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Complete List of Authors:	De Carli, Agnese; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU Andresen, Björn; Rigshospitalet, Department of Neonatology Giovannella, Martina; The Barcelona Institute of Science and Technology, ICFO, Institut de Ciències Fotòniques Durduran, Turgut; The Barcelona Institute of Science and Technology, ICFO, Institut de Ciències Fotòniques ; Institució Catalana de Recerca i Estudis Avançats (ICREA) Contini, Davide; Politecnico di Milano, Dipartimento di Fisica Spinelli, Lorenzo; Istituto di Fotonica e Nanotecnologie, Consiglio Nazionale delle Ricerche Weigel, Udo Michael; HemoPhotonics S.L. Passera, Sofia; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU Pesenti, Nicola; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU Mosca, Fabio; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU; University of Milan, Department of Clinical Sciences and Community Health Torricelli, Alessandro; Politecnico di Milano, Dipartimento di Fisica; Istituto di Fotonica e Nanotecnologie, Consiglio Nazionale delle Ricerche Fumagalli, Monica; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU; University of Milan, Department of Clinical Sciences and Community Health Greisen, Gorm; Rigshospitalet, Department of Neonatology
Keywords:	time-resolved spectroscopy, diffuse correlation spectroscopy, tissue oxygen saturation, cerebral blood flow, term infants

TITLE:

Cerebral oxygenation and blood flow in term infants during postnatal transition: BabyLux project.

Agnese De Carli[1], Bjørn Andresen[3], Martina Giovannella[4], Turgut Durduran[4,5], Davide Contini[6], Lorenzo Spinelli[7], Udo Michael Weigel[8], Sofia Passera[1], Nicola Pesenti[1], Fabio Mosca[1,2], Alessandro Torricelli[6,7] & Monica Fumagalli[1,2*], Gorm Greisen[3].

1. *NICU Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.*
2. *University of Milan, Department of Clinical Sciences and Community Health, Milan, Italy.*
3. *Deptartment of Neonatology, Rigshospitalet, Copenhagen, Denmark.*
4. *ICFO-Institut de Ciències Fotòniques, The Barcelona Institute of Science and Technology, Barcelona, Spain.*
5. *Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain.*
6. *Politecnico di Milano-Dipartimento di Fisica, Milan, Italy.*
7. *Istituto di Fotonica e Nanotecnologie, Consiglio Nazionale delle Ricerche, Milan, Italy,*
8. *HemoPhotonics S.L., Castelldefels (Barcelona), Spain.*

**Corresponding author: Monica Fumagalli, MD; NICU Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via della Commenda 12, 20122 Milan Italy – monica.fumagalli@unimi.it*

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ABSTRACT

Objectives:

A new device that combines, for the first time, two photonic technologies (time-resolved near-infrared spectroscopy and diffuse-correlation spectroscopy), was provided and tested within the BabyLux project. Aim was to validate the expected changes in cerebral oxygenation and blood flow.

Methods:

A pulse oximeter and the BabyLux device were held in place (right hand/wrist and fronto-parietal region, respectively) for 10 minutes after birth in healthy term infants delivered by elective cesarean section. Pulse oximeter saturation(SpO_2), cerebral tissue oxygen saturation(StO_2) and blood flow index(BFI) were measured over time. Tissue oxygen extraction(TOE) and cerebral metabolic rate of oxygen index($CMRO_2I$) were calculated.

Results:

Thirty infants were enrolled in two centers. After validity check of data, 23% of infants were excluded from TOE and $CMRO_2I$ calculation due to missing data. As expected, SpO_2 (estimate 3.05 %/min; CI: 2.78, 3.31 %/min) and StO_2 (estimate 3.95 %/min; CI: 3.63, 4.27 %/min) increased in the first 10 min after birth, whereas BFI (estimate $-2.84 \cdot 10^{-9}$ $cm^2/s/min$; CI: $-2.50 \cdot 10^{-9}$, $-3.24 \cdot 10^{-9}$ $cm^2/s/min$) and TOE (estimate -0.78%/min; CI: -1.12, -0.45 %/min) decreased. Surprisingly, $CMRO_2I$ decreased (estimate $-7.94 \cdot 10^{-8}$/min; CI: $-6.26 \cdot 10^{-8}$, $-9.62 \cdot 10^{-8}$ /min).

Conclusions:

Brain oxygenation and BFI during transition were successfully and simultaneously obtained by the BabyLux device; no adverse effects were recorded and the BabyLux device didn't limit the standard care.

The preliminary results from clinical application of the BabyLux device are encouraging in terms of safety and feasibility; they are consistent with previous reports on brain oxygenation during transition although the interpretation of the decreasing $CMRO_2I$ remains open.

KEY WORDS:

Near-infrared spectroscopy, diffuse correlation spectroscopy, tissue oxygen saturation, cerebral blood flow, term infant.

ABBREVIATIONS:

Absorption coefficient (μ_a), arterial oxygen saturation (S_aO_2), venous oxygen saturation (S_vO_2), blood flow index (BFI), cerebral metabolic rate of oxygen index ($CMRO_2I$), concentration of oxy-haemoglobin (O_2Hb), concentration of deoxy-haemoglobin (HHb), diffuse correlation spectroscopy (DCS), distribution of time-of-flight (DTOF), near-infrared spectroscopy (NIRS), tissue oxygen extraction (TOE), pulse oxygen saturation (SpO_2), reduced scattering coefficient (μ_s'), time-resolved spectroscopy (TRS), tissue oxygen saturation (StO_2).

INTRODUCTION:

During the last decades, progress in neonatal medicine has led to an increased survival rate of preterm infants. Despite this, the risk of brain damage and later neurodevelopmental deficits is still high and the understanding of the underlying pathophysiological mechanisms is nevertheless incomplete.[1,2] Different perinatal factors (hemodynamics, oxygen metabolism, infection-inflammation) are involved in the pathogenesis of brain damage. A more accurate identification of the leading mechanisms on a single-patient basis is desirable to provide individualized care and targeted intervention aimed to safeguard the developing brain.

The most vulnerable period is represented by the first hours and days after birth due to the risk of haemodynamic disturbances occurring during the transitional circulation combined with the impact of respiratory distress syndrome. Furthermore, critically ill premature infants have impaired cerebral autoregulation, which may expose them to both hyperoxic and hypoxic insults, both involved in brain injury.[3,4]

To that end, a continuous and non-invasive monitoring of cerebral perfusion and oxygenation has been searched for.[5]

Commercially available near-infrared spectroscopy (NIRS) devices are currently used in clinical care and in clinical trials as cerebral oximeters.[6,7] Interpretation of cerebral oxygenation as a surrogate measure of cerebral blood flow, however, depends on the assumption of stable oxygen consumption. This is relevant for instance when using NIRS to estimate cerebral autoregulation capacity or when used clinically as an indication for interventions to increase blood flow. Alternatively cerebral oxygenation may be affected by change in oxygen demand. The BabyLux project aimed to provide a non-invasive and cot-side device, that combines time-resolved NIRS (TRS), for calculation of regional oxygenation, with newly developed diffuse correlation spectroscopy (DCS), for calculation of regional perfusion, in an attempt to resolve this ambiguity.

TRS measures the attenuation, delay, and the temporal broadening of relatively short light pulses (pulse duration ~100 ps) that has passed through a diffusive medium. TRS thus has the ability to

resolve path-lengths of photons and to separate the absorption and scattering coefficients allowing for measurements of tissue oxygen saturation (StO_2).[8]

DCS studies the statistics of the diffuse coherent light into the tissue. The fluctuations of the intensity measured at the surface of the tissue are affected by the movement of the moving scatterers, mainly the red blood cells. Studying the statistics of these fluctuations allows for the quantification of the so-called blood flow index BFI, a quantity proportional to the microvascular blood flow.[9,10]

This innovative combined technology allows the calculation of cerebral metabolic rate of oxygen and, to our knowledge, only few studies have been published on this topic using combined multi-distance frequency domain NIRS and DCS.[11,12]

As direct validation of cerebral oxygenation and blood flow against a 'gold standard' is not feasible in newborn infants, we performed measurements in a clinical situation in which changes in cerebral oxygenation and brain perfusion occur and have been previously described. The aim was to obtain "expected results" according to the available evidence. We studied the postnatal transition of healthy term infants delivered by elective, uncomplicated caesarian section; in this situation, cerebral tissue oxygenation is expected to be lower than arterial saturation at all time-points, progressively rising and reaching a plateau within the first 10 minutes after birth. Moreover, small-to-moderate changes in cerebral blood flow, small changes in oxygen extraction, and no change in oxygen consumption are expected given the observations of lower cord cortisol and catecholamines levels after elective cesarean delivery compared to vaginal delivery. [13-15]

The BabyLux device provides a simultaneous measurement of regional oxygenation and perfusion and allows to disentangle the interplay between oxygen demand and perfusion, resolving the ambiguity in the interpretation of changes in regional saturation.

Aim:

The aim of this study was to validate the BabyLux device by simultaneously measuring the expected changes in cerebral oxygenation and blood flow and by calculating the cerebral oxygen metabolism.

METHODS:

Study protocol:

The study was conducted according to ISO 14155:2011 with external monitoring. Local research ethics committees approved the same study protocol in both centers (Rigshospitalet, Copenhagen, Denmark and Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy). The protocol is registered at ClinicalTrials.gov, identifier NCT02815618.

Inclusion criteria were: gestational age more than 37 weeks and planned delivery by uncomplicated elective cesarean section. Exclusion criteria were: congenital malformation apparent at birth with need for any additional assistance immediately following delivery and need for resuscitation or supplementary oxygen during the first 10 minutes after birth.

Parental consent was obtained before elective caesarean section.

The BabyLux device and the pulse oximeter (Radical 7; Masimo Corporation, Irvine, CA, U.S.A.) were both synchronized with the local clock time of the delivery room.

After birth the infant was immediately wrapped in warm towels and the head and right hand or wrist were cleaned to remove vernix and amniotic fluid (which could affect probe contact and signal quality). As soon as possible, the BabyLux probe was positioned in the fronto-parietal region of the newborn's head to measure StO_2 and BFI, and the pulse oximeter probe was placed on the right hand or wrist to measure pulse oxygen saturation (SpO_2) and pulse rate. Both probes were held in place by self-adhesive elastic bandage. For both instruments measurements lasted for at least 10 min, while standard neonatal care was given. According to international guidelines [16] we considered standard neonatal care: to warm and maintain normal temperature, to position the head in "sniffing" position, to clear secretion if needed, and to dry. If resuscitation was performed (from tactile stimulation onwards), according to our methods, the infant was excluded from the study.

In both centers timing of cord clamping was between 30 and 60 sec.

The following parameters were finally recorded over time by 10 s bins: SpO_2, pulse rate, StO_2, BFI.

Tissue oxygen extraction (TOE) was calculated as $TOE=SpO_2-StO_2$, and the cerebral metabolic rate of oxygen index ($CMRO_2I$) was calculated as $CMRO_2I=TOE \cdot BFI$

Neonatal characteristics (gestational age, birth weight, sex, Apgar score) were collected.

Instrumentation:

Two identical prototypes were built within the project and they were approved for research use according to the clinical investigation plan by the national Medical Device Agencies in both countries. The BabyLux device integrates TRS and DCS modules similar to those previously described by Torricelli *et al.*[8] and Durduran *et al.*[9], respectively. In brief, the TRS module employs pulsed lasers operating at three different wavelengths centered at about 685 nm, 760 nm, and 820 nm, respectively. The pulse duration is <100 ps, with a repetition rate of 20 MHz, and an average output power <1 mW for all wavelengths. A photomultiplier and a time-correlated single photon counting board are used to acquire the distribution of photon time of flight (DTOF) for each wavelength. The DCS module uses a continuous wave long coherence laser at 785 nm with an output power < 20 mW. Two single avalanche photodiodes and a custom-made correlator unit are used to acquire the autocorrelation of the measured light intensity. TRS and DCS share a compact and light weight fiber-optic probe, for injection and collection of the light signals into the tissue. TRS and DCS source-detector separation is 15 mm.

We have carefully evaluated the safety risk associated with the use of the pulsed laser (TRS) and continuous wave laser (DCS) according to the standard IEC 60825-1:2007. Regarding the effect on skin, for both lasers the emitting power is lower than the maximum permissible exposure (MPE) by an order of magnitude. However, as an additional precaution for heat dissipation, the DCS laser is switched off for 1 second every 9 seconds. For the effect on eye, the pulsed lasers are safe for the operator because time exposure to the laser light is shorter (0.25 s) due to the blink reflex. Conversely, for infants we can not rely on the blink reflex and/or ocular movement, therefore we cannot consider the pulsed lasers eye safe for the accidental exposure to laser light. The same happens for the DCS laser. In order to ensure safe operation of the device, proper measure of protection (i.e. a mask covering the eyes like the mask used for phototherapy) was used together with a capacitive sensor

designed to detect skin contact which is integrated in the probe head. These procedures were approved by the ethical committees and by the national medical device agencies in Italy and Denmark.

A detailed description of the BabyLux system is available in Giovannella *et al.*[17]

Data processing and quality assessment:

Processing of TRS data consists of estimating the optical properties (absorption coefficient, μ_a, and reduced scattering coefficient, μ_s') at all wavelengths, then calculating the hemodynamic parameters (concentration of oxy-haemoglobin, O_2Hb, and deoxy-haemoglobin, HHb), and finally evaluating the quality of results.

For the estimation of the optical properties, the DTOF is fitted with a model for photon diffusion in a semi-infinite homogeneous medium, after convolution with the instrument response function. The fitting procedure is described in Cubeddu *et al.*[18]

Once the estimates of μ_a at the three wavelengths are obtained, O_2Hb and HHb are calculated by means of Beer's law. Specific absorption values for hemoglobin are taken from the Prahl dataset.[19] Lipid content in neonates is limited and therefore disregarded, while water content is fixed at 90%.[20]

From O_2Hb and HHb values we obtained the total haemoglobin content $tHb=O_2Hb+HHb$, and $StO_2=100\ O_2Hb/tHb$.

The main factor affecting the quality of TRS data is the number of photon in the DTOF(N). A minimum value of $N>10^3$ was used as threshold. The quality of fitting was evaluated through the reduced chi-square χ^2 parameter. Large values ($\chi^2>10$) and very low values ($\chi^2<0.1$) were discarded since they can be indicative of poor fitting model or signal-to-noise ratio, respectively. Further criteria were set on the values for μ_s' and on the values for StO_2. Given the assumption of photon diffusion (as a rule of thumb, $\mu_s' >> \mu_a$), if at any wavelength the fitting provides too low values for μ_s' (e.g. $\mu_s' < 1\ cm^{-1}$), then there is the possibility that the use of the photon diffusion model is inappropriate and values were therefore excluded.

The normalized intensity field autocorrelation curve acquired in DCS measurements is fitted to the solution of the diffusion equation for the autocorrelation function for the semi-infinite homogeneous geometry. As the source detector separation is known and the optical properties have been estimated by TRS at 760 nm, they can be inserted in the model, enabling determination of BFI. DCS curves acquired with an intensity rate below 10 kHz were excluded, due to poor signal-to-noise ratio. Results with residuals higher than 2 SD from the mean were rejected.

For the calculation of BFI, 10 s moving average of μ_a at 760 nm was used to reduce noise propagation from TRS to DCS analysis and a fixed sample average estimate of μ_s' was used (μ_s'=7 cm^{-1}); BFI and μs' are indeed coupled in the equation describing the intensity field autocorrelation curve [21] and an eventual error in the latter is propagated in an error in the BFI [22]. Therefore using an individual estimation of μs' can increase the inter-individual variability for the BFI.

Statistics:

Descriptive analyses were obtained for the infants' neonatal characteristics. Continuous variables are described as mean (SD) or median (range), while categorical variables are expressed as number and percentage.

For SpO_2, StO_2, BFI, TOE and $CMRO_2I$ box-plots were used to show changes over time.

Over the first 10 min after birth the relationship between variables and time was studied using linear mixed-effect models with subject as random effect. Models results are expressed as estimate, 95% CI along with p-values. Values of $p < 0.05$ were considered statistically significant. Logarithmic base 10 transformation of BFI and $CMRO_2I$ data was done to normalize the right-skewed distribution of residuals.

From 10 min after birth onward, median value, 25^{th} and 75^{th} percentiles were calculated for each variable.

Statistical analyses were performed using R, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS:

Thirty infants were enrolled from October 2016 to April 2017: 14 infants in Copenhagen (CPH) and 16 in Milan (MI). Four infants were excluded: one requiring resuscitation at birth, two due to parental consent withdrawn, and one because of technical reasons (BabyLux software crash).

Mean (SD) gestational age was 38.4 (0.7) weeks [38.5 (0.8) in CPH and 38.3 (0.6) in MI]; mean (SD) birthweight was 3258g (393g) [3299g (438g) in CPH and 3225g (366g) in MI]; male (%) were 13 (50) [5 (45) in CPH and 8 (53) in MI]; median (range) Apgar 1' was 10 (8-10) [10 (9-10) in CPH and 9 (8-9) in MI]; median (range) Apgar 5' was 10 (9-10) [10 (10) in CPH and 9 (8-9) in MI].

After validity check of data, the final number of accepted measurements were 23 (88.5%) for SpO_2/pulse rate (10 in CPH and 13 in MI); 23 (88.5%) for TRS (8 in CPH and 15 in MI), 25 (96.2%) for DCS (11 in CPH and 14 in MI), 20 (76.9%) for calculated TOE and $CMRO_2I$.

Figures 1 to 5 show changes of the measured variables from the 3rd min after birth over time.

Data from birth to the 3rd min are not displayed as very few data-points were collected in that time-frame: the average starting time for BabyLux measurement was 3.5 min (SD 1.5 min) after birth (see details in supplementary material).

We analyzed changes in all parameters until the 10th min after birth: SpO_2 significantly increased over time, as well as StO_2 while BFI and TOE significantly decreased. Surprisingly, a significant decrease in $CMRO_2I$ was observed.

SpO_2 (estimate 3.05 %/min; CI: 2.78, 3.31 %/min; $p<0.001$) and StO_2 (estimate 3.95 %/min; CI: 3.63, 4.27 %/min; $p<0.001$) increased in the first 10 min after birth, whereas BFI (estimate $-2.84\cdot10^{-9}$ cm^2/s/min; CI: $-2.50\cdot10^{-9}$, $-3.24\cdot10^{-9}$ cm^2/s/min; $p<0.001$) and TOE (estimate -0.78%/min; CI: -1.12, -0.45 %/min; $p<0.001$) decreased. Also $CMRO_2I$ decreased (estimate $-7.94\cdot10^{-8}$/min; CI: $-6.26\cdot10^{-8}$, $-9.62\cdot10^{-8}$ /min; $p<0.001$).

From the 10th min onward, median SpO_2 (25th -75th percentiles) was 94.8% (92.9%-97.1%), StO_2 65.6% (59.9%-73.3%), BFI $2.50\cdot10^{-8}$ cm^2/sec ($1.88\cdot10^{-8}$-$3.46\cdot10^{-8}$), TOE 29.0% (22.7%-31.4%) and $CMRO_2I$ $6.09\cdot10^{-7}$ ($4.78\cdot10^{-7}$-$8.67\cdot10^{-7}$).

No adverse effects were recorded during the study period.

DISCUSSION:

The use of the BabyLux device during the transition period after birth was feasible; it was safe for the patients and did not limit the standard care.

The recording start time for the BabyLux device was reasonable: we obtained valid measurements in 58% of infants by 3 min after birth and in 88% of infants by 5 min. These results are similar to those reported by previous studies during transition: Urlesberger *et al*. measured 50% of infants by 3 min [23] using INVOS5100 and Baik *et al*. 79% of newborns by 3 min with NIRO.[24] Shorter starting time are reported by Ziehenberger E. *et al*, with NIRO or INVOS5100C (mean, 95 sec. and 93 sec, respectively) [25], Fauchere *et al*. with NIRO (median, 2 min; range, 1-4 min),[26] Almaazmi *et al*. with FORESIGHT (median time to signal, 63 s; interquartile range, 38-88 s),[27] and Isobe with IMUC7000 (measurement begun at 1-2.5 min).[28]

After validity check of data, 23% of infants were excluded from TOE and $CMRO_2$ calculation due to missing data (TRS in 12% and DCS in 4% of case) suggesting that technical issues still need to be improved. However, other instruments, as pulse-oximeter, routinely used in clinical practice, showed similar performances.

The recorded SpO_2 data are in line with the reference values by Dawson *et al*. for infants born by elective cesarean section.[31]

The measured changes in StO_2 and BFI are consistent with the previous reports.[23-30,32]

Cerebral StO_2 by fronto-parietal TRS sensor followed the rise in SpO_2, similarly to previous observations performed on the same population using other NIRS techniques.[23-30] Indeed, StO_2 values derived from TRS seem grossly comparable with values obtained by NIRO300,[24-26] FORE-SIGHT cerebral oximeter,[27] IMUC7000 [28] (although some of these studies censored data points where StO2 exceeded SpO2, which we did not do) but lower than values measured by INVOS5100 with neonatal sensors. [23,25,29,30] This observation is consistent with previous studies reporting

significantly higher regional StO_2 values when using pediatric and neonatal sensors compared to the INVOS5100 adult sensors.[33,34]

The derived value of TOE decreased over time in the first 10 min after birth, although a high inter-individual variability was observed. This finding is in line with previous studies that investigated changes in fractional tissue oxygen extraction (FTOE) showing a reduction in the first minutes of life, although TOE and FTOE cannot be directly compared during the sudden increase in oxygen delivery after birth.[23,35]

Cerebral blood flow (expressed as BFI) decreased by 30% over the study time. This result is consistent with a 30% decrease in cerebral blood flow velocity, measured by Doppler, previously reported in healthy term newborns.[32] This data, however, was obtained after vaginal birth and the decrease was observed from 7 to 13 min after birth. Nevertheless, a cerebrovascular response to the increase in blood oxygen content at birth is to be expected.

This is the first study in which DCS was used to measure BFI during transition after birth. BFI is an absolute quantification of cerebral blood flow with an unusual unit (cm^2/s) that differs from the conventionally reported ml/100g/min for blood flow and cm/s for blood flow velocity. However, DCS has been broadly qualitatively validated and a few in-vivo calibrations have been reported.[10] Using a calibration obtained in young piglets by comparing the BabyLux DCS with CBF measured with positron emission tomography,[38] we calculated that the median BFI value from the 10^{th} minutes after birth onward corresponded to 23.3 ml/100g/min. These results are in line with those expected in healthy term infants, taking into consideration the reported coefficient of variability and the small number of observations.[39,40]

Furthermore, BFI values measured by the BabyLux device after the 10^{th} min after birth are comparable with previously reported BFI values obtained using a combination of frequency domain NIRS and DCS systems in healthy newborns admitted to the nursery.[36,37] The BabyLux technology offers a unique possibility to obtain direct measurements of cerebral blood flow even in such a peculiar situation when no other available technology (PET, SPECT, MRI) could be used.

We expected constant $CMRO_2I$ values because infants born by uncomplicated cesarean section have low levels of catecholamine compared to those vaginally delivered and therefore are not expected to be significantly stressed or asphyxiated and therefore not to have developed an oxygen 'debt' during delivery.[14,15]

Therefore, it was surprising that we found a nearly 50% decrease in $CMRO_2I$, that was highly statistically significant, from the first minutes after birth until stabilization at about 10 minutes.

$CMRO_2I$ is a measure of oxygen metabolism and thus reflects the infants' cerebral metabolic state. Arousal occurring at birth should be associated with higher $CMRO_2I$. Our results therefore may suggest that even an uncomplicated cesarean section involve some physical stress and strain and, due to the delay in the recording start time in our study, we might have measured the descending curve associated with the gradual reduction in the alert state with cerebral activation a few minutes after birth. Alternatively, we may speculate that this unexpected result is due to an oxygenation-level dependent error of measurement of at least one of involved variables SpO_2, StO_2 or BFI, and/or an oxygenation-level dependent change in the arterio-venous ratio, i.e. the factor that relates StO_2 to arterial oxygen saturation SaO_2 and to venous oxygen saturation SvO_2 [41] All of this is really possible. Hence the physiologic interpretation of this finding is open.

In conclusion, changes in brain oxygenation and cerebral blood flow during transition were successfully and simultaneously measured by the BabyLux device in most infants. The dataset is sufficiently large to be robust. The StO_2, TOE and BFI values were plausible, although the decrease in $CMRO_2I$ was unexpected and most likely indicate some oxygenation-level dependent error in one or more of the measured variables.

These preliminary results from the clinical application of the BabyLux device are encouraging in terms of reliability, safety, and feasibility.

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COMPETING INTERESTS:

Udo Weigel is the CEO, has equity ownership in HemoPhotonics S.L. and is an employee in the company. His role in the project has been defined by the project objectives, tasks and work-packages and was reviewed by the European Commission.

What is already know on this topic:

- A continuous and non-invasive monitoring of cerebral perfusion and oxygenation has been searched for better understanding the pathogenesis of brain damage in neonates.
- Time-resolved-near-infrared spectroscopy has the ability to resolve path-lengths of photons and to separate the absorption and scattering coefficients allowing for measurements of tissue oxygen saturation.
- Diffuse-correlation spectroscopy relies on the interaction between long coherence laser light and moving scatterers, allowing for quantification of microvascular blood flow and calculation of a blood flow index.

What this study adds:

- The BabyLux device combines, for the first time, two photonic technologies (TRS/DCS), providing a non-invasive, cot-side and continuous monitoring of tissue oxygenation and blood flow.
- Cerebral tissue oxygenation and blood flow values obtained by BabyLux in term infants during transition after birth, were plausible.
- The cerebral metabolic rate of oxygen that was calculated from this data, decreased significantly: this was unexpected and the interpretation remains open.

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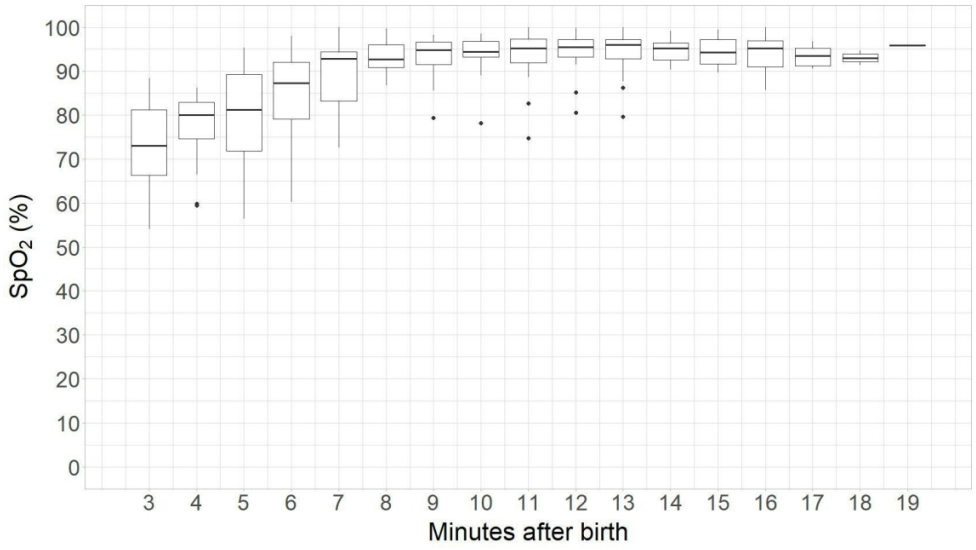

Box-plot of SpO_2 changes over time.

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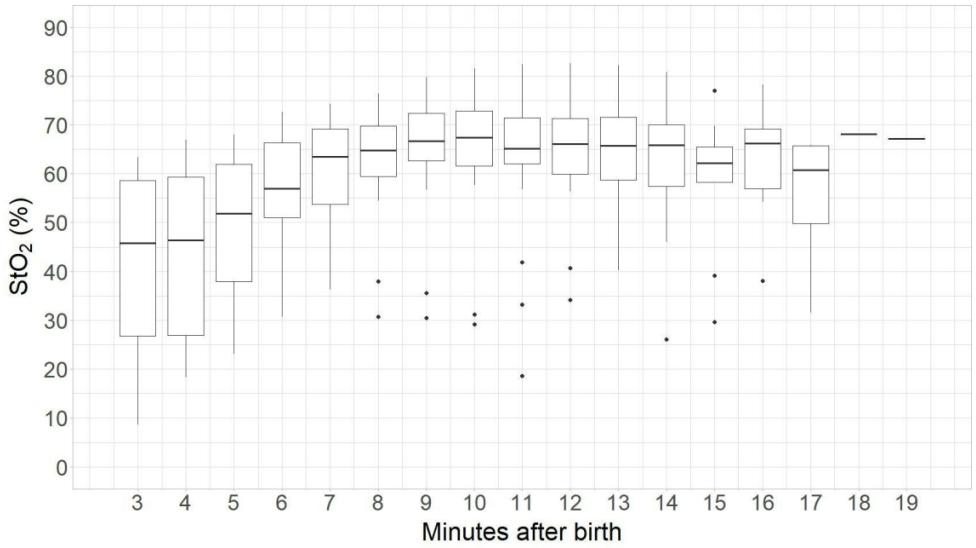

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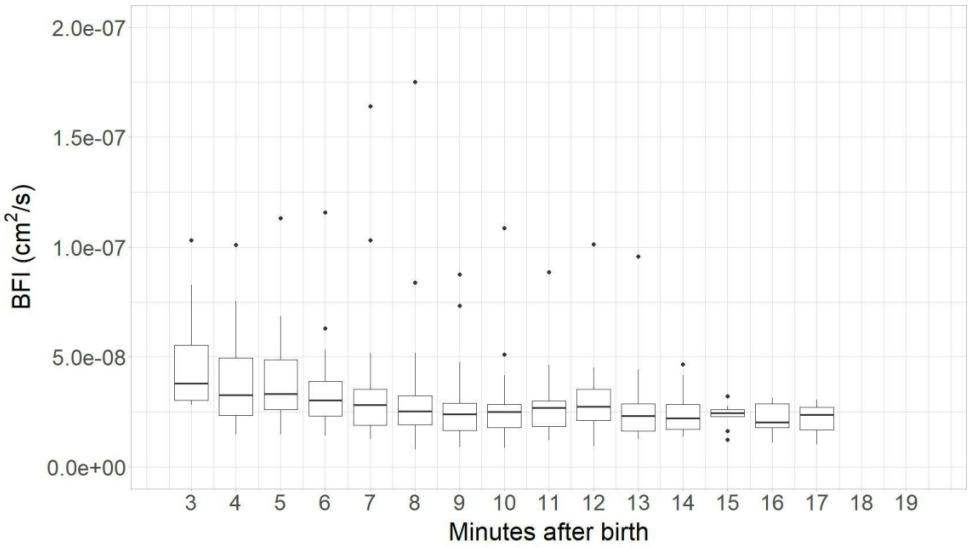

Box-plot of BFI changes over time.

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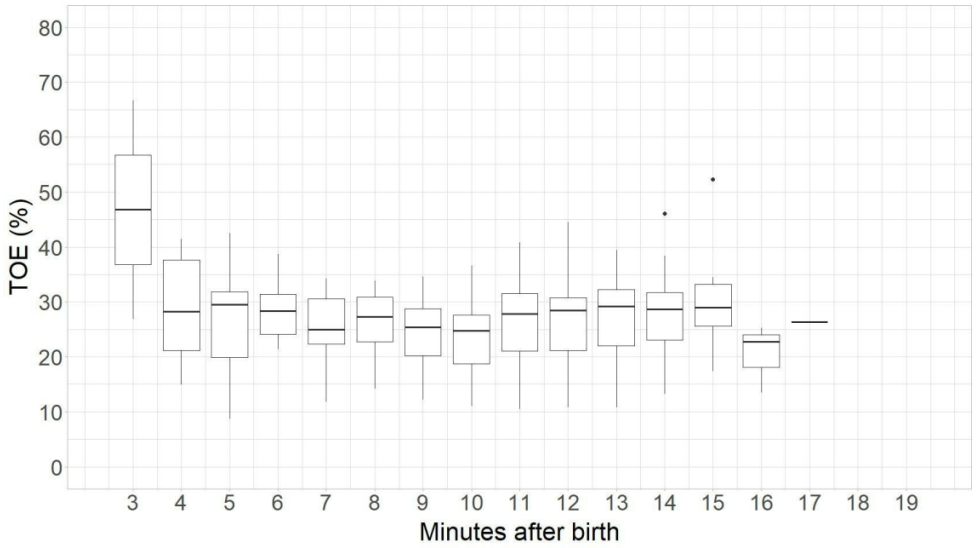

Box-plot of TOE changes over time.

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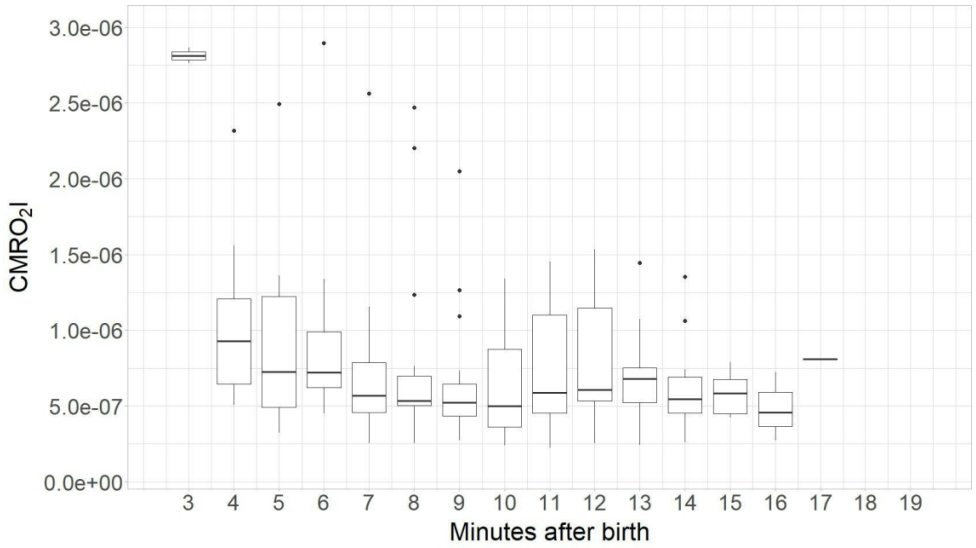

Box-plot of $CMRO_2I$ changes over time.

142x80mm (300 x 300 DPI)

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Cerebral oxygenation and blood flow in term infants during postnatal transition: BabyLux project.

SUPPLEMENTARY MATERIAL:

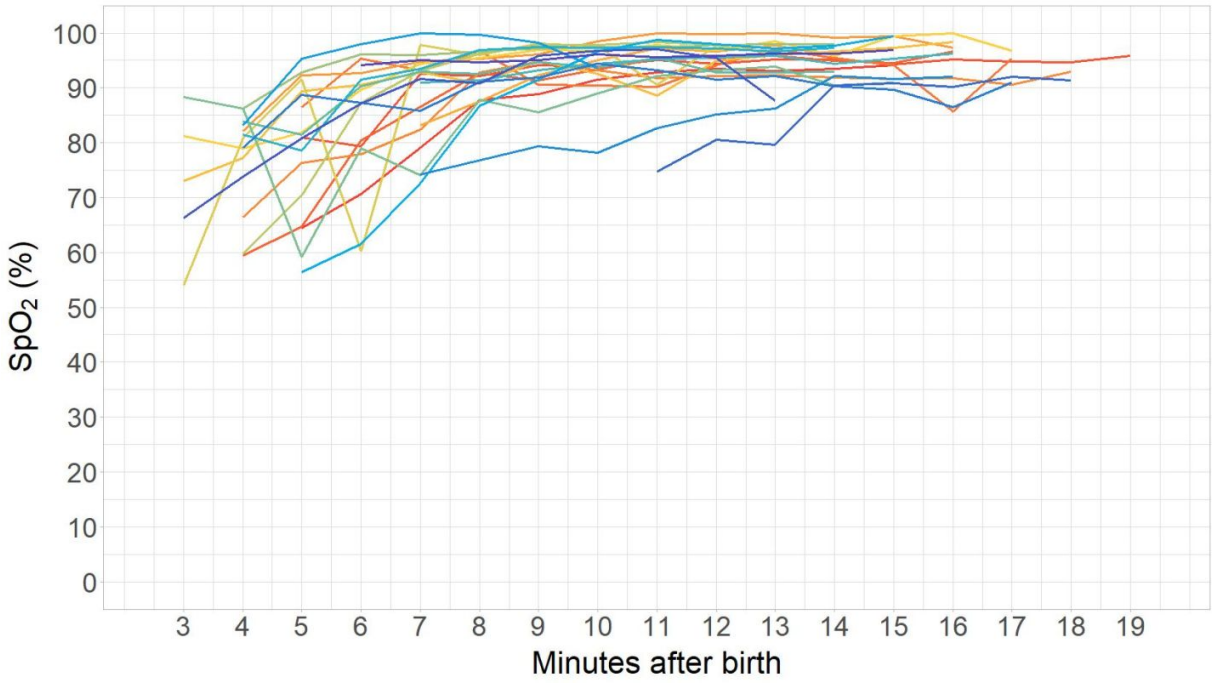

Figure 1a: SpO_2 by subject

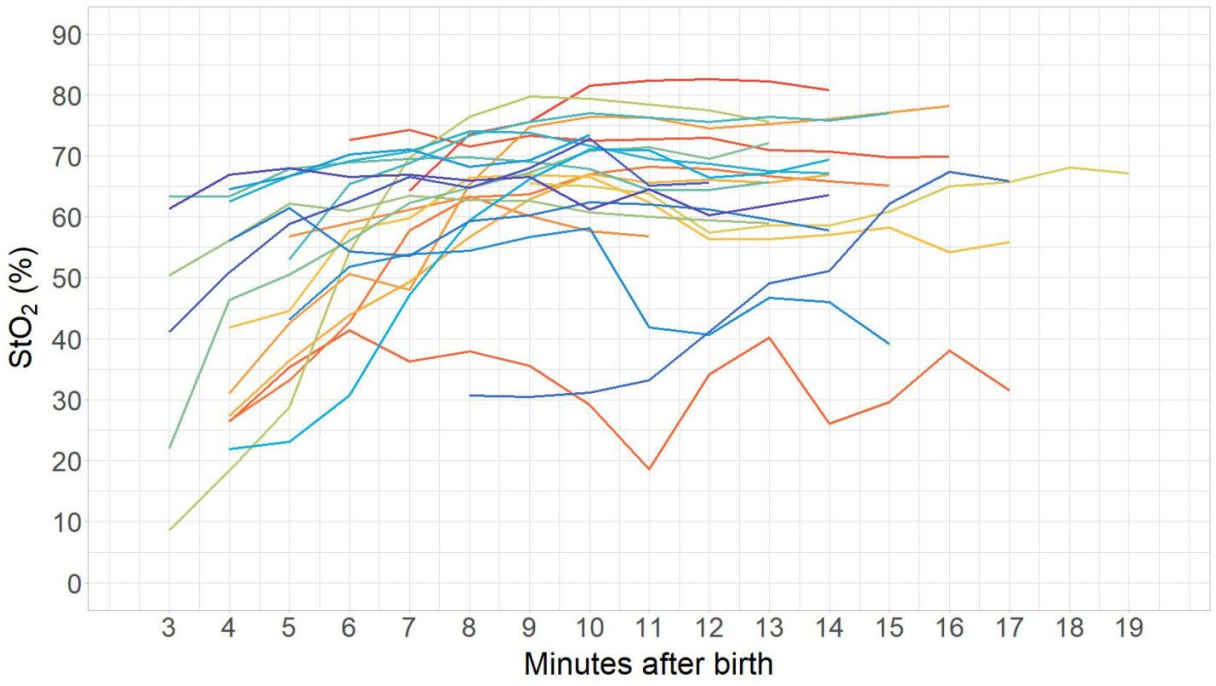

Figure 2a: StO_2 by subject

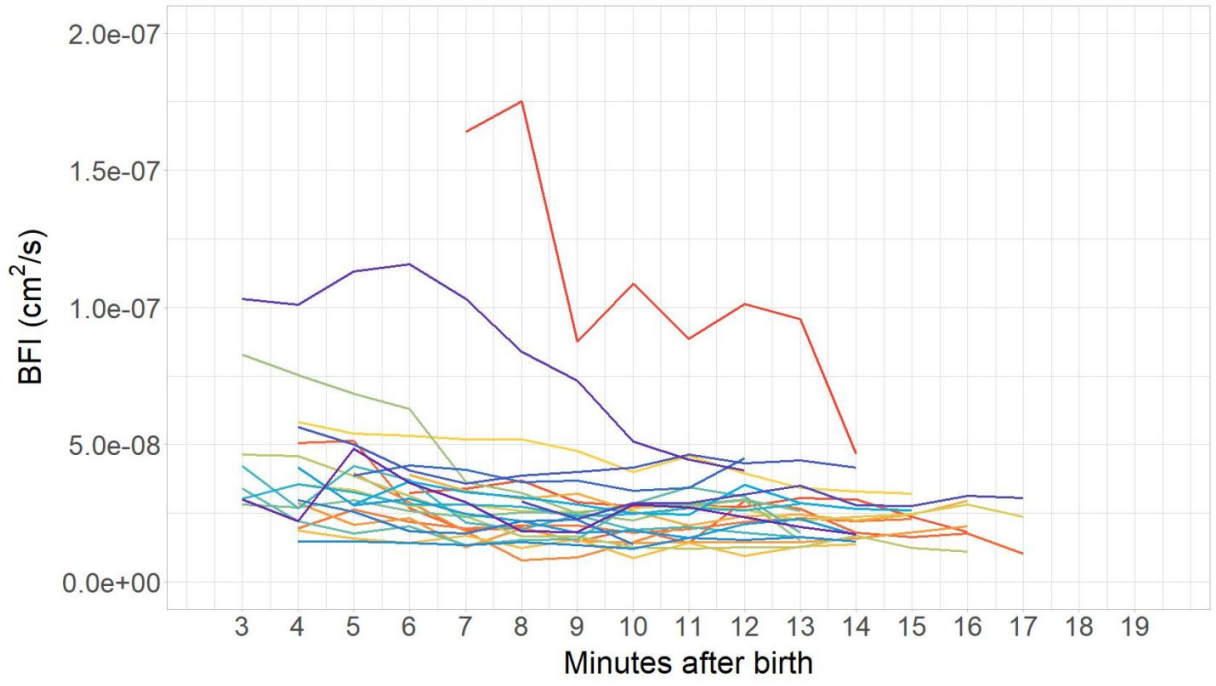

Figure 3a: BFI by subject

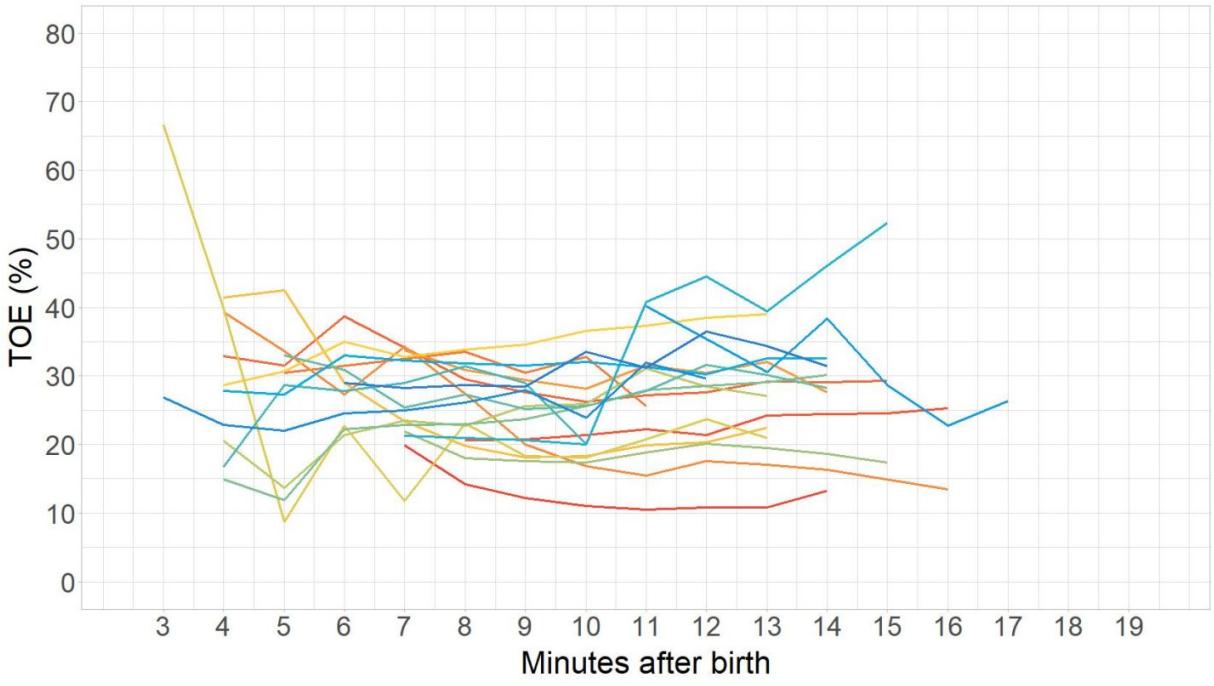

Figure 4a: TOE by subject

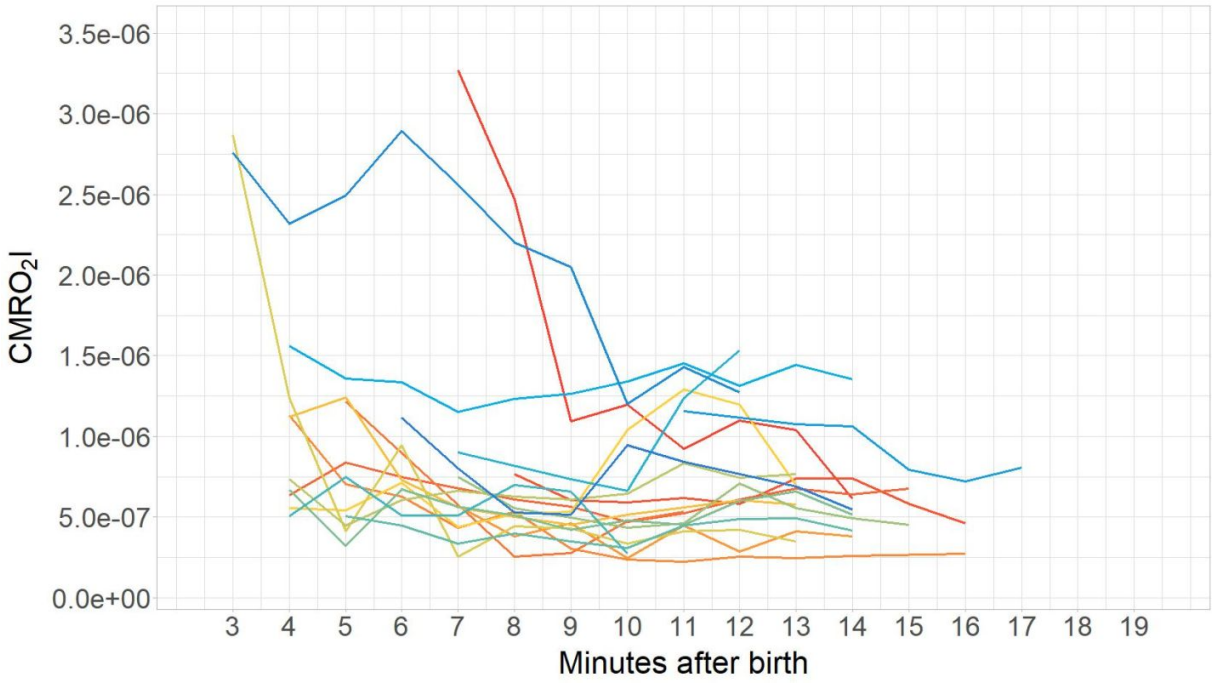

Figure 5a: $CMRO_2I$ by subject