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Clinical paper

Impact of bradycardia and hypoxemia on oxygenation in preterm infants requiring respiratory support at birth

Ilia Bresesti[a,b,c], *Alexander Avian*[d], *Marlies Bruckner*[a,b,e], *Corinna Binder-Heschl*[a,b], *Bernhard Schwaberger*[a,b], *Nariae Baik-Schneditz*[a,b], *Georg Schmölzer*[b,e,f], *Gerhard Pichler*[a,b], *Berndt Urlesberger*[a,b,*]

[a] *Division of Neonatology, Medical University of Graz, Auenbruggerplatz 34/2, 8036 Graz, Austria*
[b] *Research Unit of Cerebral Development and Oximetry, Medical University of Graz, Auenbruggerplatz 34/2, 8036 Graz, Austria*
[c] *NICU "V. Buzzi" Children's Hospital, ASST-FBF-Sacco, Via Castelvetro 32, 20154 Milan, Italy*
[d] *Institute of Medical Informatics, Statistics and Documentation, Medical University of Graz, Auenbruggerplatz 34/2, 8036 Graz, Austria*
[e] *Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital, 10240 Kingsway Avenue NW, T5H 3V9 Edmonton, Alberta, Canada*
[f] *Department of Pediatrics, University of Alberta, 10240 Kingsway Avenue NW, T5H 3V9 Edmonton, Alberta, Canada*

Abstract

Aim of the study: Analysis of the impact of bradycardia and hypoxemia on the course of cerebral and peripheral oxygenation parameters in preterm infants in need for respiratory support during foetal-to-neonatal transition.

Methods: The first 15 min after birth of 150 preterm neonates in need for respiratory support born at the Division of Neonatology, Graz (Austria) were analyzed. Infants were divided into different groups according to duration of bradycardia exposure (no Bradycardia, brief bradycardia <2 min, and prolonged bradycardia ≥ 2 min) and to systemic oxygen saturation (SpO_2) value at 5 min of life ($<80\%$ or $\geq 80\%$). Analysis was performed considering the degree of bradycardia alone (step 1) and in association with the presence of hypoxemia (step 2).

Results: In step 1, courses of SpO_2 differed significantly between bradycardia groups ($p = 0.002$), while courses of cerebral regional oxygen saturation ($crStO_2$) and cerebral fractional tissue oxygen extraction (cFTOE) were not influenced ($p = 0.382$ and $p = 0.878$). In step 2, the additional presence of hypoxemia had a significant impact on the courses of SpO_2 ($p < 0.001$), $crStO_2$ ($p < 0.001$) and cFTOE ($p = 0.045$).

Conclusion: Our study shows that the degree of bradycardia has a significant impact on the course of SpO_2 only, but when associated with the additional presence of hypoxemia a significant impact on cerebral oxygenation parameters was seen ($crStO_2$, cFTOE). Furthermore, the additional presence of hypoxemia has a significant impact on FiO_2 delivered. Our study emphasizes the importance of HR and SpO_2 during neonatal resuscitation, underlining the relevance of hypoxemia during the early transitional phase.

Keywords: Neonatal resuscitation, Degree of bradycardia, Presence of hypoxemia, Preterm infants, Respiratory support, Cerebral oxygen saturation, Cerebral oxygen delivery

* Corresponding author at: Division of Neonatology, Medical University of Graz, Auenbruggerplatz 34/2, 8036 Graz, Austria.
E-mail address: berndt.urlesberger@medunigraz.at (B. Urlesberger).

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Introduction

Continuous monitoring of heart rate (HR) and peripheral oxygen saturation (SpO_2) by using pulse-oximetry (plus ECG optionally) is currently considered standard of care during stabilization of preterm infants in the delivery room (DR). Reaching specific SpO_2 values during resuscitation is advocated, and the titration of blended supplemental oxygen accordingly is also recommended by international guidelines.[1,2] SpO_2 is widely used as a proxy for adequate ventilation and oxygenation stabilisation, whereas monitoring of HR is used as a proxy for cardio-circulatory stability.

There is still uncertainty regarding the optimal initial supplemental oxygen concentration (FiO_2) to start resuscitation in preterm infants,[3,4,5] but there are recommended SpO_2 targets to reach.[1] Increased incidence of mortality and adverse outcomes such as intraventricular haemorrhage (IVH) has been reported in those infants not reaching SpO_2 80% at 5 min after birth.[6] Increase in HR is often reflection of adequate respiratory support, but there is still an ongoing debate to define normal ranges. Nevertheless, it has been shown that preterm neonates who experience prolonged bradycardia during DR resuscitation are at increased risk for death and/or IVH.[7]

To date, the interaction of bradycardia and hypoxaemia and its effect on tissue oxygen delivery and tissue oxygenation during the immediate transition after birth is unclear. More understanding of the physiology of this interaction might explain the interplay between hypoxemia and bradycardia during neonatal resuscitation. With this aim and to detect possible regional differences, we included near infrared spectroscopy (NIRS). NIRS enables the non-invasive measurement of regional cerebral tissue oxygen saturation ($crStO_2$) and the calculation of cerebral fractional tissue oxygen extraction (cFTOE). Thus, NIRS provides information on the balance of cerebral oxygen delivery and oxygen consumption, increasing the spectrum of oxygenation parameters. NIRS has been used in neonatal research setting during postnatal transition with both preterm and term infants.[8] Typical changes of cerebral oxygenation in the first minutes after birth, as well as differences according to the need of respiratory support, have been described.[8–11] NIRS has also been successfully used to guide respiratory support and supplemental oxygen to reduce the burden of cerebral hypoxia during immediate transition and resuscitation after birth.[12]

The aim of the present study was to analyze the impact of the degree of bradycardia and the presence of hypoxemia on oxygenation parameters such as SpO_2, $crStO_2$ and cFTOE in preterm infants needing respiratory support during early neonatal transition. We hypothesized that the combination of bradycardia and hypoxaemia would be associated with significantly lower oxygenation parameters.

Methods

This study represents a retrospective analysis of four studies, conducted between December 2010 and March 2017 at the Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria.[9,10,12,13] We included preterm infants <37 weeks' gestation, who fulfilled the following criteria: (i) decision to conduct full life support, (ii) written parental consent, (iii) need for respiratory support during resuscitation, and (iv) no severe congenital malformation. The Regional Committee on Biomedical Research Ethics had approved all the studies and allowed post-hoc analysis. For all infants, maternal medical history and neonatal demographic data were documented. The included studies were designed to measure $crStO_2$ during the first 15 min after birth using NIRS. A standardized protocol was followed in all studies. In all infants, the cord was clamped within 30 s after birth. After that, the neonate was placed on the resuscitation table (CosyCot; Fisher& Paykel Healthcare; New Zealand or Giraffe incubator, GE Healthcare; United Kingdom) in supine position. A polyethylene bag was used in neonates <28 weeks' gestation. Then, a NIRS sensor was attached to the infant's left forehead. A pulse oximetry sensor (IntelliVue MP50 monitor; Philips; Netherland) was applied on the right palm or wrist to monitor SpO_2 and HR. Upper airway suction was performed as needed. Respiratory support as continuous positive airway pressure and/or positive pressure ventilation was provided via a face mask (LSR Silicon mask no. 0/0 or 0/1; Laerdal; Norway) and the 'Neopuff Infant T- Piece Resuscitator' (Perivent; Fisher& Paykel Healthcare; New Zealand) with the following starting setting: gas flow 6−8 L/min, positive end-expiratory pressure 5 cmH_2O, peak inspiratory pressure 30 cmH_2O and FiO_2 0.3. HR, SpO_2 and $crStO_2$ were recorded every second for the first 15 min after birth and stored in a multichannel system alpha-trace digital MM (BEST Medical Systems; Austria). Cerebral oxygenation was measured with INVOS 5100C (Somanetics, Troy, Michigan) or NIRO 200-NX (Hamamatsu, Japan). cFTOE was calculated for each minute as follows: (SpO_2-$crStO_2$)/SpO_2.[14] Values of $crStO_2$ higher than correspondent SpO_2 were considered artefacts and eliminated from the analysis, as well as HR and/or SpO_2 values taking longer than 5 min to be detected and displayed.

Definition of degree of bradycardia and presence of hypoxemia

We created a statistical model to first analyse the impact of the degree of bradycardia alone on oxygenation parameters (step 1), then to explore the interplay between the degree of bradycardia and the presence of hypoxemia (step 2).

Bradycardia was defined as HR < 100 bpm. Degree of bradycardia was calculated considering the sum of episodes the neonate spent with HR < 100 bpm within the first 15 min of life. Hypoxemia was considered as SpO_2 <80% at 5 min after birth.

In step 1, we divided our population of infants into three groups, according to duration of exposure to bradycardia during the first 15 min after birth: no Bradycardia (**nB**), brief bradycardia (<2 min) (**bB**) and prolonged bradycardia (≥2 min) (**pB**).

In step 2, we integrated the presence of hypoxemia using a dichotomous criterion. We divided our population into 2 groups: a group with no presence of hypoxemia (**H−**), infants had SpO_2 ≥80% at 5 min after birth; and a group with presence of hypoxemia (**H+**), infants had SpO_2 <80% at 5 min after birth.

Statistical analysis

Observed data are presented as mean ± SD or absolute frequencies and percentages. We investigated the changes in HR, SpO_2, FiO_2, $crStO_2$ and cFTOE within the first 15 min after birth using a linear mixed model with a first-order ante-dependence covariance structure. In step 1, fixed effects "time", "degree of bradycardia" (nB vs. bB vs. pB) and the interaction of these two factors were included. In step 2, the fixed effect "presence of hypoxemia" (H− vs. H+), the interaction "time with presence of hypoxemia" and the interaction "time with

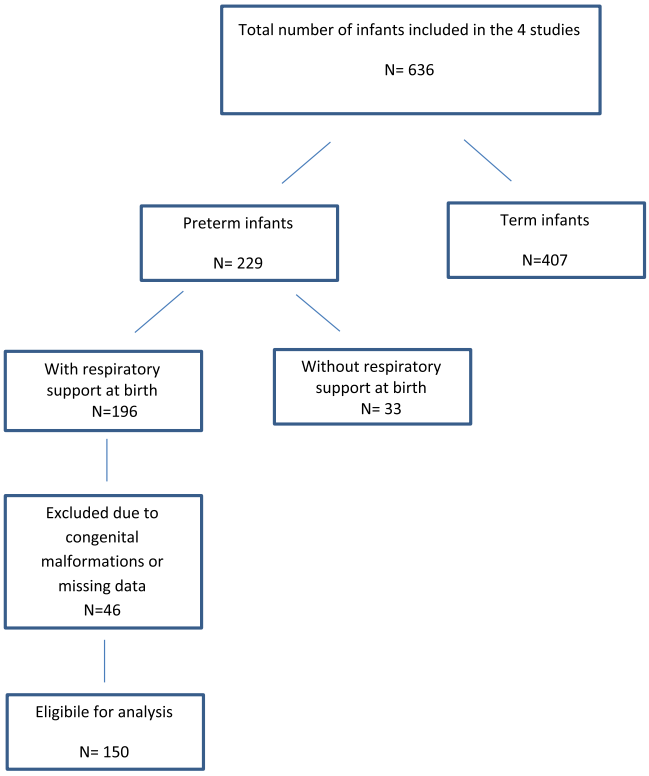

Fig. 1 – Process of infants' selection for post-hoc analysis from four studies.

degree of bradycardia with presence of hypoxemia" was added. Results are presented as estimated means and 95% confidence intervals. Post hoc analysis of differences between groups for each minute were performed. A p-value <0.05 was considered statistically significant. The statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The original four publications included 636 infants, and after selection 150 infants were analysed (Fig. 1,Table 1). Demographic data are outlined in Table 2. The cohort displayed a mean gestational age of 33 weeks and a mean birth weight of 1758 g. Only 11% of infants needed intubation. Two (1%) infants suffered from severe IVH, and the overall mortality was 3%. The mean (SD) duration until HR was displayed on the monitor was 93 (42) seconds.

Table 1 – Groups assignment (n).

	No presence of hypoxemia (H-) (71)	Presence of hypoxemia (H+) (79)
No bradycardia (nB) (46)	H-nB (26)	H + nB (20)
Brief bradycardia (<2 min) (bB) (56)	H-bB (25)	H + bB (31)
Prolonged bradycardia (bB) (56)	H-pB (20)	H + pB (28)

- **Degree of bradycardia and SpO_2at 5 min and differences in the HR course**

In step 1, courses of HR differed significantly between bradycardia groups ($p < 0.001$). Neonates in the pB group had significantly lower HR values until minute 8 compared to neonates in the nB group, and until minute 4 compared to neonates in the bB group. Neonates in the bB group had significantly lower HR values until minute 6 compared to neonates with no bradycardia. After minute 8 there were no differences between groups anymore (Fig. 2A).

In step 2, impact of degree of bradycardia on the course of HR was still present. Additionally, the presence of hypoxemia had a significant impact on the course of HR ($p = 0.013$). In the pB group, neonates with hypoxia (H+ group) had a lower HR within the first minutes (Fig. 2B). Tables of HR, FiO_2, $CrStO_2$ and cFTOE values at each minutes and statistical significance are available as Supplementary material.

- **Degree of bradycardia and SpO_2at 5 min and differences in the FiO_2course**

In step 1, courses of FiO_2 did not differ significantly between the three bradycardia groups, but there was a trend ($p = 0.058$). This trend was caused by significantly higher FiO_2 from minute 5 to 13 in pB group, and significant higher FiO_2 from minute 7 to 10 in bB group, compared to nB group. There were no differences in FiO_2 between the bB and the pB groups. (Fig. 2C).

In step 2, there was no significant impact of degree of bradycardia on the course of FiO_2. Presence of hypoxemia had a significant impact on the course of FiO_2 ($p < 0.001$). While in the H+ group neonates with no bradycardia had almost no changes in FiO_2 values, in the bB and in

Table 2 – Demographic data expressed as n (%), mean ± SD, and median (IQR); UA umbilical artery, IVH intraventricular haemorrhage.

	Total cohort	nB	bB	pB	p value	H- nB	H- bB	H- pB	p value	H+ nB	H+ bB	H+ pB	p Value
N (%)	150	46 (31%)	56 (37%)	48 (32%)		26 (17%)	25 (17%)	20 (13%)		20 (13%)	31 (21%)	28 (19%)	
Gestational age (wk)	33 (31–34)	32 (31–34)	33 (32–34)	33 (31–34)	32 (30-34)	33 (30–33)	33 (32–34)		33 (32–35)	33 (32–34)	33 (30–34)		
Birthweight (g)	1748 + 622	1669 ± 569	1812 ± 566	1710 ± 68	5	1524 ± 583	1639 ± 512	1612 ± 524		1950 ± 605	1957 ± 577	1780 ± 783	
Male	69 (46%)	22 (48%)	26 (79%)	21 (44%)		14 (54%)	12 (48%)	10 (50%)		8 (40%)	14 (45%)	11 (39%)	
APGAR 5	9 (8–9)	9 (8–9)	9 (8–9)	9 (8–9)		9 (8–9)	9 (9–9)	9 (9–9)		9 (8–9)	8 (8–9)	8 (8–9)	
APGAR 10	9 (9–9)	9 (9–10)	9 (9–9)	9 (9–10)		9 (9–9)	9 (9–10)	9 (9–10)		9 (9–9)	9 (9–9)	9 (9–10)	
UA pH	7.31 + 0.1	7.31 ± 0.1	7.31 ± 0.0	7.30 ± 0.1		7.32 ± 0.1	7.29 ± 0.0	7.31 ± 0.1		7.33 ± 0.1	7.32 ± 0.0	7.29 ± 0.1	
Intubation	16 (11%)	5 (11%)	4 (7%)	7 (15%)		5 (19%)	0	2 (10%)		0	4 (13%)	5 (18%)	
IVH any grade	6 (4%)	3 (7%)	1 (2%)	2 (4%)	0.477	3 (12%)	1 (4%)	0	0.220	0	0	2 (7%)	0.154
IVH ≥ III	2 (1%)	0	0	2 (4%)	0.116	0	0	0		0	0	2 (7%)	0.154
Death	5 (3%)	0	0	4 (8%)	0.013	0	0	1 (5%)	0.274	0	0	3 (11%)	0.058

Expressed in n (%), mean ± SD, and median (IQR).

the pB groups FiO_2 values increased after minute 6 and minute 5 respectively (Fig. 2D).

- **Degree of bradycardia and SpO_2at 5 min and differences in the SpO_2course**

In step 1, courses of SpO_2 differed significantly between bradycardia groups ($p = 0.002$). Neonates in the pB group had significantly lower SpO_2 values until minute 5 compared to nB group, and until minute 4 compared to bB group. After minute 5 there were no differences between groups (Fig. 3A).

In step 2, impact of degree of bradycardia on the course of SpO_2 was still present. Additionally, the presence of hypoxemia had a significant impact on the course of SpO_2 ($p < 0.001$). Regardless of degree of bradycardia, neonates in the H− group had higher SpO_2 values in the first minutes compared to infants in the H+ group (Fig. 3B).

- **Degree of bradycardia and SpO_2at 5 min and differences in the $crStO_2$course**

In step 1, courses of $crStO_2$ were similar between the three bradycardia groups ($p = 0.382$) (Fig. 3C).

In step 2, there was no significant impact of degree of bradycardia on the course of $crStO_2$. Presence of hypoxemia had a significant impact on the course of $crStO_2$ ($p < 0.001$). While at the beginning the increase of $crStO_2$ was comparable between both hypoxemia groups, in the H+ group this increase continued until minute 12 and in the H- group flattened at minute 6 (Fig. 3D).

- **Degree of bradycardia and SpO_2at 5 min and differences in the cFTOE course**

In step 1, courses of cFTOE were similar between the three bradycardia groups ($p = 0.878$) (Fig. 3E).

In step 2 there was no significant impact of degree of bradycardia on the course of cFTOE. Presence of hypoxemia had a significant impact on the course of cFTOE ($p = 0.045$). Because of a steeper decrease in the H+ group, this group reached stable values at minute 10, whereas the H− group reached stable values at minute 7 (Fig. 3F).

Discussion

To our knowledge, this is the first study analysing the impact of the degree of bradycardia exposure alone and in combination with the presence of hypoxemia on circulatory and oxygenation parameters in preterm infants needing respiratory support during stabilisation at birth. Analysing the degree of bradycardia alone, our results showed that it had impact on systemic oxygenation only (SpO_2). Including the presence of hypoxemia, we showed that the combination had impact on all three oxygenation parameters, confirming our hypothesis. The additional presence of hypoxaemia had a significant impact on FiO_2 delivery as well.

Degree of bradycardia

Traditionally, HR < 100 bpm during neonatal transition is considered bradycardia. However, this definition still rises concern. There is lack of evidence that this threshold value is clinically relevant. In this regard, Smit et al. have shown that healthy infants after uncomplicated birth had significantly lower HR values than defined referenced ranges, and the 10th percentile was even <100 bpm until 5 min after

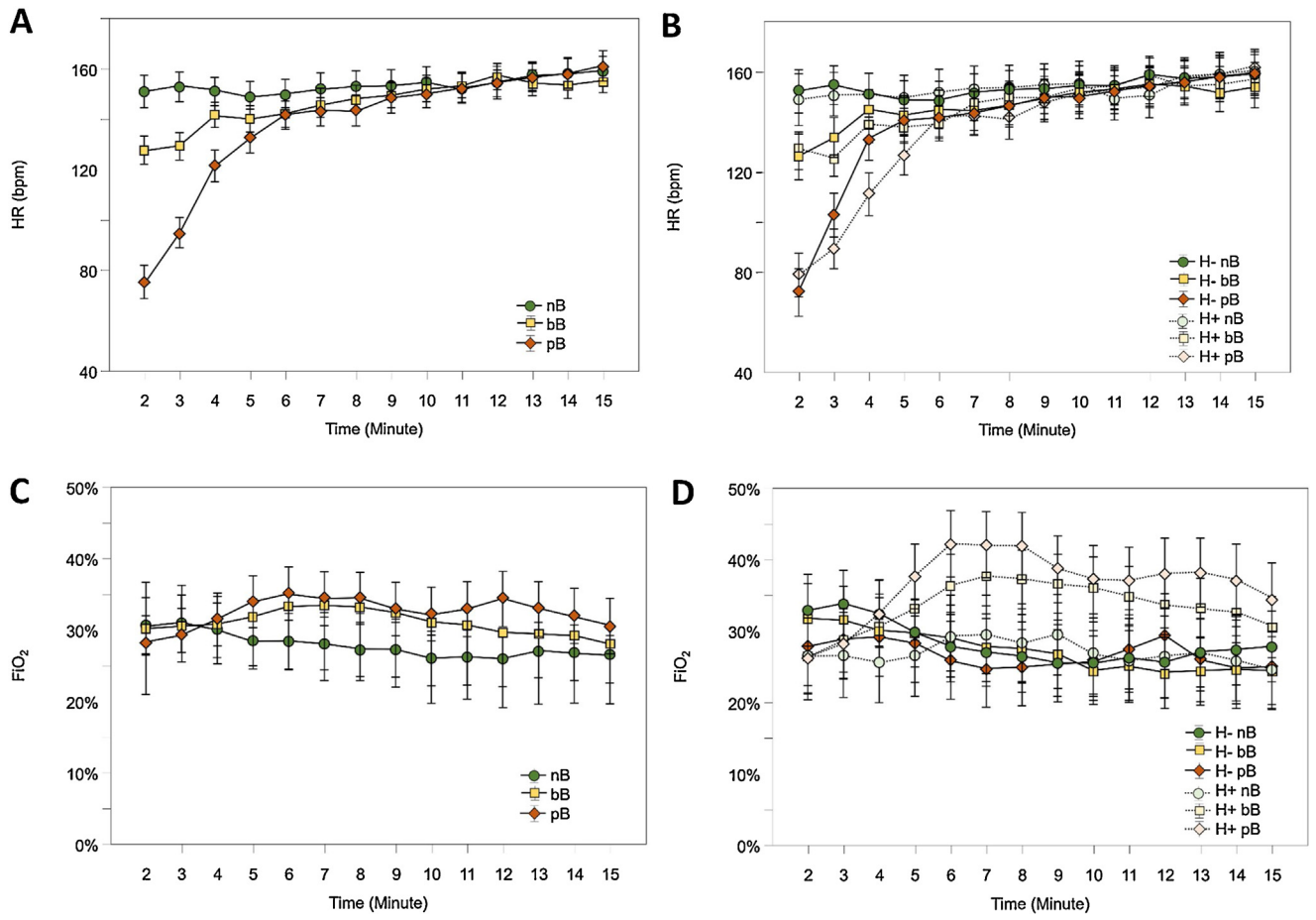

Fig. 2 – Course of HR (bpm) during the first 15 min of neonatal transitional according to (A) degree of bradycardia and (B) degree of bradycardia plus integration of presence of hypoxemia. Course of FiO_2 (%) according to (C) degree of bradycardia and (D) degree of bradycardia plus integration of presence of hypoxemia.

birth.[15] In our analysis, we considered bradycardia HR < 100 bpm using the same criteria as Kapadia and co-workers. They showed that preterm neonates who experience prolonged bradycardia during DR resuscitation have increased risk for death and for IVH.[7] However, our population is substantially different, as they analyzed only infants less than 32 weeks' gestation. In our study, most of the time spent on bradycardia was within the first minutes after birth. This finding might be explained with the slowly increasing oxygen tension during the initial aeration of the lungs, which are both known to be strong impulses for post-natal increment in HR.

We also found that only courses of SpO_2 differed significantly between the bradycardia groups. On the contrary, courses of cerebral oxygenation parameters did not show significant differences. This finding further emphasizes that cerebral oxygenation was still preserved during periods of bradycardia. Moreover, such a situation potentially even allows preservation of oxygenation capacity for the heart to be able to increase HR and overcome bradycardia. However, our findings might take into account a slight compensation by increase in FiO_2 delivered. Although courses of FiO_2 did not differ significantly between the three bradycardia groups, there was a trend to higher FiO_2 in the groups with bradycardia. Certainly, both degree of bradycardia and presence of hypoxemia trigger clinical decision to change FiO_2, then course of FiO_2 is biased by the clinical approach of the neonatologists.

Additional presence of hypoxaemia

In an individual patient analysis of 8 RCTs, Oei and co-workers found that if SpO_2 80% was not reached within 5 min after birth, there was a 2-fold risk of death and increased morbidity, such severe IVH.[6] The authors concluded that whether these findings are due to the infants' illness or to the amount of oxygen administered during stabilization remains unclear. In view of these findings, we integrated SpO_2 at 5 min into our analysis, and we used it to define presence of hypoxemia. However, again our population is substantially different, as they analyzed only infants less than 32 weeks' gestation. We found a significant impact of the combination of bradycardia and hypoxemia on all three oxygenation parameters and on FiO_2 in our cohort. Particularly, only if there was a combination of bradycardia and hypoxemia, cerebral oxygenation dropped. We previously reported that the brain had the highest saturation levels in infants during uncomplicated fetal-to-neonatal transition, indicating a preference for oxygen delivery to the brain.[11,16] The underlying mechanisms are unknown. Further we showed that in preterm infants reduced oxygen

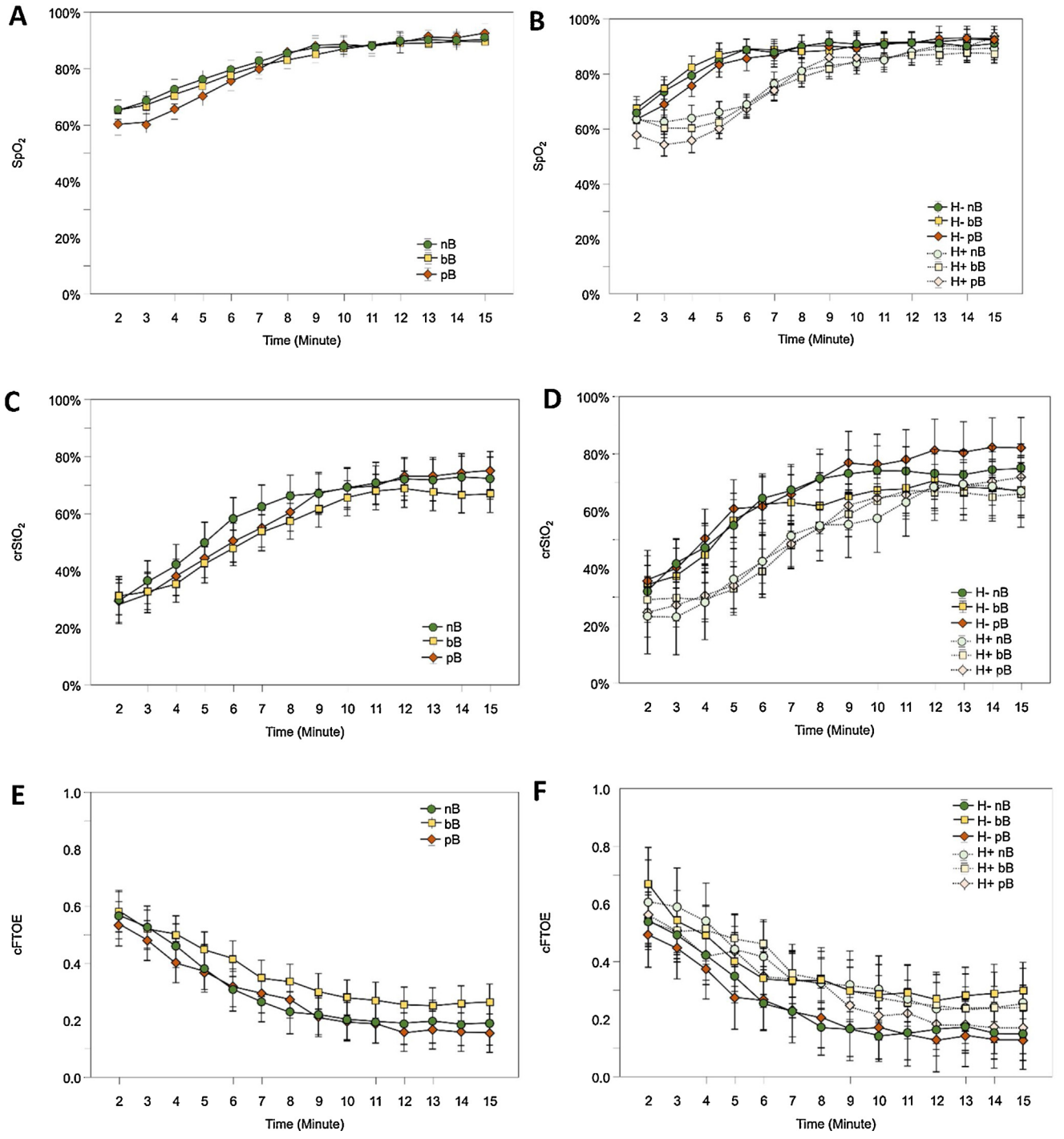

Fig. 3 – Course of SpO_2 (%) during the first 15 min of neonatal transitional phase according to (A) degree of bradycardia and (B) degree of bradycardia plus integration of presence of hypoxemia. Course of $crStO_2$ (%) according to (C) degree of bradycardia and (D) degree of bradycardia plus integration of presence of hypoxemia. Course of cFTOE according to (E) degree of bradycardia and (F) degree of bradycardia plus integration of presence of hypoxemia.

delivery to the brain was not only associated with lower $crStO_2$ values, but with changes in cerebral perfusion as well.[17] In healthy neonates, cerebral blood volume decreases significantly during fetal-to-neonatal transition, most probably due to cerebral vasoconstriction associated with the steep increase in blood oxygen tension.[18] In infants with need of respiratory support with a diminished increase in oxygen tension in the first minutes after birth, there is consecutively less change in cerebral blood volume, which may improve cerebral oxygenation by maintaining cerebral blood volume including oxygenated hemoglobin. Nevertheless, cerebral oxygenation was less challenged by degree of bradycardia as compared to additional presence of hypoxemia. No differences in course of cFTOE was seen when the neonate experience various degree of bradycardia alone. This implies that there was no increase in cerebral oxygen extraction during

bradycardia to compensate for a significant change in oxygen delivery. On the contrary, additional presence of hypoxemia resulted in a significant increase of FTOE. Recently, it has been shown that during resuscitation cFTOE was a sensible marker displaying changes in cerebral oxygen delivery during return of spontaneous circulation in a newborn asphyxiated lamb model.[19]

The present study emphasizes that the combination of both parameters is important and should be followed during neonatal resuscitation. It seems reassuring that cerebral tissue may be less challenged by bradycardia alone as compared to additional presence of hypoxaemia. This aspect strongly underlines the importance of a quick titration of FiO_2 to ensure adequate oxygen delivery within the first minutes, although often challenging for clinicians.[6,20]

Our analysis has some limitations. First, the uncertainty in the definition of bradycardia in contrast to the more structured definition of hypoxemia imposes caution in the interpretation of the results. Then, the present study is retrospective, and our findings should be confirmed by future prospective data. Our study included mainly low birth weight infants, then comparison with other studies is not appropriate especially in regard to clinical outcomes.[6,7] However, it is innovative in showing that the combination of bradycardia and hypoxemia is not only a threat for the most immature infants.

With the use of SpO_2 and FiO_2 we were only able to integrate supplemental oxygen and arterial oxygenation into our analysis, but certainly pCO_2 might have influenced cerebral perfusion too. In this regard, we showed that in healthy preterm and term infants pCO_2 levels were within normal ranges during neonatal transition.[21] Nevertheless, both pCO_2 and pO_2 levels may vary according to the efficacy of ventilatory support.[22] In addition, we did not differentiate between different respiratory support modalities, which could have influenced our data. Furthermore, blood glucose levels are associated with $crStO_2$ values,[23] but we did not integrate blood glucose levels into our model. In addition, $crStO_2$ was measured with two different devices (INVOS 5100C and NIRO 200-NX), which provide systematically different values. However, in separate analysis these tools showed very similar results.[24]

Conclusion

Our study shows that the degree of bradycardia has a significant impact on the course of SpO_2 only, but when associated with the additional presence of hypoxemia a significant impact on cerebral oxygenation parameters is observed. Furthermore, the additional presence of hypoxemia has a significant impact on FiO_2 delivered. Our study emphasizes the importance of HR and SpO_2 during neonatal resuscitation, underlining the relevance of hypoxemia during the neonatal transitional phase.

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None.

Conflict of interest

None.

CRediT authorship contribution statement

Ilia Bresesti: Conceptualization, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Alexander Avian:** Methodology, Formal analysis, Data curation, Writing - review & editing. **Marlies Bruckner:** Investigation, Writing - review & editing. **Corinna Binder-Heschl:** Investigation, Data curation, Writing - review & editing. **Bernhard Schwaberger:** Investigation, Data curation, Writing - review & editing. **Nariae Baik-Schneditz:** Investigation, Data curation, Writing - review & editing. **Georg Schmölzer:** Conceptualization, Writing - review & editing. **Gerhard Pichler:** Conceptualization, Writing - review & editing, Supervision. **Berndt Urlesberger:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2021.05.004.

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