Automated control of oxygen titration in preterm infants on non-invasive respiratory support

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ABSTRACT

Objective To evaluate the performance of a rapidly responsive adaptive algorithm (VDL1.1) for automated oxygen control in preterm infants with respiratory insufficiency.

Design Interventional cross-over study of a 24-hour period of automated oxygen control compared with aggregated data from two flanking periods of manual control (12 hours each).

Setting Neonatal intensive care unit.

Participants Preterm infants receiving non-invasive respiratory support and supplemental oxygen; median birth gestation 27 weeks (IQR 26–28) and postnatal age 17 (12–23) days.

Intervention Automated oxygen titration with the VDL1.1 algorithm, with the incoming SpO_2 signal derived from a standard oximetry probe, and the computed inspired oxygen concentration (FiO_2) adjustments actuated by a motorised blender. The desired SpO_2 range was 90%–94%, with bedside clinicians able to make corrective manual FiO_2 adjustments at all times.

Main outcome measures Target range (TR) time (SpO_2 90%–94% or 90%–100% if in air), periods of SpO_2 deviation, number of manual FiO_2 adjustments and oxygen requirement were compared between automated and manual control periods.

Results In 60 cross-over studies in 35 infants, automated oxygen titration resulted in greater TR time (manual 58 (51–64)% vs automated 81 (72–85)%, p<0.001), less time at both extremes of oxygenation and considerably fewer prolonged hypoxaemic and hyperoxaemic episodes. The algorithm functioned effectively in every infant. Manual FiO_2 adjustments were infrequent during automated control (0.11 adjustments/hour), and oxygen requirements were similar (manual 28 (25–32)% and automated 26 (24–32)%, p=0.13).

Conclusion The VDL1.1 algorithm was safe and effective in SpO_2 targeting in preterm infants on non-invasive respiratory support.

Trial registration number ACTRN12616000300471.

What is already known on this topic?

- ► Automation of oxygen delivery for preterm infants has the potential to more effectively target the desired SpO_2 range and to avoid the extremes of oxygenation.
- ► Previous automated control devices are known to be more effective than routine manual control in SpO_2 targeting, but the benefits have generally been modest.
- ► We have developed and refined a proportional–integral–derivative algorithm for automated oxygen control (VDL1.1), which now requires further evaluation.

What this study adds?

- ► Under standard clinical conditions, the VDL1.1 algorithm was considerably more effective in SpO_2 targeting than routine manual control of oxygen titration, with 23% more time in the desired SpO_2 range.
- ► The extremes of oxygenation were largely avoided, and prolonged episodes of hypoxia and hyperoxia were rare.
- ► Effective oxygen control was achieved with very few manual inspired oxygen concentration adjustments and similar exposure to oxygen.

INTRODUCTION

The conundrum of oxygen therapy for preterm infants is that while evidence favours the targeting of a predetermined range of oxygen saturation (SpO_2),[1] achieving this with any precision is beyond the capacity of bedside clinicians, despite their best efforts. Both for ventilated infants and for those on non-invasive support, manual adjustment of inspired oxygen concentration (FiO_2) is associated with a considerable proportion of time spent outside the SpO_2 target range (TR).[2–4] Automating this process has been seen as a logical goal for over four decades[5] and offers the hope of more effective SpO_2 targeting and the benefits that may follow.[6]

Numerous algorithms for automation of control of oxygen therapy now exist. Within each, an incoming SpO_2 reading is compared with a desired setpoint (either the midpoint or limits of the TR), and an updated value for FiO_2 is calculated and actuated mechanically.[6–8] Each algorithm has been found to result in more time in the SpO_2 TR, although the benefit has generally been modest.[9–22] The resultant proportion of time in the TR has been anywhere from 40% to 85%, and has been noted to be 62% in one study where a narrow SpO_2 range (span of five values) was targeted.[16]

We recently reported our preliminary clinical experience of a novel proportional–integral–derivative

(PID) algorithm for automated oxygen control in preterm infants.[23] In a 4-hour cross-over study in 20 preterm infants, time in TR (91%–95%) was 81% during the automated control periods. This study was done with a researcher monitoring device function at the bedside during the automated control periods, such that clinicians did not interact directly with the control device.

Acknowledging the information that has been gained from previous investigations of automated control algorithms in preterm infants, several outstanding questions of a practical nature remain. These include whether automated oxygen titration can function effectively (1) with differing baseline oxygen requirements, (2) in conditions of high and low frequencies of intermittent hypoxaemia (IH), and (3) during times of nursing intervention. The proportion of individual infants gaining benefit from automated oxygen control also deserves further evaluation.

Herein we report a study comparing automated oxygen control using an adaptive PID algorithm with manual oxygen control in preterm infants. We aimed to examine, under standard clinical conditions, the safety and efficacy of oxygen titration under control of the algorithm, hypothesising that automated control would afford a higher proportion of time within the SpO_2 TR.

METHODS

Study infants

We conducted a prospective cross-over study of automated oxygen control in the Neonatal and Paediatric Intensive Care Unit at the Royal Hobart Hospital. Preterm infants born at <32 weeks' gestation were eligible for inclusion if (1) ≤4 months chronological age, (2) receiving non-invasive respiratory support with continuous positive airway pressure (CPAP) or nasal high flow (HF) and (3) showing a requirement for oxygen therapy and/or a propensity to hypoxic events with or without apnoea. Each infant could be studied twice if remaining eligible.

Automated oxygen control equipment

For this study, the device used in our previous work[23 24] was modified (see online supplemental text). In brief, the previously described core PID algorithm and its enhancements were retained in full, with several additions to render the updated algorithm (VDL1.1) suitable for standard clinical conditions. These were (1) periodic update of the reference FiO_2 ($rFiO_2$), indicating baseline oxygen requirement; (2) a subroutine for long-lasting periods of missing SpO_2 signal (online supplemental table S1); (3) an apnoea-response module; (4) a suite of alarms; and (5) a user interface (online supplemental figure S1) enabling bedside staff to interact directly with the oxygen control system and to make manual adjustments to FiO_2 as appropriate.

Study procedures

Automated oxygen titration with the VDL1.1 algorithm was evaluated in a cross-over design in which a period of 24 hours of automated oxygen control was compared with two flanking periods of 12 hours of manual control, with a 30 min washout period between epochs. Bedside staff were made familiar with the functions of the oxygen control device and instructed to retain control of patient oxygenation at all times. For consistency of approach, guidelines for FiO_2 adjustment were placed at the bedside during the study (online supplemental table S2). Manual alteration of FiO_2 during automated control epochs halted algorithm-generated FiO_2 adjustments for 30 s, with the clinician-set FiO_2 then adopted at the resumption of automated control. The desired SpO_2 range was 90%–94% with alarms set at 89% and 96% (as per usual in our unit); the high SpO_2 alarm could be decommissioned if the infant was in room air. Other alarms and all other aspects of care were as per routine throughout the study. Nurse:patient ratio was 1:2.

As will be detailed in a separate report, the function of an apnoea-response module (delivering a brief pre-emptive increase in FiO_2) was evaluated in a nested study. Bedside clinicians were unaware of the status of this module, which was switched on and off in 6-hour blocks in random sequence.

Data input and collection

The SpO_2 input to the control device was sourced from a standard oximetry probe (Masimo Corp, Irvine, California, USA) routed through a cardiorespiratory monitor (Infinity Delta, Dräger Medical Australia, Notting Hill, Australia). The displayed SpO_2 value thus served as the input to the algorithm. The oximetry probe was placed in both preductal and postductal positions according to clinical need. SpO_2 averaging was set at 2–4 s to optimise precision of oxygenation monitoring and detection of SpO_2 deviations.[25] SpO_2 values were deemed missing if zero/non-numerical, or if heart rate extracted from the photoplethysmographic signal was more than 30 beats/min below the ECG heart rate.

Using methodology described previously,[23] we recorded SpO_2 and heart rate at 1 Hz. Continuous video recordings of the bedspace were made at 5 frames/s. Relevant demographic, clinical and operational data were recorded for each infant, including gestation, birth weight, and details of clinical state and level of respiratory support at the time of the study.

Data processing and statistical analysis

As described fully in the online supplemental text, data processing included aggregation of data from flanking manual oxygen control epochs to give 24 hours of recordings, generation of SpO_2 histograms and determination of (1) proportion of time in various SpO_2 ranges; (2) frequency of prolonged episodes of hypoxaemia and hyperoxaemia; (3) frequency of IH, defined as SpO_2 of <80% for 10 s[26]; (4) the number of FiO_2 adjustments; and (5) average oxygen exposure.

Data were expressed as median and IQR unless otherwise stated. Comparisons were made between automated and manual control epochs using Wilcoxon matched pairs test. The primary outcome was proportion of time in TR (TR time), defined as SpO_2 of 90%–94% when receiving oxygen and 90%–100% when in air. In the preplanned analysis of the robustness of the overall findings, the influence of demographic, clinical and operational factors on the comparative efficacy of SpO_2 targeting was examined, as were safety events (see online supplemental text).

Sample size calculation

In the initial clinical study of the forerunner oxygen control algorithm, TR time during manual oxygen control was 53%±9.4% (mean±SD).[23] Detection of an absolute increase of 10% in this proportion with 90% power and $\alpha=0.05$ would require 20 infants overall if the groups were independent and potentially fewer in view of the cross-over design.[27] Given the additional requirements of the study, in particular to test the VDL1.1 algorithm under a range of clinical conditions, we performed 60 studies requiring a minimum of 30 infants.

Results

The study was conducted from April 2017 to September 2018. A total of 60 cross-over studies were undertaken in 35 infants,

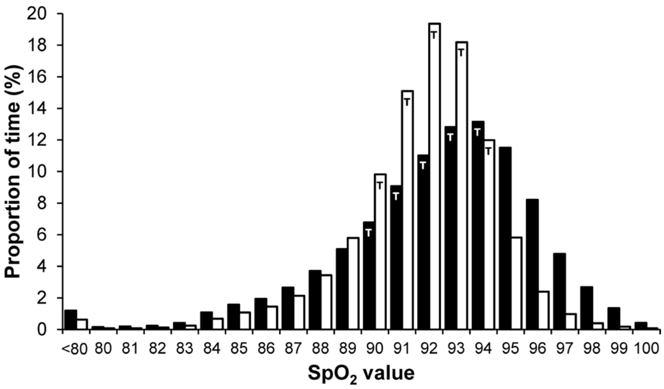

Figure 1 SpO_2 histogram comparison–time receiving oxygen. Pooled frequency histograms showing the proportion of time spent at each SpO_2 value, including only time when receiving supplemental oxygen (see online supplemental figure S3 for SpO_2 histogram including all study time). Black bars: manual control, white bars: automated control. T=SpO_2 values within the desired range (90%–94%).

with a median birth gestation of 27 weeks (IQR 26–28 weeks) and age at study of 17 (12 vs 23) days (see online supplemental table S3) for further details). Data from two flanking periods of manual control were available for 58 studies, with only a single manual control recording in two cases where respiratory support was no longer required. The proportion of missing SpO_2 signal was 2.9% overall, leaving 23.4 (23.2–23.6) hours and 23.4 (23–23.6) hours of usable time per study, and total time of 1376 and 1372 hours, for analysis of manual and automated oxygen controls, respectively.

Exemplary data recordings (online supplemental figure 2) depict the variability of SpO_2 during manual oxygen titration, which was less prominent during automated control, owing to frequent FiO_2 adjustments. The periodic adjustment of $rFiO_2$ is illustrated in online supplemental figure S2C.

SpO_2 histograms derived from pooled data including only time when receiving oxygen show a substantial increase in SpO_2 values within the TR during automated oxygen titration (figure 1), with a modal SpO_2 value at the midpoint of 92%. By contrast, manual control resulted in fewer SpO_2 values in the range of 90%–94%, a modal SpO_2 value of 94% and a skew towards hyperoxaemia. The histograms from all usable time show similar features (online supplemental figure S3).

Compared with manual control, for the study primary outcome of TR time, there was a 23% increase with automated oxygen control (table 1), and conversely less time outside the SpO_2 TR limits. Every infant gained benefit from automated oxygen titration in relation to TR time (online supplemental figure S4). SpO_2 values were also more frequently within the alarm range (89%–96%). Automated control led to a considerable diminution of time at the extremes of oxygenation (SpO_2<80% and SpO_2>98% when receiving oxygen), as well as reductions in time spent in the lesser ranges of hypoxaemia and hyperoxaemia.

Prolonged episodes of hypoxaemia and hyperoxaemia occurred with modest frequency during manual oxygen control, but were distinctly uncommon during automated control (table 2), with long-lasting hyperoxaemic episodes being virtually eliminated.

In a preplanned analysis of the robustness of the aforementioned findings, we examined whether there was an interaction of key demographic, clinical and operational factors with oxygen control mode for three important oxygenation outcome variables (figure 2). Analysis per infant (n=35), rather than per recording (n=60), did not alter the outcome differences noted for TR time (figure 2A and online supplemental table S4) nor for 30 s episodes of hypoxaemia (figure 2B) and hyperoxaemia (figure 2C). Neither gestation at birth nor age at study were covariates, whereas gender did influence the relationship between manual control values and outcome differences, with female infants showing a somewhat better response, amounting to ~1% more time in TR. Severity of lung dysfunction also demonstrated interaction, with narrowing of the TR time difference in infants for whom the baseline oxygen requirement was ≥0.35 or 0.25–0.35 (compared with FiO_2<25%), but conversely a widening of the event rate difference for hyperoxaemic episodes favouring automated control (figure 2, (online supplemental figure S5). For IH tertiles, there was an intercept difference (tertile 3 vs tertile 1, online supplemental figure S5).

During care times (3.6% of time overall), time in TR was globally reduced, but automated oxygen titration remained effective (figure 2 and online supplemental table S4 and online supplemental figure S6). The benefit of automated control was somewhat more in evidence by day than by night (figure 2), but

Table 1 SpO_2 targeting

	Manual control	Automated control	P value*
TR time†	58 (51–64)%	81 (72–85)%	<0.001 for each comparison
SpO_2 90%–94%	53 (47–58)%	69 (62–75)%	
SpO_2>94%	29 (23–37)%	15 (11–21)%	
SpO_2>94% when receiving oxygen	24 (19–30)%	6.9 (5.4–11)%	
SpO_2 in alarm range (89%–96%)	79 (74–82)%	88 (83–92)%	
SpO_2<90%	17 (12–22)%	12 (9.5–17)%	
SpO_2<80%	0.26 (0.086–0.60)%	0.085 (0.031–0.26)%	
SpO_2 80%–84%	0.47 (0.26–0.88)%	0.21 (0.085–0.36)%	
SpO_2 85%–89%	14 (10–17)%	11 (8.9–14)%	
SpO_2>96% when receiving oxygen	4.9 (3.6–9.8)%	1.1 (0.57–1.8)%	
SpO_2>98% when receiving oxygen	0.60 (0.29–1.5)%	0.13 (0.052–0.15)%	

Proportion of time (% of total usable time) within prespecified SpO_2 ranges during manual and automated oxygen control epochs, median (IQR).
*Wilcoxon matched pairs test for comparison of manual versus automated control.
†TR time: SpO_2 90%–94% when receiving oxygen, SpO_2 90%–100% when in air.
TR, target range.

Table 2 Prolonged SPO$_2$ deviations

	30 s episodes			60 s episodes		
	Manual control	Automated control	P value*	Manual control	Automated control	P value*
SpO$_2$<80% (episodes/hour)	0.25 (0.086–0.60)	0.085 (0.031–0.26)	<0.001 for each comparison	0.044 (0–0.17)	0 (0–0.085)	<0.001 for each comparison
SpO$_2$<85% (episodes/hour)	0.76 (0.35–1.5)	0.32 (0.12–0.64)		0.21 (0.086–0.47)	0.04 (0–0.13)	
SpO$_2$>96% in oxygen (episodes/hour)	1.7 (1.1–3.4)	0.14 (0.044–0.40)		0.50 (0.35–1.3)	0 (0–0.043)	
SpO$_2$>98% in oxygen (episodes/hour)	0.17 (0.085–0.52)	0 (0–0.043)		0.064 (0–0.19)	0 (0–0)	

Comparative frequency of continuous hypoxaemic and hyperoxaemic episodes (duration of 30 and 60 s) in manual and automated oxygen control epochs, median (IQR).
*Wilcoxon matched pairs test.

was similar for infants supported with CPAP or nasal HF (online supplemental table S4).

Whether expressed per individual or in pooled data, far fewer manual FiO$_2$ adjustments were required during the automated oxygen control period compared with manual control (table 3). The oxygen control algorithm generated frequent automatic FiO$_2$ alterations, reflected in a higher FiO$_2$ coefficient of variation during automated control (table 3). Oxygen titration safety events were infrequent during automated control (12 in total; see online supplemental table S5) but frequent during manual control (1011 overall). Average FiO$_2$ during the study recordings was 27% overall, and oxygen exposure did not differ between manual and automated modes of oxygen titration (table 3).

DISCUSSION

For the preterm infant with respiratory insufficiency, optimal oxygen delivery will likely be achieved by a combination of servo-controlled automated oxygen titration and prudent manual FiO$_2$ adjustments by bedside clinicians. In this cross-over study involving 35 infants, the VDL1.1 algorithm for automated oxygen control achieved a considerably higher proportion of time in the target SpO$_2$ range compared with manual control, with very few clinician-initiated FiO$_2$ adjustments during the automated control period. Considerably less time was spent in hypoxaemic and hyperoxaemic ranges, and prolonged episodes of SpO$_2$ deviation were markedly reduced. Average FiO$_2$ was equivalent during the automated and manual control periods.

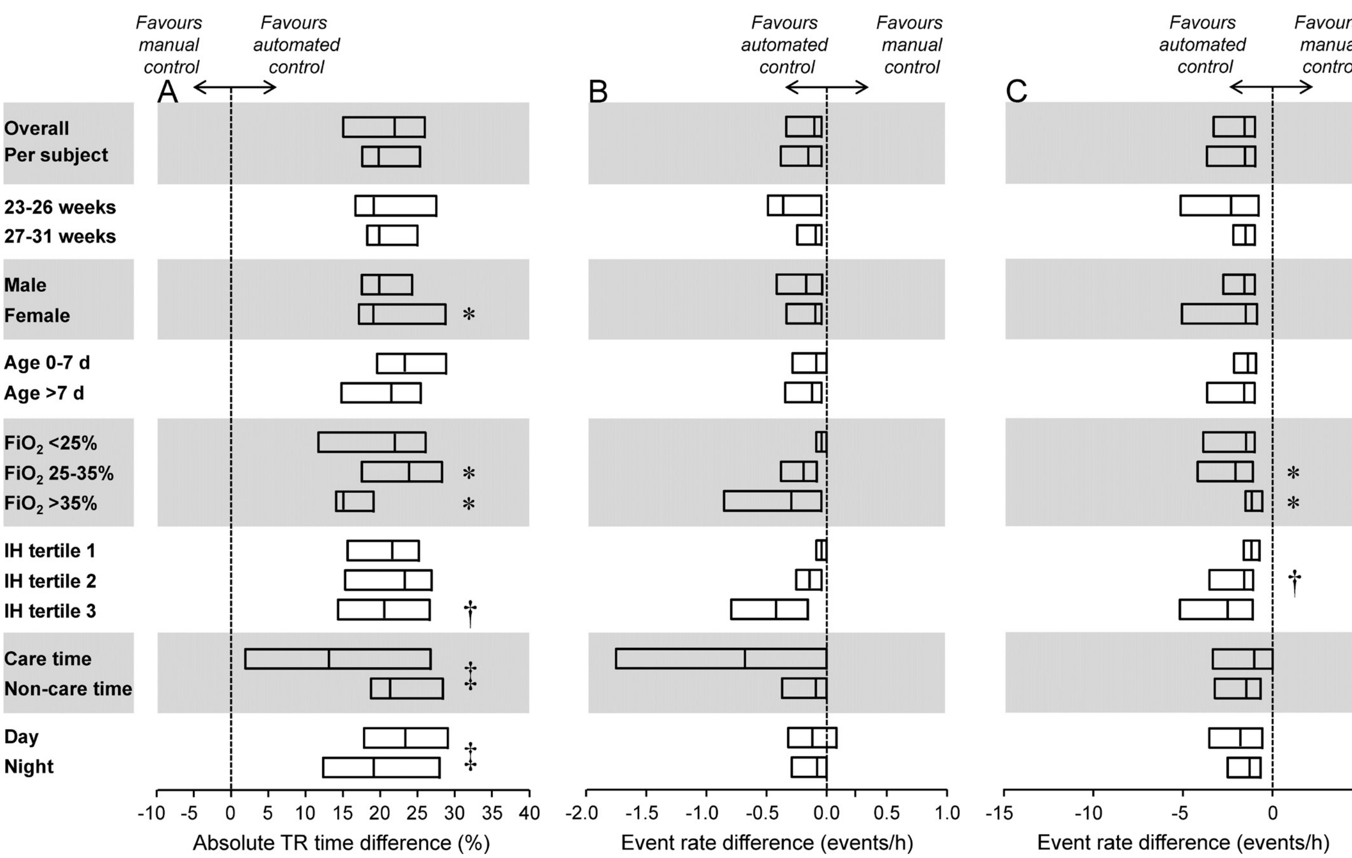

Figure 2 Oxygenation outcome differences. Boxplots (median, IQR) of difference in oxygenation outcome values between automated control and manual control, overall and by potential covariate. (A) TR time difference (manual control subtracted from automated control); (B) event rate difference for 30 s hypoxaemic episodes (SpO$_2$<80%); (C) event rate difference for 30 s hyperoxaemic episodes (SpO$_2$>96% when receiving oxygen). *Covariate found to have significant interaction in ANCOVA, p<0.05; †covariate found to have intercept difference in ANCOVA, p<0.05; ‡time compartments differ, p<0.05, Wilcoxon matched pairs test. IH: tertile boundaries 0.28 and 0.82 events/hour. ANCOVA, analysis of covariance; IH, intermittent hypoxia; TR, target range.

Table 3 FiO_2 adjustments and oxygen requirement

	Manual control	Automated control	P value*
Manual FiO_2 adjustments/hour	2.6 (1.7–3.8)	0.042 (0.031–0.13)	<0.001
Manual FiO_2 adjustments (mean/hour in pooled data)	3.2	0.11	–
Automated FiO_2 adjustments/hour	–	91 (61–130)	–
FiO_2 CV	13 (9.9–16)%	18 (13–23)%	<0.001
Average oxygen exposure	28 (25–32)%	26 (24–32)%	0.13

Frequency of FiO_2 adjustments refers to increments or decrements of 1% or more, median (IQR) unless otherwise stated.
*Wilcoxon matched pairs test.
CV, coefficient of variation; FiO_2, inspired oxygen concentration.

This study builds on our previous work examining the impact of automated oxygen control,[23] in this case with alterations to the control algorithm to render it suitable for standard clinical conditions, including updates of $rFiO_2$ and a response to protracted loss of SpO_2 signal. The combination of the forerunner PID algorithm with these additional features resulted in a 23% absolute increase in TR time, very similar to the 25% previously noted,[23] even though the oxygen control algorithm was applied under standard clinical conditions, including during times of nursing care, in the present study. The VDL1.1.algorithm was able to sufficiently adapt to the needs of a range of individuals with differing lung pathology, oxygen requirement and IH frequency, such that every infant gained an advantage.

We found the benefit of automated oxygen control over manual control to be more modest in infants where baseline FiO_2 was above 0.35, with a 15% absolute improvement in TR time for this group as against 23% overall. This may reflect a greater proportional contribution of intrapulmonary shunt (as distinct from ventilation–perfusion mismatch) to the oxygenation disturbance,[28] with an incomplete SpO_2 response to FiO_2 alterations as a result.

Manual adjustments of FiO_2 were required very infrequently during automated control with the VDL1.1 algorithm. This finding was all the more significant, given that the bedside staff were instructed to retain control of oxygenation at all times, and supplied with guidelines for oxygen titration to encourage consistency of approach. In replacing the repetitive manual task of adjusting FiO_2 with a robotic device, the need for only a handful of human interventions per day is in our view one hallmark of success. It suggests that bedside staff developed trust that oxygenation would be controlled in almost every situation, even during care times.

A notable difference in the SpO_2 histograms arising from oxygen titration by robotic device and by human, evident in many studies of different designs,[4 11 16 23 29] is that with algorithm-directed oxygen control, the SpO_2 midpoint is preferentially targeted, whereas with human control, the modal SpO_2 value is often at the upper end of the SpO_2 TR, with iatrogenic hyperoxaemia a frequent accompaniment. This should be taken into account in choosing the SpO_2 range when implementing automated oxygen control. We consider that reliable targeting of the SpO_2 midpoint by a control algorithm affords the opportunity to set a slightly higher SpO_2 TR than would be used under purely manual oxygen control. At least for the VDL1.1 algorithm, choice of a TR of 91%–95% (as in the previous study), rather than 90%–94% (present study), may lead to fewer SpO_2 values below 90% (previous study: 7.4% in pooled data,[23] current study: 12.7%) without increasing time with SpO_2 of ≥96% when receiving oxygen (4.0% in both studies).

The updating of reference FiO_2 each 30 min within the VDL1.1 algorithm is an important feature for several reasons. First, the displayed $rFiO_2$ value reflects latest demand for oxygen, and is a useful metric when set FiO_2 is changing frequently. Second, $rFiO_2$ contributes to the adaptive component of the algorithm, augmenting or tempering its response as appropriate. Finally, $rFiO_2$ is the basal value to which the calculated ΔFiO_2 is added to derive the set FiO_2 each second. Given that the ΔFiO_2 limits are −40% to +40%, it is important that $rFiO_2$ can adjust as lung disease is improving or worsening to allow sufficient leeway in responding to more pronounced SpO_2 deviations.

Our study has several limitations. The infants studied had a lower frequency of prolonged episodes of hypoxaemia than in some other studies of automated oxygen control.[16 20] Further, we focused on infants receiving non-invasive respiratory support, rather than mechanical ventilation, as the FiO_2 alterations were actuated via a motorised blender that could only be partnered with bubble CPAP or nasal HF. The mechanisms for hypoxaemia in the two settings are, however, likely very similar,[30 31] and SpO_2 targeting appears to be more difficult in infants on non-invasive support,[16] at least in part related to nurse:infant ratio.[4 32] Further, a recent cross-over study of the function of the VDL1.1 algorithm in ventilated infants also noted considerably more time in the SpO_2 TR with automated compared with manual oxygen control (88% vs 70%).[33]

CONCLUSION

The VDL1.1 oxygen control algorithm was safe and effective in SpO_2 targeting in preterm infants on non-invasive respiratory support under a range of clinical conditions.

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Contributors PAD: conceived the algorithm (with TJG) and this study, oversaw its conduct, compiled and analysed the data, wrote the first draft of the manuscript, and approved the final version. AM: conceived and developed the study equipment, assisted in conducting the study, compiled and analysed the data, edited the manuscript and approved the final version. OJL, CB and SKMA: assisted with the study conduct, reviewed and edited the manuscript, and approved the final version. RJ: identified enhancements to the automated control algorithm, reviewed and edited the manuscript, and approved the final version. CE-S: assisted in developing the study equipment, edited the manuscript and approved the final version. KL: compiled and analysed the data, edited the manuscript and approved the final version. TJG: conceived the algorithm (with PAD) and this study, oversaw its conduct, reviewed and edited the manuscript, and approved the final version.

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Competing interests The University of Tasmania and Tasmanian Health Service have jointly lodged a patent application concerning automated control of inspired oxygen concentration in the newborn infant, and have entered into a licensing agreement with SLE Limited allowing use of the VDL1.1 algorithm (as OxyGenie) in SLE respiratory support devices.

Patient consent for publication Not required.

Ethics approval The study was prospectively registered and approved by our local ethics committee. Written informed consent was obtained from parents of each enrolled infant.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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