Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Clinical quantification of SpO_2 instability using a new histogram classification system: a clinical study

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BACKGROUND: Oxygenation instability is not quantified or documented despite being common and correlated with neonatal morbidities, retinopathy of prematurity, and adverse 18-month outcomes.

METHODS: We developed a five-type SpO_2 histogram classification system based on the SpO_2 difference within the 10–90th cumulative time percentile (A) and the time percentage with SpO_2 ≤80% (B). In type 1, A is <5% and in type 5, A and B are ≥10%. We then studied consecutive 12-h SpO_2 frequency histograms in all infants ≤34 weeks gestation receiving respiratory support on day 1, over 6 months.

RESULTS: Six thousand and sixteen histograms were obtained in 73 infants, 28.9 ± 3.0 weeks gestation, and birth weight (BW) 1318.5 ± 495 g. All types were common and did not overlap. Type 3–5 ("unstable") histograms were more common in oxygen or any intubated support. Time in SpO_2 <85% and <80% progressively increased in types 3–5. Among histograms in oxygen, the mean (±SD) of SpO_2 medians was 92.8 ± 1.9. Infants ≤28 weeks exhibited three phases of SpO_2 instability (stable–unstable–stable). Those developing unstable histograms during the first week received longer ventilatory support (median [IQR], 101 [66] vs. 62 [28] days) and supplemental oxygen (62.5 [72] vs. 40.5 [40] days), and more were on ventilatory support at 40 weeks (7/15 vs. 0/10).

CONCLUSIONS: Classified SpO_2 histograms quantify and document SpO_2 instability and identify early infants at risk of prolonged respiratory support, while median SpO_2 does not.

Pediatric Research (2020) 87:716–720; https://doi.org/10.1038/s41390-019-0566-6

INTRODUCTION

Oxygen saturation (SpO_2) instability is common among premature infants, with an average of over 100 hypoxemic events per day in the first 8 weeks of life.[1] In a mouse model of bronchopulmonary dysplasia (BPD), intermittent hypoxic stress during induction of BPD potentiated oxidative stress in lung tissue, exacerbated alveolar developmental arrest[2] and was associated with delay in cerebral growth and neurodegeneration.[3] Furthermore, simulation of intermittent hypoxemia in neonatal mice resulted in permanent sensorimotor deficit and cerebral hypomyelination.[4] In premature infants, the incidence of intermittent hypoxemia has been related to retinopathy of prematurity requiring laser therapy,[1] BPD,[5,6] and adverse 18-month outcomes.[7] Various interventions such as change in ventilation mode,[8] change in position,[9] and RBC transfusion[10] have decreased the incidence of hypoxemic events in premature infants; however, the day-to-day clinical evaluation, quantification, and documentation of SpO_2 instability in the neonatal intensive care unit (NICU) is hampered by the lack of an objective tool and language.

SpO_2 histograms reveal the median SpO_2 and the presence and magnitude of SpO_2 instability over chosen periods of time ranging from the previous 30 min to 24 h.

In this manuscript, we describe a new SpO_2 histogram classification system and use it to describe the prevalence, magnitude, and natural history of SpO_2 instability in a busy level III NICU in a cross-sectional observational study.

MATERIALS AND METHODS

Study design and patients

This was a two-phase observational study conducted in the 60-bed, level III NICU at BC Women's Hospital (Vancouver, BC, Canada).

In phase 1, we developed and piloted an SpO_2 histogram classification system in a convenience sample of 29 premature infants ≤34 weeks gestation receiving respiratory support, such as continuous positive airway pressure (CPAP), non-invasive ventilation, or intubated respiratory support, during a period of 8 consecutive days. This proof-of-concept pilot was conducted to verify that five distinct histogram types, pre-defined by the study team, covered the spectrum of histograms seen and did not overlap. By the end of this phase, we made adjustments to the piloted classification system in order to simplify how each histogram type was defined (Fig. 1).

During phase 2 we prospectively applied the updated classification system to a sample consisting of all premature infants admitted between June and November of 2015 at ≤34 weeks gestation with the need for invasive or non-invasive respiratory support on day 1. Infants with congenital diaphragmatic hernia, hypoxic ischemic encephalopathy, congenital heart defect, or major congenital anomalies incompatible with life were excluded. The observation period started on the day of admission and continued until the date of discharge with participants receiving continuous pulse oximetry monitoring for the duration. Data were analyzed cross-sectionally and longitudinally.

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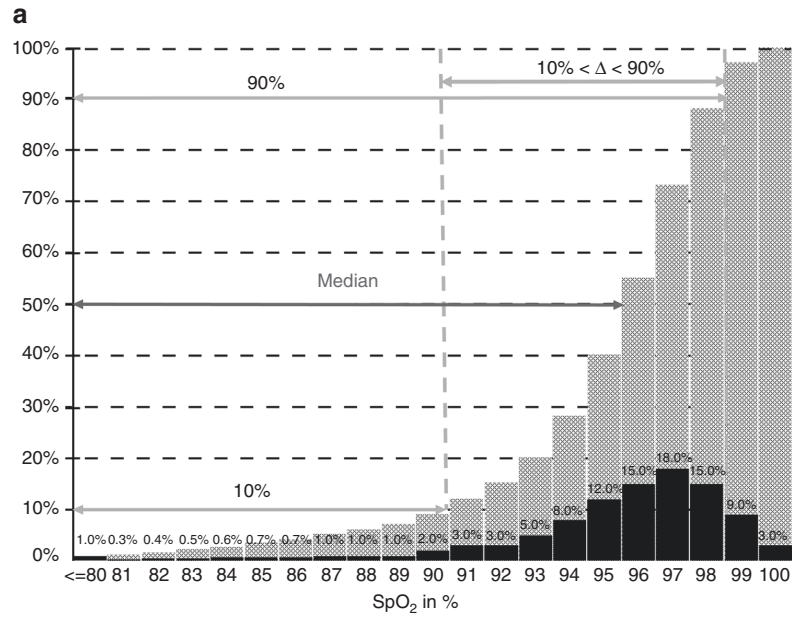
Received: 18 December 2018 Revised: 21 August 2019 Accepted: 27 August 2019
Published online: 20 September 2019



b

Type	A: # of bars between 10% and 90% (Δ)	B: % time in SpO2 ≤80%
1	<5	
2	5–9	
3	≥10	<5
4	≥10	5–9
5	≥10	≥10

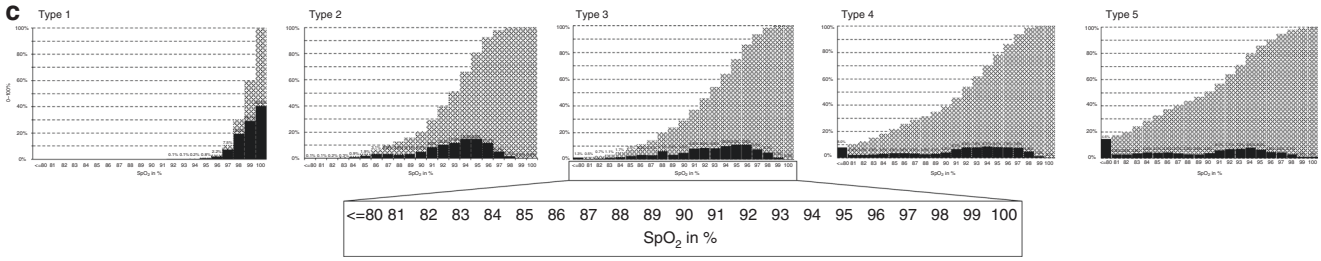


Fig. 1 The histogram classification system. **a** A sample SpO_2 histogram. SpO_2 histograms are classified by counting the number of gray bars between the 10th and 90th percentage of time and the percentage of time with SpO_2 ≤80%. The values obtained are entered into the classification table in **b**. **c** Examples of type 1–5 SpO_2 histograms

Cross-sectionally we determined the prevalence of each histogram type overall and in relation to the type of respiratory support being administered, and the mean (±SD) of the median time spent in SpO_2 ≤80%, <85%, 88–92%, 85–95%, 90–95%, and >95% for each histogram type. Longitudinally we studied the natural history of oxygenation instability among premature infants as measured by histogram type from day 1 to discharge or transfer to a level II NICU.

During the time of the study, the target SpO_2 range was 88–92%, and the alarm limits were set at 86–94% in infants where the fraction of inspired oxygen (FiO_2) was >0.21 or 86–100% in infants with $FiO_2 = 0.21$.

This was a pre-planned analysis of data obtained during a PDSA (Plan, Do, Study, Act—The W. Edwards Deming Institute, Ketchum, ID) audit aimed at increasing histogram use in the NICU, and was approved by the Institutional Review Board of our center with informed consent waived.

SpO_2 and histograms

SpO_2 was obtained continuously using pulse oximetry on the normal sensitivity setting, with a 0.5 Hz sampling rate (Radical; Masimo, Irvine, CA, USA) and was displayed with a 10-s averaging time. We used real-time 12-h histograms built with a 1-s real-time sampling rate, available as a standard option in Software Revision J.10.26, from the Phillips Intellivue MX800 monitors.

In this pragmatic study, we intended to create and use a common approach and language to document, communicate, and better understand individual oximetry data in the NICU. The pulse oximeter probe limb sitting was not standardized; the site was chosen by nursing based on nursing considerations, and nursing was responsible to obtain the best possible oximeter signal at all times. Furthermore, there were no SpO_2 validation rules, and we did not exclude areas of data dropout ($SpO_2 = 0$ and pulse rate = 0) or areas of excessive variability or consider the variables related to signal quality such as Signal IQ- signal identification and quality indicator, Signal IP- signal perfusion index, or pulse rate to heart rate correlation.

Histogram classification

In every SpO_2 histogram (Fig. 1a), the horizontal axis shows the range of the displayed SpO_2; we set the SpO_2 range from 81 to 100% and the unit width at 1%. The vertical axis shows the percentage of time. The bars in the foreground (black) show that the percentage-of-time SpO_2 values fall into each unit on the scale. The bars in the background (gray) show the cumulative percentage-of-time value, which results from adding each of the foreground bars to the sum of those to its left. The percentage of time with SpO_2 below 81% is shown as a single percentage-of-time cumulative frequency bar to the left of the 81% bar. The median SpO_2 in each histogram is the interpolated SpO_2 of the cumulative bar(s) with percentage-of-time value of 50%.

We classified SpO_2 histograms based on the number of cumulative (background) bars with percentage-of-time value >10% and <90%, and the percentage-of-time value of the cumulative frequency bar to the left of 81% (the ≤80% bar). In type 1 histograms, the number of background bars with value >10% and <90% is <5, in type 2 histograms it is 5–9, and in type 3–5 histograms it is ≥10. Type 3–5 histograms are differentiated by

the height of the ≤80% bar: in type 3 it is <5%, in type 4 it is 5–9%, and in type 5 it is ≥10% (Fig. 1b, c).

Study procedure

SpO_2 histograms were printed twice daily at pre-set times for all participating infants from the first day of life until the infant was discharged home or transferred to a different NICU.

For each histogram, the respiratory support and oxygen supplementation for the previous 12-h period were documented. Non-intubated respiratory support included heated humidified high flow by nasal cannula, CPAP, and bi-level CPAP. Intubated respiratory support included conventional ventilation, high-frequency oscillatory ventilation, and high-frequency jet ventilation. When a change in support type was made during a recorded period, the highest support given during that period was assigned.

In type 1 and 2 histograms, SpO_2 remains within a relatively narrow range, so we broadly called them Stable, while in type 3–5 histograms, SpO_2 swings more widely, so we called these Unstable histograms.

Statistical analysis

Statistical analysis was performed with the SPSS v25.0 package (IBM, Armonk, NY).

Patient demographics are shown as mean ± standard deviation (SD). Statistical analysis for the cross-sectional pathway began with simple counts to construct a frequency table of histogram types and obtain the mean (±SD) median saturation in each type. For each of six different SpO_2 ranges, graphs of the mean (±SD) percentage of time spent in the specific range were plotted, to compare histogram types. Confidence intervals (CIs) of 95% were calculated for the 85–95% range and 90–95% range.

Continuous variables were compared using Student's *t* test and categorical variables using the χ^2 and Fisher's exact tests, as appropriate. Differences were considered significant when *p* value was <0.05.

RESULTS

One hundred and sixteen infants ≤34 weeks gestation were admitted to our NICU over the 264 days of observation. Eighty nine infants needed respiratory support on day 1 of life and 16 were excluded for congenital anomalies or technical difficulties, so that 73 infants with BW 1318.5 ± 495 g and gestational age (GA) 28.9 ± 3.0 weeks were studied. We obtained and analyzed 6016 consecutive histograms, 82 ± 78 histograms per infant, over a per-patient average of 46 ± 44 days. Figure 2 shows the prevalence of each histogram type overall and in relation to the type of respiratory support being administered. The absolute and relative incidence of each histogram type is shown for each category of interest. All histogram types were common, but their prevalence was different ($p < 0.00001$). The histogram type distribution in extubated vs. intubated respiratory support was different both during periods when in $FiO_2 = 0.21$ and >0.21 ($p < 0.00001$).

In histograms obtained in FiO_2 >0.21, the overall mean (±SD) of SpO_2 medians was 92.8 ± 1.9% and was similar to that in types 2–5 histograms. This median SpO_2 lies within the alarm limits range of 86–94% used in our NICU and within the now recommended SpO_2 target of 90– 95%, but was higher than our NICU SpO_2 targets of 88–92%.

Only 56 (2%) of 2811 histograms in FiO_2 >0.21 were type 1 with a mean (±SD) of SpO_2 medians of 95.1 ± 2.6%, but in 23 of these type 1 histograms the median SpO_2 was >95% and the mean (SD) SpO_2 medians was 97.9 (0.9)%, and in 33 type 1 histograms the median SpO_2 was ≤95% and the mean (SD) SpO_2 medians was 92.9 (1.1)%.

The time spent within different saturation ranges for histograms obtained in FiO_2 >0.21 is illustrated in Fig. 3. The mean time spent in our then SpO_2 target zone 88–92% was 26 ± 11% and was similar for all histogram types, and the mean time spent in the SpO_2 85–95% alarm zone and in the 90–95% zone was 65 ± 18% and 50 ± 15%. The higher the histogram type, the more time was spent in the SpO_2 <85 and <80% zones (p <0.01). The mean difference in time >95% between type 1 vs. types 2–5 was 24% (95% confidence interval (CI) 20–28).

Histograms remained stable throughout hospital stay in 39 infants with GA 31.3 ± 1.1 and BW 1633 ± 375.5 g, whereas in 34 infants with GA 26.4 ± 2.1 and BW 957 ± 345.1 g, histograms showed an initial stable phase with only type 1 and 2 histograms, followed by an unstable phase with type 3–5 histograms and then a final stable (resolution) phase when the histogram types returned to stable.

The median (IQR) duration of the initial stable phase was 6.3 (4.1) days and the duration of the unstable phase was 49.5 (35) days. All studied infants returned to a stable (resolution) phase prior to discharge, with the exception of two infants who died during the unstable phase. In addition, one infant was transferred to a different level III NICU during the unstable phase and lost to follow-up.

Table 1 presents the respiratory outcomes of all infants born at ≤28 weeks gestation, who entered the unstable phase during the first week of life ($n = 18$), compared to infants who did not enter the unstable phase during the first week of life ($n = 10$).

DISCUSSION

The SpO_2 histogram classification system provides the clarity of a common language and reveals the presence and magnitude of SpO_2 instability, as well as the natural history among premature infants. It also shows that SpO_2 instability is common and distinct from the SpO_2 median. Further, because it is the SpO_2 median that is being targeted during clinical care, the SpO_2 median is insensitive to the degree of SpO_2 instability. Thus, our data show that for periods in FiO_2 >0.21, the overall mean (±SD) of SpO_2 medians was 92.8 ± 1.9%, and was similar to that in types 2–5 histograms. As such, the degree of SpO_2 instability needs to be documented separately and in addition to the SpO_2 median.

Our study is the first to describe and classify SpO_2 histograms in the NICU in support of clinical care. Other studies have reported on how hypoxemic events impact clinical outcomes. Poets et al.[7] in a post hoc analysis of the COT trial[11] has reported that hypoxemic events were associated with death or disability in 56.5% in the highest decile vs. 36.9% in the lowest decile of hypoxemic exposure. However, the effect of cumulative hypoxemia on death or disability was not examined. Others have shown that oxygen desaturation events are associated with the development of BPD[5] and that infants diagnosed with BPD had increased frequency and duration of intermittent hypoxemia episodes during the first 26 days of life as well as lower baseline SpO_2.[6]

We here show that unstable histograms during that first 7 days of life among extremely low gestational age newborns (ELGAN) identify infants at risk of longer ventilatory support and need for supplemental oxygen, and at increased risk of being on ventilatory support at 40 weeks.

Prospective data on how to safely and effectively decrease intermittent hypoxemia is limited partly due to the fact that these events are poorly documented and quantified. These events, observed in the presence and absence of assisted ventilation, are distinct from those due solely to immature respiratory control. Hypoxemic events in mechanically ventilated premature infants are triggered by forced exhalations that produce a decrease in lung volume with a subsequent increase in airway resistance and a drop in lung compliance.[12] While it is not yet known if newer ventilatory strategies will be able to lessen prolonged cumulative hypoxemia as detected by type 3–5 histograms, histogram type

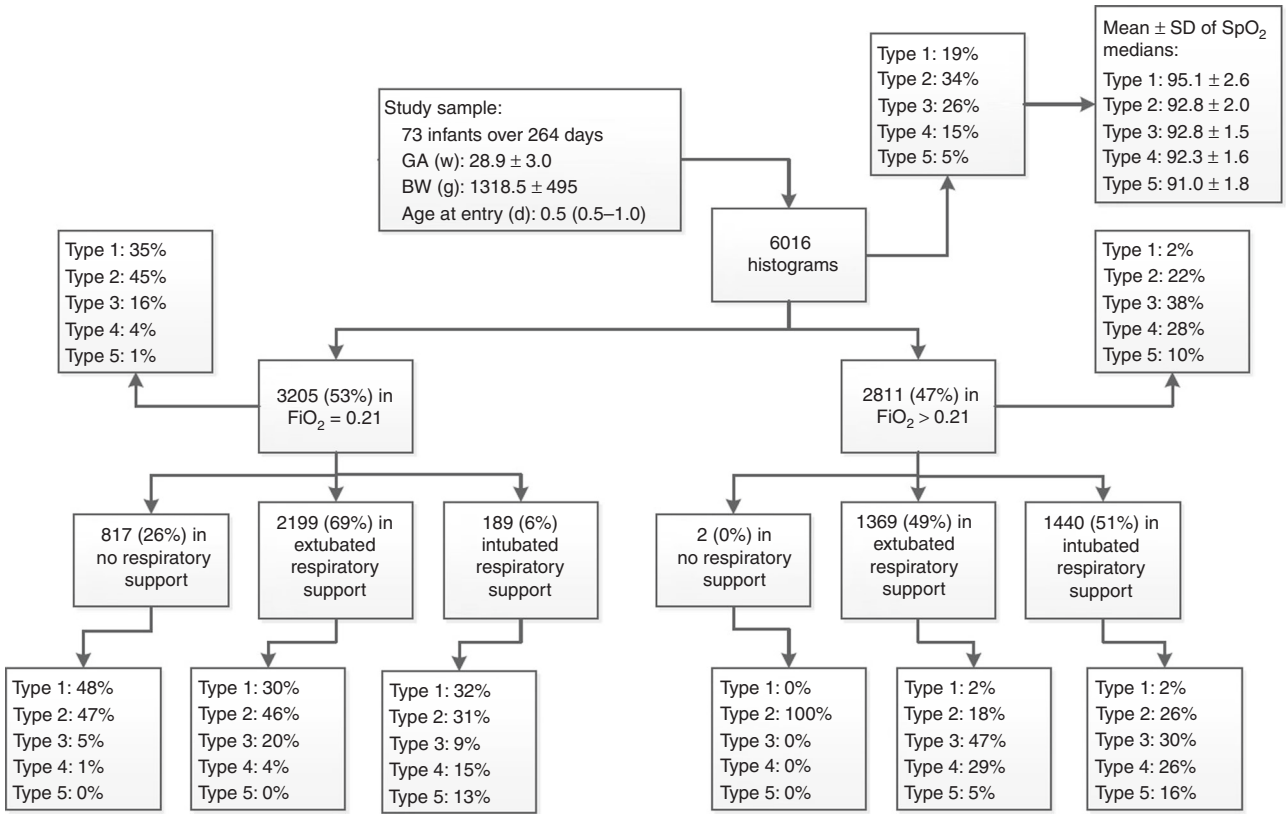


Fig. 2 Histogram prevalence study. Prevalence of each histogram type, for infants in $FiO_2 = 0.21$, $FiO_2 > 0.21$, and by form of respiratory support. The mean ± SD of the SpO_2 medians was the same in histogram Types 2–5. GA and BW are expressed as mean ± SD and age at entry as median (IQR). Supplemental oxygen by itself was not considered as respiratory support

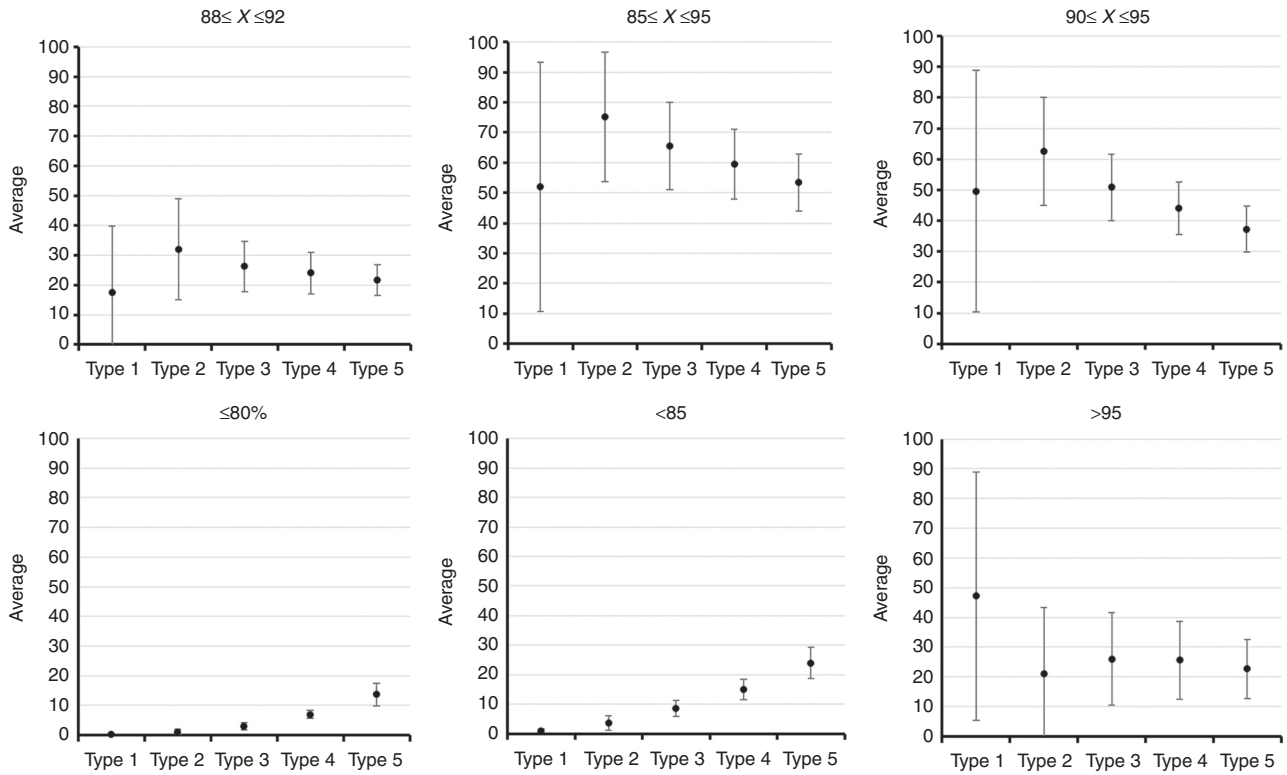


Fig. 3 Time spent in different SpO_2 ranges for each histogram type. Mean ± SD time spent within different saturation ranges for histograms obtained in $FiO_2 > 0.21$

Table 1. Characteristics and respiratory outcomes of infants ≤28 weeks gestation

	Infants who entered the unstable phase by day 7 of life, $N = 18$	Infants who did not enter the unstable phase by day 7 of life, $N = 10$	*P* value
GA (weeks), mean (±SD)	25.2 (2.0)	26.5 (1.9)	0.036
Birthweight (g), mean (±SD)	752 (237.0)	890 (467.0)	0.168
On respiratory support on day 7 (%)	18/18 (100)	10/10 (100)	1.00
On invasive support on day 7 (%)	15 (83.3)	2 (20.0)	<0.003
On supplemental oxygen on day 7 (%)	17 (94.4)	2 (20.0)	<0.001
BPD/death (%)	18 (100.0)	9 (90.0)	0.357
On supplemental oxygen at 36 weeks (%)	11 (68.8)	2 (22.2)	0.041
On supplemental oxygen at 40 weeks (%)	7 (46.7)	0 (0.0)	0.022
Off respiratory support (days), median (IQR)	101 (66.0)	62 (28.0)	0.003
Off O_2 support (days), median (IQR)	62.5 (72.0)	40.5 (40.0)	0.004
Length of unstable phase (days), median (IQR)	89.5 (67.3)	27 (46.9)	<0.001

documentation should be considered an important outcome variable in trials aimed at improving respiratory support and/or automatically regulating oxygen administration in infants.

The main limitation of our study is that we did not systematically track periods with motion artifact that potentially might have altered histogram type, but because the Masimo signal extraction technology minimizes the occurrence of artifact-based low values,[13] and because we used histograms summarizing 12 h rather than shorter periods, we think that motion artifact should have a small effect on our results. Also, our study was a descriptive study and was not powered to look for the correlation between histogram types and GA, respiratory support, and neonatal morbidities.

Displaying, describing, and documenting SpO_2 instability is now possible. If we are to improve oxygen targeting, more clinical attention needs to be paid to infants with unstable histograms. Research aimed at decreasing the prevalence of type 3–5 histograms and cumulative time in the hypoxic range is likely to improve neurodevelopmental outcomes.

AUTHOR CONTRIBUTIONS

All authors take responsibility for the reported findings and have participated in the concept and design, analysis and interpretation of data, drafting or revising, and approval of this manuscript as submitted.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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