EVALUATION OF CEREBRAL HYPOXEMIA IN EXTREMELY PRETERM INFANTS EARLY IN RESPIRATORY SUPPORT: EFFECTS OF AUTOMATED ADJUSTMENT OF INSPIRED OXYGENATION

Ilaria Stucchi[1], Francesco Cavigioli[1], Francesca Castoldi[1], Sara Gatto[1], Paola A La Verde[1], Petrina Bastrenta[1], Massimo Bellettato[2], Stefania Vedovato[2], Thomas E Bachman[3], Gianluca Lista[1]

[1]Vittore Buzzi Children's Hospital, Milan, Italy

[2]San Bortolo Hospital, Vicenza, Italy

[3]Department of Biomedical Technology, Faculty of Biomedical Engineering, Czech Technical University in Prague, Kladno, Czech Republic

Abstract

In this pilot study we aimed to evaluate the effectiveness of automated FiO_2 adjustment (A-FiO_2) in reducing the risk of cerebral tissue hypoxemia in the first weeks of life, when compensatory mechanisms that favor cerebral oxygenation are less developed. Randomized cross-over study switching between two consecutive 24-hour periods of A-FiO_2 and manual FiO_2 control. Extremely preterm infants requiring respiratory support, without significant patent ductus arteriosus were randomized in the first week of life. Masimo neonatal peripheral pulse oximeter and 5100C NIRS oximeter were used to continuously measure SpO_2 and $crStO_2$. The AVEA-CLiO ventilator was used during both automated and manual FiO_2 adjustment periods. The primary endpoint was the burden of hypoxemia calculated as the area under the two hypoxemia thresholds. Thirteen preterm infants were enrolled, with a gestational age of 26.8 ± 0.8 weeks, a birth weight of 907 ± 247 grams, an age at intervention of 7.1 ± 1.3 days, FiO_2 of 0.33 ± 0.10, and receiving respiratory support consisting of mechanical ventilation in one infant, nasal intermittent positive pressure ventilation in six infants, and nasal continuous positive airway pressure in six infants. The average FiO_2, SpO_2 and $crStO_2$ were similar during the study. Measures of hypoxemia favored A-FiO_2, including a significantly lower burden of peripheral hypoxemia (%SpO_2-hours: 3.0 ± 2.0 vs. 8.0 ± 6.1, p=0.010) and a lower burden of cerebral hypoxemia (%$crStO_2$-hours: 8.9 ± 20 vs. 20 ± 30, p=0.008)]. In this group of very young extremely preterm infants we confirmed that A-FiO_2 resulted in reduced peripheral hypoxemia. Moreover, we showed that the improvement in SpO_2 control resulted in reduced exposure to low $crStO_2$. Larger studies would be needed to determine the magnitude of the improvement and its clinical relevance.

Keywords

automated oxygen control, oxygen saturation, cerebral hypoxemia, near- infrared spectroscopy, pulse oximetry

Background

Maintenance of an appropriate level of oxygenation is an essential task in the neonatal ICU. Marginally low levels of arterial oxygenation are associated with increased mortality and marginally high with retinal and pulmonary morbidity. The standard of care for assessing arterial oxygenation is continuous noninvasive monitoring of the peripheral oxygen saturation (SpO_2) with a pulse oximeter [1]. Most new neonatal ventilators in Europe now include a feature that automates the titration of the inspired oxygen (A-FiO_2) based on the SpO_2 level. A-FiO_2 has been shown in numerous studies to increase time in the desired SpO_2 target range and reduce exposure to extremes [2]. Cerebral oxygenation is related to the arterial oxygen and blood flow. Impaired cerebral oxygenation is associated with poor neurodevelopment [3–6]. Near-Infrared Spectroscopy (NIRS) is an emerging tool for evaluating regional tissue oxygenation, and the accepted method to assess cerebral oxygenation ($crStO_2$) [1].

Lekar a technika – Clinician and Technology 2025, vol. 55(1), pp. 33–36, DOI: 10.14311/CTJ.2025.1.05
ISSN 0301-5491 (Print), ISSN 2336-5552 (Online)

The results of three studies of the effect of SpO_2 control on cerebral tissue oxygenation were not consistent. One found that a large shift in SpO_2 target range was associated with a shift in c$rStO_2$ [7]. However, two found no clear c$rStO_2$ effect associated with the use of $A\text{-}FiO_2$, despite improved SpO_2 control [8, 9]. While these studies evaluated extreme preterm infants, they were on average a month of age, a time when autoregulation of blood pressure is developed.

We sought to evaluate if the correspondence of SpO_2 and c$rStO_2$ would be more marked in week old extreme preterm infants due to their undeveloped autoregulation of blood flow.

Methods

This study reports on the pilot stage of a project intended to organize a large multicenter study in Italy to evaluate the impact of the use of $A\text{-}FiO_2$ on cerebral oxygenation of extremely preterm infants in the first weeks of life. The study was registered in the ClinicalTrials.gov database (ID: NCT02748447). Due to the disruption caused by the COVID-19 pandemic, the study was terminated.

Design

This was a randomized crossover study with two consecutive 24-hour periods. Randomization was applied using sealed envelopes. SpO_2 and c$rStO_2$ were measured for both periods, with manual and automated FiO_2 control differentiating the two arms. The SpO_2 target range was 90–95% during both arms. It was conducted in two tertiary NICU's in Northern Italy. Written consent was required and the protocol approved by the Ethics Committee of Milano Area C (approval No. 3264/2015).

Population

Infants were eligible if they were 3–10 days of age and 25–28 weeks gestational age and expected to require at least 48 hours of current level of respiratory support with AVEA ventilator (Vyaire, Yorba Linda USA). They were excluded if they had congenital anomalies or unstable hemodynamics requiring vasopressors, or a marked echocardiographic confirmed patent ductus arteriosus.

Measurements/Control

Saturation measurements were made using the Masimo SET pulse oximeter (Masimo Corporation, Irvine, CA, USA) and the Covidien 5100C pulse oximeter (Covidien, Boulder, CO, USA). The neonatal sensor for the latter was placed on the forehead. SpO_2 and c$rStO_2$ data were collected every 5 seconds automatically from the device digital outputs onto USB flash drives. All respiratory support was provided by the Vyaire AVEA-CLIO ventilator (Yorba Linda, CA, USA). The CLIO $A\text{-}FiO_2$ was activated during the appropriate 24-hour arm.

Primary End Points

These were the peripheral and cerebral burden of hypoxemia. This was defined as area under the curve (AUC) and calculated as the sum of the time below the low threshold and the actual reading for each 5-second data point. We used AUC as a more sensitive indicator of aggregate impact, and also less sensitive to arbitrary cutoffs. For SpO_2, the lower threshold was set at 88%; for example, an SpO_2 value of 70% was considered 17 below the threshold. Values below 70% were scored as 17. For c$rStO_2$, the threshold was defined as 10% below the median value for the subject in that 24-hour period (e.g. assuming a median level of 72%, threshold <62%).

Other descriptive endpoints for SpO_2 and c$rStO_2$ were stability of control (the width of the IQR) and their median. In addition, peripheral hypoxemia (SpO_2 ≤85% and ≤80%), and time in the intended SpO_2 target range were specified.

Statistical Considerations

With a planned sample size of 60 subjects, the study was projected to have greater than 90% power to detect a 5% difference in the burden of hypoxemia, with a significance level of $p<0.001$. Averages were presented as mean ± standard deviation. Differences between study arms were evaluated using a paired nonparametric test, with $p<0.05$ considered statistically significant (Wilcoxon signed-rank test, XLSTAT version 2023.1.2).

Results

Between June 2016 and November 2018, 15 infants were enrolled. One subject completed the study but there was a data collection failure. Another experienced a marked exacerbation and was withdrawn. Thus, 13 subjects completed the study and were included in the analysis. The mean gestational age of the subjects was 26.8 ± 0.8 weeks, and their birth weight was 907 ± 247 grams. They were 7.1 ± 1.3 days old at enrollment. Respiratory support modality varied, with one infant receiving invasive mechanical ventilation and the remaining infants receiving noninvasive support, including nasal intermittent positive pressure ventilation in six infants and nasal continuous positive airway pressure in six infants, with a mean FiO_2 of 0.30 ± 0.10. The first intervention arm for six of the subjects was $A\text{-}FiO_2$. The mean arterial blood pressure and

Lekar a technika – Clinician and Technology 2025, vol. 55(1), pp. 33–36, DOI: 10.14311/CTJ.2025.1.05
ISSN 0301-5491 (Print), ISSN 2336-5552 (Online)

transcutaneous CO_2 were similar during the interventions.

The primary end points were the burden of peripheral and cerebral hypoxemia. Both were reduced during *A-FiO₂* and are detailed in Table 1. Compared to manual control, the burden of peripheral hypoxemia was reduced by 62% (p=0.010) and seen in 11 of the 13 subjects. The burden of cerebral hypoxemia was reduced by 56% (p=0.015) and seen in 10 of the 13 subjects. Results of the secondary endpoints are also shown in Table 1. *A-FiO₂* was associated with a statistically significant narrower IQR for both *SpO₂* and *crStO₂*.

Table 1: Burden of Peripheral and Cerebral Hypoxemia and Oxygenation Variability.

	A-FiO₂	*M-FiO₂*	*p*
Burden hypoxemia (% *SpO₂*-hours)	3.0 ± 2	8.0 ± 6.1	0.010
Burden hypoxemia (% *crStO₂*-hours)	8.9 ± 20	20 ± 31	0.015
SpO₂ IQR width (%)	2.8 ± 0.4	3.5 ± 0.8	0.022
crStO₂ IQR width (%)	7.0 ± 1.9	8.7 ± 2.6	0.041

The burden of hypoxemia is reported as *SpO₂-hours* for peripheral and *crStO₂-hours* for cerebral. The values are presented as mean ± standard deviation.

Fig. 1 depicts the absolute difference in the burden of peripheral and cerebral hypoxemia for each subject.

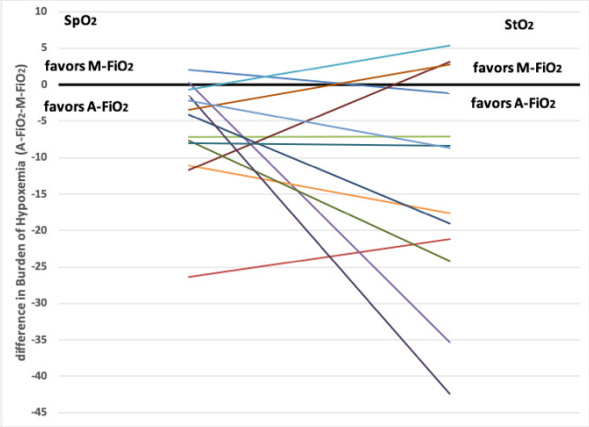

Fig. 1: Individual effect of A-FiO₂ on burden of hypoxemia.

As detailed in Table 2, the *SpO₂*, *crStO₂* and *FiO₂* were nearly identical during manual and auto control. However, control of *SpO₂* was slightly better during *A-FiO₂*, though the differences did not reach statistical significance.

Discussion

We evaluated 13 extremely preterm infants in the first weeks of life in a physiological crossover study. We found improvements in *SpO₂* control associated with automated *FiO₂* control translated to a reduction in cerebral hypoxemia.

Table 2: Comparison of Oxygenation Control and Hypoxemia Metrics During Automated and Manual FiO₂ Control.

	A-FiO₂	*M-FiO₂*	*p*
SpO₂ Target Range (% time)	81.0 ± 8.9	77.0 ± 11.5	0.51
SpO₂ <90 (% time)	12.8 ± 9.3	13.6 ± 6.0	0.81
SpO₂ ≤85 (% time)	1.8 ± 1.4	3.2 ± 2.4	0.09
SpO₂ ≤80 (% time)	0.45 ± 0.47	0.87 ± 0.91	0.10
FiO₂ % (median)	34.0 ± 14.5	33.0 ± 10.3	0.80
SpO₂ % (median)	93.0 ± 1.0	93.0 ± 0.8	0.46

Percent time associated with various *SpO₂* thresholds for hypoxemia. The *SpO₂* target range is 90–95%, plus >95% without supplemental oxygen. The values are presented as mean ± standard deviation.

Three other small single site crossover studies evaluated the relative effectiveness of *SpO₂* control and its association with cerebral oxygenation [7–9]. The subjects in all three were extremely preterm infants about a month after birth. Schmid evaluated 16 infants at two different *SpO₂* target ranges [7]. The actual separation was 2% *SpO₂*. They reported statistically significant decreases in peripheral hypoxemia of 40% and a 34% reduction in the burden of cerebral hypoxemia [7]. The other studies evaluated the impact of better *SpO₂* control using *A-FiO₂* and its association with improved cerebral hypoxemia [8, 9]. Both studies reported similar results. They found *A-FiO₂* increased time in the *SpO₂* desired target range, but there was no statistically significant improvement in cerebral hypoxemia. They both reported small reductions in peripheral hypoxemia of about 30%, but much smaller improvements in cerebral hypoxemia of about 10%. The trends in the 3 studies are comparable to ours [7–9]. We reported a larger, but not significant decrease in peripheral hypoxemia of about 45%, but in contrast a statistically significant marked reduction in the burden of peripheral and cerebral hypoxemia of 62% and 56%, respectively. In the aggregate these studies suggest that increases in peripheral hypoxemia increase cerebral hypoxemia. The magnitude of the effects in cerebral hypoxemia that we reported suggests that the effect is more marked when the autoregulatory system is less developed. However, we cannot rule out that the magnitude of the peripheral improvement was also a contributing factor.

We used AUC to quantify the burden of hypoxemia. This is used commonly for NIRS assessments [7–9] but is not typically used for *SpO₂*. We reasoned that its use for the burden of peripheral hypoxemia would be a more sensitive than traditional cutoffs (e.g., <target range, ≤85%, ≤80%) in that the risk of arterial hypoxemia increases linearly with decreasing *SpO₂* [10]. In fact, we

Lekar a technika – Clinician and Technology 2025, vol. 55(1), pp. 33–36, DOI: 10.14311/CTJ.2025.1.05
ISSN 0301-5491 (Print), ISSN 2336-5552 (Online)

found that while the traditional metrics of SpO_2 ≤85% and ≤80% reflected a trend favoring $A\text{-}FiO_2$, and the AUC <88% was statistically significant. Since we found that AUC of low SpO_2 was associated with cerebral hypoxemia, we suggest that it might be a better metric for exposure to hypoxemia in assessing the effectiveness of $A\text{-}FiO_2$ systems.

Conclusion

In contrast to other studies, we found that $A\text{-}FiO_2$ use was associated with the improved cerebral oxygenation. We believe this is reflective of our evaluation of infants in their first week when autoregulation of blood flow is less developed. Another reason might be chance, as all these studies were quite small [7–9]. Larger studies are needed to confirm and quantify our conclusion. Finally, outcome studies are needed to quantify the association of cerebral and peripheral oxygen saturation with both respiratory and neurological outcome.

Acknowledgement

We recognize the parents of the subjects their consent.

Conflict of Interest and Funding

TB and GL have received support from the manufacturers, but none was received in support of this project. The other authors report no potential conflicts.

Data sharing

Data is available upon reasonable request.

References

[1] Sweet DG, Carnielli VP, Greisen G, Hallman M, Klebermass-Schrehof K, Ozek E, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update. Neonatology. 2023 Feb 15;120(1):3–23. DOI: 10.1159/000528914

[2] Stafford IG, Lai NM, Tan K. Automated oxygen delivery for preterm infants with respiratory dysfunction. Cochrane Database of Systematic Reviews. 2023 Nov 30;11(11): CD013294. DOI: 10.1002/14651858.CD013294.pub2

[3] Tombolini S, De Angelis F, Correani A, Marchionni P, Monachesi C, Ferretti E, et al. Is low cerebral near infrared spectroscopy oximetry associated with neurodevelopment of preterm infants without brain injury? Journal of Personalized Medicine. 2022 Mar 22;12(5):625–9. DOI: 10.1515/jpm-2021-0498

[4] Vesoulis ZA, Mathur AM. Cerebral Autoregulation, Brain Injury, and the Transitioning Premature Infant. Frontiers in Pediatrics. 2017 Apr 3;5:64. DOI: 10.3389/fped.2017.00064

[5] Katheria AC, Stout J, Morales AL, Poeltler D, Rich WD, Steen J, et al. Association between early cerebral oxygenation and neurodevelopmental impairment or death in premature infants. Journal of Perinatology. 2021 Apr;41(4):743–8. DOI: 10.1038/s41372-021-00942-w

[6] Greisen G, Hansen ML, Rasmussen MI, Vestager M, Hyttel-Sørensen S, Hahn GH. Cerebral Oximetry in Preterm Infants-To Use or Not to Use, That Is the Question. Frontiers in Pediatrics. 2022 Feb 2;9:747660. DOI: 10.3389/fped.2021.747660

[7] Schmid MB, Hopfner RJ, Lenhof S, Hummler HD, Fuchs H. Cerebral desaturations in preterm infants: a crossover trial on influence of oxygen saturation target range. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2013 Sep;98(5): F392–8. DOI: 10.1136/archdischild-2012-303136

[8] Waitz M, Schmid MB, Fuchs H, Mendler MR, Dreyhaupt J, Hummler HD. Effects of automated adjustment of the inspired oxygen on fluctuations of arterial and regional cerebral tissue oxygenation in preterm infants with frequent desaturations. The Journal of Pediatrics. 2015 Feb;166(2):240–4. DOI: 10.1016/j.jpeds.2014.10.007

[9] Gajdos M, Waitz M, Mendler MR, Braun W, Hummler H. Effects of a new device for automated closed loop control of inspired oxygen concentration on fluctuations of arterial and different regional organ tissue oxygen saturations in preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2019 Jul;104(4):F360–5. DOI: 10.1136/archdischild-2018-314769

[10] Bachman TE, Newth CJ, Iyer NP, Ross PA, Khemani RG. Hypoxemic and hyperoxemic likelihood in pulse oximetry ranges: NICU observational study. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2019 May;104(3): F274–9. DOI: 10.1136/archdischild-2017-314448

Ilaria Stucchi M.D.
Department of Neonatology
Vittore Buzzi Children's Hospital
Via Castelvetro 32
Milan, Italy

E-mail: ilaria.stucchi@asst-fbf-sacco.it

Lekar a technika – Clinician and Technology 2025, vol. 55(1), pp. 33–36, DOI: 10.14311/CTJ.2025.1.05
ISSN 0301-5491 (Print), ISSN 2336-5552 (Online)