

# **The risk for hyperoxia after extra oxygen therapy for apnea, bradycardia, cyanosis in preterm infants**

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## INTRODUCTION

The incidence of prematurity, defined by the World Health Organization as the delivery of the fetus at <37 completed weeks of gestation is 7.1 % and has not changed over the years. A smaller proportion, 1.1 %, is born extreme premature (<32 weeks).(1) One of the most common and resilient problems in preterm infants is apnea of prematurity (AOP)(2). AOP is defined as a respiratory pause > 20 seconds or when this pause is combined with cyanosis, pallor, hypotonia and/or bradycardia.(3) If an infant does not respond to tactile stimulation, interventions such as mask ventilation and an increase in fractional oxygen are necessary. The incidence of AOP is inversely correlated with gestational age and birth weight, nearly all infants born at <29 weeks gestation exhibit AOP and 7% at 34-35 weeks gestation (2). The immature respiratory center is one of the factors explaining the frequent occurrence of apnea's and are sometimes difficult to treat.

AOP is often combined with bradycardia and cyanosis (ABC) and can result in morbidity, which includes ROP, impaired growth, longer term cardio respiratory instability and poor neurodevelopmental outcome (4). The risk for hypoxic episodes increases when oxygen saturations drop  $\leq 80\%$  for  $\geq 10$  seconds. Preterm infants often receive extra oxygen as intervention for ABC, which can lead to hyperoxia. Oxygen can be toxic to living cells, particularly in high concentrations. The risk for hyperoxia increases when an arterial blood saturation ( $SpO_2$ ) increase of  $>95\%$  for  $\geq 10$  seconds (4). Hyperoxia has been shown to be an important pathogenetic factor for bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) (5) and is also correlated with cerebral palsy (6).

Monitoring the  $SpO_2$  of these infants is, therefore, important and considered standard of care in the neonatal intensive care unit (NICU). To achieve adequate oxygen delivery, without creating episodes increasing the risk for hypoxia or hyperoxia, oxygen levels are often monitored by continuous non-invasively pulse oximetry (7). The optimal oxygen saturation values for premature infants remain largely undefined but ranges between 85% to 93% have been associated with improved neurodevelopmental outcome (8).

One of the biggest challenges for a neonatal nurse is try to stay within these narrow target oxygen saturation ranges. Increasing the Fraction of Inspired Oxygen ( $FiO_2$ ) is often needed, but may unintendedly result in hyperoxia. The long-term consequences of frequent apnea's are attributed to the occurrence of bradycardia and cyanosis (4), it is possible that (iatrogenic) hyperoxia also contributes to this when extra oxygen is given after AOP.

### **PROBLEM STATEMENT**

There are several studies reporting the occurrence of oxygen saturations > 95%. (9-11) Also, poor compliance regarding alarm limit settings, which could lead to hyperoxia, have been observed. (12-14) There is however barely data available how frequently hyperoxia occurs after apnea's, the duration of these episodes and how this is related to the occurrence and duration of cyanosis during apnea's. A high occurrence of hyperoxia after apnea's could potentially lead to a different view in the pathophysiology of the long term consequences of apnea's. Also, this study could lead to more awareness among caregivers in neonatal wards concerning hyperoxia after apnea's and effort should be undertaken in avoiding this.

### **AIM**

This study therefore aimed to investigate the occurrence and duration of hyperoxia in preterm infants treated with extra oxygen given after an apnea.

### **REASERCH QUESTIONS**

1. What is the occurrence and duration of hyperoxia in preterm infants treated with extra oxygen given after an ABC,
2. How long does hyperoxia last and how does this correlate with the duration of bradycardia and cyanosis Are there differences in the characteristics of ABC's and oxygen therapy when
  - a. hyperoxia occurs or not
  - b. hyperoxia occurs and ambient air or supplemental oxygen was given before ABC occurred.

### **METHOD**

This retrospective, descriptive single-centre study was performed in the Neonatal Intensive Care Unit (NICU) of Leiden University Medical Center, the Netherlands, which is a tertiary level perinatal center with an average of 400 intensive care admissions a year. Approval was obtained from the ethical review board of Leiden University Medical Center (C12.168).

#### *Participants*

All infants, with a gestational age (GA) < 32 weeks at birth, born between October 2011 and October 2012, supported with nasal Continuous Positive Airway Pressure (nCPAP) were evaluated. Infants with major congenital heart disease were excluded; different oxygen saturations and separate guidelines for oxygen supply are followed for this group. Clinical parameters of each infant were stored every minute, and collected in Patient Data

Management System (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). Only the ventilators in the intensive care were connected to PDMS, therefore only infants receiving nCPAP in the ICU were included.

#### *Procedure*

In all infants ABC's (Apnea's associated with bradycardia ( $\leq 80$  beats per minute) and hypoxia (oxygen desaturation  $\leq 80\%$ ) where extra oxygen was given, were identified. The data collection started with an ABC, hyperoxia (oxygen saturation  $\geq 95\%$ ) was measured after the addition of extra oxygen and stopped at the time when the oxygen supply was back at the baseline at the time the ABC occurred (figure 1).

Figure 1

#### *Data collection*

ABC's were retrieved in two ways: 1) apnea was noted in the respiratory chart in PDMS. As this was not always registered exact on the time point the apnea occurred, the moment of hypoxia combined with bradycardia was retrieved which was the closest to the registered apnea, 2) apnea was not noted, but respiratory rate in PDMS was zero and combined with bradycardia and hypoxia.

With every ABC the following characteristics were noted: the duration and depth of bradycardia, the duration and depth of hypoxia, the amount of baseline oxygen and extra oxygen given, the duration of extra oxygen given (measured from the start of extra oxygen after the ABC until oxygen was titrated to the baseline oxygen), if hyperoxia occurred and the duration of hyperoxia. Characteristics of ABC's and oxygen therapy were compared when a) hyperoxia occurred or not, and b) when hyperoxia occurred but ambient air or extra oxygen was given as baseline (oxygen therapy before ABC).

### *Statistical analyses*

Quantitative data are expressed as median and interquartile range (IQR), or number (percentage) where appropriate. ANOVA, independent samples Mann-Whitney U test were used for comparisons between hyperoxia or not, and occurrence of hyperoxia in baseline oxygen requirements (ambient air or supplemental oxygen). The correlations between duration of bradycardia, hypoxia and hyperoxia were investigated using Pearson product-moment correlation coefficient for normal distributions or Spearman's rank when normal distribution could not be assumed. *p*-values less than 0.05 were assumed as statistically significant.

Statistical analysis was performed by IBM SPSS Statistics version 20 (IBM Software, NY, USA, 2012).

## **RESULTS**

From October 2011 until October 2012 194 infants < 32 weeks gestation were admitted to the NICU and received nCPAP during their admission. One infant had a congenital heart disease and was excluded. In total, charts of 193 infants were reviewed for ABC where extra oxygen was given. In 56/193 infants 257 ABC's occurred where oxygen was increased, Patients characteristics are shown in table 1. The depth of bradycardia was 70 (63-76) bpm with a duration of 1(1-1) minute. The depth of hypoxia was 68 (61-73)% with a duration of 2 (1-2) minutes. The baseline level of oxygen before ABC occurred was 23 (21-28)% and increased to 39 (30-67)% after the ABC (absolute increase of 16%). The duration of titrating down the oxygen to the baseline was 14 (4-52) minutes (table 1).

Table 1

### **ABC's with no hyperoxia versus hyperoxia**

Hyperoxia occurred in 79% (202/257) of the ABC's where oxygen was increased and lasted 13 (4-30) minutes. When comparing ABC's where hyperoxia occurred with ABC's where hyperoxia did not occur, no differences were observed in the duration of bradycardia (1(1-1) vs 1 (1-1) min; ns), depth of bradycardia (70 (63-77) vs 70 (63-76) bpm; ns), hypoxia (2 (1-2) vs 2 (1-2) minutes; ns), depth of hypoxia (69 (62-73) vs 68 (61-73)%; ns), in baseline oxygen

level (23 (21–28)% vs 23 (21-33)%; ns) and oxygen increase (37 (30 – 65)% vs 45 (34-68)%; ns) (table 2). After extra oxygen was given, the time needed to return to baseline level was longer in ABC's with hyperoxia than without (20 (8-80) vs 2 (2-3) minutes;  $p < 0.001$ ) (table 2). There was no correlation between the duration of hyperoxia and hypoxia ( $r = -0.05$ ; ns) or bradycardia ( $r = -0.05$ ; ns).

Table 2

#### **ABC's with hyperoxia and baseline level: ambient air versus extra oxygen**

In 52% (105/202) of ABC's with hyperoxia ambient air was given as baseline oxygen level and in 48% (97/202) extra oxygen was given as baseline level before the ABC occurred. No differences were observed in the duration and depth of bradycardia 1 (1-1) vs 1 (1-1) min; ns and 70 (64-76) vs 70 (62-75) bpm; ns). The duration and depth of hypoxia lasted longer in ABC's where extra oxygen was at baseline level versus the duration where ambient air was given as baseline level (2 (1-2) vs 2 (1-3) min;  $p=0.001$  and 68 (63-75) vs 67 (58-73)%;  $p=0.05$ ). Although there were no differences measured in the time needed to return to baseline level (22 (8-101) vs 19 (8-63) min; ns), the duration of hyperoxia lasted much longer when ambient air was given compared when extra oxygen was given as baseline level (14 (5-40) min vs 8 (4-26) min;  $p < 0.05$ ) (table 3). There was a correlation between the baseline oxygen level before ABC and the duration of hyperoxia after ABC ( $r=0.2$ ;  $p < 0.01$ )

Table 3

## DISCUSSION

In this retrospective study in preterm infants on CPAP we observed that when extra oxygen was given for treating ABC's, hyperoxia frequently occurred and lasted significantly longer than the bradycardia or hypoxia. The duration of hyperoxia was not correlated to the duration of bradycardia or hypoxia, but there was a correlation with the baseline oxygen level before ABC. Hyperoxia lasted longer when patients were in ambient air before the ABC. Also, when hyperoxia occurred, we recorded a significantly longer time needed to titrate oxygen back to the baseline level than after ABC's where hyperoxia did not occur. Our findings reflect a low compliance of caregivers in our unit preventing hyperoxia by manual adjust oxygen therapy adequately. Caregivers should be more aware of the dangers of not only the ABC, but also for the risk for hyperoxia that could occur after the ABC.

The high incidence of hyperoxia in our unit is comparable to what has been reported in previous studies.(9-11) However, this is the first study describing hyperoxia after oxygen has been increased when ABC's occur and how long the hyperoxia last. Our results nicely show that nurses responded fast to an incident (ABC), but the oxygen therapy is not carefully titrated once the incident is over. The compliance of nurses could be affected by the nurse:patient ratio which is variable in our unit, on average 1:2. Sink *et al.* specified oxygen saturation ranges by nurse: patient ratio. The percentage of time oxygen saturation was above the target ranges increased from 51% to 82% when nurse:patient ratio increased from 1:1 to 1:3. (10)

Another factor that could explain the high occurrence and long duration of hyperoxia is setting the alarm limits incorrect. Previous studies have reported a low compliance for alarm limits for pulse oximetry. (12-14) Clucas *et al.* (2007) investigated the nursing compliance with alarm limits for pulse oximetry in preterm infants and categorized the oxygen requirements into approximate tertiles as low (22%-23%), moderate (24%-29%) and high (> 29%). Observations taken for infants requiring high levels of supplemental oxygen, the upper alarm limit was set correctly in 35,7%, compared with 23,6% in the moderate group and 6,2% in the low oxygen group.(12) The low compliance for alarm settings could explain our observation that the duration of hyperoxia was significantly longer when infants were in ambient air before the ABC occurred and alarm limits were not adjusted when extra oxygen was started (from 85-100% to 85-95%).

The long term consequences of ABC's for preterm infants has been well established.(4) Most caregivers are aware that frequent bradycardia and hypoxia can result in morbidity,

which includes ROP, impaired growth, longer term cardio respiratory instability and poor neurodevelopmental outcome. (4). However, hyperoxia has been shown to be an important pathogenetic factor for similar morbidities. (5, 6) In this study, we observed that hyperoxia occurs often directly after ABC and even lasted longer than the ABC, it will be difficult to distinguish the effect of bradycardia, hypoxia and also the hyperoxia on the long term morbidity. We speculate that when considering the long-term consequences of ABC in preterm infants, it is possible that iatrogenic hyperoxia that often follows after an ABC could also play an important role.

Probably due to the lack of proper guidelines for titrating oxygen, oxygen saturations are frequently above target ranges when it is controlled manually by nursing staff. Nurses easily administer large amounts of oxygen in order to prevent hypoxia. Observational data showed that manual  $\text{FiO}_2$  adjustments in preterm infants varied widely in frequency and step size by caregivers.(11) It is possible that, when manual adjustments of  $\text{FiO}_2$  are standardized, fluctuations of saturations will decrease, reducing the periods of hypoxia and hyperoxia. Lau *et al.* implemented a  $\text{SpO}_2$  targeting protocol and developed an algorithm for titrating  $\text{FiO}_2$ , and found sustainable improvement in maintaining  $\text{SpO}_2$  within the target range: The percentage of high  $\text{SpO}_2$  levels was markedly reduced to between 0 and 15%. Ford *et al.* showed that education and training was effective in improving the maintenance of the intended range of  $\text{SpO}_2$  from a very low 20% of the time to approximately 42% of the time. This was largely the result of a reduction in the proportion of time with  $\text{SpO}_2$  above the intended range from 78% to nearly 37% of the time.(15) However, other studies reported that knowledge about the risk of hyperoxia did not reduce the time preterm infants spent oxygen saturations above the target ranges.(16, 17)

Another possibility to improve our care in oxygen therapy is to replace manual adjustments by caregivers with an automated regulation of the fraction of inspired oxygen. Several studies have shown oxygen saturations were less variable and more often maintained within target ranges when oxygen therapy is automatically adjusted instead of manually. (18-21) However, whether automated oxygen regulation will improve long term morbidity in preterm infants, is still a subject for further research.(22)

The study is limited by the small sample size; only infants where data was available in PDMS were included. This could have led to a bias as these were the more preterm infants admitted to the NICU. It is possible that the occurrence of hyperoxia after ABC is lower when we could have included all preterm infants, including the infants admitted in the step down unit receiving nCPAP, low flow or oxygen therapy. However, we do not expect that this will

influence the incidence considerably as the more preterm infants we reported have more frequently ABC's than the stable preterm infants.

### **CONCLUSION**

In preterm infants treated with CPAP, hyperoxia occurs often after oxygen therapy for ABC's and the duration was longer than the bradycardia and hypoxia. The duration of hyperoxia was much longer in infants breathing ambient air compared to infants who had extra oxygen before ABC occurred. It is possible that not only the bradycardia and hypoxia that occurs with the ABC could play a role in the long-term consequences of apnea's, but also the iatrogenic hyperoxia after the ABC.

### **RECOMMENDATIONS**

NICU professionals, should be more aware of the occurrence of hyperoxia after ABC's when extra oxygen is given and more vigilance is needed for alarm settings and titrating oxygen back to baseline as soon as possible. This could be reached by more training, education and a low nurse:patient ratio or by replacing the manual by automatic adjustments.

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Figure 1

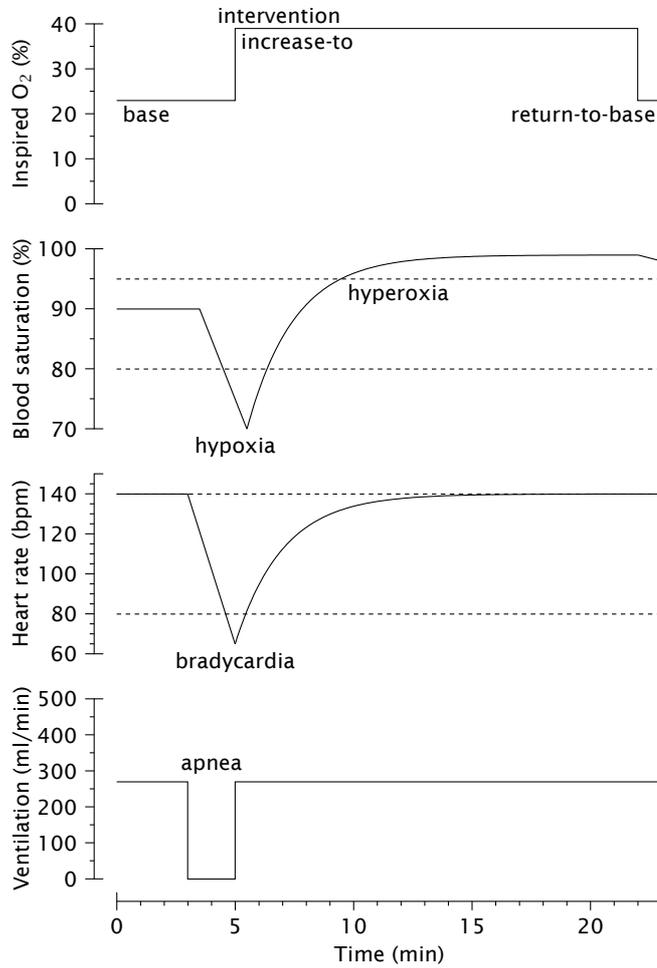


Figure 1 Measuring hyperoxia

**Table 1**

Table 1 Baseline Characteristics Patient and ABC's

Characteristics Patients	N=56	Characteristics ABC's	N=257
Gestational Age GA, days	197 (183-206)	Depth of bradycardia (bpm)	70 (63-76)
Birth Weight, gram	908 (800-1167)	Duration bradycardia (min)	1 (1-1)
Males, %	52	Depth of hypoxia (%)	68 (61-73)
Apgar 5 minutes, median (range)	8 (5-10)	Duration hypoxia (min)	2 (1-2)
Singletons, %	41	Baseline oxygen level (%)	23 (21-28)
Caesarean Delivery, %	50	Max increase oxygen level (%)	39 (30-67)
Mortality %	7	Duration titration to baseline oxygen level (min)	14 (4-52)
BPD <sub>moderate-severe</sub> %, at 36 weeks GA	7	Characteristics ABC's	N=257
ROP $\geq$ stage 3 (%)	7	Depth of bradycardia (bpm)	70 (63-76)
NEC $\geq$ stage 2a (%)	5	Duration bradycardia (min)	1 (1-1)
IVH grade $\geq$ 2 (%)	18	Depth of hypoxia (%)	68 (61-73)
Apnea per infant	1 (1-6)	Duration hypoxia (min)	2 (1-2)

Data are expressed as median (IQR), unless specified otherwise.

**Table 2**

Table 2 Total group no hyperoxia vs hyperoxia

Characteristics ABC and oxygen support (median (IQR))	No hyperoxia N= 55	Hyperoxia N= 202	p-value*
Depth of bradycardia (bpm)	70 (63-77)	70 (63-76)	ns
Duration bradycardia (min)	1 (1-1)	1 (1-1)	ns
Depth of hypoxia (%)	69 (62-73)	68 (61-73)	ns
Duration hypoxia (min)	2 (1-2)	2 (1-2)	ns
Baseline oxygen level (%)	23 (21-33)	23 (21-28)	ns
Max increase oxygen level (%)	45 (34-68)	37 (30-65)	ns
Duration titration to baseline oxygen level(min)	2 (2-3)	20 (8-80)	< 0.001
Duration hyperoxia (min)	-	13 (4 -30)	

\* Independent samples Mann-Whitney U test

**Table 3**

Table 3 Group hyperoxia: baseline ambient air vs supplemental oxygen

Characteristics ABC and oxygen support (median (IQR))	ambient air N= 105	extra oxygen N= 97	p-value*
Depth of bradycardia (bpm)	70 (64-76)	70 (62-75)	ns
Duration bradycardia (min)	1 (1-1)	1 (1-1)	ns
Depth of hypoxia (%)	68 (63-75)	67 (58-73)	0.05
Duration hypoxia (min)	2 (1-2)	2 (1-3)	0.001
Baseline oxygen level (%)	21 (21-21)	28 (25-34)	< 0.001
Max increase oxygen level (%)	32 (27-45)	44 (35-77)	< 0.001
Duration titration to baseline oxygen level (min)	22 (8-101)	19 (8-63)	ns
Duration hyperoxia (min)	14 (5-40)	8 (4-26)	< 0.05

\* Independent samples Mann Whitney U test

## **DUTCH SUMMERY**

**Titel:** Het risico op hyperoxie na extra zuurstof therapie voor apneus bij te vroeg geboren kinderen

**Inleiding:** Premature kinderen met apneus, gecombineerd met bradycardie en cyanose (ABC), krijgen vaak extra zuurstof. De gevolgen op lange termijn van frequente ABC's worden vaak toegeschreven aan bradycardie en hypoxie. Het is bekend dat extra zuurstoftherapie het risico op hyperoxie verhoogt. Het optreden en de duur van hyperoxia nadat ABC's is onbekend.

**Doel:** Het optreden en de duur van de hyperoxie onderzoeken nadat extra zuurstof voor ABC's is gegeven en hoe/of dit gerelateerd is aan de duur van bradycardie en of cyanose.

**Onderzoeksvragen:** Wat is het optreden en de duur van hyperoxie bij premature kinderen behandeld met extra zuurstof, gegeven na een ABC en hoe lang duurt hyperoxie in vergelijking met de duur van bradycardie en cyanose en hoe zijn deze gecorreleerd?

**Methode:** Een retrospectief onderzoek in de neonatale intensive care unit van het Leids Universitair Medisch Centrum werd uitgevoerd. In een jaar tijd werden alle ABC's van kinderen <32 weken zwangerschap, ondersteund met nasale Continuous Positive Airway Pressure (nCPAP), geïdentificeerd. In ABC's waar zuurstoftoevoer werd verhoogd, werden bradycardie (<80bpm), cyanose (<80%) en hyperoxie (> 95%) en hun correlatie onderzocht.

**Resultaten:** In 56/193 opgenomen kinderen, hebben zich 257 ABC's voorgedaan waar zuurstoftoevoer werd verhoogd. Hyperoxie na ABC's werd gemeten in 79% (202/257). De duur van hyperoxie was langer dan bradycardie en cyanose (13 (4-30) vs 1 (1-1) vs 2 (1-2) minuten,  $p < 0,001$ ). Er was geen correlatie tussen de duur van cyanose-hyperoxie en bradycardie-hyperoxie. Hyperoxie na ABC's duurde langer wanneer kinderen omgevingslucht kregen dan wanneer zij al extra zuurstof ontvingen vóór ABC. (15 (5-38) min vs 6 (3-24) min;  $p < 0,01$ ).

**Conclusie:** Bij premature kinderen aan nCPAP, treedt frequent hyperoxie op nadat zuurstoftoevoer is verhoogd na ABC's. Hyperoxie duurt langer dan bradycardie en cyanose tijdens ABC.

**Aanbevelingen:** NICU verpleegkundigen moeten waakzamer zijn in het titreren van zuurstof na de ABC's.

**Trefwoorden:** prematuur, baby, intensive care, hyperoxie, zuurstof

## **ABSTRACT**

**Title:** The risk for hyperoxia after extra oxygen therapy for apnea in preterm infants

**Introduction:** Preterm infants with apnea's combined with bradycardia and cyanosis (ABC), often receive extra oxygen. The long-term consequences of frequent ABC's are often attributed to bradycardia and hypoxia. It is known that extra oxygen therapy increases the risk for hyperoxia. The occurrence and duration of hyperoxia after ABC's is unknown.

**Aim:** To investigate occurrence and duration of hyperoxia after extra oxygen for ABC's and how this is related to the duration of bradycardia and/or cyanosis.

**Research questions:** What is the occurrence and duration of hyperoxia in preterm infants treated with extra oxygen given after an ABC and how long last hyperoxia when compared to the duration of bradycardia and cyanosis and how are these correlated?

**Methods:** A retrospective study in the neonatal intensive care unit of Leiden University Medical Center was performed. In a years' period all ABC's of infants < 32 weeks gestation supported with nasal Continuous Positive Airway Pressure (nCPAP) were identified. In ABC's where oxygen was increased, moments of bradycardia (< 80bpm), cyanosis (< 80%) and hyperoxia (> 95%) and their correlation were investigated.

**Results:** In 56/193 admitted infants, 257 ABC's occurred where oxygen supply was increased. Hyperoxia occurred in 79% (202/ 257) after ABC's. The duration of hyperoxia was longer than bradycardia and cyanosis (13 (4–30) vs 1 (1-1) vs 2 (1-2) minutes;  $p < 0.001$ ). There was no correlation between duration of cyanosis-hyperoxia and bradycardia-hyperoxia. Hyperoxia lasted longer after ABC's when infants received ambient air than when extra oxygen was given before ABC occurred. (15 (5–38) min vs 6 (3–24) min;  $p < 0.01$ ).

**Conclusion:** In preterm infants supported with nCPAP, hyperoxia after extra oxygen supply for ABC's was frequent and lasted longer than bradycardia and cyanosis during ABC.

**Recommendations:** NICU caregivers should be more vigilant in titrating extra oxygen after ABC's.

**Keywords:** preterm, infant, nursing, hyperoxia, oxygen