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APNEA WITHIN THE FIRST YEAR OF LIFE IN PREMATURE INFANTS WITH BRONCHOPULMONARY DISPLASIA AND PULMONARY HYPERTENSION

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Infants with severe and moderate bronchopulmonary dysplasia (BPD) are characterized by long-term persistence of apnea of prematurity and often have a pulmonary hypertension (PH). Respiratory pauses, accompanied by intermittent hypoxia, do not clinically manifest themselves, therefore cardiorespiratory monitoring (CRM) is required. We hypothesized that the persistent of apnea, as the cause of hypoxemia episodes, may be associated with the persistence of PH in infants with BPD. **The aim** of the study was to evaluate the dynamics of cardiorespiratory parameters and to study the relationship between obstructive apnea and PH during the first year of life of premature infants with BPD + PH. **Materials and methods.** CRM was performed in 58 infants were born at 26 0/7-31 0/7 weeks gestation and with birth weight less than 1500 grams, before discharge from the hospital (35-44 weeks of post menstrual age). 14 infants did not have BPD (group without BPD). 44 infants had BPD and 17 of them had a complication of this disease PH (BLD + PH group). Other infants with BPD did not have PH (BLD-PH group). Eight infants with BPD also underwent a study at home (aged 9 to 10 months of life). **Results.** Preterm infants with BPD + PH were more significant decrease in the average SpO_2, higher desaturation index and more a number of desaturation episodes of <10% compared to infants with BPD-PH and without BPD. There was no difference in the apnea/hypopnea index and frequency of occurrence of different types of apnea between groups. There was no difference in cardiorespiratory performance in infants with BPD+PH compared to infants with BPD-PH in 9-10 months of life. **Conclusions.** There was a positive dynamics of cardiorespiratory parameters in infants with BPD+PH in 9-10 months after discharge from the hospital. The number of infants with an index of OA> 1/hour is higher in the group BPD+LH.

Keywords: prematurity; bronchopulmonary dysplasia; pulmonary hypertensia; apnea; cardiorespiratory monitoring.

ОСОБЕННОСТИ АПНОЭ У ДЕТЕЙ ПЕРВОГО ГОДА ЖИЗНИ, РОДИВШИХСЯ НЕДОНОШЕННЫМИ И СТРАДАЮЩИХ БРОНХОЛЕГОЧНОЙ ДИСПЛАЗИЕЙ И ЛЕГОЧНОЙ ГИПЕРТЕНЗИЕЙ

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Дети с тяжелым и среднетяжелым течением бронхолегочной дисплазии (БЛД) характеризуются длительной персистенцией апноэ недоношенных и чаще имеют осложнение заболевания в виде развития вторичной ле-

гочной гипертензии (ЛГ). Однако для анализа и мониторирования истинных респираторных пауз требуется проведение кардиореспираторного мониторирования (КРМ), поскольку дыхательные паузы, сопровождающиеся интермиттирующей гипоксией, часто клинически себя не проявляют. Мы предположили, что наличие апноэ как причины эпизодов гипоксемии может быть ассоциировано с персистенцией ЛГ у детей с БЛД. **Целью исследования** была оценка динамики кардиореспираторных показателей и изучение взаимосвязи наличия апноэ и ЛГ у детей первого года жизни, родившихся недоношенными и страдающих БЛД, осложненной ЛГ. **Материалы и методы.** Было проведено КРМ 58 детям, родившимся на 26 0/7–31 0/7 неделях гестации и с массой тела при рождении менее 1500 г, непосредственно перед выпиской из стационара (35–44 недели постменструального возраста). 14 детей не имели БЛД (группа без БЛД). У 44 детей была диагностирована БЛД, причем 17 из них имели осложнение в виде развития ЛГ (группа БЛД + ЛГ). Другие дети с БЛД не имели ЛГ (группа БЛД – ЛГ). Также восьми детям с БЛД было проведено КРМ в домашних условиях (в возрасте 9–10 скорригированных месяцев жизни). **Результаты.** У недоношенных детей с БЛД + ЛГ отмечалось более значимое снижение средней SpO_2, большее значение индекса десатурации и числа эпизодов десатурации < 10 % по сравнению с детьми с БЛД – ЛГ и без БЛД. Не получено разницы по индексу апноэ/гипопноэ и частоте выявления разных видов апноэ между группами. При этом дети с БЛД + ЛГ чаще имели индекс обструктивных апноэ > 1/ч (диагностически значимое количество обструктивных апноэ), чем дети в других группах. Не получено разницы в кардиореспираторных показателях у детей с БЛД + ЛГ по сравнению с детьми с БЛД – ЛГ в 9–10 скорригированных месяцев жизни. **Выводы.** Отмечается положительная динамика кардиореспираторных показателей у детей, страдающих БЛД + ЛГ, через 9–10 месяцев после выписки из стационара. Число детей с индексом ОА > 1/ч больше в группе с БЛД + ЛГ.

Ключевые слова: недоношенные дети; бронхолегочная дисплазия; легочная гипертензия; апноэ; кардиореспираторное мониторирование.

INTRODUCTION

Preterm birth is a major cause of death and a significant cause of long-term loss of human potential amongst survivors all around the world. Complications of premature birth are the single largest direct cause of neonatal deaths and the second most common cause of under-5 deaths after pneumonia [11].

Bronchopulmonary dysplasia (BPD) is a serious chronic lung disease in premature infants and is especially common in extremely low birth weight infants, who have had respiratory distress syndrome and perinatal infections [16, 19].

Pulmonary hypertension (PH) is a well-known complication of BPD that occurs in 4% of infants with mild BPD and 33% of infants with moderate and severe BPD [5]. Mortality from this disease is 33–48% within 2 years without treatment [15]. Development of PH is associated with impaired growth and a remodeling of pulmonary vessels and is supported by permanent or intermittent episodes of hypoxia/hypercapnia and vasoconstriction, which are typical for BPD [6]. Immature respiratory control, the predisposition for the upper airway obstruction from muscle hypotension, small diameter of airways, prolonged intubation with subsequent inflammation, and narrowing of the upper airway also contribute to the development of intermittent hypoxia. According to the literary sources, several parameters must be simultaneously recorded with the possibility of a specialist analyzing the episodes for the analysis and monitoring of respiratory pauses because these pauses accompanied by intermittent hypoxia are not often clinically manifested. One study found that recording respiratory pauses using bedside cardiac monitors or by nursing staff is ineffective [7]. Polysomnography (PSG) and cardiorespiratory monitoring (CRM) are the most objective methods to record respiratory pauses and intermittent hypoxia. However, PSG is difficult in premature infants. CRM is acceptable for these patients. We presumed that apnea that causes episodes of hypoxia might be associated with PH persistence in infants with BPD. We also analyzed the CRM data in BPD patients at 9–10 corrected months of age to assess the dynamics of cardiorespiratory parameters.

This study aimed to evaluate the dynamics of cardiorespiratory parameters and to study the interrelationship between apnea and PH in premature infants with PH-associated BPD within the first year of life.

MATERIALS AND METHODS

We examined 58 infants born at 26 0/7–31 0/7 weeks of gestation with a birth weight <1500 from 2015 to 2017 at Perinatal Center and Sleep Laboratory of Almazov National Medical Research Centre (Saint Petersburg, Russia). BPD was diagnosed in 44 infants according to Jobe and Bancalari definition (2001) [13] and definition of Russian Respiratory Society (2008) [1]. All 58 infants received 4- to 6-h daytime CRM while sleeping without oxygen support and SpO_2 routine monitoring just before

discharge from the hospital (35–44 weeks of postmenstrual age (PMA)). The parents of infants gave informed consent for monitoring.

We also performed CRM eight BPD infants at 9–10 corrected months of age. In these cases, monitoring was conducted at home for 8–10 hours at night.

The exclusion criteria were premature infants with congenital abnormalities of the upper and lower respiratory tracts, hemodynamically significant congenital heart defects (except patent ductus arteriosus), diaphragmatic hernia, phenotypic signs of chromosomal abnormalities, congenital endocrine diseases (congenital hypothyroidism), tracheostomy.

We used Embletta device (Natus Medical Incorporate, Pleasanton, CA, USA) and recorded nasal airflow, pulse oximetry, one electrocardiography (ECG) channel and chest and abdominal movements. The results were analyzed by RemLogic program. After it a specialist analyzed these results too. The infants' mothers kept a patient monitoring diary, developed by the research team, in which they recorded the patient's periods of sleep, awake periods and feeding. Later a specialist guided by this diary when decoding and evaluating of monitoring records. Feeding, specialists examinations and awake periods were excluded from the analysis during decoding and evaluating monitoring data. CRM did not was performed on routine ophthalmologic examination day because frequency of apnea increased after ophthalmoscopy [8].

Apnea was determined according to the criteria of The American Academy of Sleep Medicine (the 2012 edition) for count the incidence of sleep breathing disordered in children regardless of age [9]. Central apnea (CA) was associated with simultaneous absent respiratory movements and airflow in the upper airway; obstructive apnea (OA) was associated with absent respiratory movements but save of airflow in the upper airway; mixed apnea (MA) was associated with periods of presence or absence of respiratory movements but save of airflow in the upper airway.

The data were statistically processed using a personal computer and SPSS v. 16.0 (SPSS Inc., Chicago, IL, USA). Indicators of descriptive statistics, such as the median (me), minimum (min), and maximum (max), were calculated using nonparametric methods with samples that did not correspond to a normal distribution. Mann–Whitney criteria were used to compare the quantitative variables; the Mann–Whitney and Wilcoxon criteria were used for repeated studies. Statistically significant differences were considered when $p < 0,05$.

RESULTS

We examined 44 infants with BPD, 31 of whom had persistent oxygen dependence at 36 weeks of PMA and 14 had no BPD (non-BPD group), before discharge from the hospital. Artificial lung ventilation (ALV) was applied to 37 (84%) infants with BPD and 3 (21%) infants without BPD during the early neonatal period because of respiratory distress syndrome and prenatal pneumonia. PH was diagnosed in 17 infants who were oxygen dependent at 36 weeks of PMA and developed moderate or severe BPD, based on echocardiography (systolic pulmonary artery pressure ≥35 mm Hg and mean pulmonary artery pressure ≥25 mm Hg [4]) and clinical characteristics (the infants were treated with sildenafil) (BPD + PH group). Most of BPD + PH infants were males and had a lower gestational age, lower body weight at birth and longer periods of ALV and oxygen dependent than infants without BPD and with BPD not complicated by PH (BPD – PH group) (Table 1). In our study, 38% of infants had BPD + PH. The data obtained are consistent with the data in literature.

Based on the monitoring results, the group of infants with BPD + PH had lower average SpO_2 (93.6% [89.0–96.6%]) than BPD – PH group (97.2% [89.7–98.7%]) and infants without BPD (97.5% [96.3–98.7%]) ($p = 0.0003$) (Fig. 1). Also infants with BPD + PH had higher oxygen desaturation index (ODI) and more desaturation episodes <10% than infants in other groups. At the same time, there was not differ in apnea/hypopnea index (AHI) and the occurrence of apnea episodes among these groups (Table 2).

Apnea is expected in premature infants less than 36 weeks of PMA, and CA can be determined in infants within the first year of life. The pathology of the condition is the presence of obstructive apnea. We focused our attention on a large number of hypopnea and central apnea in individual infants in the study groups, which were associated with episodes of periodic breathing and CA and are considered to be physiological for this age period and do not require treatment [3]. These groups did not differ on OA index ($p = 0.6$), but it should be noted that the tendency for OA was identified in infants with BPD + PH. Five infants with BPD + PH had OA index more than 1 per hour (a diagnostically significant value), and 3 infants had higher OA index (2.5, 5.8, and 8.6/h). Only three of 27 BPD – PH patients had OA index >1/h. All infants without BPD

Table 1 (Таблица 1)

Clinical data depending on BPD and PH presence
Клинические данные в зависимости от наличия бронхолегочной дисплазии и легочной гипертензии

Parameters / Параметры Me (min-max)	Without BPD / Без БЛД (n = 14)	BPD – PH / БЛД – ЛГ (n = 27)	p*	BPD + PH / БЛД + ЛГ (n = 17)	p**
Male, *N* (%) / Мальчики, *N* (%)	7 (50 %)	15 (56 %)	0.75	13 (77 %)	0.05
Gestational age at birth (weeks) / Гестационный возраст (нед.)	29 (26–32)	28 (23–31)	0.01	26 (23–29)	0.001
Birth weight (g) / Масса тела при рождении (г)	1160 (750–1490)	970 (590–1370)	0.2	750 (540–1130)	0.003
ALV (days) / Длительность ИВЛ (сут.)	0 (0–1)	2 (0–33)	0.09	15 (0–53)	< 0.001
O_2 suppl. (days) / O_2-зависимость (сут)	0 (0–19)	41 (0–70)	< 0.001	84 (42–133)	< 0.001

Note: the significance of differences; * $p < 0.05$ when comparing groups BPD – PH and without BPD; ** $p < 0.05$ when comparing the group of BPD + PH with groups with BPD – PH and without BPD.
Примечание: БЛД — бронхолегочная дисплазия; ЛГ — легочная гипертензия; ИВЛ — искусственная вентиляция легких; значимость различий: * $p < 0{,}05$ при сравнении групп БЛД без ЛГ и без БЛД; ** $p < 0{,}05$ при сравнении группы БЛД + ЛГ с группами с БЛД без ЛГ и без БЛД

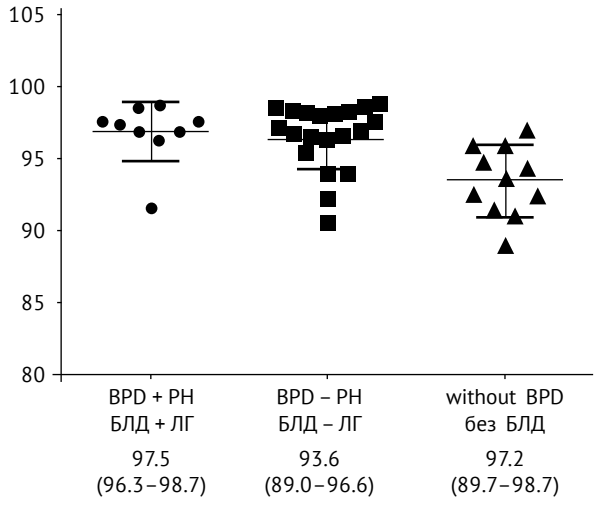

Fig. 1. Average oxygen saturation in infants depending on BPD and PH presence (p = 0.0003)
Рис. 1. Средняя сатурация кислорода у детей в группах в зависимости от наличия бронхолегочной дисплазии и легочной гипертензии (p = 0,0003): БЛД — бронхолегочная дисплазия; ЛГ — легочная гипертензия

had OA index less than 1/h. The differences in the number of infants with OA index >1/h was statistically significant between these groups ($p < 0.05$).

One infant with OA index 5.8/h underwent repeated examinations at 1 and 3 months after discharge from the hospital, during which OA was not recorded.

There was no statistically difference in respiratory data between infants without BPD and BPD – PH group of infants.

Table 2 (Таблица 2)

Respiratory data before discharge from the hospital depending on BPD and PH presence
Респираторные данные перед выпиской из стационара в зависимости от наличия бронхолегочной дисплазии и легочной гипертензии

Parameters / Параметры Me (min-max)	Without BPD / Без БЛД (n = 14)	BPD – PH / БЛД – ЛГ (n = 27)	p*	BPD + PH / БЛД + ЛГ (n = 17)	p**
Desaturation index (events/hour) / ИД (событий/ч)	20 (1.1–58.8)	24.6 (1.0–104.5)	0.2	43 (13.3–133.5)	0.04
Desaturation 0–5 % (events/hour) / Десатурация 0–5 % (событий/ч)	13.6 (0.7–28.5)	14.4 (0.5–46.2)	0.2	22.5 (8.7–46.2)	0.009
Desaturation 5–9 % (events/hour) / Десатурация 5–9 % (событий/ч)	4.1 (0.2–26.4)	8 (0.3–64.8)	0.2	19 (3.8–72.3)	0.05
Desaturation 10–20 % (events/hour) / Десатурация 10–20 % (событий/ч)	0.1 (0–7.7)	0.8 (0–32.3)	0.2	1 (0–18.2)	0.2
AHI (events/hour) / ИАГ (событий/ч)	5.2 (0–42.3)	8.2 (0–38.6)	0.4	13.4 (0.4–95.2)	0.1
Hypopnea (events/hour) / Гипопноэ (событий/ч)	4.2 (0–20.9)	1.5 (0–73.1)	0.7	2.2 (0–61.2)	0.6
Central apnea (events/hour) / ЦА (событий/ч)	0.5 (0–4.8)	1.1 (0–25.5)	0.2	3.1 (0–95.2)	0.1
Obstructive apnea (events/hour) / ОА (событий/ч)	0 (0–2)	0 (0–1.9)	0.9	0 (0–8.6)	0.6
Mixed apnea (events/hour) / СмА (событий/ч)	0 (0–0.3)	0 (0–0.8)	0.1	0 (0–5.9)	0.2

Note: the significance of differences: * $p < 0.05$ when comparing groups BPD – PH and without BPD; ** $p < 0.05$ when comparing the group of BPD + PH with groups with BPD – PH and without BPD.

Примечание: значимость различий: БЛД — бронхолегочная дисплазия; ЛГ — легочная гипертензия; ИД — индекс десатурации; ЦА — центральное апноэ; ОА — обструктивное апноэ; * $p < 0,05$ при сравнении групп БЛД без ЛГ и без БЛ; ** $p < 0,05$ при сравнении группы БЛД + ЛГ с группами с БЛД без ЛГ и без БЛД

We performed CRM at home on six BPD infants and two BPD + PH infants at 9–10 corrected months of age. There was a positive dynamic such as increase average SpO_2 to ≥94%, a absence of obstructive apnea, a decreases ODI (6.5/h [1.3–21.2/h]) and AHI (2.3/h [0–10.2/h]), and the number of 5–9% desaturation episodes (1.4/h [0–7.5/h]). Our results confirmed with single literature data and devoted to the study of age-related changes in the pulmonary reserve in premature infants with chronic lung diseases [2]. Five infants had AHI > 1/h resulting from CA (two infants with PH). There are no standards for the occurrence of CA in infants in this age group.

DISCUSSION

In our study infants with BPD + PH differed from infants in other groups by having lower average oxygen saturation, higher ODI and more desaturation episodes <10%, which is most likely a result of structural and functional immaturity of the lung followed by postnatal deterioration of angiogenesis and alveoli formation.

Dynamic examination of patients revealed an improvement in cardiorespiratory parameters in infants with BPD + PH, but more extensive prospective studies are necessary to assess CRM data in this group of patients at a later age.

Support of necessary level of SpO_2 in premature infants with BPD (from 92 to 96% [20]) can improve growth of infants, reduces the severity of PH symptoms and reduces the risk of sudden death associated with hypoxemia [21]. Studies conducted on rats have shown that intermittent hypoxia can have a detrimental effect on cognitive function because of increased oxidative stress and inflammation [18], while studies on premature infants under NICU have indicated a negative effect of hypoxemic events on clinical outcomes [12]. Monitoring respiratory pauses, especially in infants with BPD + PH, for which it is important to support of necessary level of oxygen saturation (≥95% [22]), is significant for timely correction therapy.

In our study, there is a correlation between the presence of obstructive apnea and PH in premature infants with BPD; the number of infants who had an OA index > 1/h was greater in the BPD + PH group. There is limited information on the occurrence of OA in infants of this age category [14]. Previous studies that examined obstructive apnea during sleep focused on children >2 years old [10]. The recommendations of The American Academy of Pediatrics are intended for children >1 year old [17]. This is due to the difficulty in using PSG or CRM on these patients.

There was no statistically significant difference in respiratory rates among the groups; however, the CA index was higher in infants in the BPD + PH group. Perhaps this is a result of a more immature control of breathing in these infants because of birth before 28 weeks of gestation.

There were several limitations to this study. The first, the study comprised a small sample size. The second, some parents often failed to monitor their infant or these infants were living in another region of Russia and we couldn't have a chance to monitor them. In addition, monitoring the infants at home created a problem because it was nearly impossible to constantly monitor an infant while the parents were asleep, which led to periodic difficulties in the interpretation of the results.

CONCLUSIONS

Premature infants with BPD + PH had a more significant decrease in average SpO_2, a greater ODI and a greater number of desaturation episodes <10% compared to infants with BPD – PH and infants without BPD. There was no difference in AHI and frequency of occurrence of different types of apnea among the groups.

The number of infants with an OA index > 1/h was greater in the BPD + PH group. In addition, there was a positive dynamic among cardiorespiratory parameters in infants with BPD + PH at 9–10 corrected months of age.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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