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Systematic Underestimation of Oxygen Delivery in Ventilated Preterm Infants

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Key Words
Bronchopulmonary dysplasia · Oxygen saturation · Oxygenation · Prematurity · Ventilation

Abstract
Background: Emerging evidence indicates that hyperoxia is a risk factor for bronchopulmonary dysplasia, a common multifactorial long-term complication of prematurity. To date, the equivalence between set and delivered oxygen (O_2) in ventilated preterm infants has not been rigorously studied. ***Objectives:*** To test the hypothesis of systematic underestimation of O_2 delivery in extremely low birth weight (ELBW) infants during long-term ventilation. ***Methods:*** Actually achieved O_2 concentrations were measured and compared to the set inspired oxygen fraction (FiO_2). A total of 108 O_2 measurements were carried out during the ventilation of 54 ELBW infants: O_2-Δ error (i.e., the difference between O_2 concentrations achieved by the ventilator and set FiO_2) was the main study outcome measure. ***Results:*** Systematic O_2-Δ errors were found, with mean values of +9.52% (FiO_2 0.21–0.40), +2.10 (FiO_2 0.41–0.60), +2.86% (FiO_2 0.61–0.80), and +0.016% (FiO_2 0.81–1.0; $p < 0.0001$). Theoretical simulations from the observed data indicate that, if not corrected, systematic O2-Δ errors would lead to a non-intentional total O_2 load of 1,202.9 (FiO_2 0.21–0.40), 252.46 (FiO_2 0.41–0.60), 342.85 (FiO_2 0.61–0.80), and 2 (FiO_2 0.81–1.0) extra liters/kg body weight/100 ventilation hours. ***Conclusions:*** Systematic underestimation of the O_2 delivered by infant ventilators can potentially lead to surprisingly large increases in total O_2 load during long-term ventilation of ELBW infants, especially in the lower FiO_2 range (i.e., 0.21–0.40). Underestimation of true O_2 delivery can potentially lead to unrecognized high O_2 loads, and more pronounced and prolonged hyperoxia.

Introduction

Emerging evidence indicates that hyperoxia is a risk factor for bronchopulmonary dysplasia (BPD), a common multifactorial long-term complication of prematurity [1]. Adequate ventilation requires delivering the correct volume of gas in the right dose and time to ensure sufficient oxygen (O_2) delivery to critical organs. In particular, O_2 is widely used in the neonatal intensive care unit (NICU). However, as O_2 is a drug with significant side effects, its stringent control is a prerequisite for tai-

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lored resuscitation and ventilation of newborn infants [2, 3]. The aim of the present study was to test the hypothesis that systematic underestimation of O_2 release occurs during long-term ventilation of extremely low birth weight (ELBW) infants admitted to a tertiary level NICU.

Methods

The source of O_2 was a hospital wall supply connection delivering 100% piped O_2 to the infants via endotracheal tubes. Commercially available NICU ventilators either for conventional assisted ventilation or high frequency ventilation, regularly checked by the manufacturer's technical staff, were used during the study. The O_2 concentration (% purity) supplied by the NICU ventilators was measured by an Ohmeda 5120 Oxygen Analyzer (Datex-Ohmeda, Louisville, Colo., USA), with the oximeter's probe applied in a sterile fashion to the O_2 nozzle, immediately upward to the connection with the endotracheal tube. For the measurements of O_2 concentrations, the endotracheal tube was briefly disconnected from the nozzle, with the infant being temporarily ventilated on an AMBU bag by the neonatologist in charge. The mean time needed for each measurement was approximately 8 s. All readings were performed in triplicate, and mean values were considered for data analysis. Mean intra- and inter-assay coefficients of variation (CV) for oximeter accuracy were 1.5 and 2.0%, respectively. Results of oximeter calibration at ambient air (liquid air hospital source; n = 120 readings) and in a bag containing 100% O_2 (n = 120 readings) were 21 ± 0.24 and 100 ± 0.02% (mean ± SD), respectively. In pilot studies, 3 different Ohmeda 5120 Oxygen Analyzers gave similar results, with a mean error shift within ±1% (n = 120 readings on room air, and n = 120 readings on 100% O_2 bags). O_2 concentrations measured in the gas within the incubators (as well as in the air around the infant's nostrils and mouth) were constantly at 21 ± 0.18% (mean ± SD) regardless of the set inspired O_2 fraction (FiO_2) or O_2 concentration given to the infant, or other ventilatory variables.

Therefore, the O_2 microenvironment was considered to be constantly room air (i.e., FiO_2 0.21) and most likely did not confound the O_2 readings in the NICU ventilators used. Given that the O_2-air gas mix follows the ideal gas law, its state is determined by its pressure, volume, and temperature: $p \cdot V = n \cdot R \cdot T$, where p is the pressure (Pa), V is the volume (m^3), n is the amount of substance (mol), T is the temperature (C), and R is the gas constant (i.e., 8.3143 $m^3 \cdot Pa \cdot C^{-1} \cdot mol^{-1}$ or 0.082057 liters atm mol^{-1} C^{-1}). As a consequence, we investigated the possible influences of airflow pressure and temperature on the released O_2 volume by recording temperature and pressure data during ventilation, and by determining the O_2-Δ error distributions at different FiO_2 values while maintaining both constant temperature and flow end-pressure of the O_2-air gas mix by using NICU ventilators connected to inflatable bags. All determinations were carried out independently by a single experienced technician who was unaware of the currently set FiO_2 value. Saturimetric pO_2 (SaO_2)was determined using a Masimo SET Radical pulse oximeter (Masimo Corp., Irvine, Calif., USA) with the sensor placed randomly on either of the infant's feet. Target SaO_2 was 88–92% in infants with a postmenstrual age of <32 weeks and 90–94% in infants with a postmenstrual age of ≥32 weeks [4].

O_2 measurements involved 54 ELBW infants (male = 28; female = 26; mean gestational age at birth 27.41 ± 1.82 weeks; birth weight 784.5 ± 168.6 g) on long-term assisted ventilation. The O_2-Δ error (i.e., the absolute difference between O_2 concentrations released by the ventilator and set FiO_2, expressed as percentages of set FiO_2, was the main study outcome measure. In order to test whether systematic O_2-Δ errors could influence arterial O_2 tension (PaO_2), PaO_2 and SaO_2 were measured with a blood gas analyzer (ABL 700 , Radiometer, Copenhagen, Denmark) using radial artery blood samples obtained from the ventilated infants, and subsequently the PaO_2/SaO_2 ratio was calculated. PaO_2, SaO_2 and PaO_2/SaO_2 ratios in ventilated ELBW infants (n = 54) were compared to those of a control ELBW population (n = 52) on long-term nasal continuous positive airway pressure (N-CPAP).

Data Analysis

Data distribution was assessed using the D'Agostino-Pearson test (i.e., $p > 0.05$ indicating normal distribution) and results are expressed as mean ± SD, or median (interquartile range), as appropriate. The relationship between set FiO_2 and achieved O_2 concentrations was tested by linear regression analysis. The observed O_2-Δ errors for four different FiO_2 ranges (i.e., 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.0) were evaluated using Kruskal-Wallis analysis of variance, and post-hoc differences were assessed by the Mann-Whitney U test. A two-tailed test p value of <0.05 was considered to indicate statistical significance. The MedCalc® ver. 9.2.0.2 statistical software package (MedCalc. Software, Mariakerke, Belgium) was used.

Results

A total of 108 O_2 measurements were carried out at different time points during long-term ventilation, and four different FiO_2 ranges (0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.0) were evaluated.

The mean temperature of the O_2-air gas mix given to the infants was 35.0 ± 0.13°C. In the SIMV mode, mean values for ventilatory variables were PIP 17.95 ± 1.28 mm Hg, PEEP 3.55 ± 0.51 mm Hg, IT 0.35 ± 0.021 s, and RR 39.9 ± 10.5 BPM, while in the HFV mode the ventilatory variables were: ΔP 22.43 ± 4.23 mm Hg, MAP 13.22 ± 1.23 mm Hg, IT 0.35 ± 0.021, and frequency 15.0 ± 0.01 Hz. Systematic differences between set FiO_2 values and O_2 concentration actually achieved by the ventilator were present, with the O_2-Δ error's average skewed on the positive axis (H test = 69.0252; DF = 41, p = 0.0039; fig. 1).

Deviations from the set concentrations were particularly evident for lower FiO_2 ranges. Average O_2-Δ errors were +9.52% (interquartile range +5.71 to +13.3%), +2.10 (0 to +6.67%), +2.86% (–0.97 to +4.77%), and +0.016% (–6.68 to +4.44%) for the 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.0 FiO_2 ranges, respectively (H test = 39.8387;

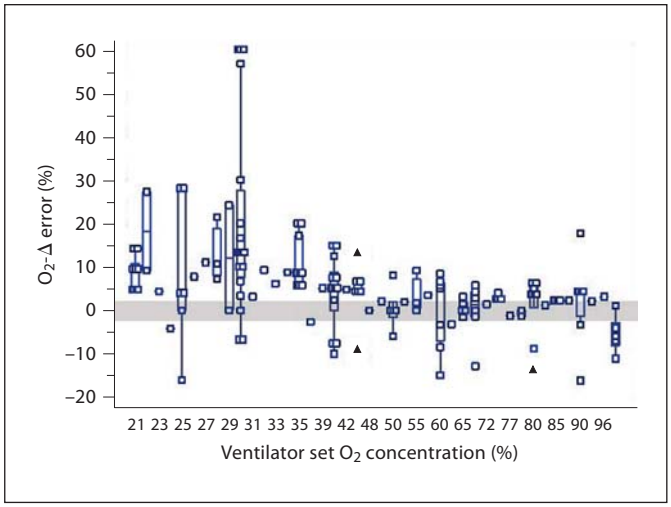

Fig. 1. O_2-Δ errors (i.e., actually delivered O_2 concentrations on the Y axis, box-and-whisker plots) as a function of set FiO_2 values (X axis). The horizontal grey bar indicates the 0 ± 2% error interval reference. Each central box shows the values from the lower to upper quartile (25–75%), with the middle line representing the median value. A line extends from the minimum to the maximum value, excluding 'outliers' (i.e., as defined as a value that is smaller than the lower quartile – 1.5 times the interquartile range, or larger than the upper quartile + 1.5 times the interquartile range) values which are displayed as separate triangular points (▲).

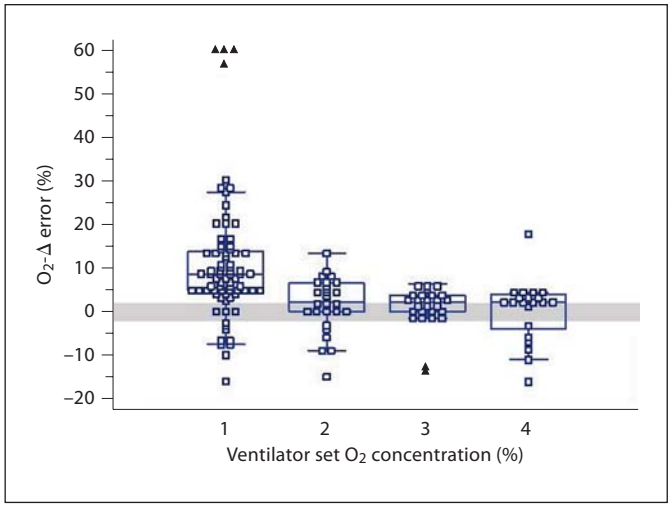

Fig. 2. O_2-Δ errors (i.e., actually delivered O_2 concentrations on the Y axis, box-and-whisker plots) as a function of four programmed FiO_2 ranges. The horizontal grey bar indicates the 0 ± 2% error interval reference. Each central box shows the values from the lower to upper quartile (25–75%), with the middle line representing the median value. A line extends from the minimum to the maximum value, excluding 'outliers' (i.e., as defined as a value that is smaller than the lower quartile – 1.5 times the interquartile range, or larger than the upper quartile + 1.5 times the interquartile range) values which are displayed as separate triangular points (▲).

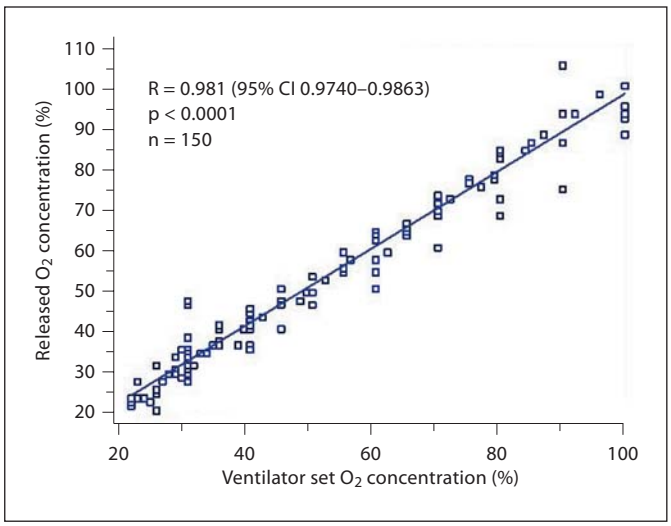

Fig. 3. Linear regression between achieved O_2 (Y axis, %) concentrations as a function of set FiO_2 (X axis, %).

DF = 3, $p < 0.0001$; fig. 2). O_2-Δ errors were consistent and reproducible within a ±1.14% shift. O_2-Δ errors were present notwithstanding a strong linear relationship between programmed and actually achieved O_2 concentrations (r^2 = 0,9625, n = 150 data points, $p < 0.0001$; fig. 3).

The results of a bench test with the same NICU ventilators connected to inflatable bags maintaining temperature and pressure as constants, revealed no significant association between the recorded Δ errors as a function of variable FiO_2 values (median error +4.76%, 95% CI 3.75–6.25%) and temperature or pressure (r = 0.00, p = 1.0; n = 105 data points; data not shown). Significantly higher PaO_2 (61.25 ± 8.66 vs. 48.15 ± 8.26 mm Hg, p = 0.0002), and PaO_2/SaO_2 ratios (0.6858 ± 0.061 vs. 0.5095 ± 0.042, $p < 0.0001$), associated with comparable SaO_2 values (92.0 ± 9.81 vs. 89.0 ± 7.41, p = 0.1324), were found in the study population on long-term ventilation as compared to an ELBW population on long-term N-CPAP. Theoretical simulations based on the observed data indicate that, if not corrected, O_2-Δ errors could lead to total administration of 1,202.9 (FiO_2 0.21–0.40), 252.46

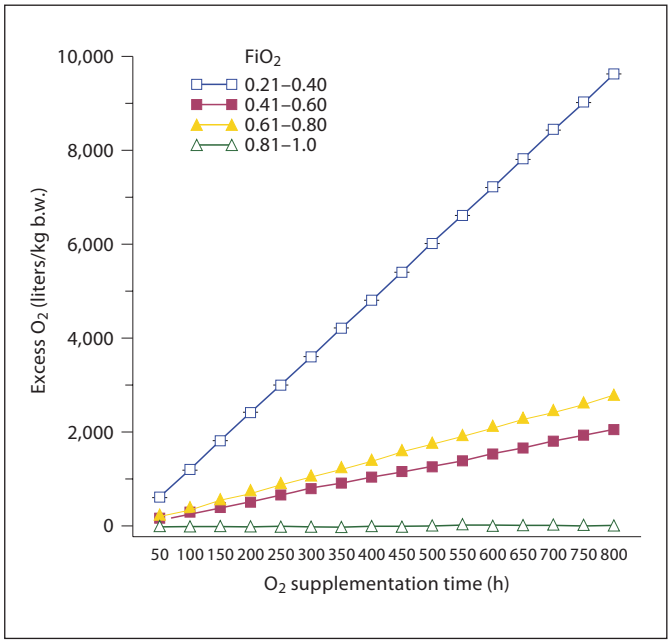

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Fig. 4. Simulations for excess O_2 supplied to infants during long-term ventilation as a function of FiO_2 category according to the observed findings. The results are based on a simulated airflow value of 2 liters/kg body weight per min.

(FiO_2 0.41–0.60), 342.85 (FiO_2 0.61–0.80), and 2 (FiO_2 0.81–1.0) excess O_2 liters/kg body weight/100 ventilation hours (fig. 4).

Discussion

Our findings indicate that, despite an apparently correct O_2 release, on the first glance negligible but systematic underestimations of the truly delivered O_2 can potentially lead to surprisingly large differences in the O_2 load actually received by preterm ELBW infants during long-term ventilation. The results of simple bench tests indicated that O_2-Δ errors, while independent of the temperature and pressure of the O_2-air mix, were significant and most consistent in the lower (i.e., 0.21–0.40) FiO_2 values range; importantly, ELBW infants are most commonly ventilated with low FiO_2 (< 0.40) in order to prevent oxygen toxicity. It is well known that systematic errors are consistent and repeatable, whereas random errors arise from random fluctuations in the measurements. If the delivered FiO_2 is higher than the set FiO_2, systematic O_2 errors, albeit of small entity, are of particular relevance in a NICU setting. In spite of the fact that it is important to know the exact dosing of a drug, such as oxygen, experts might argue over the clinical consequences that follow such an overestimation. As long as the FiO_2 is used to regulate SaO_2 and PaO_2, it would not matter too much clinically. However, as soon as FiO_2 is used to release clinical actions or when applying the oxygenation index, our findings could be quite relevant clinically.

The occurrence of systematic errors can produce a kind of 'domino effect' where changes, small in themselves, will propagate similar changes nearby in a linear sequence. Periods of O_2 supplementation in the order of 400–700 h are not uncommon in ELBW infants undergoing assisted ventilation. It seems obvious that, if not properly monitored and adjusted, the systematic underestimation of O_2 delivery we describe might translate into large differences in total O_2 liters received in excess during long-term ventilation, potentially leading to unrecognized chronic hyperoxia. This concern is supported by the statistically higher PaO_2 and PaO_2/SaO_2 ratios observed in the ELBW population on long-term assisted ventilation, as compared to ELBW infants on long-term N-CPAP.

Emerging evidence challenges the use of 100% O_2 concentrations in newborn resuscitation [3–5]. In particular, a brief O_2 exposure of only a few minutes during resuscitation of moderately asphyxiated term neonates has been reported to exacerbate oxidative stress up to 4 weeks after birth [6]. Moreover, high-oxygen resuscitation impairs cerebral blood flow in preterm newborns [7], promotes reperfusion injury, and causes brain damage in animal models [8]. Detrimental effects of neonatal resuscitation with pure oxygen in the delivery room right after birth also has been confirmed by evidence of direct myocardial and renal tubular damage following 100% O_2 resuscitation of severely depressed term infants [9].

In contrast, the pathophysiology potentially related to systematic underestimation of the O_2 load in extremely preterm infants on long-term ventilation remains unknown to date. Acute and chronic hyperoxia are not exactly comparable, because adaptive mechanisms ensue in the latter condition leading to changes in the architecture of the lung [10] and potentially other organs.

Prior research indicates that neonatal exposure to 65% oxygen has negative effects on lung architecture and the breathing pattern of adult mice [11], and more recently, repetitive hyperoxia has been shown to depress respiration in newborn mice [12]. Hyperoxia can disrupt vascular and alveolar growth in the developing lungs [13], and

trigger hyperoxic lung inflammation and injury in the extremely premature infants [14], likely contributing to the development of BPD.

Our observations underline the clinical importance of testing rather than assuming the equivalence between set FiO_2 and actually achieved O_2 concentrations when using ventilators for newborns. Indeed, the present study identifies systematic O_2-Δ errors as an insidious and previously unrecognized risk factor for prolonged hyperoxia, potentially playing a role in the pathogenesis of BPD in extremely preterm infants on long-term ventilation. Nevertheless, it should be emphasized that systematic O_2-Δ errors are potentially preventable, either by means of routine checks by NICU operators or through a more stringent quality control of the O_2 release from the industrial NICU ventilators and gas technology. The results of the theoretical simulations seem to suggest that accuracy in the O_2 release regulation should be pushed forward to an order of at least 0.01, a figure comparable to the minimum observed average O_2-Δ error, for any given FiO_2 value. In fact, the envisaged accuracy would theoretically lead to 0.72 (FiO_2 0.21–0.40), 1.21 (FiO_2 0.41–0.60), 1.69 (FiO_2 0.61–0.80), and 2.17 (FiO_2 0.81–1.0) excess O_2 liters/kg body weight/100 ventilation hours, thus curtailing by approximately 200 times the average excess O_2 volume supply, from 297.65 to 1.45 O_2 liters/100 ventilation hours. It is likely that lower PaO_2 (45–65 mm Hg) and SaO_2 (82–92%) goals, together with higher $PaCO_2$ (42–60 up to 70 mm Hg) limits should be followed for ELBW infants at high risk of oxygen toxicity/ventilator injury [5]. However, in order to avoid both hypoxia or/and hyperoxia in long-term ventilated extremely preterm infants, new evidence-based guidelines on the goals of assisted and spontaneous ventilation are necessary. In the near future, reliable markers of plasma and tissue oxidative stress (e.g., intra-erythrocyte and plasma non-protein-bound iron, F2-isoprostanes, protein carbonyls and 4-hydroxynonenal as well as vascular endothelial growth factor, i.e., a biomarker of neoangiogenesis) may be used to monitor pathological processes associated with chronic hyperoxia.

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