Automated Oxygen Control in Neonatology

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Acknowledgements and Disclosures

Thank you to the organisers for the invitation

I will discuss the neonatal use of automated oxygen control systems and have received financial support from the following companies

- Inspiration Healthcare plc (Oxygenie)
- Vapotherm (OAM)

I have received financial support from the following companies, but will not be discussing their products:

- Chiesi – Curosurf surfactant
- Biofloratech Ltd – Labinic probiotic

Background

SpO_2 is the best current continuous measure to achieve normoxia

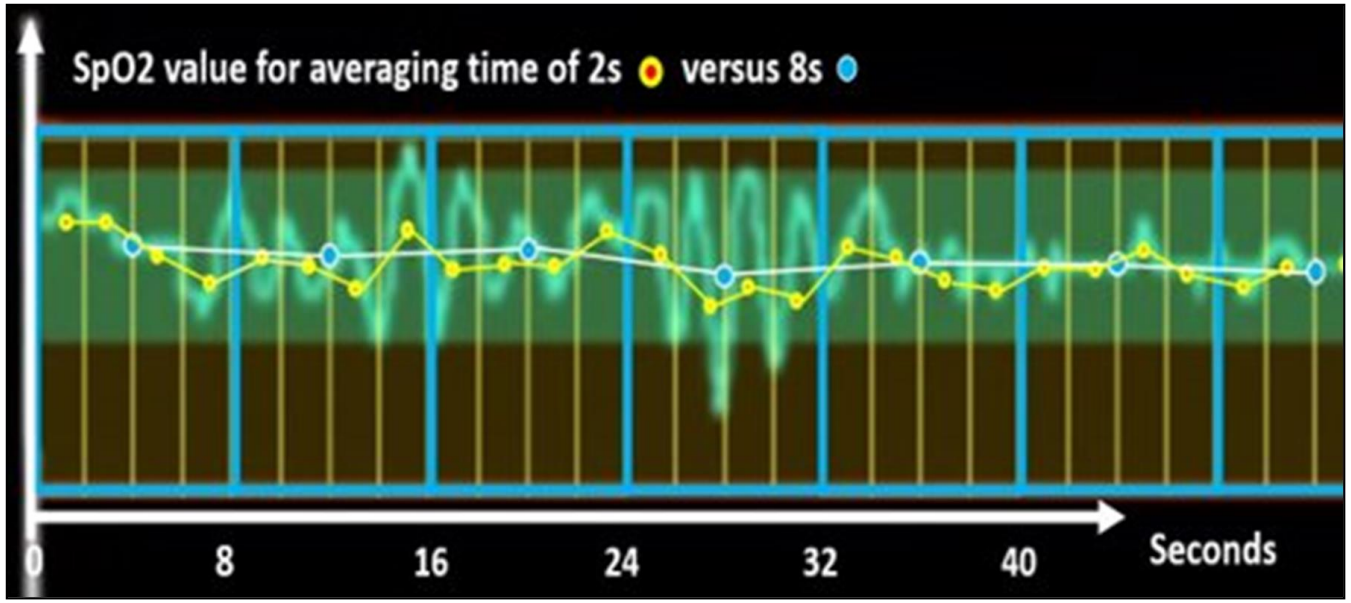
NeOProM studies - 91-95% group had lower mortality than 85-89%

Hyperoxia increases the risk of acute and chronic lung disease, ROP, red blood cell oxidative stress, cardiac dysfunction and neurodevelopment abnormalities

Hypoxia increases NEC, cerebral palsy and mortality. Increased levels of damaging free radicals as oxygenation restored increases inflammation, and vascular remodelling occurs in the longer term

Intermittent Hypoxia

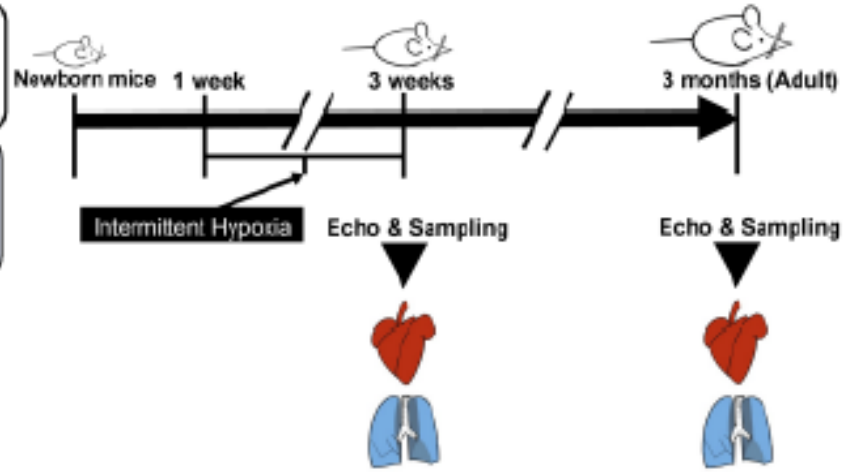
- No standard definition
- Alarm and averaging settings vary
- Staff perceptions of need for intervention vary
- Charts under-record event incidence (Brockmann PE 2013)



Methods

Murine Intermittent Hypoxia (IH) Model

Groups:
Normoxia, Normoxia+IH,
Hyperoxia, Hyperoxia+IH



In vitro IH model
Pulmonary microvascular endothelial cells (PMECs)

Groups:
Normoxia, Normoxia+IH,
Hyperoxia, Hyperoxia+IH

Outcomes

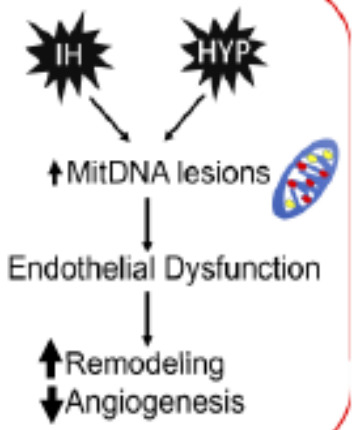
In vivo: Intermittent Hypoxia

- ↑ Lung MitDNA lesions
- ↑ Pulmonary vascular remodeling
- ↓ Lung angiogenesis
- Changes persist into adulthood
- Short term cardiac dysfunction
- Worse with concomitant hyperoxia (HYP) exposure

In vitro: Intermittent Hypoxia

- ↑ PMEC MitDNA lesions
- ↓ PMEC angiogenic potential
- Worse with concomitant hyperoxic exposure

Mechanism

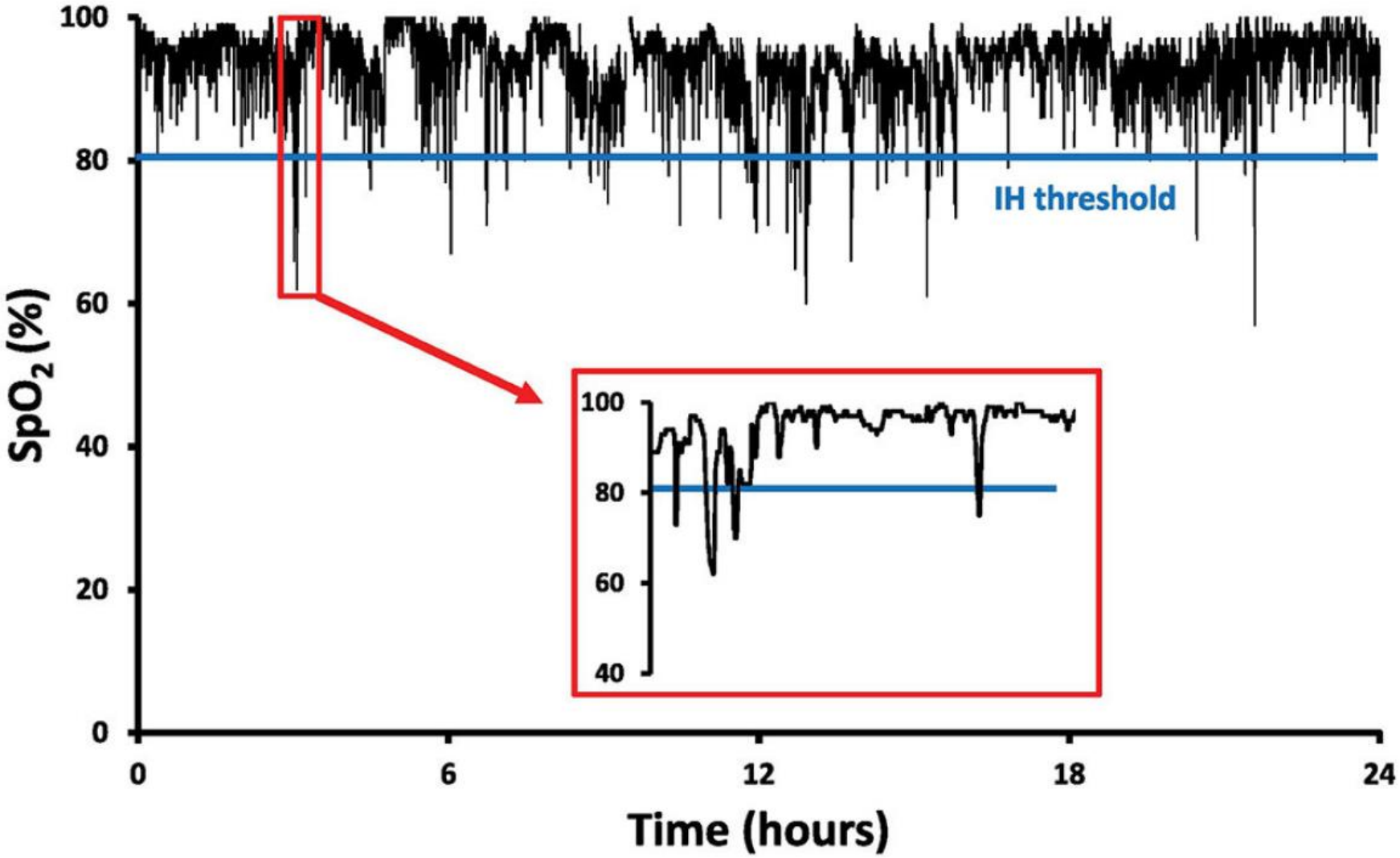


Conclusion

Neonatal IH alters lung endothelial cell function, induces mitDNA damage, and causes persistent impairment in lung vascular growth. Moreover, when superimposed on hyperoxia, neonatal IH induces a severe lung vascular phenotype that is characteristically seen in preterm infants with PH.

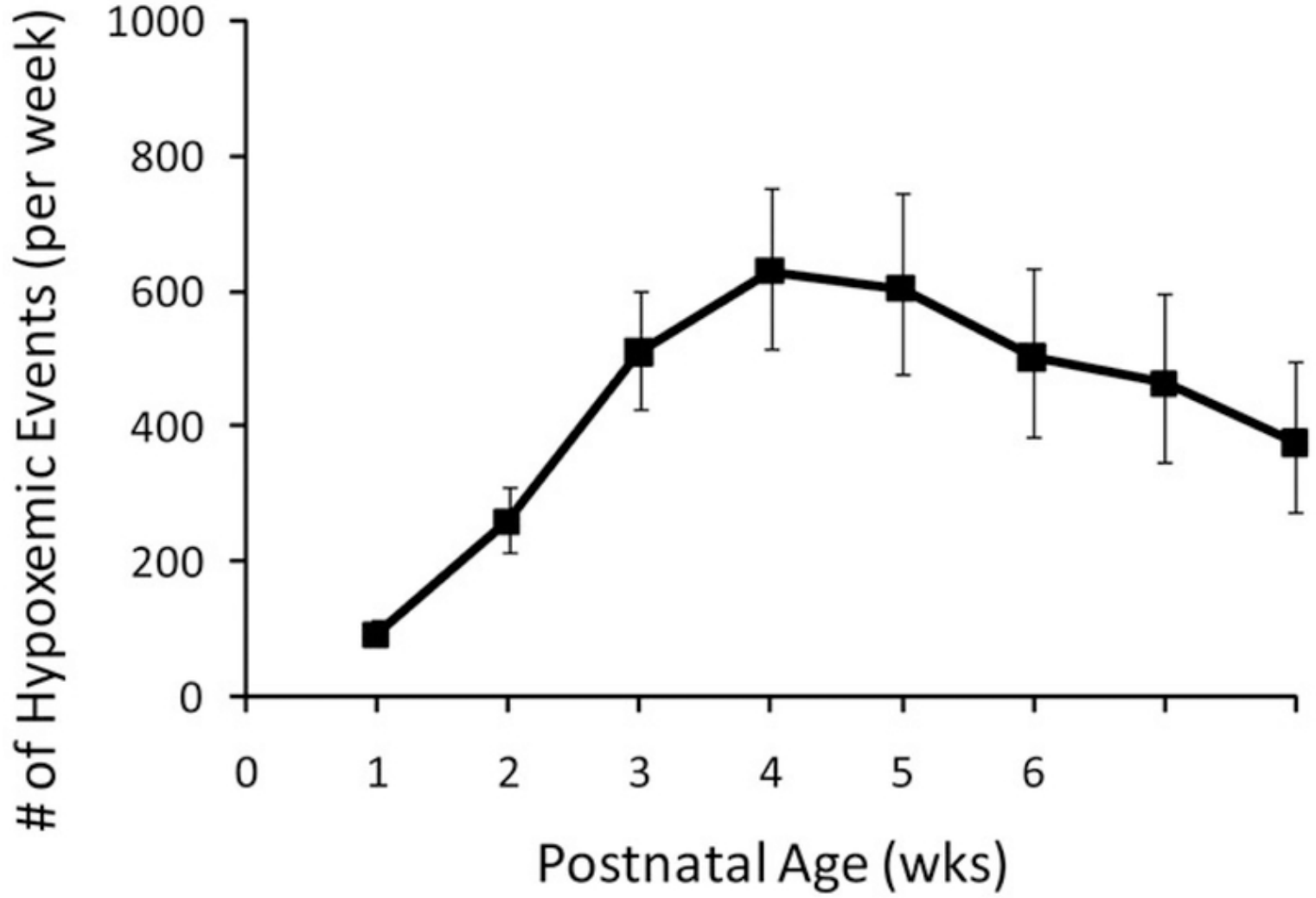
Damianos A, et al. Neonatal intermittent hypoxia persistently impairs lung vascular development and induces long-term lung mitochondrial DNA damage. J Appl Physiol. 2022 Nov 1;133(5):1031-1041

Frequency of IH events



Di Fiore JM 2021

Increase in IH events over time



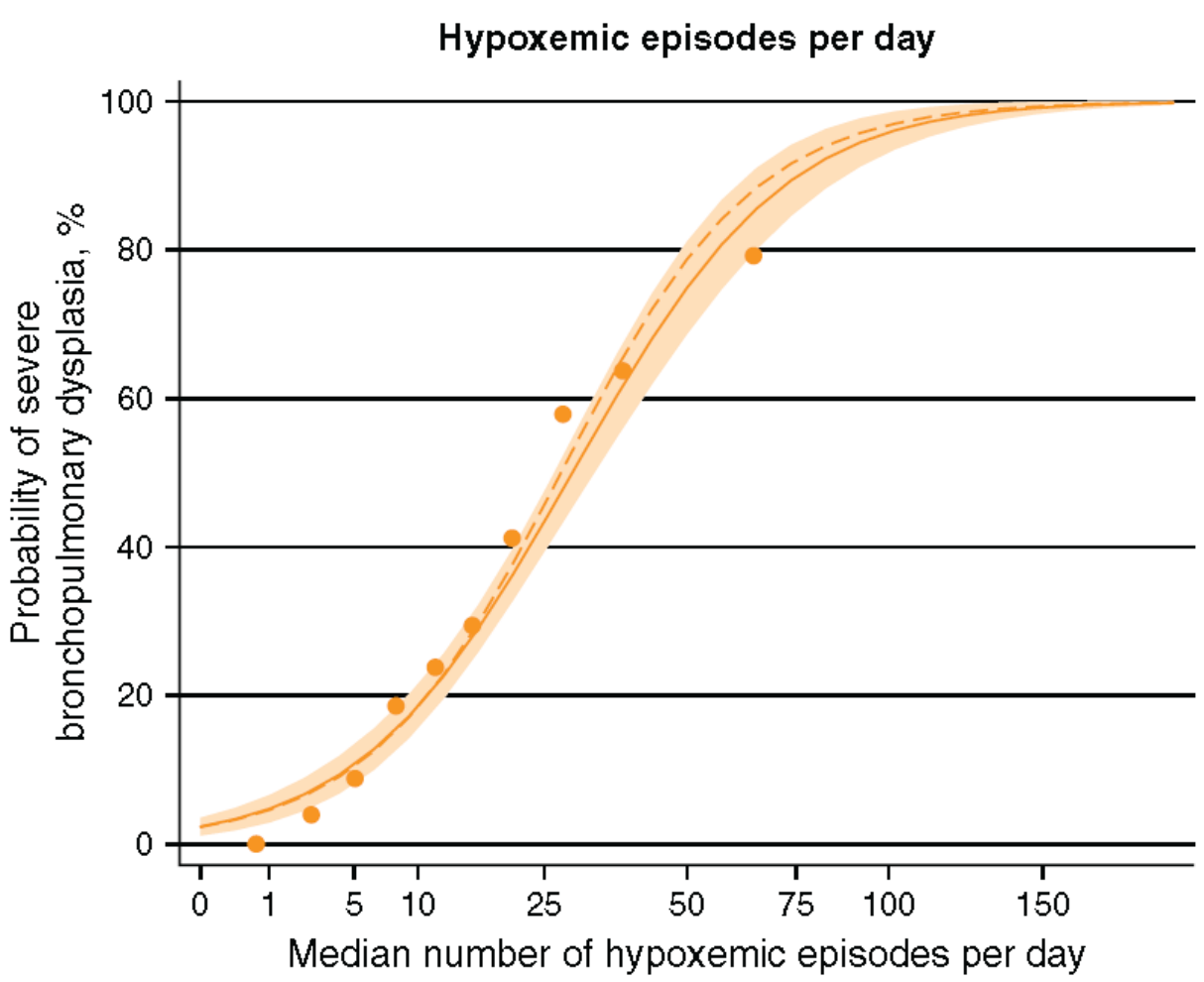
mean+95% confidence interval

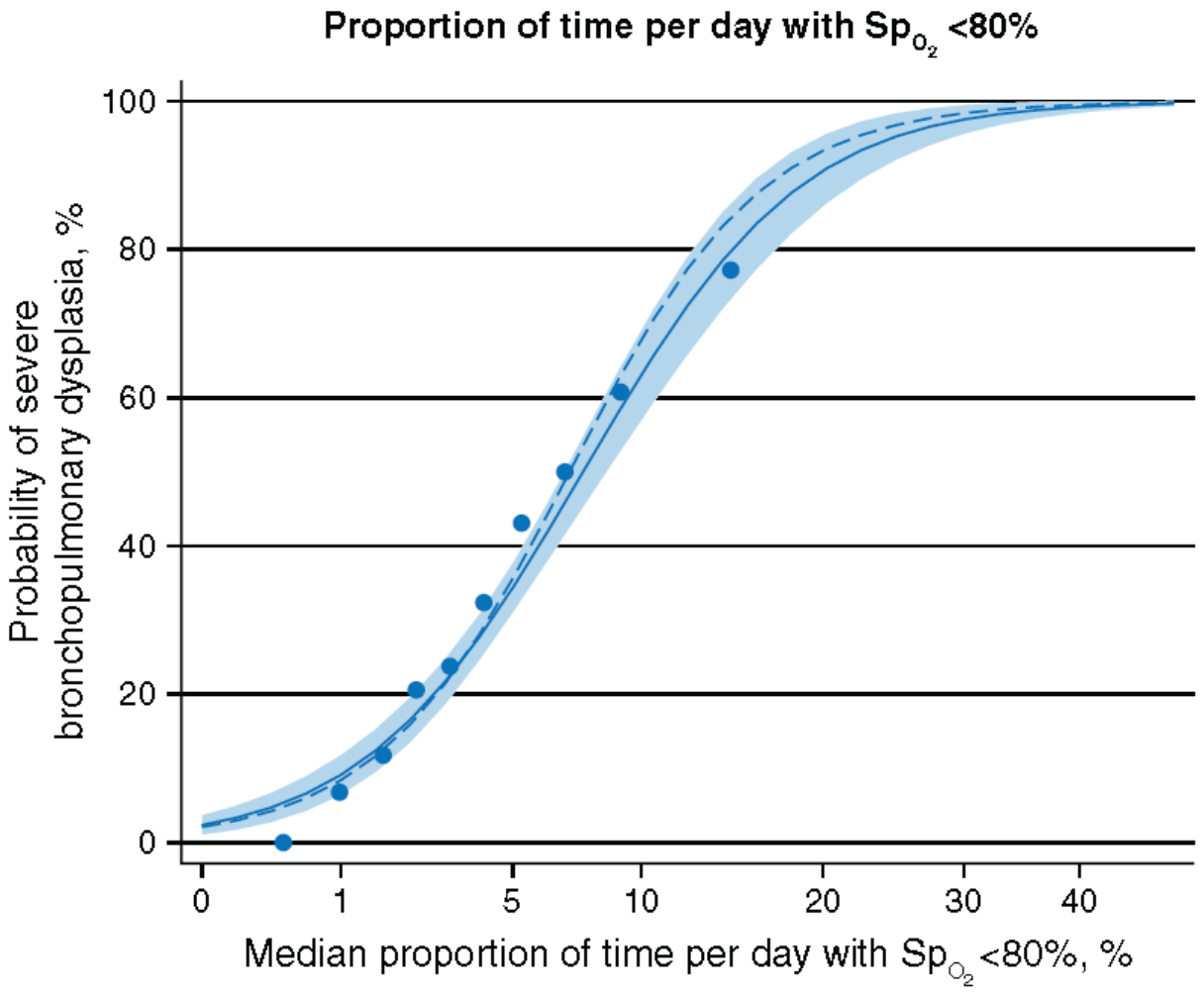
Di Fiore JM 2010

Important outcomes associated with IH

- Severe ROP (Di Fiore JM 2010)
- Sleep-disordered breathing (Di Fiore JM 2019)
- BPD (Fairchild KD 2019; Raffay TM 2019; Jensen EA 2021)
- Death or neurodevelopmental disability (Poets CF 2015)

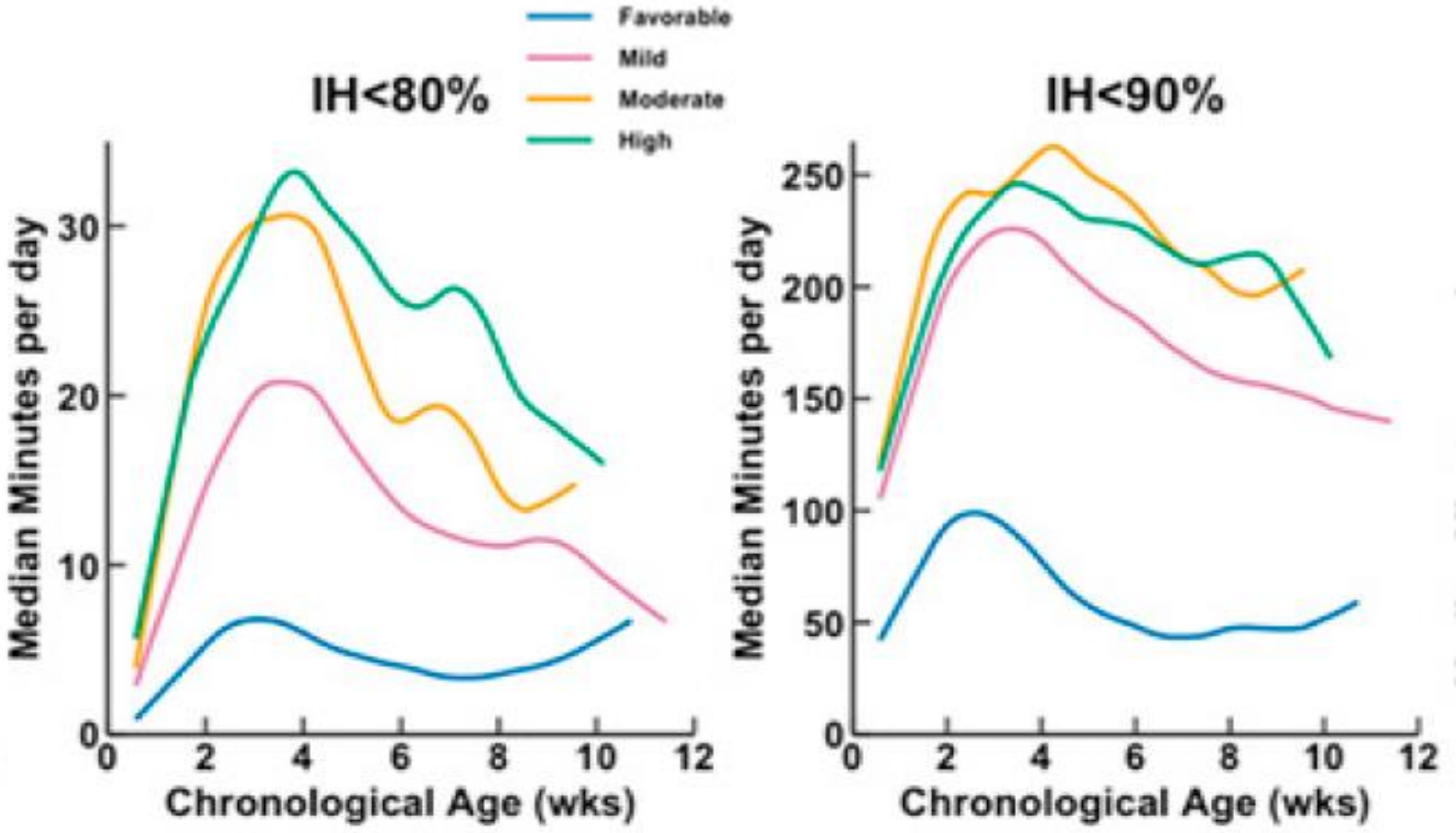
BPD and IH – prediction of risk





Jensen EA 2021

Intermittent Hypoxia – Pre-Vent Study



(Ambalavanan et al 2023)

Control of Oxygen

- Control of oxygenation is part of our ventilation optimisation strategy
- It is not about <u>just</u> staying in the target range
- It is also about minimising hypoxic and hyperoxic episodes – frequency, depth and duration

LEONI PLUS
CLAC inside

Vapotherm®
Oxygen Assist Module

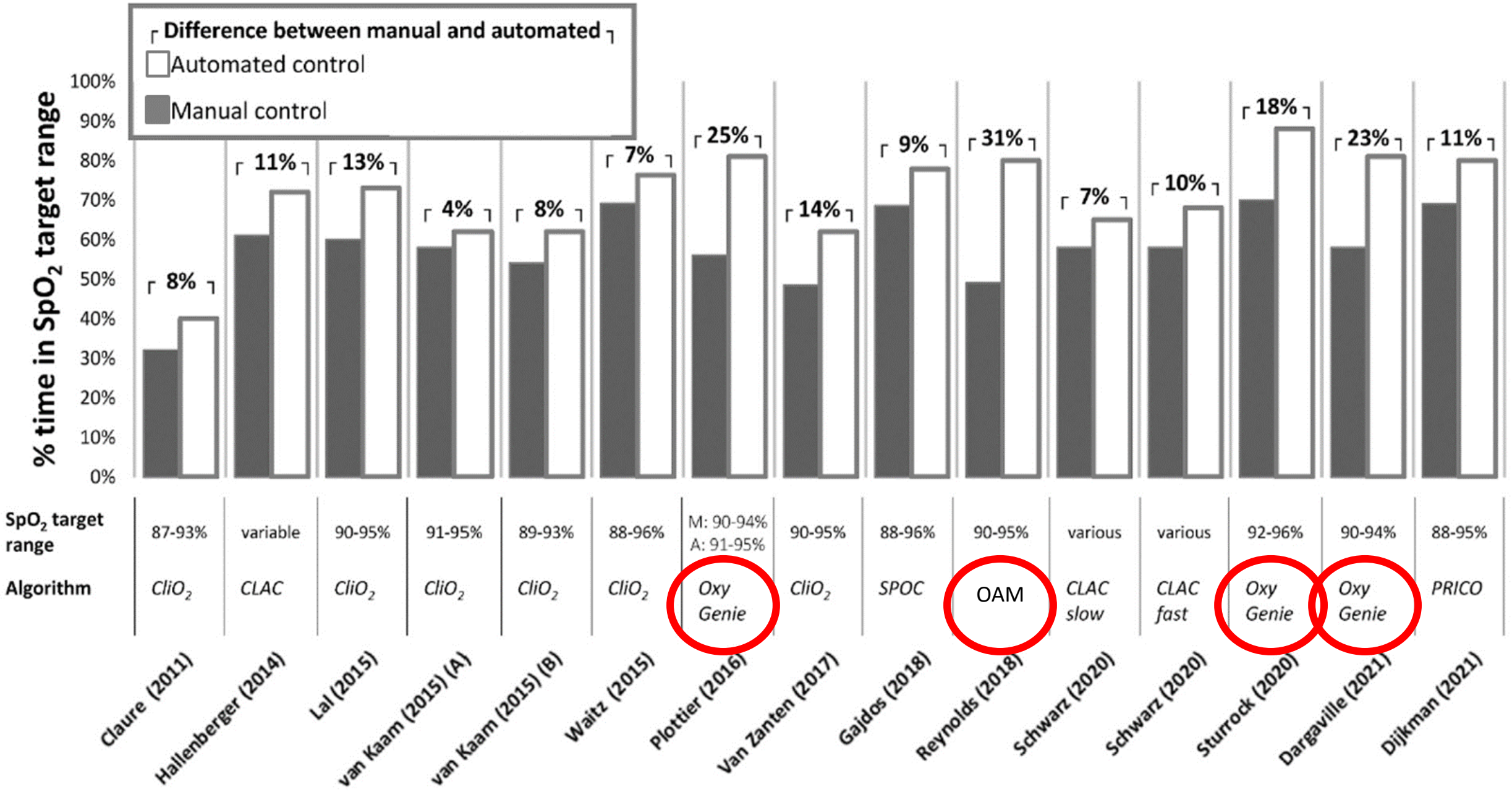
PRICO

OxyGenie®
Inspired Oxygen Control

Sophie
SPO2C inside

CLiO2™
AVEA®

Evidence for effectiveness of O_2 Controllers



(Dargaville PA 2021)

Automated vs manual oxygen control in preterm infants: SR & Meta-analysis

13 trials enrolling 343 preterm infants on respiratory support.

Auto controllers for the range SpO_2 90-95%

- Increased time spent within the TR (p = .008)
- Reduced the time of hypoxia <80% (p<0.0001)
- Reduced the time of hyperoxia >98% (p = .009)
- Reduced number of manual adjustments (p = .002)

Attenuation of intermittent hypoxia events

Abdo M et al. J. Maternal-Fetal & Neonatal Medicine 2021

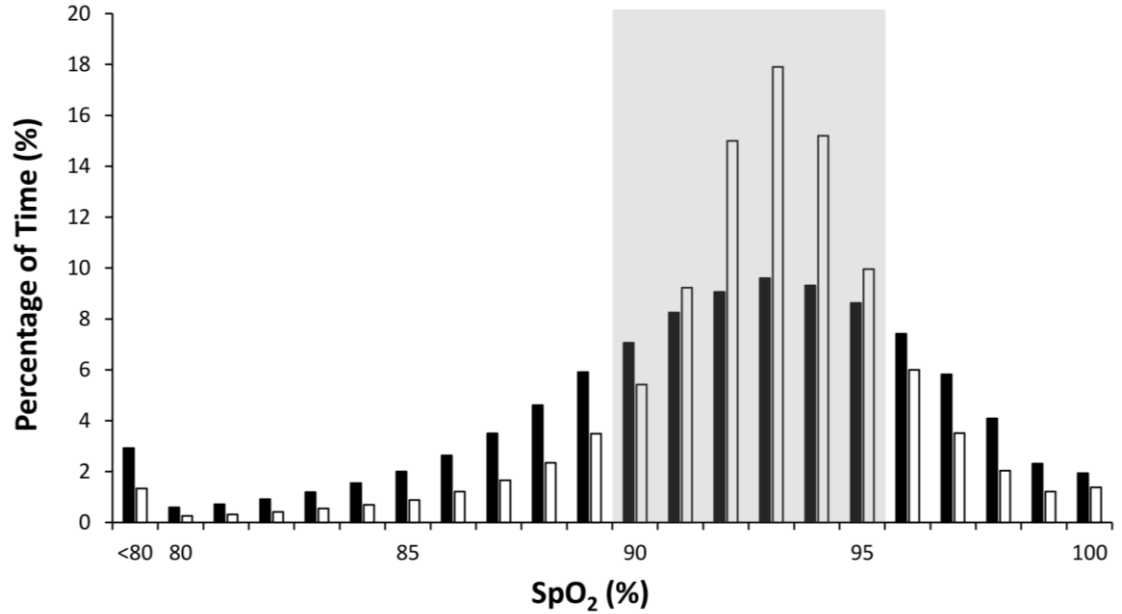
Original article

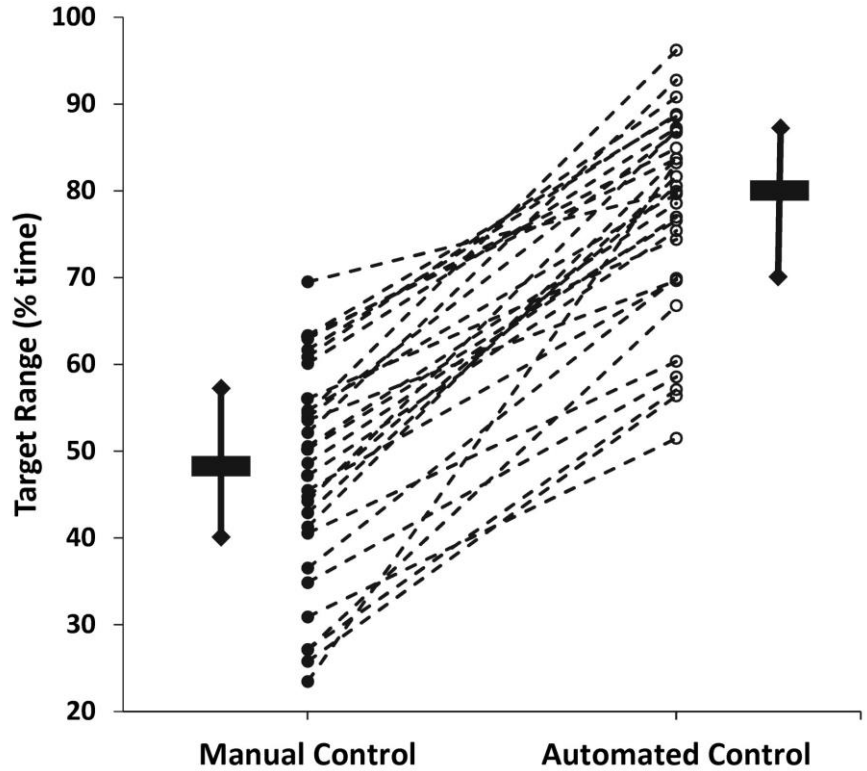
Randomised cross-over study of automated oxygen control for preterm infants receiving nasal high flow

Peter R Reynolds,[1,2] Thomas L Miller,[3,4] Leonithas I Volakis,[5] Nicky Holland,[1] George C Dungan,[5,6] Charles Christoph Roehr,[7,8] Kevin Ives[7]

- Prospective, two-centre, order-randomised, 24-hr crossover trial
- N=30 preterm infants requiring at least FiO_2 ≥25% and at least 12 FiO_2 changes
- Vapotherm OAM ("IntellO_2") algorithm

Category	Automated control	Manual control	P values*
Target SpO_2 range†			
Episodes/hour (counts)	41 (32–52)	38 (32–46)	0.0387
Average episode duration (s)	70 (49–99)	48 (31–61)	<0.0001
Per cent time in range (%)	80 (70–87)	49 (40–57)	<0.0001
SpO_2>95%‡			
Episodes/hour (counts)	37 (30–46)	18 (13–25)	<0.0001
Average episode duration (s)	12 (9.5–14)	48 (34–68)	<0.0001
Per cent time in range (%)	12 (8.9–16)	23 (15–41)	<0.0001
SpO_2>98%‡			
Episodes/hour (counts)	4.5 (1.8–8.5)	5.5 (1.9–14)	0.572 (NS)
Average episode duration (s)	6.4 (5.1–7.0)	24 (20–32)	<0.0001
Per cent time in range (%)	0.68 (0.29–1.4)	3.7 (1.2–9.9)	<0.0001
SpO_2<range			
Episodes/hour (counts)	27 (22–30)	24 (21–26)	0.082 (NS)
Average episode duration (s)	17 (15–21)	42 (29–50)	<0.0001
Per cent time in range (%)	12 (8.8–17)	28 (17–36)	<0.0001
SpO_2<80% for ≥60 s			
Total number of episodes§	0 (0–1.3)	5 (2.8–14)	<0.0001
Average episode duration (s)¶	0 (0–69)	119 (97–148)	<0.0001





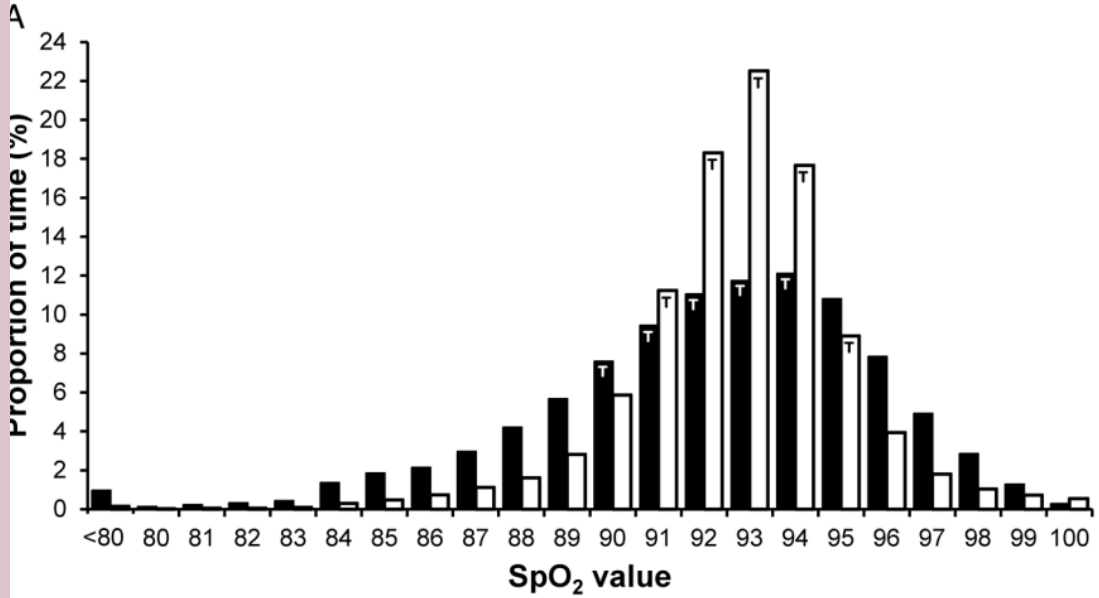
Clinical evaluation of a novel adaptive algorithm for automated control of oxygen therapy in preterm infants on non-invasive respiratory support

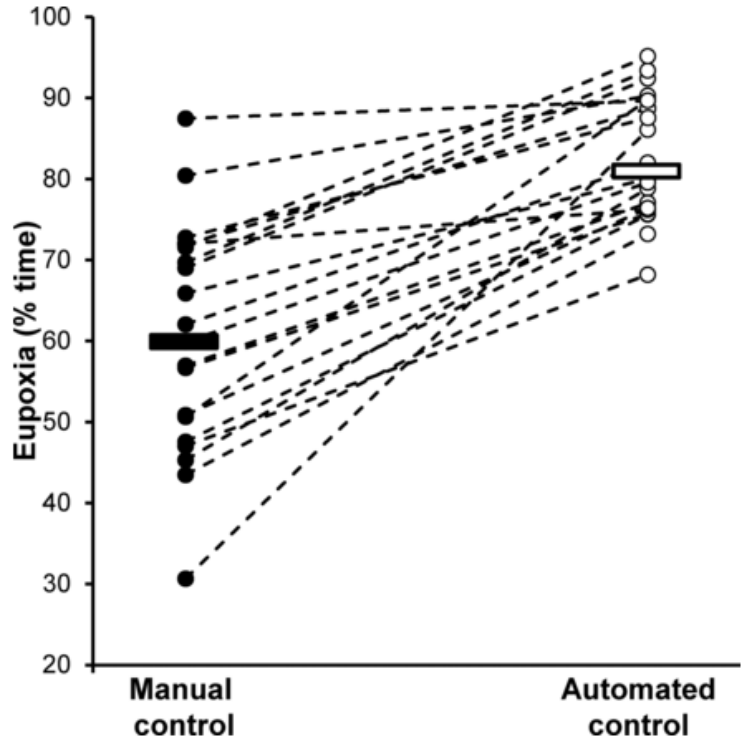
Gemma K Plottier,[1,2] Kevin I Wheeler,[3] Sanoj K M Ali,[1,2] Omid Sadeghi Fathabadi,[4] Rohan Jayakar,[4] Timothy J Gale,[4] Peter A Dargaville[1,5]

- Prospective, single-centre, order-randomised, 24-hr crossover trial
- N=20 preterm infants requiring oxygen
- VDL 1.0 algorithm ("Oxygenie")

Table 1 Oxygen saturation (SpO_2) targeting

	Manual control	Automated control	p Value*
SpO_2 in target range	55 (46–60)%	78 (75–87)%	0.0001
SpO_2 below target range	19 (12–27)%	14 (7.8–19)%	0.0027
SpO_2 above target range	25 (23–35)%	5.1 (3.1–6.9)%	0.0003
Eupoxia	56 (48–63)%	81 (76–90)%	<0.0001
SpO_2 in alarm range (89%–96%)	81 (70–83)%	93 (90–98)%	0.0006
SpO_2 in alarm range or higher when in air	81 (73–83)%	95 (92–98)%	<0.0001
SpO_2<80%	0.7 (0.10–1.3)%	0 (0–0.17)%	0.0006
SpO_2 80%–84%	2.6 (1.2–3.2)%	0.39 (0.10–0.67)%	0.0001
SpO_2 85%–88%	10 (6.8–15)%	3.5 (1.1–5.8)%	0.0002
SpO_2 97%–98% when in oxygen	5.0 (3.2–7.9)%	0.71 (0.28–1.5)%	0.0001
SpO_2 99%–100% when in oxygen	0.46 (0.22–1.4)%	0 (0–0.12)%	0.0010





Summary: Oxygenie vs OAM

	Hypoxia	**Hyperoxia**	**In range**
Manual	19-28%	23-25%	49-55%
OAM	12%	12%	80%
Oxygenie	14%	5.1%	78%

Author	Title	Journal
Kaltsogianni *et al*	Closed-loop oxygen system in late preterm/term, ventilated infants with different severities of respiratory disease	Acta Pediatrica 2023
Salverda *et al*	Clinical outcomes of preterm infants while using automated controllers during standard care (OxyGenie and CLiO2).	Arch Dis Child Fetal Neonatal Ed. 2023
Ali *et al*	Preliminary study of automated oxygen titration at birth for preterm infants.	Arch Dis Child Fetal Neonatal Ed. 2022
Salverda *et al*	Comparison of two devices for automated oxygen control in preterm infants: a randomised crossover trial.	Arch Dis Child Fetal Neonatal Ed. 2022
Dargaville *et al*	Automated control of oxygen titration in preterm infants on non-invasive respiratory support	Arch Dis Child Fetal Neonatal Ed. 2022
Salverda *et al*	The effect of automated oxygen control on clinical outcomes in preterm infants: a pre- and post-implementation cohort study	Eur J Pediatr. 2021
Sturrock S *et al*	A randomised crossover trial of closed loop automated oxygen control in preterm, ventilated infants	Acta Paediatr. 2021
Plottier G *et al*	Clinical evaluation of a novel adaptive algorithm for automated control of oxygen therapy in preterm infants on non-invasive respiratory support	Arch Dis Child Fetal Neonatal Ed. 2017
Dargaville *et al*	Development and preclinical testing of an adaptive algorithm for automated control of inspired oxygen in the preterm infant	Arch Dis Child Fetal Neonatal Ed. 2017

Clinical Outcomes and AOC

FiO2-C study

- Initial planned recruit 2340 infants <28 weeks gestation
- Randomisation to automated oxygen control with any CE-marked algorithm/device, or to routine manual oxygen control.

The primary outcomes are:

- death or any of severe ROP, BPD or NEC.
- death or any of i) language/cognitive delay, ii) motor impairment, iii) severe visual impairment or iv) hearing impairment, at 2 years corrected gestational age.

- The trial commenced in July 2018; poor recruitment, has stopped early

$CLiO_2$™ vs Oxygenie™

	OXYGENIE	$CLIO_2$	P
N=242	N=121	N=121	
Gestational Age	28+3	27+5	0.09
Birth Weight	1034	1011	0.60
Time in target range	71.5%	51.3%	**<0.001**
Hypoxia (SpO_2<80%) / Hyperoxia (SpO_2>98%)	0.7 / 1%	1.2 / 4%	**<0.001**
Invasive ventilation days, median (IQR)	0 (0–4.2)	2.1 (0–8.4)	**0.012**
CPAP days, median (IQR)	8.4 (4.8–19.8)	16.7 (6.3–31.1)	**<0.001**
Died, n (%)	7 (5.8)	3 (2.5)	0.34
Retinopathy of prematurity			
Early Treatment indicated n (%)	5 (4.5)	13 (11.2)	0.09
Received laser coagulation, n (%)	1 (0.9)	10 (8.6)	**0.008**
Intraventricular haemorrhage (≥stage 2), n (%)	27 (22.5)	18 (14.9)	0.21
Days in NICU, median (IQR)	28(15 – 42)	40(25 – 61)	**<0.001**

Salverda HH, et al. ADC FNE. 2023:108(4);394

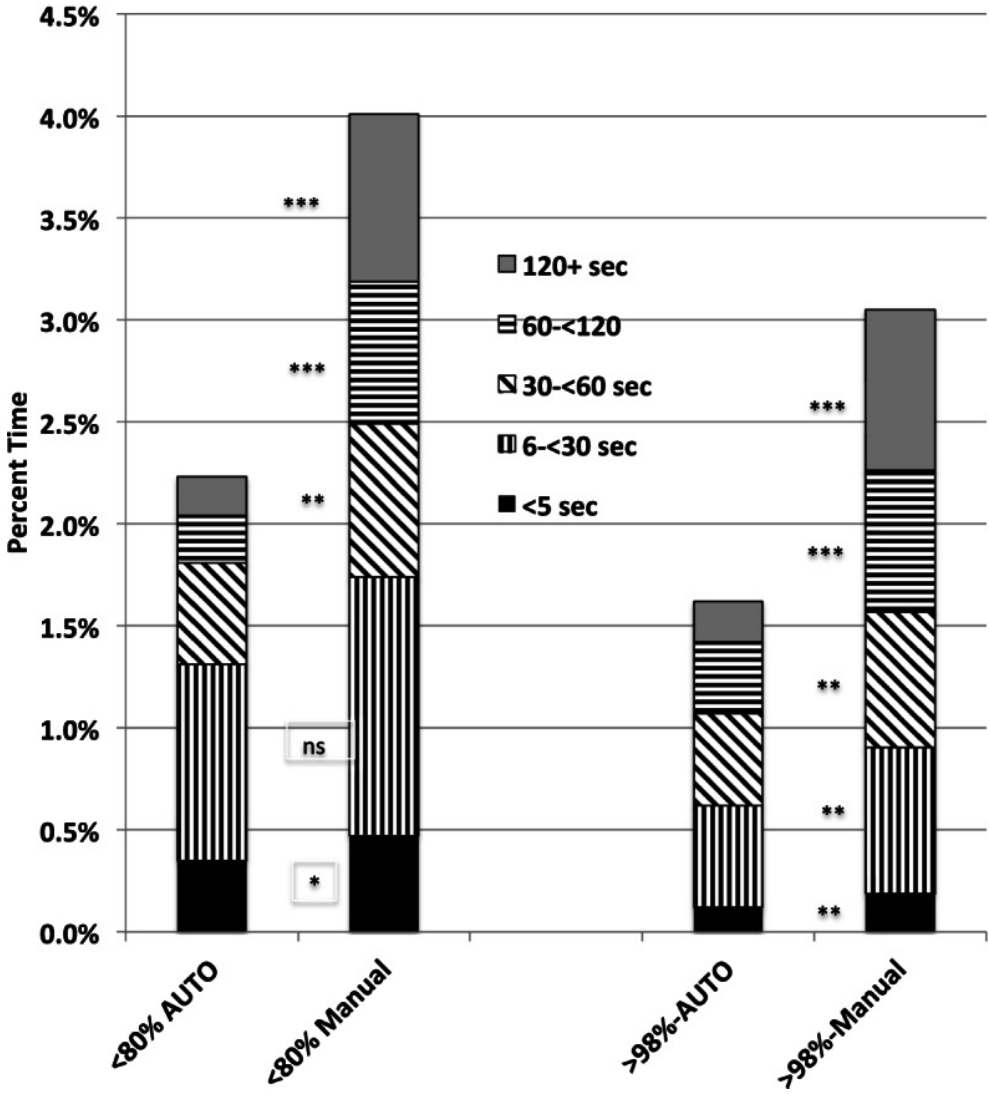
Cochrane Meta-analysis 2023

- 13 studies, 339 infants
- Improved time in target range
- Reduced hyperoxia
- Probably reduced hypoxia
- No clear effect on clinical outcomes

Stafford IG et al. Cochrane Database Syst Rev. 2023 Nov 30;11(11):CD013294

Frequency of hypoxic & hyperoxaemic episodes

- 58 babies <32 weeks studied on non-invasive ventilation
- Randomised to 24hrs on manual or automated O_2 control
- Episodes at extremes (>98% or <80%) were less common in automated control
- Long episodes (>30 seconds) were less common in automated control



Nair V, et al. Arch Dis Child Fetal Neonatal Ed. 2023 Mar;108(2):136-141

Outcomes at 2-years

- Neurodevelopmental outcomes at 2 years of age were compared for infants born at 24–29 weeks gestational age before (2012–2015) and after (2015–2018)
- The primary outcome was a composite (death or severe impairment)
- 289 in the pre-AOC; 292 in the post-AOC epochs
- Outcome of mortality /severe NDI 17.9% pre-AOC (41/229) vs. 24.0% (47/196) post-AOC (p = 0.12)
- Limitations of retrospective study and use of different devices acknowledged

Salverda HH, *et al*. Eur J Pediatr. 2023 Apr;182(4):1593-1599

Why have trials not shown improved clinical outcomes?

- Outcomes depend on more than just oxygenation
- Influence of frequency and durations of IH events not tested in studies
- Rapid improvements in neonatal care influence outcomes
- Some adverse outcomes are rare, so very large sample sizes would be needed
- Risk of patients lost to follow-up in retrospective studies may not be random

Situations where auto-oxygen is helpful

- During handling: examinations, cares, nappy changes, parent skin-to-skin
- During procedures
  - Ultrasound scans
  - Umbilical / long line insertion
  - LISA procedure for surfactant
  - Cannulation / lumbar puncture / X-ray / Lung ultrasound etc
- Frequent desaturations (e.g. shunting) – compliance will still be better than manual control
- Where nursing staff are busy!

Summary

- Not all automated oxygen controllers are the same
- Characteristics "out of target range" should be considered
- Intermittent hypoxia and hyperoxia are (perhaps most) important
- Use of AOC should be throughout the "oxygen journey"
- Consider the additional benefits:
  - Reduction in nursing workload
  - Greater stability during procedures

Thank you

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