Cardio-respiratory events in preterm infants during the transitional period.

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Abstract

Objective

To investigate the features of cardio-respiratory events (CRE) in preterm infants during the transitional period, and to evaluate whether different neonatal characteristics may correlate with CRE type, duration and severity.

Study design

Infants with gestational age (GA) <32 weeks and/or birth weight <1500g were enrolled in this observational prospective study. Heart rate (HR) and peripheral oxygen saturation (SpO₂) were recorded continuously over the first 72 hours. CRE ≥ 10 sec were clustered into isolated desaturation (ID, SpO₂<85%), isolated bradycardia (IB, HR<100 bpm or <70% of baseline) or combined desaturation/bradycardia (DB) and classified as mild, moderate or severe. The daily incidence of ID, IB and DB was analyzed. The effect of relevant clinical variables on CRE type and severity was assessed using generalized estimating equations.

Results

Of 1050 events analyzed, ID were the most frequent (n=625) and IB the least common (n=171). CRE significantly increased from day 1 to 2 (p=0.028). One in 5 CRE had severe characteristics; event severity was highest for DB (p<0.001). Compared with other event types, DB incidence inversely correlated with GA (p=0.029) and was higher with CPAP (p=0.002). The presence of a hemodynamically significant patent ductus arteriosus was associated with ID occurrence (p=0.001) and longer CRE duration (p=0.003).

Conclusions

CRE during transition show different types, duration and severity. Neonatal characteristics play a significant role in the determination of CRE features, strengthening possible importance of a tailored clinical approach to reduce the hypoxic burden in preterm infants aged 0-72h.

List of abbreviations:

CPAP: continuous positive airway pressure

CRE: cardio-respiratory events

DB: combined desaturation and bradycardia

GA: gestational age

GEE: generalized estimating equations

HR: heart rate

hsPDA: hemodynamically significant patent ductus arteriosus

IB: isolated bradycardia

ID: isolated desaturation

PDA: patent ductus arteriosus

SpO₂: peripheral arterial oxygen saturation

uREDF: umbilical reversed end-diastolic flow

VLBW: very-low-birth-weight

Introduction

Despite continuous improvements in neonatal care, preterm birth is still burdened by significant clinical complications and represents a major risk factor for neurodevelopmental impairment (1).

Cardio-respiratory events (CRE), defined as intermittent hypoxic and/or bradycardic episodes, are very common among preterm infants (2). Poor respiratory drive, increased metabolic oxygen consumption and the reduced total blood oxygen carrying capacity of this population significantly enhance CRE frequency and severity (3).

Evidence from animal models have shown that CRE, either alone or combined to specific clinical factors (i.e., intrauterine growth restriction, respiratory support modality, need for supplemental oxygen, etc.), can initiate a pathological cascade that leads to an increased production of reactive oxygen species, with possible detrimental effects on several neonatal outcomes (4). In particular, an association between intermittent hypoxic events and the development of retinopathy of prematurity (ROP) has previously been described, with evidence of a positive correlation between ROP severity, event duration and the depth of hypoxemia (5). A number of studies have also suggested the critical influence of CRE on early brain development, showing a relationship between hypoxic burden and poor neurodevelopment (6–8). A possible role for hypoxic events during the first months of life on the development of bronchopulmonary dysplasia has been recently reported in very-low-birth-weight (VLBW) (9) and extremely preterm neonates (10).

The transitional period, defined as the first 72 hours after birth, is a critical phase of physiological adaptation and affects several organ systems, most notably the heart and the lungs. In particular, the dynamic cardiovascular changes that are typical for the transition from a fetal to a neonatal circulation enhance preterm infants' cardiorespiratory instability (11), which, in turn, may contribute to the clinical relevance of CRE during this period.

The combination of hypoxemia and bradycardia that occurs during CRE results in intermittent fluctuations of cerebral perfusion and oxygen delivery. This may affect cerebrovascular autoregulation, as suggested by the correlation between early hypoxic burden and the rates of

intraventricular hemorrhage (12,13), whose risk is highest during the transitional period (14). Furthermore, a lower rate of survival at 90 days has been observed in preterm small-for-gestational-age infants who experienced a higher CRE number during transition (15).

Most of the available literature on CRE features in the preterm population and the related clinical outcomes, however, are based on infants aged a few weeks or older, with limited data from the transitional period (2,4). Moreover, whether CRE features may be associated with specific neonatal characteristics has not been investigated yet. Therefore, this study was aimed to characterize CRE during the transitional period in VLBW preterm infants, and to evaluate whether different neonatal characteristics may correlate with CRE type, duration and severity.

Methods

Study population and Ethics

Infants born at S. Orsola-Malpighi Hospital between February 2018 and August 2019 were consecutively enrolled in this observational, prospective study according to the following criteria: gestational age (GA) <32 weeks' gestation and/or birth weight <1500 g, 0-12 hours of life. Major congenital malformations, including congenital heart disease, were exclusion criteria. For the sake of data homogeneity, infants requiring mechanical ventilation during the study period were ruled out from the study. Moreover, in order to reduce the impact of feeding modality on CRE occurrence, enteral feeds during the study period were administered as gravity boluses (16).

This study was conducted in conformity with the principles and regulations of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of St. Orsola-Malpighi Hospital, Bologna (Italy) and is registered in the Protocol Registration System ClinicalTrials.gov (NCT04123691). Written informed consent was obtained from the parents/legal guardians of each infant.

CRE analysis

Peripheral oxygen saturation (SpO₂) and heart rate (HR) were collected using a pulse oximeter Masimo Radical 7 (Masimo Corporation, Irvine, CA, USA) with a SpO₂ averaging time set at 2 sec, connected via a RS232 cable to a laptop running ICM+ ® (<https://icmplus.neurosurg.cam.ac.uk/>; Cambridge Enterprise, UK). ICM+ ® is an analytical software allowing a real-time multiparametric data collection and a retrospective trace analysis. Raw HR and SpO₂ data were continuously recorded with a 1-Hz sampling frequency from the time of enrolment up to 72 hours of life using this software. ECG monitoring, synchronized with the pulse oximeter via the ICM+ software, was also performed; time periods showing a HR discrepancy >20% between the two devices were considered as likely artefacts and ruled out from data analysis.

ICM+ graphical traces (Figure 1; online) and spread sheet outputs were analyzed to identify the following CRE types: isolated desaturations (ID), defined as SpO₂ <85% (16,17); isolated bradycardias (IB), defined as any HR fall <100 bpm or >30% below the baseline before the event (16,18,19); combined desaturation and bradycardia (DB), if the two events occurred within a 30-sec time window (20). Combined events were further stratified according to the timing of bradycardia onset: before desaturation onset (type 1), after desaturation onset, but before its nadir (type 2), and concomitant or subsequent to desaturation nadir (type 3) (21).

Event duration was calculated as the period spent below the SpO₂/HR thresholds used for CRE definition. Due to their doubtful clinical significance, events <10 sec were ruled out from the study (17). Based on the combination of SpO₂/HR nadir and their duration, CRE were defined as mild (duration ≤60 sec and SpO₂ nadir 80-84% and/or HR 80-99 bpm or 30-50% below the pre-event baseline), moderate (duration 61-120 sec and/or SpO₂ nadir 70-79% and/or HR nadir 60-79 bpm or 50-70% below the pre-event baseline) and severe (duration >120 sec and/or SpO₂ nadir <70% and/or HR nadir <60 bpm (22)).

Neonatal clinical characteristics

The following antenatal and neonatal data were recorded: GA, antenatal steroids (complete course vs. incomplete course or not given) evidence of reversed end-diastolic flow at antenatal umbilical Doppler (uREDF) (present vs. absent); ventilatory status over the first 72 hours of life (continuous positive airway pressure [CPAP] vs. low flow nasal cannulas or self-ventilating in air [SVIA]).

A screening echocardiogram aimed at evaluating the ductal status was routinely performed at the time of enrolment using an ultrasound scanner CX50 (Philips Healthcare) with a 12-MHz probe, and repeated 6-12 hourly in the presence of a patent ductus arteriosus (PDA) or 12-24 hourly if there was no evidence of PDA.

The ductal diameter was measured from the high parasternal view at the point of maximum constriction, caring to avoid color-Doppler interference outside the vessel wall. The ductal flow pattern was evaluated from the parasternal short axis using continuous-wave Doppler and, based on the ratio of end-diastolic to peak-systolic velocity, was defined as pulsatile (≥ 0.5) or restrictive (< 0.5) (23). Blood flow velocity in the descending aorta and in the anterior cerebral artery was measured using pulsed-wave Doppler from low subcostal sagittal view and from sagittal view through the anterior fontanel, respectively. The left atrium to aortic root (LA:Ao) ratio was measured on M-Mode scans obtained from the parasternal long axis view using the leading-edge-to-leading-edge technique. Based on the abovementioned echocardiographic features, the ductal status was defined as follows: no evidence of PDA (noPDA), restrictive PDA (rPDA; restrictive shunt pattern and LA:Ao ratio < 1.5), haemodynamically significant PDA (hsPDA; pulsatile shunt pattern and LA:Ao ratio ≥ 1.5 or evidence of reversed end-diastolic flow either in the descending aorta or in the anterior cerebral artery (23,24).

Statistical analysis

Generalized estimating equation (GEE) models were used to analyze the effect of GA, uREDF, antenatal steroids, ductal and ventilatory status on the occurrence of CRE types (ID, IB, DB) and severe events using binomial distribution/logit link, respectively. In these models, the PDA status of

and the ventilatory support were used as time-dependent covariates and the events were nested within individuals.

The analytical strategy used in the present study was aimed at improving estimation efficiency and therefore power. In particular, the working correlation structure of our GEEs was accurately chosen (25) and the autoregressive correlation model, which is appropriate when time-varying outcomes or covariates are investigated (26), was used. Moreover, a robust estimation of standard errors was performed (27), and the standard errors were adjusted for the number of non-redundant parameters. A GEE model with gamma distribution/log link was used to evaluate the relation of different neonatal characteristics and event types with event duration.

Variations in the number of ID, IB and DB over the 3 days of life, adjusted for the effective hours of recording, were analyzed using Repeated Measures ANOVA (RM-ANOVA). IBM SPSS, version 25.0, was used for the statistical analyses. The significance level was set at $p < 0.05$.

Results

Thirty-two neonates were enrolled during the study period (Figure 2; online). The characteristics of the study population are detailed in Table 1. None of the enrolled infants experienced perinatal asphyxia or required inotropes during the period of evaluation. All the small-for-gestational-age (SGA) infants included in the present study showed evidence antenatal uREDF; for this reason, the latter condition was included in the GEE models described below.

Overall, 1050 events were recorded; of these, ID were 625 (59.5%), IB 171 (16.3%) and 254 (24.2%) were combinations of the two events (BD). For BD, the timing of bradycardia in relation to desaturation was examined: bradycardia onset preceded desaturation onset in 164 (65.1%) events, whereas the onset of bradycardia occurred after desaturation onset, but before its nadir in 77 (30.6%) events. Bradycardia onset followed desaturation nadir only in a very limited number of DB ($n=11$, 4.4%).

The mean CRE number/patient/day is illustrated in Figure 3. The results of RM-ANOVA showed that the mean number of events increased significantly from day 1 to day 2 ($p=0.028$) and then remained stable. On day 1 and day 2, ID were significantly more frequent than DB and IB ($p<0.001$), while on day 3 DB and ID were more frequent than IB.

The results of GEE models evaluating the impact of different neonatal characteristics on the event types are reported in Table 2. A significant effect was found between the ductal status and incidence of ID; this effect was significantly higher in the presence of a hemodynamically significant or restrictive duct as compared to a closed duct. The incidence of DB showed a significant inverse relationship with the infants' GA. Moreover, this event type was significantly more frequent with CPAP compared to NC or SVIA periods. DB was less frequent in the presence of a hsPDA. The incidence of IB was also significantly lower in the presence of a hsPDA compared to a closed duct. For a better understanding of this finding, baseline HR values in infants with hsPDA, rPDA and noPDA were compared using a GEE model, which showed that hsPDA was associated with significantly higher baseline HR values compared to noPDA ($B=10.897$, 95% CI 4.99-16.80, $p<0.001$), while no difference was observed between rPDA and noPDA ($p=0.205$).

With respect to the event duration, DB were the longest episodes, whereas IB showed the shortest length (Figure 4; online). The GEE results showed a significantly increased duration for combined events compared to ID ($B=22.06$, 95% CI 11.51-32.61, $p<0.001$) and IB ($B=34.81$, 95% CI 18.84-50.79, $p<0.001$); there was also a significant association between hsPDA and event duration ($B=22.465$, 95% CI 7.41-37.51, $p=0.003$).

Based on the combination of SpO₂, HR nadir and event duration, CRE were stratified according to their severity; 431 out of 1050 events (41%) were mild, 407 (38.8%) moderate and 212 (20.2%) severe. The results of the GEE model are shown in Table 3 and indicate that, after adjusting for neonatal characteristics, DB events were significantly more severe compared to ID, while IB exhibited milder features than ID.

Discussion

This study shows that during the transitional period in preterm infants CRE are of different types, duration and severity, and specific characteristics, such as GA, non-invasive ventilatory support and ductal patency, play a significant role in the determination of CRE features. To the best of our knowledge, this is the first study describing CRE features during transition and analyzing the impact of different neonatal characteristics in the determination of event types, duration and severity.

Most of the available literature on CRE in the preterm population is mainly derived from intermittent periods of evaluation over the first weeks or months of life (2,4). In these studies, the variability in the infants' characteristics (e.g., gestational and post-conceptual age, ventilatory status, ongoing medications etc.), together with the use of different CRE definitions, all contribute to the heterogeneity of current evidence.

Due to the immaturity of their physiology the transition from a fetal to a neonatal circulation often results in important hemodynamic and respiratory changes in preterm infants, which contribute to their vulnerability to cardio-respiratory instability during the first 72 hours of life. The incidence of intermittent hypoxic events during the first 72 hours of life in preterm infants <28 weeks' gestation has also been associated with an increased incidence of symptomatic childhood wheezing at 2 years of age (28) and with lower survival rates at 90 days in the small-for-gestational-age cohort (15).

In the present study, isolated desaturations were the most frequent event during the transitional period, and the incidence of this event type was significantly increased in infants with echocardiographic evidence of a PDA. As shown in Table 1, the prevalence of ductal shunting was highest in the first 24 hours of life, which is consistent with previous data from the transitional period (29). The echocardiographic scans performed during the study period ruled out the presence of persistent pulmonary hypertension and documented a predominantly left-to-right trans-ductal shunt in infants with a PDA. However, during this period transient right-to-left trans-ductal shunts may occur, as a consequence of the more gradual decrease of pulmonary vascular resistance after preterm birth (30) or as a result of breathing-related fluctuations in intra thoracic pressure (31), resulting in fleeting

hypoxemia. The hypoxemic nature of these episodes may be also accountable for the longer event duration observed in infants with an hsPDA. The possibility of right-to-left shunts resulting in isolated hypoxic episodes, not accompanied by bradycardia, has also been proposed by Poets et al in infants and young children (20). To the best of our knowledge, the relationship observed between ID and the presence of a PDA represents a novel finding and, given the unfavorable influence of early hypoxia on preterm infants' outcomes (13,15), warrants further investigation.

The typical manifestation of an apneic episode is the concomitant occurrence of bradycardia and desaturation (32). In the present study, a significant inverse correlation between the incidence of DB and the infants' GA was observed. This is consistent with data by Fairchild et al (33), suggesting immaturity of central breathing control and of respiratory reflexes on the occurrence of CRE (32).

A significantly higher incidence of DB was also observed in infants on CPAP, independently of GA. By providing distending pressure and increasing the functional residual capacity, CPAP is often adopted in the presence of frequent apneic spells (34); from this perspective, the observed association would not be causal, but it may rather result from the therapeutic use of this ventilatory modality in order to reduce the apneic burden. An increased burden of bradycardias has also been reported by MacLaren et al as a consequence of orbital compression from the CPAP fixation straps, resulting in a vagal overstimulation (35); the same mechanism was also previously reported to induce central apneas in premature neonates (36).

For DB events, the temporal relationship between bradycardia and desaturation was also analyzed: we observed that the bradycardia onset occurred most frequently after the desaturation onset, but before its nadir, whereas hypoxia with subsequent bradycardia was observed only in a small number of DB. This finding supports an apneic etiology for most combined events. Primary cardiac hypoxia resulting in bradycardia represents a less common mechanism, possibly involved in less than one third of the combined events observed in the present study. Similar results were previously reported by Hiatt et al, who analyzed a pool of apneic episodes, describing a prompt HR fall after the onset of apnea but before the pO₂ decrease (37), and by Carbone et al, who observed the HR drop before SpO₂

fall in more than half of apneic episodes (38). Conversely, Schmid and colleagues reported a slightly more frequent number of combined events with simultaneous onset of bradycardia and desaturation (21) compared to the present findings; however, the authors also included in their study mechanically ventilated infants, in which CRE may entail different underlying mechanisms.

The CRE showing the longest duration and the highest severity were combined desaturation and bradycardia, independent of other neonatal characteristics. Assuming the underlying apneic nature of DB, these findings are consistent with previous evidence according to which the duration of apneic events represented the main determinant for the concomitant occurrence of bradycardia (18) and for SpO₂ and HR nadirs (38). It is possible that the HR drop occurring during combined events results in a transient decrease in cardiac output, thus contributing to reduce oxygen delivery to end-target organs leading to a deeper fall in SpO₂.

In the present study, IB were the least frequent events, with an incidence similar to that previously reported by Poets et al (20). This event type was far less common in infants with echocardiographic evidence of an hsPDA. To better understand this finding, baseline HR values were compared between noPDA and hsPDA infants, with a significantly higher baseline HR seen in the latter group which is consistent with previous evidence (39,40). We hypothesize that the hemodynamic disturbances secondary to the presence of a hsPDA may be accompanied by an increase of basal sympathetic tone. This may inhibit the occurrence of bradycardic spells, more likely resulting from transient exacerbations of vagal activity (41).

Finally, the daily incidence of CRE throughout the first 72 hours of life was examined; a lower number of total CRE was observed during the first 24 hours, with ID being the most common and DB the least frequent within this time window. As recommended by current guidelines on the management of respiratory distress (42), prophylactic caffeine for prevention of apnea-of-maturity was started soon after birth in all the enrolled infants at a loading dose of 20 mg/kg, followed by maintenance of 5 mg/kg/day from day 2 onwards. Consistent with the findings of a recent meta-

analysis (43), the administration of the loading caffeine dose in the first day of life may have had a role in the observed lowest incidence of DB, which is the typical manifestation of apnea (20).

Intermittent CRE often result in the alternance between hypoxia and subsequent hyperoxia. This is a known risk factor for the development of prematurity-related neurological complications, such as IVH and periventricular leukomalacia (PVL).

The association between intermittent hypoxia and PVL has been previously demonstrated in animal models (44-46). By disrupting the physiological glial differentiation and repair, the ensuing oxidative stress has been proposed as a leading translational mechanism for the development of periventricular white matter injury during the neonatal period (47). In the present cohort, however, the possible association between CRE burden and later PVL development was not evaluated as, among the enrolled infants, only one developed PVL during hospital stay as a consequence of a late-onset infection of central nervous system. The study was also not powered to detect more subtle longer term neurodevelopmental sequelae resulting from white matter injury.

A significant association between the occurrence of IVH and the hypoxic burden in preterm neonates during the first 24 hours of life has been reported (13). Intermittent hypoxia, together with other risk factors, such as the immaturity-related impairment of cerebral autoregulation in response to cerebral blood flow fluctuations and other hemodynamic disturbances (e.g., myocardial dysfunction, ductal shunt etc.) (48,49), can contribute to the development of IVH during transition. The concomitant occurrence of hypoxemia and bradycardia may further affect the delicate balance between cerebral autoregulation and hemodynamic instability during this period, with possible implications for IVH development. This study investigated the occurrence and the characteristics of CRE in relatively stable preterm infants, therefore the low incidence of IVH observed in the study population is not surprising. Further studies, inclusive of ventilated infants are required to understand the relationship between CRE, autoregulatory stability and the prevalence of IVH.

Of note, the prevalence of SGA/uREDF in the study cohort was noticeably high, allowing a deeper focus on the possible association between this condition and CRE characteristics. This data reflects

the characteristics of the local neonatal population: the hospital where the study was conducted is a referral center for placental-related pregnancy complications, which represent a leading cause of preterm birth in our NICU.

An important limitation of the present study is the lack of concomitant respiratory plethysmography which would have allowed differentiating between apneic and non-apneic events, or polysomnography, which would have helped discriminating among central, obstructive and mixed apneas, providing additional information on CRE etiology during transition; however, for technical reasons, a simultaneous monitoring of breathing activity and nasal airflow throughout the first 72 hours after birth, synchronized and integrated with pulse oximeter data, was not feasible.

There are also possible limitations related to the use of the pulse oximeter which have previously been described, including the presence of motion artefacts and the influence of different data averaging intervals on the observed SpO₂ nadir and duration (50). To address these issues, the pulse oximeter was set on the lowest data-averaging interval and synchronized with ECG monitoring in order to rule out possible artefacts.

This study shows that CRE during the transitional period have a complex etiology and clinical significance. In particular, our findings indicate that the presence of a PDA is associated with a higher burden of hypoxic episodes which, in part, may represent the clinical manifestation of transient right-to-left transductal shunting. The inverse relation observed between the incidence of combined DB and GA reflects the physiological immaturity of different systems, including the complex mechanisms of breathing control, whereas the higher incidence of these events in infants on CPAP likely ensues from the therapeutic use of this ventilatory modality against apneic spells, although a causal relationship entailing vagal overstimulation may also be postulated.

Despite the limitations previously acknowledged, the present data provides useful information, not only to disentangle the physiological mechanisms underlying the different types of CRE occurring during the first 72 hours of life, but also to potentially predict specific CRE patterns based on the infant's characteristics. This is important in order to optimize the complex early clinical management

of these infants, with the aim of facilitating a more tailored clinical approach to very preterm infants during such a delicate period in life. Combined continuous evaluation of cardiovascular parameters and end-target organ oxygenation during CRE occurrence would help to better clarify the hemodynamic impact of CRE during transition.

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Figures

Figure 1 (online). Examples of ICM+ traces for peripheral oxygen saturation (SpO₂) and heart rate values (HR, obtained by ECG; BPM, obtained by pulse oximeter) showing isolated desaturation (A), combined desaturation and bradycardia (B) and isolated bradycardia (C).

Figure 2 (online). Flow chart of the study enrolment.

Figure 3. Mean number of cardio-respiratory events (CRE), overall and by type of event (ID, isolated desaturation; DB, desaturation + bradycardia; IB, isolated bradycardia) in each day of life. Bars represent 95% confidence intervals (CI).

Figure 4 (online). Event duration according to the event type (ID, isolated desaturation; DB, desaturation + bradycardia; IB, isolated bradycardia). The central line in the boxplot is the median, the margins of the box are the 25th and the 75th percentile and the ends of the whiskers represent one and a half times the interquartile range ($1.5 \times \text{IQR}$).

Table 1. Clinical characteristics of the study population at birth and during the study period.

Clinical characteristics (n=32)			
Gestational age (weeks)			
Mean ± standard deviation (SD)	30.6 ± 2.3		
Range (min-max)	24+4 - 33+1		
Birth weight (g)			
Mean ± SD	1275 ± 319		
Range (min-max)	675 - 1852		
Sex (males), n (%)	19 (59.3%)		
Twinhood, n (%)	10 (31.2)		
Delivery mode (C-section), n (%)	30 (93.8)		
Antenatal steroids, n (%)			
Complete course	26 (81.2)		
Incomplete course or not given	6 (18.8)		
Apgar at 5', mean ± standard deviation (SD)	9 ± 1		
Abnormal antenatal umbilical Doppler, n (%)	14 (43.8)		
Small for gestational age, n (%)	11 (34.4)		
Monitoring period (hours of life)	0-24h	24-48h	48-72h
Weight (g), mean ± SD	1268 ± 323	1220 ± 325	1160 ± 318
Status of ductus arteriosus, n (%)			
Haemodynamically significant	12 (37.5)	6 (18.8)	2 (6.3)
Restrictive	15 (46.9)	9 (28.1)	5 (15.6)
Closed	5 (15.6)	17 (53.1)	25 (78.1)
Ventilatory support, n (%)			
Continuous Positive Airway Pressure	28 (87.5)	23 (71.9)	17 (53.1)
Nasal cannulas	0 (0)	1 (3.1)	5 (15.6)
Self-ventilating in air	4 (12.5)	8 (25)	10 (31.3)
Intraventricular hemorrhage, n (%)			
Subependimal hemorrhage	2 (6.3)	2 (6.3)	3 (9.4)
Grade 1-2	2 (6.3)	2 (6.3)	3 (9.4)
Grade 3-4	0 (0)	0 (0)	0 (0)

Baseline peripheral oxygen saturation (%), mean $\pm$ SD	96.6 $\pm$ 2.9	96.2 $\pm$ 3.4	95.7 $\pm$ 2.8
Baseline heart rate (bpm), mean $\pm$ SD	153.5 $\pm$ 15	149.1 $\pm$ 18.3	152.7 $\pm$ 18.5

Table 2. Results of generalized estimating equation models for each event type. Abbreviations: GA, gestational age; uREDF, antenatal umbilical reversed end-diastolic flow; PDA, patent ductus arteriosus; CPAP, continuous positive airway pressure; SVIA, self-ventilating in air; OR, odds ratio; CI, confidence interval.

<i>Event type</i> <i>Variable</i>	Isolated desaturation				Desaturation + bradycardia				Isolated bradycardia			
	<i>OR</i>	<i>95% CI</i>		<i>P-value</i>	<i>OR</i>	<i>95% CI</i>		<i>P-value</i>	<i>OR</i>	<i>95% CI</i>		<i>P-value</i>
GA, weeks	1.161	0.985	1.367	0.075	0.852	0.740	0.982	0.027	0.968	0.806	1.163	0.731
uREDF	0.819	0.348	1.925	0.646	0.896	0.413	1.943	0.781	1.557	0.687	3.530	0.289
no uREDF§	1				1				1			
Antenatal steroids, complete course	0.988	0.497	1.966	0.974	0.848	0.480	1.499	0.571	1.356	0.742	2.477	0.322
Antenatal steroids, incomplete course or not given§	1				1				1			
PDA, hemodynamically significant	4.519	1.845	11.066	0.001	0.301	0.120	0.758	0.011	0.295	0.143	0.610	0.001
PDA, restrictive	2.598	1.243	5.430	0.011	0.430	0.237	0.782	0.006	0.559	0.255	1.227	0.147
Closed duct§	1				1				1			
CPAP	0.532	0.174	1.622	0.267	3.911	1.573	9.725	0.003	0.912	0.252	3.304	0.888
Nasal cannulas or SVIA§	1				1				1			

Table 3. Results of generalized estimating equation model predicting severe cardio-respiratory events. Abbreviations: GA, gestational age; uREDF, antenatal umbilical reversed end-diastolic flow; PDA, patent ductus arteriosus; CPAP, continuous positive airway pressure; SVIA, self-ventilating in air; OR, odds ratio; CI, confidence interval.

Variable	OR	95% CI	P- value
GA, weeks	1.028	0.897-1.178	0.688
uREDF	1.216	0.721-2.052	0.463
no uREDF§	1		
Antenatal steroids, given	0.831	0.349-1.980	0.677
Antenatal steroids, incomplete course or not given§	1		
PDA, hemodynamically significant	1.580	0.795-3.140	0.191
PDA, restrictive	1.645	1.130-2.394	0.009
Closed duct§	1		
CPAP	1.401	0.731-2.686	0.310
Nasal cannulas or SVIA§	1		
Isolated bradycardia	0.377	0.182-0.778	0.008
Desaturation + bradycardia	3.022	2.062-4.428	<0.001
Isolated desaturations§	1		