Closed-loop automated oxygen control in preterm ventilated infants: a randomised controlled trial

Ourania Kaltsogianni ,[1,2] Theodore Dassios ,[1,2] Allan Jenkinson ,[1,2] Eleanor Jeffreys,[1,2] Kenta Ikeda ,[3] Masashiro Sugino ,[4] Anne Greenough [1,2]

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[1]Department of Women and Children's Health, School of Life Course and Population Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK
[2]Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London, UK
[3]Department of Neonatology, Tokyo Women's Medical University Adachi Medical Center, Adachi City, Tokyo, Japan
[4]Neonatology, Shikoku Medical Center for Children and Adults, Zentsuji, Kagawa Prefecture, Japan

Correspondence to
Dr Theodore Dassios;
theodore.dassios@kcl.ac.uk

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ABSTRACT

Objective To compare the duration of mechanical ventilation between preterm infants receiving closed-loop automated oxygen control (CLAC) or manual oxygen control.

Design Randomised controlled trial.

Setting Tertiary neonatal unit in London, UK.

Patients Infants (n=69) with a median (IQR) gestational age of 27.0 (25.6–29.0) weeks studied at a corrected postmenstrual age of 27.6 (25.9–29.1) weeks.

Interventions Infants were randomised to CLAC or manual oxygen control within 48 hours of initiation of mechanical ventilation if less than 7 days of age until successful extubation.

Main outcome measures Duration of mechanical ventilation.

Results The CLAC infants (n=34) compared with those who received manual control had a shorter duration of mechanical ventilation (median (range): 11 (1–57) vs 40 (3–134) days, p=0.027), a shorter duration of supplemental oxygen (median (range): 33 (0–100) vs 47 (3–335) days, p=0.031), a lower incidence of bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age (55% vs 83.9%, p=0.015) and fewer required home oxygen (26.5% vs 51.4%, p=0.016). In the CLAC infants, the time spent in the target oxygen range (91%–95%) was increased (p<0.001) and the times spent in hypoxaemia (peripheral oxygen saturation level (SpO_2)<85%) and hyperoxaemia (SpO_2>95%) were reduced (p<0.001).

Conclusions Use of CLAC in preterm, ventilated infants was associated with improved achievement of oxygen saturation targets, shorter durations of mechanical ventilation and supplemental oxygen treatment and a lower incidence of BPD. These results need to be replicated in larger multicentre studies before any change in routine practice could be recommended.

Trial registration number NCT05030337.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Closed-loop automated oxygen control (CLAC) improves compliance with achievement of peripheral oxygen saturation targets and prevents hypoxaemia and hyperoxaemia, with fewer manual adjustments to the inspired oxygen concentration in preterm infants, compared with manual oxygen control.

⇒ The available evidence on the effect of CLAC on longer term outcomes is limited.

WHAT THIS STUDY ADDS

⇒ In a randomised controlled trial, CLAC was associated with reductions in the durations of mechanical ventilation and supplemental oxygen, the need for home oxygen and the incidence of bronchopulmonary dysplasia in preterm ventilated infants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND POLICY

⇒ This study demonstrated that use of CLAC improves respiratory outcomes in preterm ventilated infants. If these results are replicated in larger studies, CLAC should then be introduced into clinical practice.

INTRODUCTION

Many preterm infants require respiratory support in the newborn period and, although they are increasingly managed on non-invasive support, some require mechanical ventilation.[1] Premature, ventilated infants frequently develop complications. The most common adverse outcome is bronchopulmonary dysplasia (BPD), particularly if prolonged mechanical ventilation is needed.[2] This can result in increased long-term respiratory and neurological morbidity.[3] Other complications include retinopathy of prematurity (ROP)[4] and intracerebral haemorrhage.[5] Therefore, optimising neonatal ventilation and reducing its duration should be a high priority in the management of preterm neonates.

Ventilated infants frequently require supplemental oxygen, but its use can result in the development of reactive oxygen species and further increase the risk of complications.[6] Targeting oxygen therapy to maintain peripheral oxygen saturation levels (SpO_2) within a predefined range can maximise the benefits of increased oxygen delivery to the tissues while minimising the risk of complications. Closed-loop automated oxygen control (CLAC) systems improve compliance with oxygen target achievement and prevent hypoxaemia and hyperoxaemia in preterm infants receiving invasive or non-invasive support, with fewer manual adjustments to the inspired oxygen concentration (fraction of inspired oxygen (FiO_2)).[7–12] It is unclear, though, whether CLAC is associated with any important clinical benefits. The majority of studies to date have had a crossover design, with a short study period, and were not sufficiently powered to detect significant differences in long-term outcomes.[9] In our own experience, the use of CLAC appeared to reduce the duration of mechanical ventilation. Furthermore, previous studies reported that CLAC

could facilitate earlier weaning of the FiO_2 when compared with manual control, which is a major determinant of an infant's readiness for extubation.[13 14] It is, therefore, possible that use of CLAC would reduce the duration of mechanical ventilation. The aim of this study was to test that hypothesis in a randomised controlled trial (RCT), that is, CLAC compared with manual oxygen control would be associated with a reduction in the duration of mechanical ventilation in ventilated infants born at less than 34 weeks of gestation.

Patients and methods

A non-blinded, RCT was undertaken at a tertiary neonatal unit (King's College Hospital NHS Foundation Trust, London, UK) between September 2021 and March 2025. Ventilated infants born below 34 weeks of gestation and within 48 hours of initiation of mechanical ventilation and less than 14 days of age were eligible for the study. We had initially planned to recruit infants less than 31 weeks of gestation, but sought ethical consent to amend the protocol to recruit infants less than 34 weeks when an audit demonstrated a relatively high number of infants also ventilated at the more mature gestational age.

Infants with major congenital abnormalities or who were receiving high frequency oscillatory ventilation (as depending on their underlying condition, might need different oxygen saturation targets) were excluded. The study was registered on ClinicalTrials.gov database (registration number: NCT05030337). Written, informed parental consent was obtained before recruitment.

Infants were randomised to receiving either CLAC (intervention group) or manual (control group) adjustment of the oxygen concentration from recruitment to successful extubation[15] that was defined as no need for reintubation within the subsequent 48 hours.[16] Infants who failed extubation continued in their initial study arm. If an infant was successfully extubated, the study was completed. Infants ventilated beyond day 28 of life were studied until their first extubation attempt. The nurse-to-patient ratio was determined by the patient's acuity and was 1:2 for all patients during the study according to the unit protocol.

Extubation was considered, as per unit policy, if the fraction of inspired oxygen (FiO_2) was<0.4, the infant had acceptable blood gases (ie, a pH>7.25 and an arterial pressure of CO_2<8.5 kPa) and their breathing rate was above the set ventilator rate.

Infants were ventilated on pressure-limited timed-cycled or volume-targeted ventilation using SLE6000 neonatal ventilators (Inspiration Healthcare, South Croydon, UK) and ventilation settings were manually adjusted by the clinical team as per the unit's protocol. Our pulse oximetry oxygen saturation targets in infants born at less than 34 weeks gestational age were 91%–95% with a low alarm limit of 90% and a high of 98%. For the duration of the study, participants were connected to the standard bedside monitor (Philips IntelliVue MX750) and an SpO_2 cable (SLE uSPO_2 cable) which was connected to the ventilator for continuous recording of SpO_2 and FiO_2 levels (standard care). The Philips monitor uses the Nellcor Neonatal SpO_2 sensor. The SLE cable uses Masimo SET Neonatal Pulse Oximetry Adhesive Sensor. There was usually a difference of 1%–2% in SpO_2 levels displayed with the Masimo probe providing lower readings. The 'SLE' SpO_2 function would activate an alarm for an SpO_2 below or above the target range. The clinical team would react to the bedside monitor that represented standard care, but any alarms from the ventilator would also be noted. Analysis was performed on data obtained via the 'SLE' SpO_2 cable that was connected to the Masimo oximeter. Oxygen saturation monitoring could be either preductal or postductal unless there was a difference between them, then preductal readings would be obtained. In addition to standard care, infants in the intervention group were connected to the Oxygenie Auto-O_2 closed-loop oxygen saturation monitoring software (Inspiration Healthcare, South Croydon, UK) which uses a proportional-integral-derivative algorithm.[17]

Manual adjustments to the FiO_2 were allowed at any point during the study, including the infants receiving automated oxygen control as per the clinician's discretion.

Data were downloaded directly from the ventilator and consisted of second-by-second recordings of ventilator settings and paired SpO_2 and FiO_2 results until day 28 of life or until successful extubation, whichever came first. Data collected were the proportion of the time spent below the target oxygen saturation range (SpO_2<91%) and in hypoxaemia (SpO_2<85%), the percentage of time spent within the target oxygen range (SpO_2: 91%–95%), and in hyperoxaemia (SpO_2>95%). When infants were weaned to room air (FiO_2: 0.21), an SpO_2 above target range was considered as being within target range as the FiO_2 could not be weaned any further. The unit's protocol for oxygen titration was to adjust the FiO_2 as required to maintain the SpO_2 within the target range. This approach was taken during the manual and automatic oxygen control periods.

A potential risk in the intervention group could be the masking of an increased oxygen requirement as oxygen saturation levels remained within their target range. The CLAC system, however, has an alarm set to be activated if there is an increase in FiO_2 of 30% from the baseline oxygen requirement.

Demographic and outcome data were collected from the clinical records which included gestational age, birth weight, postnatal age and weight at study enrolment, use of antenatal steroids, mode of delivery, doses of surfactant, administration of postnatal corticosteroids, birth plurality and diagnoses at enrolment were recorded for each infant. Outcome data were reviewed when all participants had reached a postmenstrual age of 36 weeks at least.

Systemic corticosteroids were administered to infants who remained ventilated beyond the first week of life[18] with an FiO_2 requirement>0.60 and a mean airway pressure>10 cm H_2O. Intravenous dexamethasone was given over a 9-day tapering course with a cumulative dose of 2.7 mg/kg.[19]

The primary outcome was the duration of mechanical ventilation. The secondary outcomes were the percentage of time spent within target oxygen saturation range, the time spent in hypoxaemia or hyperoxaemia, the number of days requiring supplementary oxygen, the incidence of BPD at 36 weeks post menstrual age (PMA), the length of neonatal unit stay and need for home oxygen. BPD severity was categorised according to the definition proposed at the National Heart, Lung and Blood Institute-sponsored workshop in year 2000.[19]

Sample size calculation

In a cohort of 368 preterm infants born between 24 and 30 weeks of gestation, the SD of the duration of mechanical ventilation was 3.83 days.[20] The median duration of ventilation was 12 days (mean 19 days). Randomisation of 70 infants (35 in each group) would allow detection of a reduction in the duration of mechanical ventilation of 3 days with 90% power and a significance level of 5%.

Analysis

The data were assessed for normality with the Kolmogorov-Smirnov test and found not to be normally distributed.

Table 1 Demographics according to randomisation. Data are presented as the N (%) or medians (range)

	Infants randomised to CLAC*	Infants randomised to manual oxygen control
Number of infants	34	35
Male sex	14 (41.2)	17 (48.6)
Gestational age (weeks)	27.6 (22.4–33.6)	26.6 (22.7–31.7)
Gestational age≥30 weeks	5 (14.7)	2 (5.7)
Birth weight (g)	873 (510–1900)	783 (475–1685)
Birth weight z-score	−0.205 (−3.51 to 1.62)	−0.26 (−2.39 to 1.55)
Prolonged rupture of membranes (>18 hours)	8 (23.5)	4 (11.8)
Completed antenatal steroids	22 (64.7)	21 (60)
Doses of surfactant administered	1 (1–2)	1 (1–3)
APGAR score at 1 min	4 (1–9)	5 (1–8)
APGAR score at 5 min	8 (2–10)	8 (2–10)
Day of life at study	1 (1–14)	2 (1–9)
Corrected gestational age at study entry	28.1 (22.4–33.6)	27.1 (22.9–31.7)
Hours ventilated at study entry	15 (2–320)	27 (2–168)
Received treatment for PDA†	8 (23.5)	13 (37.1)
Received systemic corticosteroids	10 (29.4)	14 (40)
IVH grade III‡ or IV/PVL§	8 (23.5)	10 (28.6)
Day of life at first extubation attempt	4 (1–52)	12 (2–107)
Extubation success	23 (67.6)	23 (65.7)
Survived to discharge	27 (79.4) One inpatient at the time of analysis	27 (77.1) Three inpatients at the time of analysis
Postmenstrual age at discharge (weeks)	40.4 (35.6–58.7)	42.3 (35.3–68.3)
Weight at discharge (g)	2890 (1850–5595)	3030 (1800–6170)
Home oxygen	9 (26.5)	18 (51.4)

*Closed-loop automated oxygen control.
†Patent ductus arteriosus.
‡Intraventricular haemorrhage.
§Periventricular leukomalacia.
APGAR, appearance, pulse, grimace, activity, respiration; NS, non-significant.

Differences in continuous data were tested for statistical significance using the Mann-Whitney U test. Categorical data were assessed using the χ^2 test. The analysis was undertaken using IBM SPSS V.28.0.1.1 (SPSS, Chicago, Illinois, USA). Patients' data were analysed according to their randomised assignment group. Imputation of missing data was not performed. A p value of <0.05 was considered statistically significant.

RESULTS

Informed consent was obtained from 70 parents. One infant was subsequently excluded due to underlying congenital cytomegalovirus infection that was diagnosed after randomisation. There were 34 infants in the intervention group and 35 in the control group. The 69 infants had a median gestational age of 27.0 (IQR 25.6–29.0) weeks and median birth weight of 795 g (650–1105 g) and were studied at a median corrected postmenstrual age of 27.6 (25.9–29.1) weeks (table 1).

There were no episodes when an increased oxygen requirement was missed during the use of automated oxygen control. There were no significant differences in the ventilator settings of the two groups at the beginning of the study (table 2) and at the time of first extubation attempt (online supplemental table 1). Ventilator data were truncated to 28 days for a total of 26 infants (10 in the intervention group and 16 in the manual oxygen control group).

The median percentage of time spent below the target SpO_2 range (SpO_2<91%) and in hypoxaemia (SpO_2<85%) was significantly lower for infants receiving CLAC (p=0.004 and p<0.001, respectively; table 3) compared with manual oxygen control, but the median FiO_2 delivery during hypoxaemia (p=0.159) was not significantly higher. Infants in the intervention group spent a greater proportion of their time within the target SpO_2 range (91%–95%), (p<0.001). The median FiO_2 requirement to achieve peripheral oxygen saturations within the target range

Table 2 Ventilator settings of the infants at the beginning of the study. Data are presented as median (range)

	Infants randomised to CLAC	Infants randomised to manual oxygen control	P value
Mean airway pressure (cm H_2O)	9 (7–15)	9.5 (5.4–14)	0.894
Positive inspiratory pressure (cm H_2O)	25 (12–30)	25 (15–30)	0.142
Positive end expiratory pressure (cm H_2O)	5 (5–7)	5 (4.7–6.5)	0.380
Inspiratory time (seconds)	0.4 (0.35–0.45)	0.4 (0.34–0.5)	0.348
Rate (breaths per minute)	40 (30–60)	45 (30–60)	0.97
Inspired oxygen concentration (%)	25 (21–65)	25 (21–60)	0.943

CLAC, closed-loop automated oxygen control.

Table 3 Hypoxaemia and hyperoxaemia by randomised mode. Data are presented as the medians (range)

	CLAC	Manual oxygen control	P value
% time below target range*	8.9 (0–6.4)	15.7 (0.5–39.6)	**0.004**
% time in target range†	87.5 (52.4–99.0)	59.3 (27.3–99.5)	**<0.001**
% time above target range‡	4.4 (0–19.7)	20.9 (0–40.5)	**<0.001**
% time with SpO_2<85%	0.3 (0–6.4)	1.6 (0–6.3)	**<0.001**
SpO_2 % during hypoxaemia§	89 (86–90)	89 (86–91)	0.095
FiO_2 % during hypoxaemia	32 (24.5–96)	32 (21–65)	0.159
SpO_2 % in target range	94 (93–99)	94 (93–98)	0.114
FiO_2 % in target range	22 (21–60)	30 (21–56)	0.201
SpO_2 % during hyperoxaemia¶	96 (96–98)	97 (95–99)	**<0.001**
FiO_2 % during hyperoxaemia	25.5 (22-57)	35 (23–55)	**0.014**

P-values< 0.05 appear in bold.
*SpO_2<91%.
†SpO_2: 91%–95%.
‡SpO_2>95%.
§SpO_2<85%.
¶SpO_2>95%.
CLAC, closed-loop automated oxygen control; FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation level.

did not differ significantly between the groups (p=0.201). The time spent in hyperoxaemia (SpO_2>95%) was significantly lower during CLAC (p<0.001) and the median FiO_2 delivery during hyperoxaemia was lower (p=0.014).

CLAC was associated with a lower median duration of mechanical ventilation (p=0.027; table 4), and median duration of supplemental oxygen (p=0.031; online supplemental figure 1), and median time to first extubation attempt (p=0.018; figure 1). The incidences of BPD (p=0.015) and the combined outcome of moderate/severe BPD or death at 36 weeks PMA (p=0.008) were lower. In addition, fewer infants in the intervention group were discharged on home oxygen (p=0.016). The median length of neonatal unit stay (p=0.205) and the incidence of ROP requiring treatment (p=0.168) did not differ significantly between the two groups.

DISCUSSION

We have demonstrated in an RCT that automated oxygen control was associated with shorter durations of mechanical ventilation and supplemental oxygen, a reduced incidence of BPD and number of infants discharged on home oxygen.

In agreement with previous studies in preterm infants,[7–12 21] use of CLAC was associated with improved achievement of oxygen saturation targets and reduced hyperoxaemia. In our study, CLAC was associated with a significantly reduced time spent below the target oxygen range (SpO_2<91%) and the time spent in hypoxaemia (SpO_2<85%) over a period of 28 days. In some studies,[22–26] automated oxygen control reduced the percentage of time spent below the targeted SpO_2 range, but in others, it was less effective than manual control.[13 27–30] More recent evidence suggests that the relative effect of CLAC on oxygen saturation targeting varies over time. Time-based analysis of data from an RCT in preterm infants receiving non-invasive respiratory support demonstrated that automated oxygen delivery increased the time spent below the target SpO_2 range at the start of its use that gradually decreased over time, whereas for infants on manual oxygen control, hypoxaemia progressively increased.[31]

Manual control can be a relatively subjective intervention and more frequent manual adjustments might result in greater time spent within target range. Other studies have reported that the percentage time spent within the target SpO_2, ranged from 35% to 80% using manual control, so our median percentage time in range of 59.3% using manual control is not out of proportion compared with current clinical practice.[12]

Our findings confirm our hypothesis that the improvement in achieving oxygen saturation targets during CLAC resulted in earlier extubation. Indeed, for infants randomised to CLAC, the median time spent within the target oxygen range increased by 28%, days on oxygen were reduced and the time to first extubation attempt was almost halved with similar ventilation settings at the time of extubation and extubation success rates. This

Table 4 Primary and secondary outcomes by randomised mode. Data are presented as the medians (range)

	Infants randomised to CLAC	Infants randomised to manual oxygen control	P value
Duration of mechanical ventilation (days)	11 (1–57)	40 (3–134)	0.027
*BPD of any severity among infants who survived to discharge	16 (55)	26 (83.9)	0.015
Moderate/severe BPD	14 (41.2)	26 (74.3)	0.008
Death	5 (14.7)	4 (11.4)	
Days of supplemental oxygen	33 (0–100)	47 (3–335)	0.031
Length of neonatal unit stay (days)	79 (16–209)	103 (43–321)	0.205
Treatment for †ROP	4 (13.8)	6 (19.4)	0.168

*Bronchopulmonary dysplasia.
†Retinopathy of prematurity.
BPD, bronchopulmonary dysplasia; CLAC, closed-loop automated oxygen control; ROP, retinopathy of prematurity.

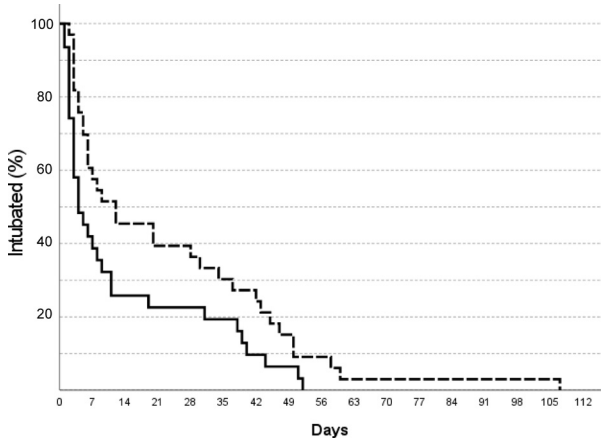

Figure 1 Kaplan-Meier plot for time to first extubation. The dashed line corresponds to infants randomised to manual oxygen control and the solid line to infants receiving automated oxygen control.

suggests that the clinicians had responded to the overall improvement in oxygen saturation levels and oxygen requirements.

In a retrospective cohort study comparing outcomes pre and post implementation of automated oxygen control as standard care for a total of 588 preterm infants (293 pre-implementation vs 295 in the post-implementation cohort), there was a significant reduction in the duration of mechanical ventilation (mean (SD) days: 4.7±8.3 vs 6.4±10.1, p=0.029) post implementation, but no significant effects on morbidity or mortality at hospital discharge[32] or neurodevelopmental outcomes at 2 years of age.[33] The study, though, was limited by its retrospective design, changes to neonatal care during the study span and its limited power to detect differences in outcomes including BPD, ROP, necrotising enterocolitis, intraventricular haemorrhage and periventricular leukomalacia.[32] Moreover, an RCT including 44 preterm infants receiving invasive or non-invasive respiratory support reported that rates of BPD (38.1% vs 47.4%, p=0.75) and severe ROP (5% vs 21%, p=0.18) were smaller among infants randomised to CLAC versus manual oxygen control, but the differences were not significant.[34] BPD is a multifactorial disease, and the sample size required to demonstrate differences in that outcome could exceed a single unit capacity. Therefore, we based the size of our study on detecting a difference in the duration of mechanical ventilation, a meaningful clinical outcome and directly related to the development of BPD.[2] It should be noted that our sample size calculation was based on a population of infants with a gestational age of less than 30 weeks. In our study, however, we pragmatically included infants up to 34 weeks so that the study population could be achieved at a single centre level within a reasonable time frame. The median gestation, however, of the infants was 27 weeks with an upper quartile of 29 weeks. It follows, thus, that the great majority of our included infants were within the gestational range of the infants in the study we used to calculate our sample size.[20]

The difference in the median duration of mechanical ventilation between the CLAC and the manual control groups in our study was larger than anticipated. It potentially was augmented by some differences in the demographics between the two groups such as the gestational age, the incidence of male sex and the presence of PDA. Furthermore, a greater proportion of the CLAC infants had prolonged rupture of the membranes. There may be a risk of confounding due to some imbalances in the demographics of the two groups.

We should note that our study was powered to detect a difference in the duration of mechanical ventilation and not to detect a difference in BPD, which is a complex outcome and is due to multiple interrelated parameters and would require significantly larger population. Our finding, thus, of a significantly shorter duration of ventilation coupled with the unexpected but significant finding of a decreased incidence of BPD potentially highlights the contribution of prolonged invasive ventilation in the pathophysiology of BPD. We acknowledge that our findings should be explored in larger studies whose sample size would be calculated around this important outcome.

This study has strengths and some limitations. It is the first randomised controlled trial to report on the effect of CLAC on the duration of mechanical ventilation and longer-term respiratory outcomes. Most infants were randomised within 48 hours of initiation of mechanical ventilation and all remained in their initial study arm until they were successfully extubated. Therefore, we had more data points for analysis compared with previous crossover studies.[9] The study was not powered to detect differences in the incidence of BPD, but we did demonstrate a significant association and have suggested a plausible explanation. Automated oxygen control devices differ regarding their effect on the time spent in target SpO_2 range in preterm infants[35 36] and, therefore, use of a different controller may have had a different impact on clinical outcomes. Our study is a single centre one with a relatively small sample size, so our results should be replicated in larger multicentre studies before they can be considered applicable to routine clinical practice.

In conclusion, use of CLAC in a randomised trial was associated with reductions in the durations of mechanical ventilation and supplemental oxygen, the incidence of BPD and the need for home oxygen in preterm ventilated infants.

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ORCID iDs
Ourania Kaltsogianni https://orcid.org/0000-0001-9381-5521

Theodore Dassios https://orcid.org/0000-0001-5258-5301
Allan Jenkinson https://orcid.org/0000-0003-2667-2190
Kenta Ikeda https://orcid.org/0009-0009-3744-6739
Masashiro Sugino https://orcid.org/0000-0002-8172-3379
Anne Greenough https://orcid.org/0000-0002-8672-5349

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