Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences
Tome 76, No 3, 2023

MEDICINE
Clinical medicine

OXYGENATION INDEX – AN OBJECTIVE INDICATOR OF THE SEVERITY AND TREATMENT EFFECT OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

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Received on March 24, 2020
Presented by D. Damianov, Member of BAS, on June 30, 2020

Abstract

The basis of PPHN pathogenesis is Right-to-Left shunt due to suprasystemic pulmonary pressure. Treatment of PPHN is complex and frequently ineffective. Medicaments influencing PPHN pathogenesis are pulmonary vasodilators. First-choice medicament is inhaled nitric oxide. The main thesis of the current study is: Overcoming pulmonary vasoconstriction by means of iNO will lead to the improvement of oxygenation and contribute to more immediate termination in newborns ventilatory support. The strategy is successful – infants from the iNO group quite logically require less ventilatory support compared to the control group, as evident by statistically significant differences in OI at the 24th and 48th hours. Oxygenation Index (OI) is an objective criterion that provides important information about the severity of PPHN and the effect of treatment applied. iNO decreases statistically significant OI at the 1st, 24th and 48th hour after initiation of the therapy. Treatment with iNO results in a more rapid hemodynamic stabilization of patients than conventional therapy of PPHN.

Key words: oxygenation index, persistent pulmonary hypertension, inhaled nitric oxide, newborn, objective criterion

Introduction. Life-threatening respiratory failure, resulting from persistent high pulmonary vascular resistance and right-to-left shunt through the arterial

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DOI:10.7546/CRABS.2023.03.13

canal, foramen ovale and intrapulmonary vessels is defined as persistent pulmonary hypertension of the newborn (PPHN) [1,4,9,10]. Most commonly, PPHN is associated with the following three etiological factors [8,9]:

- Acute occurring vasoconstriction of the pulmonary vessels;
- Hypoplasia of the pulmonary vascular bed;
- Idiopathic pulmonary hypertension.

Objectively, oxygenation (severity of the disease) is determined using the following indices:

- **Oxygenation index (OI)** = FiO2 × mean airway pressure × 100 / PaO2; **P/F ratio**: PaO2/FiO2 – the ratio between the partial arterial pressure of O2 and the concentration of the supplied inspiratory O2 [3];
- **Oxygenation saturation index (OSI)** [8] – in contrast to other indices, it is non-invasive and is calculated by the following formula:
  - Mean airway pressure MAP × FiO2 × 100 / preductal SpO_2.
  - OI ≈ 2 × OSI [8].

Treatment of PPHN is complex and often ineffective. The basis of PPHN pathogenesis is Right-to-Left shunt due to supra-systemic pulmonary pressure. Medicaments affecting PPHN pathogenesis are pulmonary vasodilators. First-choice medicament is inhaled nitric oxide [7,12]. Patients showing good effect of iNO therapy are referred to as the "responder" group. In clinical practice, the effect of the drug is considered to be good in case of reducing OI by more than 20% or disappearing the difference between preductal and postductal oxygen saturation after the onset of iNO therapy. According to literature data, about 40% of newborns treated with PPHN do not respond to inhaled nitric oxide therapy [11].

Patients and methods (Table 1).

iNO group – 12 newborns: Infants with PPHN and gestational age of over 34th gestational week in critical condition, despite optimal mechanical ventilation. iNO therapy is initiated after echocardiographic examination to exclude cyanotic heart disease and to diagnose PPHN.

Control group – 20 newborns: A study of infants with PPHN, at gestational age of over 34th gestational week, in critical condition, supported only by optimal mechanical ventilation.

No statistically significant difference is found between the two groups in terms of **gestational week**: mean gestational age of the first group A is 36 ± 2 weeks and of the control one is 37 ± 1 week.

There is no statistically significant difference between both groups regarding birth weight: the average weight of the first group A is 2739 ± 539 g, while the range values of the control group are 3026 ± 629 g. Infants with IUGR in both groups are 18.75%, half of which have a weight of less than 3rd percentile for the respective gestational age.

In both groups, male sex is predominant, but there is no statistically significant difference in the newborns included in the study ($p = 0.703$).

Table 1

Perinatal characteristics of infants

Characteristic*	iNO gr. ($n = 12$)	Control gr. ($n = 20$)	P
Weight (g)	2739 (1730–3500)	3026 (2050–4220)	0.199
Gest. age (g.w.)	36 (34–38)	36 (34–40)	0.428
Male, n (%)	9 (75)	13 (65)	0.703
IUGR, n (%)	1 (8)	5 (25)	0.097
Apgar score, 1 min	<7 (2–7)	<7 (0–7)	0.231
Apgar score, 5 min	<8 (5–9)	<8 (3–9)	0.603
pH	7.25 (7.00–7.40)	7.30 (6.9–7.41)	0.286
MFI,n (%)	8 (66)	13 (65)	0.963
Diabetes, n (%)	3 (25)	4 (20)	0.735
Caesarean section, n (%)	12 (100)	20 (100)	

IUGR – intrauterine growth retardation; MFI – maternal-fetal infection
*Data are presented as average value within range in brackets or as number and % (in brackets)

All newborns in both groups are born by Caesarean section. The infants in both groups have data for moderate intrapartal asphyxia according to the values of Apgar score on the 1st min. Apgar score on the 5th min is more than 7 and again no significant difference is observed between the two groups ($p = 0.286$).

Results and discussion. The PPHN severity is based on the value of the **OI.** According to the OI, PPHN is defined as:

- Mild PPHN <15 OI
- Moderate PPHN 15≥25 OI
- Severe PPHN 25≥40 OI
- Very severe PPHN> 40 OI

The analysis of OI after initiating mechanical ventilation identifies the following features:

iNO group:

- Highest percentage of infants with very severe PPHN – 58%;
- No infants with mild PPHN;
- Infants with perinatal asphyxia combined with infection have the highest OI;
- Two of the infants with the highest OI – exitus letalis, before initiating treatment.

Control group:

- There are newborns with mild PPHN – 10%;
- Newborns with very severe PPHN are 25%;
- Severe PPHN newborns are prevalent – 45%;

- In this cohort newborns with infection, MAC and asphyxia have the highest OI;
- Both newborns with a very high OI at the onset of the disease and the ones with a low OI have poor outcome.

Infants, included in the study, are monitored for OI values dynamically within 72 h after initiation of therapy and/or until discontinuation of mechanical ventilation. Figures 1 and 2 demonstrate the dynamics of OI in both patient groups.

When analyzing the OI dynamics in both groups of patients, the following features are identified:

- OI values decrease over time in both groups; one patient from the control group turns out to be an exception having severe asphyxia and MAC at birth with poor outcome and exitus letalis prior to the 48th hour after birth.

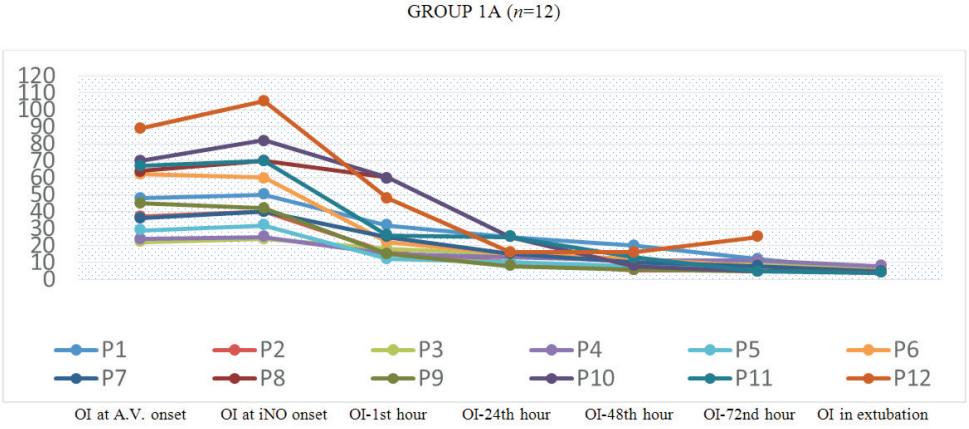

Fig. 1. OI dynamics in iNO group; A.V. – artificial ventilation; OI – oxygenation index

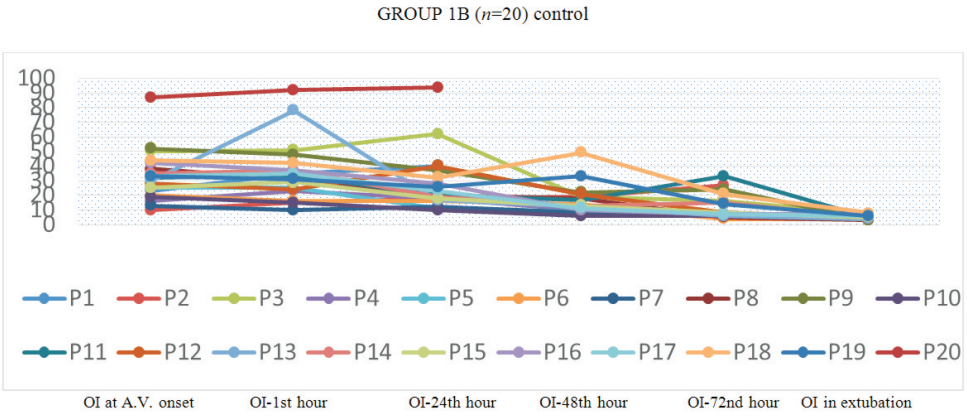

Fig. 2. OI Dynamics in Control group; A.V. – artificial ventilation; OI – oxygenation index

- In iNO group, OI values are higher at iNO therapy initiation compared to the onset of assisted ventilation; i.e. the patients' condition progressively exacerbates.
- Extubation OI values are lower than 10 in both patient groups.
- A sharp decline in OI values has been observed in iNO group at the first hour of therapy.
- Repeated sharp decline in OI has also been observed at the 24th hour in iNO group.
- In the control group, the decrease in OI values is gradual, with fluctuations of rising in some patients at 1st, 24th and 48th hours after initiation of assisted ventilation.
- At 1st, 24th and 48th hours the average OI values are significantly higher in the control group (Table 2).

T a b l e 2

Mean OI value in both groups

Group		n	Mean	Std. Deviation	Std. Error Mean	p	p MW-test
OI at the onset of A.V.	iNO	**12**	**49.417**	**20.9782**	**6.0559**		
	Control	20	32.750	17.2318	3.8531	**0.021**	**0.023**
OI 1st hour	iNO	**12**	**29.083**	**17.4171**	**5.0279**		
	Control	20	35.400	20.2573	4.5297	0.376	0.293
OI 24th hour	iNO	**11**	**16.09**	**6.252**	**1.885**		
	Control	20	28.05	19.959	4.463	**0.021**	**0.016**
OI 48th hour	iNO	**11**	**10.86**	**4.313**	**1.301**		
	Control	18	16.89	10.278	2.423	**0.077**	**0.050**
OI 72nd hour	iNO	**11**	**9.32**	**5.763**	**1.738**		
	Control	18	12.28	8.662	2.042	0.325	0.585
OI in extubation	iNO	**10**	**5.10**	**1.197**	**0.379**		
	Control	17	5.00	1.414	0.343	0.853	0.796

A.V. – artificial ventilation, OI – oxygenation index, MW-test – Mann–Whitney test

Concerning the OI dynamics, the following conclusions can be drawn:

- OI is higher in the iNO group compared to the control group only in initiating artificial ventilation.
- In iNO group OI within the first hour is lowered almost twice (from 49 to 29 on average), which corresponds to 41%; the logical conclusion is that the newborns in the treatment group appear to be "responders", since they have more than 20% decline in OI.
- In the control group OI in the first hour has a higher average value than when initiating assisted ventilation.

- At the 24th hour the decline of OI in iNO group is 68% compared to the initial value, while in the control group – only 15%; the same tendency has been observed at the 48thhour. These are also the time intervals in which there is a statistically significant difference between both groups
- After the 48th hour the decrease in OI values in the two groups does not differ.
- The infants of both groups have been extubated at relatively low OI values; the explanation of this fact regarding iNO group is associated with an increased risk of occurrence of "rebound" effect, i.e. re-deterioration of the condition with iNO dose reduction.

Conclusion. The basic thesis of the current study is: Overcoming pulmonary vasoconstriction by means of iNO will lead to the improvement of oxygenation and promote more immediate termination of the ventilatory support of the infants. The strategy is successful – infants from the iNO group quite logically require less ventilatory support compared to the control group, as evident by statistically significant differences in OI at the 24th and 48th hours. The mean duration of iNO therapy in our study is 98 ± 12 hours, which is similar to that reported by KINSELLA et al. [6] (95 ± 13 hours) and FINER et al. [2] (91 ± 67 hours SD).

Another important result of the study is that iNO toxicity is similar to that reported by other authors [5]. Methaemoglobin levels do not exceed 5% in any patient (average – 1.42%, levels 0–3.5%). The incidence of hemorrhagic manifestations has not been increased during iNO therapy.

OI is most commonly used to assess the severity of hypoxic respiratory failure and PPHN in neonatal intensive care units. This index is considered to be a better indicator of lung damage compared to the P/F ratio. The explanation of this is that the value of the mean airway pressure (MAP) is used to calculate OI, which in turn is an important indicator of oxygenation. At this stage, both the clinical protocols used in practice and the protocols in clinical randomized trials use OI to assess therapy for hypoxic respiratory failure and PPHN.

There are several limitations of the OI usage in neonatal intensive care units:

- The method is invasive and requires either a permanent arterial catheter or frequent sampling of arterial blood.
- It is calculated intermittently only at the hours when blood and gas analysis is performed.
- The location of the arterial catheter is important – preductal or postductal.
- It is not entirely clear to what extent the value of OI correlated with the severity of pulmonary disease or pulmonary vascular resistance in PPHN.

For these reasons, to assess the therapeutic effect of iNO other methods are being examined. One of the most commonly used is the Oxygen Saturation Index, which unlike OI is non-invasive [8]. Despite the many advantages of this method, we have chosen to trust OI in the present study for the following reasons:

- OI is the index used by all major randomized clinical trials for the therapeutic effect of iNO in PPHN.
- OSI does not correlate with values of pulmonary vascular resistance in PPHN and is not a reliable indicator for assessing the severity of disease at very low or very high values of preductal SpO2.

Oxygenation Index is an objective criterion that provides significant information about the severity of PPHN and the effect of treatment applied. iNO decreases statistically significant OI at the 1st, 24th and 48th hours after initiation of therapy. Treatment with iNO results in a more rapid hemodynamic stabilization of patients in comparison with conventional treatment of PPHN. In Bulgaria iNO is used for the first time in infants with Pulmonary hypertension, that is often observed after cardiac surgery. This is a very effective treatment, established almost 10 years ago by Prof. Lacheva in the National Heart Hospital. The current trial is the first that represents the usage of iNO in the Neonatal intensive care unit in newborns with PPHN. This treatment has been conducted for 5 years now and at this particular moment is considered the most effective for severe PPHN.

REFERENCES

[1] Cabral J. E., J. Belik (2013) Persistent pulmonary hypertension of the newborn: recent advances in pathophysiology and treatment, J. Pediatr. (Rio J), **89**(3), 226–242.

[2] Finer N. N., N. Evans (2015) Inhaled nitric oxide for the preterm infant: evidence versus practice, Pediatrics, **135**(4), 754–756.

[3] Gien J., J. P. Kinsella (2016) Differences in preductal and postductal arterial blood gas measurements in infants with severe congenital diaphragmatic hernia, Arch. Dis. Child. Fetal Neonatal Ed., **101**, F314–F318.

[4] Hernandez-Diaz S., L. J. Van Marter, M. M. Werler, C. Louik, A. A. Mitchell (2007) Risk factors for persistent pulmonary hypertension of the newborn, Pediatrics, **120**(2), e272–e282.

[5] Neonatal Inhaled Nitric Oxide Study Group (1997) Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure, N. Engl. J. Med., **336**, 597–604.

[6] Kinsella J. P., R. H. Steinhorn, U. S. Krishnan et al. (2016) Recommendations for the use of inhaled nitric oxide therapy in premature newborns with severe pulmonary hypertension, J. Pediatr., **170**, 312–314.

[7] Konduri G. G. (2004) New approaches for persistent pulmonary hypertension of newborn, Clin. Perinatol., **31**, 591–611.

[8] Rawat M., P. K. Chandrasekharan, A. Williams, S. Gugino, C. Koenigsknecht et al. (2015) Oxygen Saturation Index and Severity of Hypoxic Respiratory Failure, Neonatology, **107**, 161–166.

[9] Steinhorn R. H., K. N. Farrow (2007) Pulmonary hypertension in the neonate, NeoReviews, **8**, e14–e21.
[10] Teng R. J., T. J. Wu (2013) Persistent pulmonary hypertension of the newborn, J. Formos. Med. Assoc., **112**(4), 177–184.
[11] Thelitz S., J. M. Bekker, B. Ovadia, R. B. Stuart, M. J. Johengen et al. (2004) Inhaled nitric oxide decreases pulmonary soluble guanylate cyclase protein levels in 1-month-old lambs, J. Thorac. Cardiovasc. Surg., **127**, 1285–1292.
[12] Tworetzky W., J. Bristow, P. Moore, M. M. Brook, M. R. Segal et al. (2001) Inhaled nitric oxide in neonates with persistent pulmonary hypertension, Lancet, **357**(9250), 118–120.

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