

The Administration of 100% Oxygen and Respiratory Drive in Very Preterm Infants at Birth

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Abstract

Aim: To retrospectively investigate the changes of SpO₂ and respiratory drive in preterm infants at birth after administration of 100% oxygen.

Methods: Respiratory parameters, FiO₂ and oximetry of infants <32 weeks gestation before and after receiving FiO₂ 1.0 were reviewed during continuous positive airway pressure (CPAP) or positive pressure ventilation (PPV).

Results: Results are given as median (IQR) or percentages where appropriate. Suitable recordings were made in 50 infants (GA 27 (26–29) weeks), 17 received CPAP and 33 PPV. SpO₂ increased rapidly in the first minute after FiO₂ 1.0 and remained stable. The duration of FiO₂ 1.0 tended to be shorter in the CPAP group than in the PPV group (CPAP vs. PPV: 65 (33–105) vs. 100 (40–280) s; $p=0.05$), SpO₂ >95% occurred more often in PPV group (53% vs. 69%) and lasted longer (70(40–95) vs. 120(50–202) s). In CPAP group, minute volume increased from 134 (76–265) mL/kg/min 1 minute before to 240 (157–370) mL/kg/min ($p<0.01$) 1 minute after start FiO₂ 1.0 and remained stable at 2 minutes (252 (135–376) mL/kg/min; ns). The rate of rise to maximum tidal volume increased (from 13.8 (8.0–22.4) mL/kg/s to 18.2 (11.0–27.5) mL/kg/s; $p<0.0001$) to 18.8 (11.8–27.8) mL/kg/s; ns). In the PPV group respiratory rate increased from 0(0–4) to 9(0–20) at 1 minute ($p<0.001$) to 23 (0–34) breaths per minute at 2 minutes ($p<0.01$).

Conclusion: In preterm infants at birth, a rapid increase in oxygenation, resulting from a transient increase to 100% oxygen might improve respiratory drive, but increases the risk for hyperoxia.

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Introduction

Hyperoxemia may lead to hyperoxia causing oxidative stress and tissue injury which should be avoided in infants at birth [1,2]. Meta-analyses indicate that resuscitation of term infants at birth with air significantly reduced mortality compared with those resuscitated with fraction of inspired oxygen (FiO₂) of 1.0 [1–6]. International resuscitation guidelines now recommend term infants should start in air [2,7,8]. Less clinical data are available for preterm infants, but guidelines now recommend to use oxygen judiciously during stabilization of preterm infants at birth [2,7–9].

Since SpO₂ percentiles were introduced [10] lower SpO₂-targets in the first minutes after birth are accepted. However, hypoxia inhibits breathing movements in the fetus [11]. Although O₂ sensitivity of infants changes in days-weeks after birth [12] and most preterm infants breathe at birth [13,14], it is not known when the hypoxia-mediated switch from respiratory suppression to stimulation occurs. Possibly hypoxia immediately after birth will produce a weakened or absent respiratory drive as shown in preterm lambs [12]. In contrast, it has been shown in asphyxiated

term infants [15] and animals [16] that applying 100% oxygen with no titration delayed the time of the first breath.

From 2008 until 2010, the local guidelines of the Royal Women's Hospital (Melbourne, Australia) and the Leiden University Medical Center (Leiden, the Netherlands) recommended starting in air and switching to FiO₂ 1.0 if needed and then titrating down in preterm infants at birth. An oxygen saturation (SpO₂) ≤70% at 5 minutes was used to increase FiO₂ [10]. The immediate switch to 100% was a pragmatic choice, but immediate FiO₂ reduction was advocated once the infant was stabilized.

Our aim was to investigate the change in SpO₂ and respiratory drive in preterm infants right after birth in the delivery room after switching from air to FiO₂ 1.0.

Methods

The local institutional review boards (IRBs) of the Leiden University Medical Center (Commissie Medische Ethiek, Leids Universitair Medisch Centrum) and Royal Women's Hospital (the

Table 1. Baseline characteristics for preterm infants breathing on CPAP and infants receiving positive pressure ventilation when a FiO₂ of 1.0 was started.

Characteristics	breathing on CPAP	Positive pressure ventilation	p-value
	N = 17	N = 33	
Gestational age, wk, mean (SD)	28.9 (1.5)	27.1 (2.1)	<0.01
Birth weight, g, mean (SD)	1073 (227)	993 (311)	<0.0001
Male Sex (%)	10 (60)	16 (49)	ns
Caesarean (%)	8 (47)	18 (54)	ns
Apgar at 1 min, median (IQR)	6 (5–7)	4 (2–6)	<0.05
Apgar at 5 min, median (IQR)	8 (8–8)	7 (6–8)	<0.05

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Human Research Ethics Committee, Royal Woman's Hospital) approved physiological- and video recordings at birth in the delivery room when respiratory support was necessary for research purposes. Written parental consent to use the recordings for research was obtained after birth. A retrospective study was performed in both hospitals with data collected between 2008 and 2010. During the period of data collection local guidelines recommended that support was started with air and switched to FiO₂ 1.0 when: 1) cardiac massage was needed, 2) positive pressure ventilation (PPV) was administered for 1 minute and heart rate (HR) was <100 beats per minute (bpm) or 3) SpO₂ <70% at 5 minutes. FiO₂ was then titrated down as quickly as possible (when SpO₂ >90%). Recordings were only made when the research team was available.

Respiratory support was delivered with a T-piece resuscitator (Neopuff, Fisher & Paykel, Wellington, New Zealand) and face mask. Local resuscitation guidelines recommended to start PPV (20–25/5 cmH₂O) in preterm infants during apnea or HR<100 bpm. In breathing infants and HR>100 bpm, CPAP (5–6 cmH₂O) is given. Changing pressures was left to the discretion of the caregiver.

The use of a respiratory monitor (Acutronic Medical Systems AG, Hirzel, Switzerland), a Masimo SET pulse oximeter (Masimo Radical, Masimo Corporation, Irvine CA, USA), an oxylog (Teledyne, Poway CA, USA) and Spectra program (Spectra, Grove Medical Limited, Hampton, UK) for physiological recordings has been described in detail in previous publications [13].

All recordings of infants born at <32 weeks gestation between 2008 and 2010 were reviewed. Using video and respiratory function monitoring other interventions were identified performed during the analyzed period. Infants receiving FiO₂ 1.0 were identified and divided into two groups. This was based on the type of respiratory support they received around the time point FiO₂ 1.0 was started: group 1) infants were breathing on continuous positive airway pressure (CPAP) and group 2) received positive pressure ventilation (PPV).

In all infants we recorded when FiO₂ was increased to 1.0, for what reason(s) (e.g. low HR, low SpO₂), duration and the downward titration rate of FiO₂ 1.0. Furthermore we noted the increase in SpO₂ duration of SpO₂ >95%. We used SpO₂ >95% as an indication for increased risk for hyperoxia.

In group 1 (CPAP group) the effect of FiO₂ 1.0 on respiratory drive was investigated. To measure the change in respiratory effort, we analyzed the respiratory rate (RR), expired tidal volume (V_{te}), minute volume (MV) and the rate of rise to maximum tidal volume (mL/kg/second) during inspiration from 1 minute before until two minutes after starting FiO₂ 1.0 (which served as a control

period). To measure the maximum rate of tidal volume increase we used spontaneous breaths without mask leak (V_{ti} = V_{te}).

In group 2 (PPV group) the tidal volumes and rate of rise will be influenced by the positive pressure ventilation given and we only analyzed RR of the spontaneous breaths from 1 minute before until two minutes after starting FiO₂ 1.0. Breaths in between and coinciding with inflations were identified according to previous described methods [15]. In apneic infants, starting time of breathing was noted.

As changing of FiO₂ can influence flow and volume measurements [17–19], the respiratory monitor was tested in vitro by delivering a constant tidal volume using a glass syringe and different gas conditions. The results were used to give the following corrections: at FiO₂ 1.0, both inspired and expired tidal volumes were corrected by –6% when using cold dry gas and by –10% when heated gas was used.

Data are presented as mean (± SD) or median (IQR) where appropriate. Differences were analyzed with a paired samples t-test for parametric data or a Wilcoxon signed rank test for non-parametric data where appropriate using (SPSS for Windows, version 17.0.0, Chicago, IL, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

Data from 80 recorded infants were reviewed, 30 were excluded (no respiratory support (n = 10), no supplemental oxygen (n = 7), low quality recordings (n = 12) and 1 infant was born dead). Thus, 50 infants with GA 27 (26–29) weeks were analyzed (table 1); during the study window (1 minute before–2 minutes after start of oxygen) 17 breathed on CPAP (CPAP-group) and 33 received PPV (PPV-group).

The infants in the CPAP-group did not receive PPV during or after the study window. In both groups ventilation pressures were not increased during the study window. (pressures given: CPAP-group CPAP level 5.3 (4.6–5.9) cmH₂O, PPV-group; PIP 21.6 (20.3–24.9) cmH₂O and PEEP 4.2 (3.5–4.7) cmH₂O) and no readjustments of mask position were observed. After the study window 1 infant of the CPAP-group was intubated, but reason was unclear. In the PPV-group, 5 infants were intubated after the study window for apnea and low SpO₂ despite FiO₂ 1.0. Cardiac massage was not provided to any infant.

Supplemental oxygen

In the CPAP-group FiO₂ 1.0 was started 300 (225–315) seconds after birth and was given for 65 (33–105) seconds. FiO₂ was

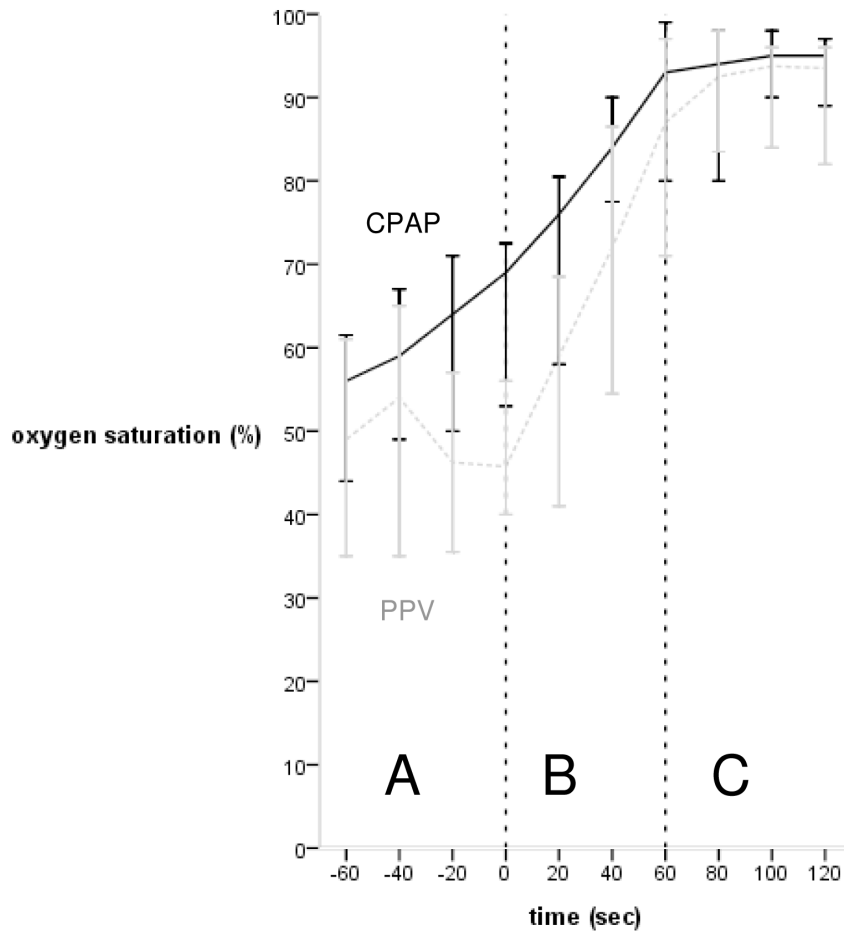


Figure 1. Oxygen saturation (%) of infants on CPAP and infants needing PPV in the minute before and 2 minutes after start of FiO₂ 1.0. Black = CPAP-group, light grey = PPV-group, (A) minute before start FiO₂ 1.0, (B) first minute after start FiO₂ 1.0, (C) second minute after start FiO₂ 1.0.

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weaned in 20 (5–60) seconds to 21 (21–21) %. In all infants oxygen was started for low SpO₂ and HR was >100 bpm.

In the PPV-group FiO₂ 1.0 was started 180 (120–270) seconds after birth and was given for 100 (40–280) seconds. FiO₂ was weaned in 25 (10–47) seconds to 21 (21–30)%.

Oxygen saturation

In all patients the fastest increase in SpO₂ occurred in the first minute after starting oxygen (figure 1) (CPAP-group: from 62 (16)% to 87 (12)% at 1 minute after and to 93 (5)% at 2 minutes after starting oxygen, PPV-group: from 45 (19)% to 80 (24)% (p<0.001) after 1 minute and to 87 (19)% after 2 minutes (figure 1).

SpO₂ >95% occurred in 9/17 (53%) infants of in group 1 and in 23/33 (69%) infants of group 2. The starting point and duration of SpO₂ >95% are depicted in figure 2

Changes on respiratory drive when breathing on CPAP

In the CPAP-group, increasing FiO₂ to 1.0 increased RR from 30 (18–41) 1 min before to 35 (24–45) breaths per minute (ns) 1 minute after to 39 (31–44) breaths per minute (p<0.05) in the 2nd minute.

V_te and MV increased significantly in 1st minute after increasing FiO₂ to 1.0 and remained stable in the 2nd minute

(V_te: from 4.9 (2.3–8.8) mL/kg to 6.7 (3.6–10.4) mL/kg (p<0.001) to 6.5 (3.7–10.2) mL/kg (ns); MV: from 134 (76–265) mL/kg/min to 240 (157–370) mL/kg/min (p<0.01) to 252 (135–376) mL/kg/min (ns)).

The rate of rise to maximum tidal volume increased from 13.8 (8.0–22.4) mL/kg/s in the minute before to 18.2 (11.0–27.5) mL/kg/s (p<0.0001) in the minute after increasing FiO₂ to 1.0 and remained stable at 18.8 (11.8–27.8) mL/kg/s (ns) in the 2nd minute.

Changes on respiratory drive when receiving PPV

PPV was given in 23 apneic infants and in 10 infants for poor respiratory drive. Apneic infants started breathing 80 (50–180)s after FiO₂ 1.0 and at that moment SpO₂ was 87% (11) and HR 147 (19) bpm.

RR increased from 0 (0–4) 1 min before to 9 (0–20) breaths per minute (p<0.001) 1 minute after to 23 (0–34) breaths per minute (p<0.01) in the 2nd minute after switching to FiO₂ 1.0.

Discussion

We investigated the influence of switching from air to FiO₂ 1.0 on SpO₂ and respiratory drive in preterm infants at birth. Most infants with SpO₂ near the 10th percentile had a good HR but FiO₂ was increased to 1.0 because of low SpO₂. After increasing

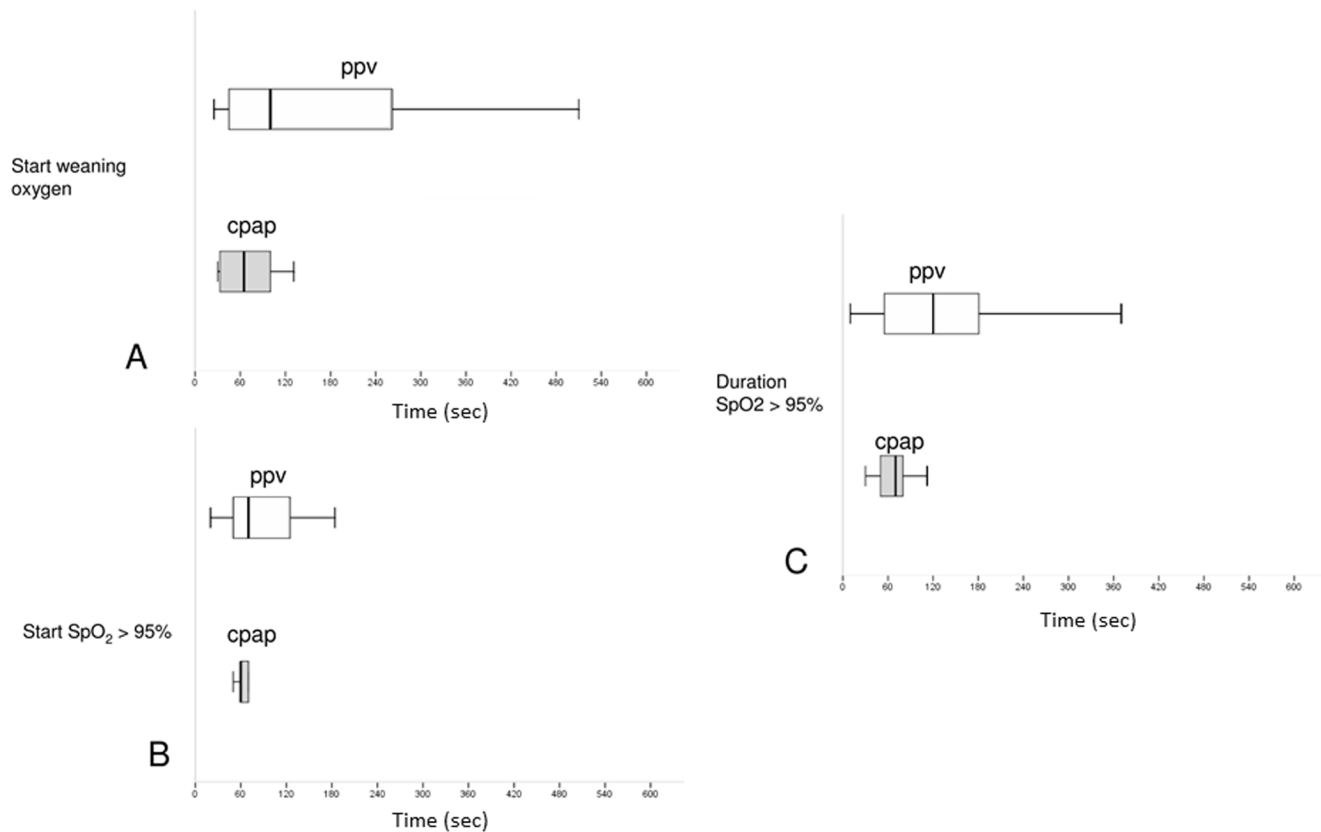


Figure 2. Box plots showing median (IQR) starting time of weaning FiO_2 1.0 (A), starting time of $\text{SpO}_2 > 95\%$, (B) in seconds after FiO_2 1.0 is started and duration of $\text{SpO}_2 > 95\%$, (C) in infants on CPAP and infants needing PPV. Grey = CPAP-group, white = PPV-group. doi:10.1371/journal.pone.0076898.g002

FiO_2 to 1.0, respiratory drive improved simultaneously with a rapid increase in SpO_2 . However, $\text{SpO}_2 > 95\%$ occurred in the majority of infants, especially in the infants who received PPV, which probably reflects the difficulty of simultaneously performing PPV and titrating oxygen. These observations suggest that targeting a higher percentile as currently recommended in international guidelines [7,8] (25th–50th percentile) might improve respiratory drive. A more stepwise increase in FiO_2 and more diligence in reducing FiO_2 , for example when $\text{SpO}_2 > 85\%$, could reduce the risk of hyperoxia.

We observed that preterm infants started to breathe more vigorously, as indicated by an increased rate and effort, once FiO_2 was increased and SpO_2 improved. Antenatally, hypoxia suppresses fetal breathing movements [11] whereas postnatally hypoxia stimulates breathing. The sensitivity increases during days-weeks after birth [12]. However, the mechanisms driving the large inspiratory efforts and controlling the switch to continuous breathing after birth are unknown, although increasing arterial PO_2 may be involved [20]. We speculate that infants in our study, who failed resuscitation with air, respiratory support was insufficient to aerate the lung and supplemental oxygen was required to compensate. We suggest that the resulting increase in oxygenation increased drive from the respiratory center and respiratory effort, which increased lung aeration and FRC. This would explain why FiO_2 1.0 was only required for a short time and could be rapidly weaned allowing most infants to remain stable with little extra oxygen. Although our weaning rate was fast, studies comparing high versus moderate FiO_2 levels in preterm infants found similar levels of FiO_2 at 10 minutes [9,21–23].

Experimental studies have shown that pulmonary vascular resistance at birth is related to ventilation onset and oxygen had little impact [24–26]. Also, Sobotka et al. found that increasing FiO_2 to 1.0 in hypoxic lambs just after birth improved blood oxygenation, but had no effect on lung compliance and pulmonary blood flow [25]. This supports the hypothesis that increased oxygenation after FiO_2 1.0 is achieved by increasing the partial pressure gradient for oxygen diffusion compensating the ventilation-perfusion mismatch due to low FRC [25].

The reported V_t increased in infants on CPAP could be explained by improved lung compliance. However, volume increase occurred right after increasing FiO_2 and remained stable in the minute thereafter. Also, RR increase cannot be explained by improving compliance. Alternatively, increased pressures could have elevated V_t , but these remained unchanged. Increasing FiO_2 increases gas density which can influence measurements [17–19]. However, after correction, tidal volumes remained significantly larger after FiO_2 1.0 and when considering the rate of rise is also increased it is more likely to be the infant's own effort.

Although studies showed it is feasible to support preterm infants at birth with a FiO_2 of < 1.0 , most infants starting with low FiO_2 levels needed an increased FiO_2 (0.45–0.6) to reach target SpO_2 levels [21,22]. However, the different approaches make it difficult to compare these studies with our observational data reported in this study. We often observed SpO_2 below target. Therefore, starting in air may not be the right approach. Although it is unclear how detrimental a short period of FiO_2 1.0 is at birth (1–2 minutes), more vigilance in preventing SpO_2 levels $> 95\%$ is needed [2].

In line with our recent report [13], we observed that oxygen use was not always according to the guidelines. Oxygen was given earlier or later than recommended. In the PPV-group a SpO₂ >95% occurred more often and lasted longer, increasing the chances of hyperoxia. These observations may indicate the algorithm was difficult to follow. This will become even more difficult if separate SpO₂ targets for each minute after birth are defined and may lead to a change in focus away from adequate ventilation. Adding an extra person to the resuscitation team could be helpful.

Limitations

The retrospective nature of the study and the relative small sample size precludes any hard conclusion regarding respiratory drive and oxygenation. Recording respiratory parameters at birth is challenging, similar studies do not include large number of infants [27–31]. The infants included in this study is a sample of the preterm infants born in the hospitals and a selection bias could have occurred. However, the sample was randomly chosen as recordings were performed if the research team was available. The

observed variation in starting time of FiO₂ 1.0 complicates comparing with the respiratory drive of infants receiving air. Also, the observational nature of this study prevented us to have a control group of infants needing no support. However, we were interested in the effect of FiO₂ 1.0 and measurements before starting oxygen served as a control period.

Conclusions

We observed that during respiratory support of preterm infants switching from air to FiO₂ 1.0 increased the risk for hyperoxia. No hard conclusions can be drawn, but our observations might suggest that respiratory drive increased after supplemental oxygen was given and oxygenation improved. The role of SpO₂ levels in stimulating respiratory drive at birth merits further investigation.

Author Contributions

Conceived and designed the experiments: JV PD SH AP. Performed the experiments: JV PD AP. Analyzed the data: JV NN AP. Wrote the paper: JV MS SH FW PD AP.

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