Sleep of the prematurely born infant

Sonia Scaillet [a], Aline Vuckovic [b], Caroline Haegenmacher [c], Driss Qachri [c], Claire Lelong [c], Daphne Vens [c]

[a] Queen Fabiola Children's University Hospital, sleep unit, Brussels
[b] Queen Fabiola Children's University Hospital, neonatal intensive care unit, Brussels
[c] Queen Fabiola Children's University Hospital, pediatric intensive care unit, Brussels

Sonia.scaillet@huderf.be

Keywords

Prematurity, apnea of prematurity, polysomnography, positive pressure respiratory support, maturation

Abstract

Introduction
Prematurely born infants (PBI) very often present apnea during sleep. These events can still be detected at term equivalent age (TEA), with variable impact on ventilation. An immature respiratory control is responsible for these events, which disappear as the infant matures. This observational study describes polysomnographic results for a cohort of 12 PBI who were examined at TEA and again 11 weeks later.
Method
A cohort of 12 extreme preterm (average gestational age of 27 weeks) infants were followed by the HUDERF sleep unit as they received a cardio-respiratory monitor for home uses during sleep.
Polysomnography 1 (PSG1) was performed at TEA for the 12 infants. 10 of these 12 infants had another PSG (PSG2) 11 weeks later.
Results
All infants presented with apnea of prematurity at TEA, which significantly decreased at PSG2. Respiratory rates and heart rates both decreased significantly, while saturation in oxygen was not significantly different when compared between PSG1 and PSG2.
Discussion
Poorly tuned chemo and mechanoreceptors together with a highly pliable thorax, immature lungs and suboptimal central respiratory control are responsible for the apnea. These respiratory events disappear as the child matures.
Lower heart and respiratory rates at PSG2 reflect the maturing parasympathetic system.
Conclusion
Apnea in PBI result from suboptimal respiratory central control. They can result in a vicious cycle where hypoxia increases, thereby further destabilizing respiratory control. Further studies are necessary to investigate the feasibility of home use of respiratory support in the case of oxygen dependency in PBI.

Introduction

There is compelling evidence that sleep in children is essential to consolidate learning and memory . It is a time of rest for the body which allows for processing of daytime experiences. The conscious is disconnected and all vital functions are taken care of by the autonomic nervous system (ANS).

For the PBI, taking care of the vital functions poses a major problem : all systems are immature and still developing, including the ANS. The PBI spends most of his time in the state of sleep, which itself looks very different to what we understand by « sleep ».

The continuous period of sleep during night time that we have come to cherish as a refuge after the busy daytime hours is for the PBI fragmented and filled with cardiorespiratory events. Sleep is said to be unconsolidated (figure 1).

Perhaps this particular sleep architecture, littered with arousals and awakenings is necessary to allow for the preservation of vital functions : stimulants such as caffeine has saved many PBI just as it has saved many weary vehicle drivers at night. The awake state allows for better control of breathing, a key function often compromised during sleep of the PBI. Thus, the fragmented sleep observed in the PBI could be a necessary condition to help maintain adequate oxygenation.

The study of sleep using polysomnography informs about the state of vital functions. It is a very complete tool to evaluate both cerebral and ventilatory activities. The electroencephalogram (EEG) reflects the sleep state, and the eventual reaction to a potentially dangerous cardio-respiratory event. All other sensors measure ventilation directly or indirectly. Thus, the impact of sleep disordered breathing can be observed, and the ANS can be evaluated in its response to the many cardiorespiratory challenges faced by the PBI.

Apnea of prematurity are frequent, and their number increases as the gestational age decreases. These apnea can be central (no respiratory effort observed), obstructive (respiratory effort visible on the thoracic and abdominal belts) or mixed. The airflow measurements complete the information obtained by the thoracic and abdominal belts to identify the type of apnea observed.

All are apnea of immaturity, as they arise from suboptimal central responses to poorly tuned chemo and baro-receptors.

The upper airways have to be maintained open by the ANS, which can be almost non-operational in the PBI. Physiological hypercapnia during sleep maintains breathing movements. These movements disappear if chemoreceptors are not fine-tuned enough to maintain this relative hypercapnia, hence the frequent central apnea that can be observed in sleep of the PBI.

The obstructive respiratory events result from the periodic collapse of the upper airways that an immature ANS is not able to maintain open in a continuous manner.

These respiratory events can be more or less well tolerated. Often, they do not have any observable repercussions but sometimes they are accompanied by bradycardia and deep desaturation in oxygen.

The only way for the PBI to resolve a badly tolerated respiratory event is to have an arousal or an awakening. But again, these arousal reactions, which can be lifesaving, are sometimes inexistent, or very late in coming, creating a dangerous vicious circle (1). The late arousal response increases the hypoxia, which impacts negatively on central control, thereby increasing its instability (figure 2).

Figure 1: *hypnogram showing unconsolidated sleep at Term Corrected Age (TCA).*

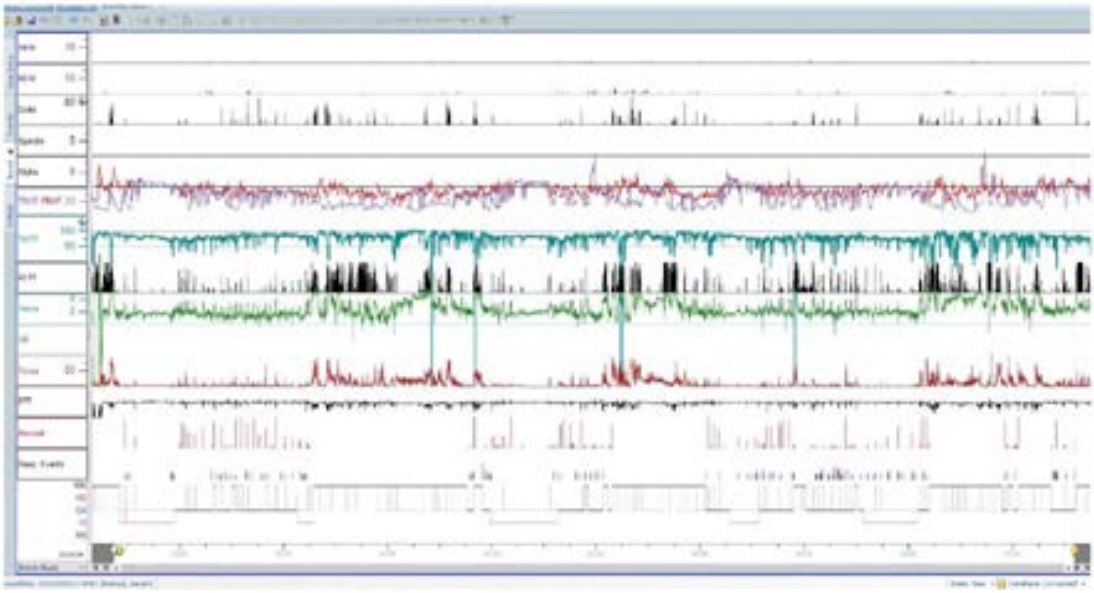
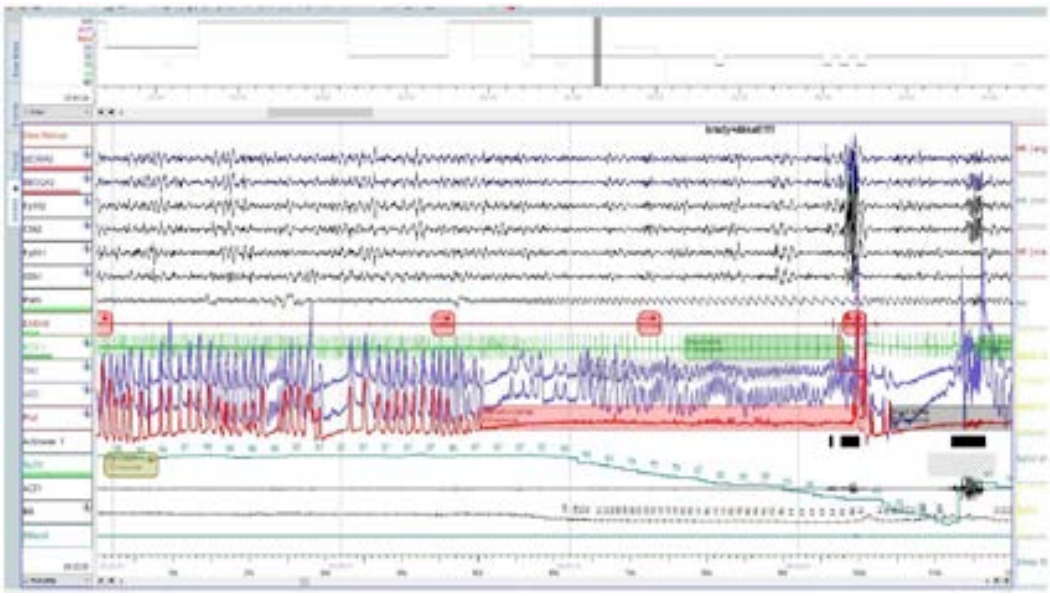


Figure 2: *A poorly tolerated obstructive apnea (OA) at TCA. The OA lasted 50 seconds and was accompanied by deep desaturation (minimum 23%) and a bradycardia (44 beats/minute) before the child finally reacted.*



The use of oxygen, CPAP (continuous positive airway pressure) and caffeine all help in maintaining proper oxygenation during sleep, providing optimal conditions for immature control centers.

Polysomnographic studies have shown that supplemental oxygen significantly decreases the amount of apnea of prematurity, suggesting that reducing hypoxemia optimizes central respiratory control (3).

Recently, NIV (noninvasive ventilation) in the form of BIPAP (bilevel positive airway pressure) has been used with promising results to allow discharge from the neonatal unit without supplementary oxygen. This method both keeps the upper airways open, and recruits pulmonary function that may otherwise be underused, thus optimizing breathing (2).

Discussion on home use of NIV during sleep of the PBI is outside the scope of this article, but there is evidence that it has a normalizing effect on sleep, as is demonstrated in figure 3, where the use of BIPAP results in the disappearance of the apnea.

Apnea of prematurity should therefore not be ignored, as they are a manifestation of central control instability.

Knowing when this instability becomes unmanageable for the PBI is impossible to predict, but outside stressors such as viral infections could very well tip the scale to a life threatening situation. Intermittent hypoxia associated with these apnea could also have long term effects on cognitive development, long after they have disappeared from sleep. Thus, their detection and treatment should be a priority (4).

This study describes the polysomnographic features of 12 infants born between June 2019 and November 2020 after an average of 27 weeks of gestation. The recordings were done at term equivalent age upon request from the neonatal unit (NICU), which corresponded to the time of discharge from the NICU (PSG1). Ten of these infants had another polysomnography 2 to 3 months after the first one (PSG2). It is usual for the sleep unit to program a PSG on average 21/2 months after the one performed at TEA to monitor maturation. The results of the PSG2 help guide the decision to maintain or not the surveillance by cardio-respiratory monitor during sleep. The population characteristics are shown in table 1.

Figure 3A: *PSG performed in a PBI re-admitted one week after discharge from the neonatal unit for alarms on the CR home monitor and a suspicion of viral infection: mean oxygen saturation during sleep 90%, with 48 minutes spent <90%. She has periodic breathing (figure 4) with an index of central apnea of 80.6 central apnea/hour of sleep (maximum length of the central apnea: 11 seconds) and a high number of obstructive and mixed apnea, with a combined index of 49.6/hour.*

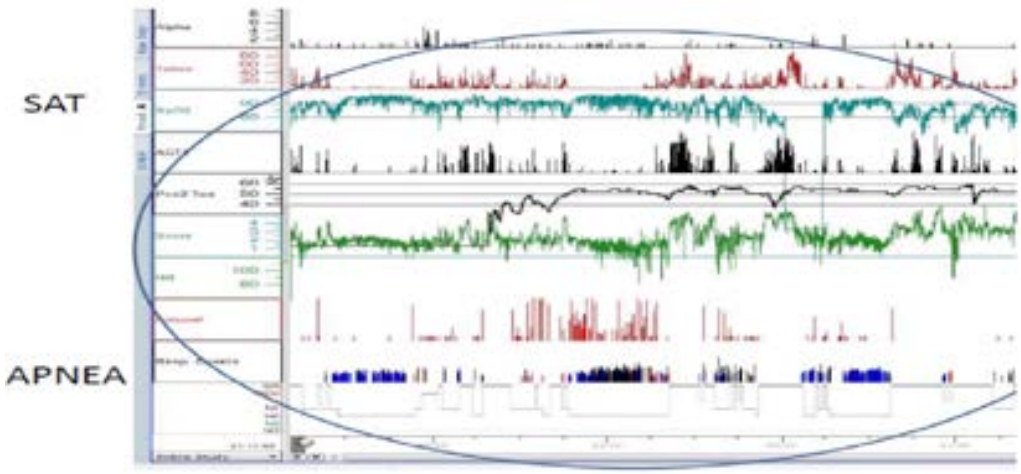


Figure 3B: *Same child with BIPAP (6 days after the PSG described in figure 3A): normalisation of the oxygen saturation (mean :96%) and the disappearance of the apnea. The child went home with the NIV, and used it during sleep for one month.*

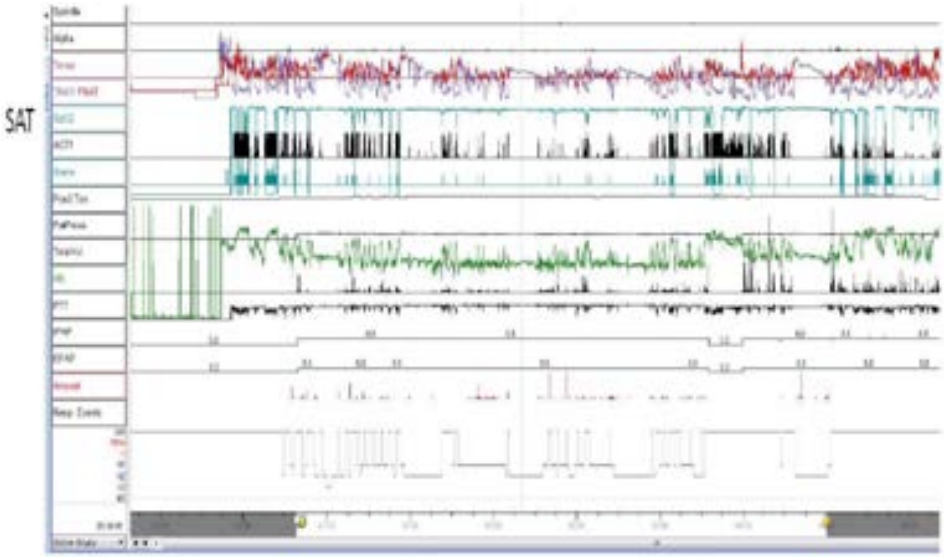
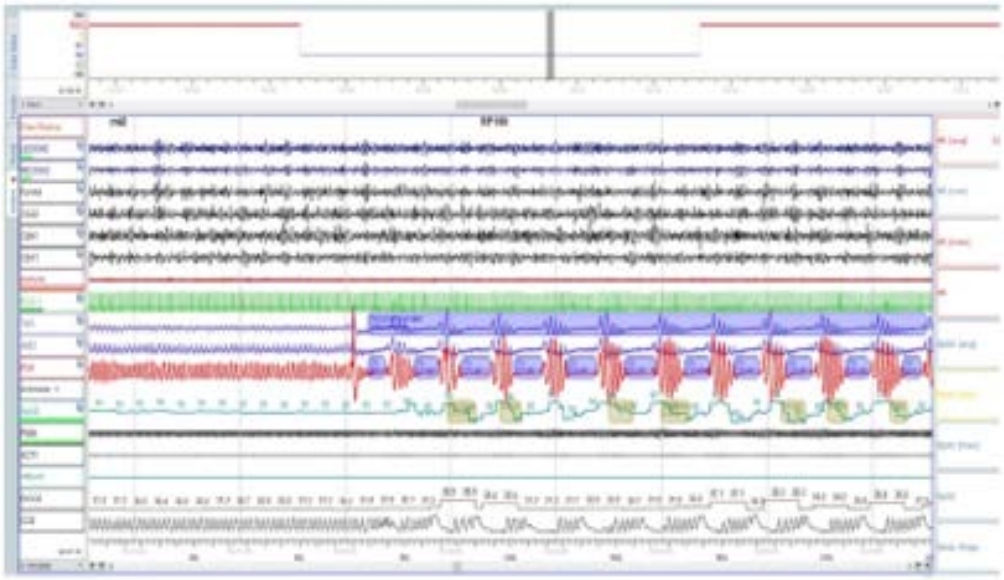


Figure 4: *Periodic breathing*



Results

All 12 infants were discharged from the neonatal unit with a cardio-respiratory monitor to be used at home during sleep. One infant also received a CPAP for home use, which she used one month, then did not tolerate it any longer. A second polysomnography (PSG2) was performed one month after she stopped using it.

Another infant was re-admitted one week after discharge from the neonatal unit for alarms on the home cardio-respiratory monitor and a suspicion of viral infection. No germs were identified, but as she could not be weaned off the supplemental oxygen, she left the hospital with an NIV.

During the hospitalization, she had a polysomnography to evaluate her ventilation during sleep, as the PSG performed at discharge from the neonatal unit (PSG1) did not show major signs of respiratory insufficiency. Another one was also performed to titrate her NIV (figure 3).

Again, the devise was used for a month, then the child did not tolerate it any longer. A final PSG (PSG2) was performed one month after that.

PSG2 was scheduled on average 2 and ½ months after PSG1 for all infants, but 2 infants left the cohort and handed their cardio-respiratory monitor before the scheduled date. Thus, the statistical analysis was performed on 10 infants.

The PSG results for the 12 infants performed at TEA at a mean corrected age of 39.3 weeks (PSG1) and those for the 10 of the 12 infants at a mean corrected age of 50.6 weeks (PSG2) are presented in table 2.

Table 1: characteristics for the 12 infants at PSG1 and the 10 infants at PSG2

	Mean	Median (min – max)
Gestational age (weeks)	26.8	26.5 (24 – 31)
Weight at birth (gr)	849	805 (494 – 1380)
Corrected age at PSG1(weeks)	39.3	39.5 (36 – 41)
Weight at PSG1 (gr)	2894	2840 (2355 – 3610)
Corrected age at PSG2 (weeks)	50.6	49.6 (45 – 57)
Weight at PSG2 (gr)	5400	5372 (4180 – 6600)

Table 2

	PSG1 Mean (min-max)	PSG 2	P (Student T-test, paired) 10 pairs
N (N° of infants)	12	10	
Sleep efficiency (SE)	71.8 (44-86)	74.8 (34-99)	0.189 (NS)
Saturation in oxygen (NREM)			
Mean	97.3 (95-100)	97.6 (95-99)	0.313
Lowest	73.3 (65-89)	78.4(69-87)	<0.01
% TST spent <90%	1.2 (0-3.2)	0.7 (0-2)	0.150
% TST spent between 91- 94%	6.6 (0.1-14)	4.8 (0-14)	0.270
Breathing rate (cycles/min) (RR)			
Min	58 (35-82)	39 (25-56)	<0.01
Max	76 (42-110)	45 (29-72)	<0.01
Delta RR	18 (3-36)	6.5(2-16)	0.010
Mean heart rate (beats/min)	147 (134-160)	126 (111-142)	<0.01
Min	81 (48-116)	84 (46-114)	0.056
Apnea			
Central (number/hour of sleep)*	8.7 (2.5-26.2)	5.2 (0-12)	0.016
Obstructive (number/hour of sleep)	6.8 (0-17.4)	2.4 (0-10)	<0.01

NREM: non-rem sleep or quiet sleep; TST: total sleep time

*Data on central apnea (CA) indices for one child who presented at PSG1 a large amount of periodic breathing (resulting in a CA index of 92.3 CA/hour of sleep) is not included, as none of the other infants presented with such a large amount periodic breathing at PSG1. That infant was discharged from the neonatal unit with a CPAP. The statistical analysis of CA data is therefore performed on 9 paired infants and not 10.

Discussion

There is a significant decrease in the number of both central apnea and obstructive apnea between PSG1 (performed at term equivalent age or TEA) and PSG2 (performed on average 2 1/2 months after PSG1).

Apnea of prematurity are well known in the neonatal units and attributed to the immature control of the respiratory system, combined with immature lungs and soft pliable thorax. Several treatments are routinely used to counteract their effect, such as prone positioning, oxygen supplementation, CPAP and xanthine use.

Most neonatal units monitor these apneic events using pulse oximeter, as they are often accompanied by intermittent oxygen desaturations and bradycardia. A polysomnography examination at the time of discharge from the neonatal unit, at term equivalent age (TEA), allows for in detail analysis of different cardio-respiratory parameters, thereby evaluating the infant's capacity for adequate response to the various apneic events that may occur during sleep.

In one case, the infant was discharged with a CPAP treatment, as he presented with an abnormally high amount of both central and obstructive events during sleep. These events were short, and were associated with intermittent hypoxia (during periodic breathing, figure 4), even though the overall average saturation during sleep time remained within normal values. It has been proposed that episodic hypoxia/reoxygenation cycles have the potential to sustain a pro-inflammatory cascade with resultant multisystem morbidity (4).

The use of CPAP diminished greatly the appearance of these apneic events, both central and obstructive, treating the intermittent hypoxia (IH). This suggests that CPAP treatment improves overall oxygenation, thereby optimizing central respiratory control.

All infants at PSG1 exhibited apnea of prematurity, some more than others. And all infants showed a significant decrease in these events at PSG2 ($p<0.05$), reflecting the maturation of respiratory control.

It is noteworthy that one infant was rehospitalized just one week after discharge, for a suspicion of viral infection, but no germs were identified. The child remaining oxygen dependent, a PSG was requested (figure 3A), which showed a marked increase in the apneic events when compared with PSG1 at discharge. It is proposed that in this case the infant had entered a vicious cycle of respiratory control destabilization, brought about by some inflammatory event (1). The use of oxygen stabilized the situation somewhat, but the use of NIV completely resolved the problem, resulting in the disappearance of the apneic events and the regularization of the oxygen saturation (fig 3B). The child was discharged with NIV, which was used for a period of one month.

This case raises the question whether apnea of prematurity are as benign as is generally thought. Certainly all premature infants will exhibit them, but when exactly must they be considered potentially dangerous? The answer perhaps lies in the way the infant is able to respond to the event. Figure 2 illustrates one obstructive respiratory event which lasted a very long time (50 seconds) before the child responded with an arousal, lifting the obstructive apnea. The deep desaturation and bradycardia that accompanied the event reflects the inability for this child to deal with such events.

So, it is not the number of apnea per se that can be worrisome, but rather how the child responds to the event that determines his ability to deal with an immature respiratory control.

As the infants mature from PSG1 to PSG2 the heart and respiratory rates significantly diminishes, as expected with the maturation of respiratory

control centers in the brain stem and the development of the autonomous nervous center (ANC).

A typical feature of respiratory rates (RR) at PSG1 is their increased variability, when compared with variability at PSG2 (delta RR, p=0.01), reflecting cardio-respiratory instability.

Heart rate variability studies have proven to be an important tool in the study of the ANC in term and preterm born infants (5). It was shown that an increasing postnatal age is associated with an increase in parasympathetic activity.

Moreover, gestational age at birth influences maturation of autonomic cardiovascular control, as preterm born infants exhibit less heart rate variability at TEA when compared with term born infants. The authors proposed that this increased immaturity of cardiovascular control when compared with term born infants could contribute to the increased risk of SIDS that premature infants face (6).

The significantly lower heart rate observed at PSG2 when compared to values observed at PSG1 can therefore be interpreted as reflecting the increased parasympathetic activity that establishes itself in the first months of life.

Sleep efficiency (SE) is a parameter that reflects the amount of time the child is actually asleep during the recording of the PSG. To obtain this parameter, the EEG during the recording has to be scored (active, quiet sleep or awake) and a ratio is established between the time spent asleep versus awake. During the first months of life infants do not have consolidated sleep, as they sleep a lot but not in a continuous manner. The sleep efficiency at PSG1 (72%) was not very different to that observed at PSG2 (75%) indicating that they were still unable to sleep through the night at 50 weeks corrected age.

There is some evidence that term babies are already able to sleep through the night at 2 months of age, but there is a lack of serious studies on the subject. Moreover, PSG sleep studies in the laboratory promote uncomfortable conditions for sleep, that may or may not be well tolerated by the infant, thus influencing the sleep efficiency results. A SE above 70% in sleep laboratory conditions can therefore be considered normal for preterm born infants at PSG1 and PSG2.

The oxygen saturation results are also not very different between PSG1 and PSG2 : this is to be expected, as this is a parameter which will determine the infant's ability to leave the neonatal unit. The value shown in table 2 are only those obtained during NREM (or quiet) sleep, which are short periods of uninterrupted sleep with few or no apnea. REM sleep (or active) is littered with micro-arousals and apnea, making oxygen measurements difficult and unreliable. Therefore for the sake of comparison between PSG1 and PSG2 only oxygen saturation in NREM sleep is presented.

Conclusion

Polysomnography studies are a precious tool to evaluate the cardio-respiratory immaturity that these infants invariably have when leaving the neonatal unit. And even though it is impossible to predict how a particular infant will react when confronted with an outside stressor (such as a viral infection), it is safe to presume that it will impact negatively on the infant's central respiratory control, placing the child in a potentially dangerous situation.

Further studies are necessary to evaluate noninvasive ventilation for home use during sleep as a potential treatment for infants who cannot be weaned off oxygen.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES:

1. Di Fiore JM, Martin RJ, Gauda EB. Apnea of prematurity – Perfect storm. Respir Physiol Neurobiol. 2013;189(2):213-22.
2. Vuckovic A, Scaillet S, Haggenmacher C, Johansson A. Discharge from the neonatal intensive care unit with noninvasive respiratory support : an 11-year experience in a tertiary pediatric care center in Belgium. Presentation at the 7th Congress of the European Academy of Paediatric Societies; 2018 Oct 30-Nov 3; Paris, France.
3. Simakajornboon N, Beckerman RC, Mack C, Sharon D, Gozal D. Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in preterm infants. Pediatrics 2002;110(5):884-8.
4. Martin RJ, Wang K, Koruglu O, Di Fiore J, Prabha KC. Intermittent Hypoxic Episodes in Preterm Infants : Do they matter ? Neonatology. 2011;100(3):303-10.
5. Cardoso S, Joao Silva M, Guimaraes H. Autonomic nervous system in newborns: a review based on heart rate variability. Childs Nerv Syst. 2017;33(7):1053-1063.
6. Fyfe KL, Yiallourou SR, Wong FY, Odoi A, Walker AM, Horne RS. The effect of gestational age at birth on post-term maturation of heart rate variability. Sleep. 2015;38(10):1635-44.