the reconstruction during the severe hypoglycemic event.

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