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A COMPREHENSIVE PROGRAM OF OPTIMIZATION THE BRAIN OXYGEN STATUS IN NEWBORNS WITH RESPIRATORY DISORDERS BASED ON TARGETING REGIONAL OXYGENATION

Abstract. NIRS provides the ability to obtain information about the brain oxygen status non-invasively. Therefore, potentially, this technology can make it possible to correct therapy that affects the blood and oxygen supply to the brain.

The aim of our study was to develop a guideline for a dynamic monitoring of the oxygen status based on regional oxygenation data, as well as an effective therapeutic tool for newborns with respiratory distress.

78 newborns with respiratory disorders were included (37 late preterm and 41 full-term) in this observational cohort study. In addition to a standard cardiorespiratory monitoring, a simultaneous monitoring of abdominal and cerebral oxygenation was performed during the early neonatal period.

The developed treatment guideline was based on a multisystem approach in diagnosis and optimization of the brain oxygen delivery and consumption. The proposed algorithm focused on maintaining an adequate perfusion pressure, cardiac output, oxygen, and carbon dioxide content in the arterial blood in newborns with respiratory disorders.

Implementing the developed treatment guideline in the neonatal intensive care units should increase the treatment effectiveness in newborns with respiratory disorders.

Implementation developed treatment guideline in the neonatal intensive care units should increase the effectiveness of treatment in newborns with respiratory disorders.

Keywords: near infrared spectroscopy, newborn, oxygen status, respiratory disorders, treatment guideline

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ИНТЕГРИРОВАННАЯ ПРОГРАММА ОПТИМИЗАЦИИ КИСЛОРОДНОГО СТАТУСА ГОЛОВНОГО МОЗГА У НОВОРОЖДЕННЫХ С РЕСПИРАТОРНЫМИ РАССТРОЙСТВАМИ ПО ДАННЫМ РЕГИОНАЛЬНОЙ ОКСИГЕНАЦИИ

Аннотация. Использование метода NIRS позволяет неинвазивно получать информацию о кислородном статусе головного мозга, а следовательно, проводить коррекцию терапии, влияющей в том числе на кровоснабжение и доставку кислорода к головному мозгу.

Цель исследования – разработать интегрированную программу динамического контроля кислородного статуса с учетом данных региональной оксигенации, а также комплекс эффективных лечебных мероприятий у новорожденных с респираторными расстройствами.

В исследование было включено 78 новорожденных детей с клинико-лабораторными проявлениями дыхательного расстройства. На протяжении раннего неонатального периода в дополнение к стандартному мониторингу кардиореспираторного статуса проводили параллельное измерение абдоминальной и церебральной оксигенации.

Разработанная программа основана на мультисистемном подходе к диагностике и оптимизации доставки и потребления кислорода головным мозгом посредством поддержания адекватного перфузионного давления, сердечного выброса, содержания кислорода и углекислого газа в артериальной крови новорожденных с респираторными расстройствами.

Включение в интегрированную программу мониторинга кислородного статуса, динамического контроля региональной оксигенации, а также разработанного на его основе комплекса эффективных лечебных мероприятий позволит повысить эффективность проводимого лечения у новорожденных с респираторными расстройствами.

Ключевые слова: спектроскопия в близком к инфракрасному спектру, новорожденный, доставка кислорода, потребление кислорода, практические рекомендации

Для цитирования: Интегрированная программа оптимизации кислородного статуса головного мозга у новорожденных с респираторными расстройствами по данным региональной оксигенации / Д. Н. Санковец [и др.] // Вес. Нац. акад. навук Беларусі. Сер. мед. навук. – 2021. – Т. 18, № 1. – С. 16–24 (*на англ.*). https://doi.org/10.29235/1814-6023-2021-18-1-16-24

Introduction. Despite the fact that NIRS technology (near-infrared spectroscopy) introduced into clinical practice almost 40 years ago, it is only in the last decade has becoming more common in the neonatal intensive care unit (NICU) [1]. As we know, NIRS provides continuous non-invasive measurement of regional tissue oxygenation (rSO_2), and its ease of use and high potential for practical healthcare has contributed to its wider implementation in the management of critical ill patients, especially preterm in NICU. The benefits of NIRS implementation in a comprehensive newborn monitoring program described earlier, however, evidence supporting the potential utility of NIRS independently, or in conjunction with other modalities is growing [2, 3].

Awareness of the importance of interpreting physiological data in context of each patient has led to a change the clinical paradigm from a "one size fits all" approach to a personalized one focused on achieving the optimal functional level of vital systems in individual infant. As a result, the problem facing many clinicians is the interpretation of this relatively new monitoring method. Both discrete and trend values are rich in information, however, in contrast to the well-known pulse oximetry, rSO_2 is determined by a wider range of physiological determinants [4]. In this context, correct interpretation of the NIRS-derived data, on the one hand will have fundamental importance for provide the appropriate interventions, and on the other, it will allow looking at the pathophysiology of disease from a different angle.

The aim of our study was to develop a guideline for dynamic monitoring of oxygen status based on rSO_2 data, as well as an effective therapeutic tool for newborns with respiratory distress.

Materials and research methods. From February 2013 to March 2016, we conducted this observational cohort study in our NICU in the National Scientific Practical Centre "Mother and Child". Seventy-eight newborns with respiratory disorders were enrolled (37 late preterm and 41 full-term). Recording the data began from the moment of birth (in the delivery room or operating room) and dynamically continued for the first 7 days of life.

Inclusion criteria: gestation age from 30 to 42 weeks; presence of respiratory distress requiring any respiratory support (oxygen therapy, non-invasive ventilation, conventional and high-frequency mechanical ventilation); arterial line for direct blood pressure and blood gases monitoring. Infants with congenital heart disease, multiple congenital malformations, history of sepsis, and surgical pathology were excluded.

In addition to standard cardiorespiratory monitoring, a simultaneous monitoring of abdominal and cerebral oxygenation were performed by the "INVOS 5100C" (Covidien, Medtronic, USA) with the Pediatric SomaSensor (SAFB-SM).

Unlike pulse oximetry (SpO_2), NIRS expresses full tissue hemoglobin oxygenation without subtraction of non-arterial data (venous and capillary). Thus, NIRS reflects the ratio of oxygenated to total hemoglobin for the mixed arterial, capillary, and venous vascular compartment underlying a given probe [1]. Regional oxygenation reflect the oxygen saturation in the venous (70 to 80 %), arterial (20 to 25 %) and capillary (5 %) [5]. Hence, as NIRS provides mainly information about hemoglobin oxygenation in post-capillary tissues, regional oxygenation can be considered as surrogate measures of the local oxygen utilization.

To assess cerebral oxygenation ($crSO_2$), the NIRS sensor was placed on the forehead, in the case of abdominal oxygenation ($abdSO_2$) – on the midline of the abdomen, above the pubic region (Fig. 1). All staff members attending were trained to use the device.

To better understand the balance between brain oxygen delivery and oxygen consumption, we used the cFTOE (cerebral fractional tissue oxygen extraction) then can be calculated from $crSO_2$ and arterial oxygen saturation: $(SpO_2 – crSO_2)/SpO_2$.

From clinical experience, cFTOE, calculated on the basis of NIRS and pulse oximetry data, showed a significant correlation with FTOE calculated during direct (invasive) measurement of oxygen content in venous and arterial blood in neonatal piglet model [6]. Thus, an increase in FTOE suggests an increase

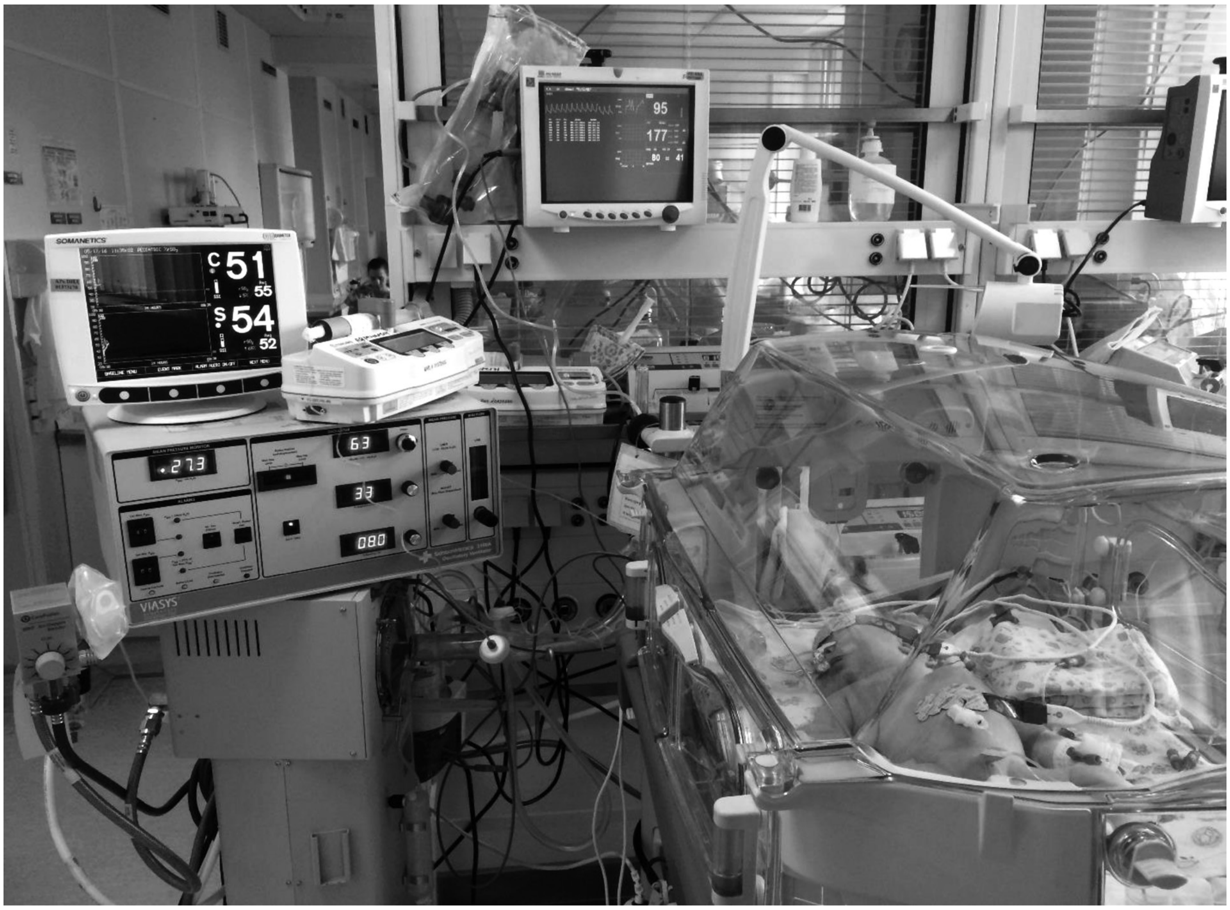

Fig. 1. Cardiorespiratory monitoring and probe positions during NIRS

in the oxygen extraction by the tissues due to higher oxygen consumption in relation to oxygen delivery, while a decrease suggests less oxygen use compared to the supply. This also relatively compensates for low arterial oxygen content, as is often the case in newborns with lung disease or congenital heart defects [7].

To assess systemic perfusion, another NIRS-derived coefficient was used SCOR (splanchnic-cerebro oxygenation ratio). SCOR can be calculated from cerebral and abdominal regional oxygenation: $abdSO_2/crSO_2$.

In addition to the aforementioned NIRS data, we also analyzed the following: $crSO_2$min is the daily minimal $crSO_2$, $crSO_2$max is the daily maximum $crSO_2$, $\Delta crSO_2$ is the daily amplitude of cerebral regional oxygen saturation (calculated as the difference between $crSO_2$max and $crSO_2$min), $abdSO_2$min is daily minimal $abdSO_2$, $abdSO_2$max is the daily maximum $abdSO_2$, $\Delta abdSO_2$ is the daily amplitude of abdominal regional oxygen saturation (calculated as the difference between $abdSO_2$max and $abdSO_2$min).

To minimize the impact of third-party factors monitoring was carried out during calm patient state (without sedation), outside the phototherapy period and began at least one hour after enteral feeding [2, 8].

Respiratory and hemodynamic support was carried out in accordance with the local NICU guidelines and the clinical protocols for intensive care in neonatology (order of the Ministry of Health of the Republic of Belarus dated January 28, 2011, No. 81).

Evaluation of blood gas parameters was performed with “ABL – 835 Flex” (Radiometer, Denmark). After collection arterial blood samples were immediately injected into a co-oximeter. We evaluated: PaO_2 – oxygen tension, mmHg, ctO_2 – the total content of oxygen, ml/dl, Lactate – lactate concentration, mmol/l, pH – the negative logarithm of the hydrogen ion activity, $PaCO_2$ – carbon dioxide tension, mmHg, p50 – oxygen tension at 50 % saturation of blood, mmHg. Paired assessments of blood gas parameters and regional oxygenation undertaken whenever an ABG was conducted as part of necessary patient care.

Echocardiography (ECHO) measurements were performed using commercially available Philips HD 11 XE (USA) in M-, B-, Doppler modes and in tissue Doppler imaging mode. For quantitative assessment of left ventricular function were used the common echocardiographic parameters: fraction shortening (FS), ejection fraction (EF). Pulmonary hypertension was defined based on the ratio of pulmonary artery pressure to systemic blood flow. Assessment of pulmonary artery pressure was carried out by tricuspid regurgitation peak velocity or by Kitabatake's method.

Data are presented as mean values ± SD for normally distributed continuous variables and median (interquartile range) when the distribution was skewed. Differences between the two groups were assessed using Mann–Whitney *U*-test for non-parametric data, Student's *t*-test for parametric data or χ^2-test for categorical measurements. A correlation analysis was performed to investigate if there was an association between between regional oxygenation and red blood cell parameters, as well as arterial blood gas data. Correlations were performed using Spearman's rank correlation coefficient (ρ) or Pearson's correlation where appropriate. The pre- and post-transfusion values of all measurements were compared using Wilcoxon matched pairs test. To identify physiological determinants of cerebral oxegenation and cFTOE simultaneous multiple linear regression was performed. Checking for multicollinearity before building a multiple regression model was carried out based on the analysis of the Variance Inflation Factor and the correlation matrix. To calculate the probability that a stabilization of the cardiorespiratory status (weaning from inotropes/vasopressors and mechanical ventilation) will occur at certain points in time, the Kaplan–Meier method was used. To compare groups a log-rank test was performed. $p < 0.05$ was considered statistically significant. The statistical analyses were performed using MedCalc 19.1 (MedCalc Software Ltd., Ostend, Belgium).

Results and its discussion. In this study 78 newborn infants with respiratory disorder requiring respiratory support (non-invasive, conventional or high-frequency oscillatory lung ventilation) were included. According to the tasks of the study, clinical and statistical hypotheses were made. The flow chart of the study was developed (Fig. 2).

Condition of all included newborns considered as severe because of profound pulmonary insufficiency with hemodynamic instability. All patients were provided with central venous catheter for inotropic and vasopressor support. Clinical characteristics of patients are outlined in the Table.

First we checked the assumption that regional oxygenation's data could be used as a tool for estimation the effectiveness of respiratory and hemodynamic support. We revealed that $\Delta crSO_2$ has statistically significant differences depending of initial clinical status at the beginning of intensive care and in the period of further stabilization. Patients with more severe clinical status had more statistically significant daily shifts of $crSO_2$ ($p < 0.0001$). Patients who was stabilized (weaning from inotropes/vasopressors and mechanical

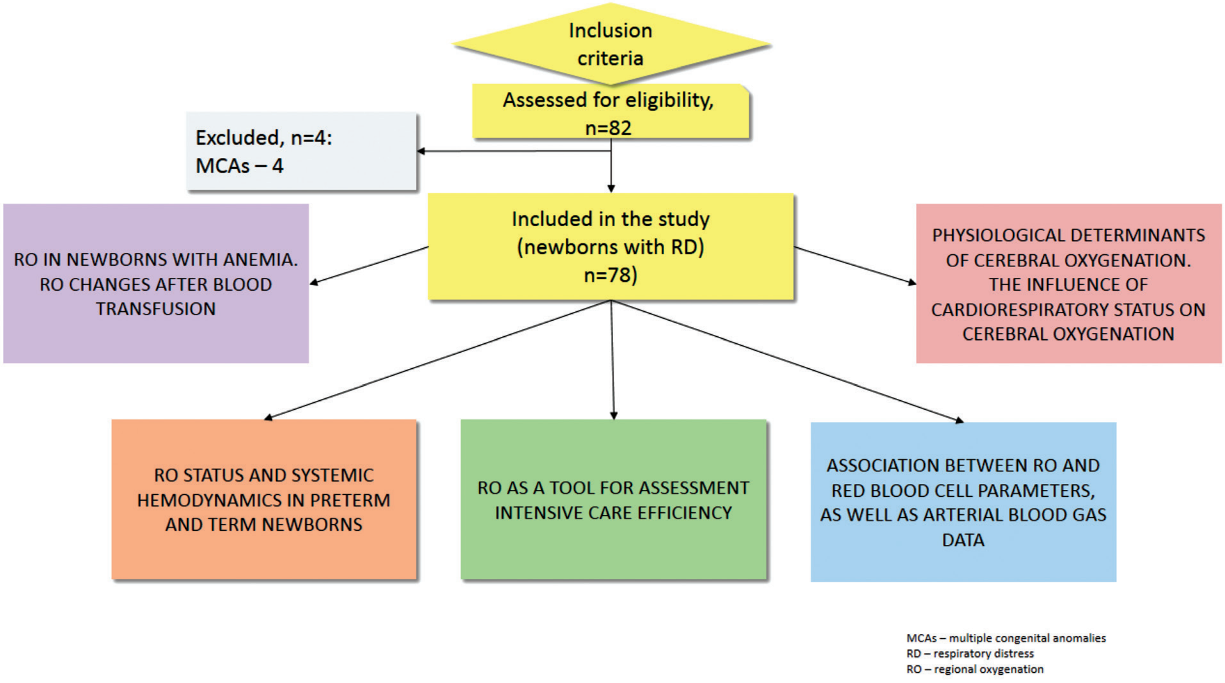
Inclusion criteria
Assessed for eligibility, n=82
Excluded, n=4: MCAs – 4
Included in the study (newborns with RD) n=78)
RO IN NEWBORNS WITH ANEMIA. RO CHANGES AFTER BLOOD TRANSFUSION
PHYSIOLOGICAL DETERMINANTS OF CEREBRAL OXYGENATION. THE INFLUENCE OF CARDIORESPIRATORY STATUS ON CEREBRAL OXYGENATION
RO STATUS AND SYSTEMIC HEMODYNAMICS IN PRETERM AND TERM NEWBORNS
RO AS A TOOL FOR ASSESSMENT INTENSIVE CARE EFFICIENCY
ASSOCIATION BETWEEN RO AND RED BLOOD CELL PARAMETERS, AS WELL AS ARTERIAL BLOOD GAS DATA
MCAs – multiple congenital anomalies
RD – respiratory distress
RO – regional oxygenation

Fig. 2. Study flow chart

Main clinical characteristics of studied patients

Characteristic	Value
Gestational age, weeks:	37 (34; 39)
preterm, *n*	37
term, *n*	41
Birth weight, g	2994.6 ± 678.6
Apgar score at 1 min	8 (6; 8)
Sex, *n*:	
male	46
female	32
Delivery mode, *n*:	
vaginal delivery	25
Cesarean section	53
Respiratory support, *n*:	
non-invasive	2
CMV	56
HFO	20
Hemodynamic support, *n*:	
none	4
dopamine	42
dopamine + (adrenaline/noradrenaline)	32
Clinical diagnosis, *n*:	
congenital pneumonia	38
unspecified intrauterine infection	8
respiratory distress syndrome (RDS)	4
congenital pneumonia + RDS	28

ventilation) to 96 hours of life had $\Delta crSO_2$ lower than those, who was stabilized to 7 days of life as well as those who did not reach hemodynamic stability in early neonatal period 8 (5; 15) % vs 11 (8; 14) and 13 (9; 22) % respectively. Moreover, we found that premature infants with $\Delta crSO_2 \leq 20$ % in the first day of life had probability of reaching cardio-pulmonary stability in early neonatal period 3.3 times higher (95 % CI (1.5–6.9), $p_{log-rank} = 0.0023$) compared with patients with $\Delta crSO_2$ more than 20 % during the 1st day of life.

Both very low and very high values of daily $crSO_2$ could contribute to the increase of $\Delta crSO_2$. As target we considered $crSO_2$ and cFTOE values 78 ± 7 % and 0.22 ± 0.07 which are stated to be “physiologic” according the literature and confirmed by us during pilot study [9, 10].

Cerebral oxygenation levels laying out of physiologic values give us signs of imbalance between oxygen delivery and consumption so multisystem assessment of patient is needed (Fig. 3).

Estimation of hemodynamic status. Cerebral autoregulation is known to be a mechanism that allows to mitigate effects of systemic pressure fluctuations on brain blood flow. That’s why $crSO_2$ levels below physiologic range in patient with systemic hypotension are most likely to indicate loss of auto-regulation and require immediate intervention to increase cardiac output and tissue perfusion. As we established, the negative relationship between the blood lactate level and the value of the $crSO_2$, as well as the positive one with cFTOE indirectly confirm this fact [11]. Increase of lactate (traditional marker of hypoperfusion and tissue hypoxia) is accompanied, under equal conditions, by a reduction in the supply of oxygen to tissues and an increase in O_2 extraction. As a results, we will see certain $crSO_2$ changes reflecting impaired oxygen status of the brain. As the first markers of systemic hypoperfusion we recommend to use indicators widely available in everyday clinical practice: prolonged capillary refill time, oliguria and arterial lactate.

According to our data, the SCOR coefficient is a useful clinical tool to evaluate end-organ hypoperfusion. As we found SCOR below 0.80 indicated hypoperfusion with a sensitivity of 53.4 % and a specificity of 85.9 % [12].

Bedside echocardiography is an integral part of the modern approach in assessing hemodynamic status in newborns [13]. But ECHO data also add useful information about the effectiveness of oxygen delivery to the brain. In particular, our study found that the systolic function of left ventricle was positively

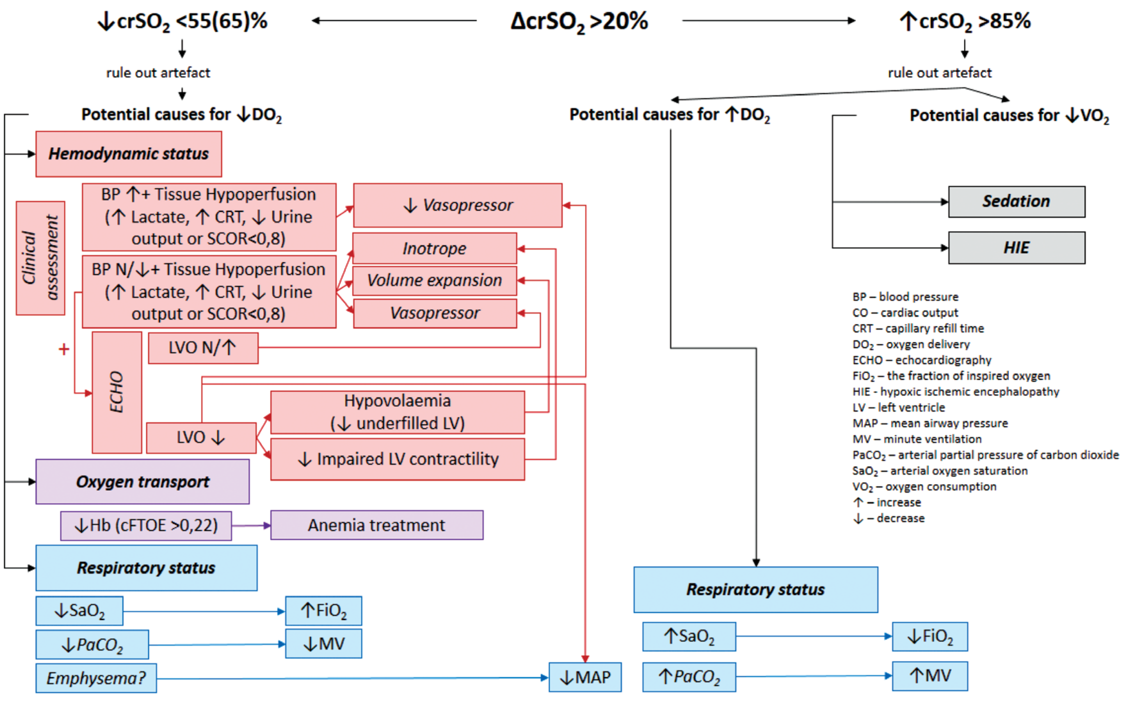
↓$crSO_2$ <55(65)%
$\Delta crSO_2$ >20%
↑$crSO_2$ >85%
rule out artefact
rule out artefact
Potential causes for ↓DO_2
Potential causes for ↑DO_2
Potential causes for ↓VO_2
Hemodynamic status
Clinical assessment
BP ↑+ Tissue Hypoperfusion (↑ Lactate, ↑ CRT, ↓ Urine output or SCOR<0,8)
BP N/↓+ Tissue Hypoperfusion (↑ Lactate, ↑ CRT, ↓ Urine output or SCOR<0,8)
↓ Vasopressor
Inotrope
Volume expansion
Vasopressor
+
ECHO
LVO N/↑
LVO ↓
Hypovolaemia (↓ underfilled LV)
↓ Impaired LV contractility
Oxygen transport
↓Hb (cFTOE >0,22)
Anemia treatment
Respiratory status
↓SaO_2
↑FiO_2
↓$PaCO_2$
↓MV
Emphysema?
↓MAP
Sedation
HIE
Respiratory status
↑SaO_2
↓FiO_2
↑$PaCO_2$
↑MV
BP – blood pressure
CO – cardiac output
CRT – capillary refill time
DO_2 – oxygen delivery
ECHO – echocardiography
FiO_2 – the fraction of inspired oxygen
HIE - hypoxic ischemic encephalopathy
LV – left ventricle
MAP – mean airway pressure
MV – minute ventilation
$PaCO_2$ – arterial partial pressure of carbon dioxide
SaO_2 – arterial oxygen saturation
VO_2 – oxygen consumption
↑ – increase
↓ – decrease

Fig. 3. A comprehensive program for improving of cerebral oxygenation in newborns with respiratory disorders

correlated with cerebral oxygenation (for EF: $r = 0.42$, $p = 0.006$; for FS: $r = 0.44$, $p = 0.005$) and negatively correlated with cFTOE (для EF: $r = –0.42$, $p = 0.007$; for FS: $r = –0.44$, $p = 0.005$).

It has been proved that the use of both dopamine and epinephrine for early systemic hypotension in newborn improves brain perfusion and oxygenation [14]. Noteworthy that vasopressors use (epinephrine and norepinephrine) for hemodynamic instability in newborns increase preload because of α-adrenoreceptor mediated peripheral vasoconstriction. As a result, heart contractility (and eventually brain perfusion) could be compromised so echocardiographic assessment of such patients is required. As our study shows, newborns received combination: dopamine ≥10 mcg/kg·min and epinephrine (norepinephrine) ≥0.05 mcg/kg·min, had highest level mean arterial pressure and at the same time lowest level of $crSO_2$ and closed to minimal indicators of left ventricle's function (EF and FS) [15]. In addition, the use of epinephrine and norepinephrine in newborn infants, even in case of reduced peripheral vascular resistance (dopamine-refractory distributive shock), may involve adverse changes in the oxygen status of the brain [16]. Thus, in our view, diminishing the dose of vasopressor (if already used) in case of low cardiac output and decreased cerebral oxygenation seems a reasonable tactic.

Evaluation of blood oxygen transport. We found statistically significant correlations between $crSO_2$ and cFTOE on the one hand, and erythrocyte count, hemoglobin, and hematocrit on the other, confirming the statement that $crSO_2$ depends on the appropriate delivery of oxygen to the brain [11]. We have shown that tissue oxygenation impairment in newborns with respiratory distress and anemia manifests not only with such invasive criteria like decrease of systolic blood pressure or arterial lactate elevation but also non-invasive indicators like falling of $crSO_2$ and increase of cFTOE.

It is known that NIRS data tended to return to normal after the correction of the anemia [17]. It has also been found that a newborn with a cFTOE > 0.22 is 3.5 times more likely to have anemia requiring blood transfusion [17]. Additionally, as we have shown earlier, correction of hemoglobin by blood transfusion in full-term newborns with hemolytic anemia also was accompanied by increase of $crSO_2$ [18]. So it is clear that NIRS can be used in NICU not only for early diagnosis of tissue oxygen imbalance because of anemia, but also for monitoring of the effectiveness of blood transfusion.

Evaluation of respiratory status. It is widely known now that $PaCO_2$ is a major determinant of cerebral perfusion and consequently oxygen status of the brain [19]. Significant positive correlation between $PaCO_2$ and $crSO_2$ also confirms this statement [11, 15]. It is extremely important in case of mechanical ventilation in newborns because it could be accompanied with inadvertent hyperventilation and hyperoxia [15].

For example, we established by ROC-analysis that $crSO_2 \leq 66$ % in infant on ventilation and combined inotropic support may indicate the presence of hypocapnia with sensitivity of 40.0 % and specificity of 100 % (AUC = 0.670, $p = 0.0343$) [15]. Thus, in our opinion, the reduction of the minute volume of ventilation is justified not only in the case of hypocapnia, but also in clinical situation when $PaCO_2$ approaches the lower limits and simultaneously the $crSO_2$ is below physiologic range.

Lung ventilation has negative influence on systemic hemodynamics and brain blood flow because of increase of intrathoracic pressure reducing preload (and eventually cardiac output) and hampering venous return from the brain [20]. Our previous study about predictors of $crSO_2$ in newborns on respiratory support revealed that $crSO_2$ was inversely correlated with mean airway pressure [15]. This means that when patient on ventilation have a downward $crSO_2$ trend (especially when left heart contractility decreased) lung emphysema should be excluded and MAP should be diminished.

Until recently, pulse oximetry was the only effective method of controlling oxygen supply to meet metabolic needs. Despite that, monitoring SpO_2 solely do not provide the information about adequacy of oxygen supply of the brain. As widely known, the most typical response on the desaturation in newborn patients is giving an additional oxygen. Almost every time when stable desaturation occurs the fraction of oxygen received by patient is increased by 10–20 % or more until SpO_2 is getting to be in physiological range.

Studies of desaturation episodes mainly focus on the harmful effects of hypoxia and hypoxia-ischemia [21]. However, the oxygen supply to the central nervous system can reach potentially dangerous levels in the post-hypoxic reperfusion, especially in patients with hyperoxia, which, according to our data, is typical for patients with the most compromised cardio-therapy status [15].

However, according to the results of our research, there were no statistically significant relationship between the PaO_2 and saturation of the arterial blood and $crSO_2$, which is consistent with the observations of C. Hunter [11, 22]. But it is necessary to note that if SaO_2 >90 %, and PaO_2 exceeds 80 mmHg oxyhemoglobin dissociation curve becomes relatively flat and a further increase of PaO_2 has a relatively minor effect on oxygen saturation of the blood. Since study participants had median values of SaO_2 and PaO_2 significantly above the physiologic range, this may partly explain the lack of a statistically significant relationship.

Another one reason for above physiological $crSO_2$ is a low oxygen extraction in the brain, in front of its adequate delivery (severe hypoxic-ischemic encephalopathy, profound anesthesia) [2, 23].

Considering all of the above, if patient on respiratory support has stable cerebral hyperoxia the first step to consider is the lowering oxygen fraction not only in cases when SpO_2 is above physiologic range but when it closer to them. The vasodilation effect of hypercarbia should also be taken into account, so in the case of CO_2 biuld-up with an accompanying cerebral hyperoxia, an increase of minute ventilation is justified as an appropriate step.

Conclusion. No doubt cerebral hypoxia or hyperoxia of newborn could lead to irreversible brain damage [24–26].

Our novel diagnostic and treatment guideline is based on integrated estimation and optimization of brain's oxygen supply and consumption via maintaining proper perfusion pressure, cardiac output, O_2 and CO_2 arterial content in newborns with respiratory distress.

In our research total oxygen consumption of the newborn's brain was not measured directly. Thus, all conclusions about oxygen extraction are based on a reasonable assumption, about a fairly stable O_2 metabolism in the brain.

We determined minor differences of $crSO_2$ and cFTOE in term and late pre-term newborns but physiological determinants of brain's oxygen status were independent of the gestational age [15, 27]. Thus, our approach is applicable to both term and late-term newborns with respiratory disorders in early neonatal period.

It is also important to note that routine manipulations performed in the NICU, such as changes in body position, repositioning or aspiration from the endotracheal tube, withdrawal of blood from umbilical catheters, may adversely affect cerebral hemodynamics and oxygenation [14, 28, 29]. As these changes are usually temporary, they have not been taken into account.

As oxygen status of the brain of a newborn child with respiratory disorders is a continuum and almost all patients have a combination of several reasons for imbalance between oxygen supply and consumption of oxygen by the brain, selection of separate components in proposed program of stabilization of cerebral oxygen status is highly conditional.

If $crSO_2$ lays out the specified physiological range and intervention is needed we recommend step-by-step approach: only one action at time, then re-evaluation in 30–60 min and another action.

It is very important to have an ECHO available to assess patient's hemodynamics.

Our integral approach to monitoring of oxygen status with dynamic control of regional oxygenation as well as complex of effective interventions allow clinicians to be more effective in management of newborn patients with respiratory disorders.

Conflict of interests. The authors declare no conflict of interests.

References

1. Sood E. D., Benzaquen, J. S., Davies R. R., Woodford E., Pizarro C. Predictive value of perioperative near-infrared spectroscopy for neurodevelopmental outcomes after cardiac surgery in infancy. *Journal of Thoracic and Cardiovascular Surgery*, 2013, vol. 145, no. 2, pp. 438–445e1. https://doi.org/10.1016/j.jtcvs.2012.10.033

2. Sankovets D. N., Gned'ko T. V., Svirskaya O. Ya. Near-infrared spectroscopy (NIRS) – new paint in the neonatologist palette. *Neonatologiya: novosti, mneniya, obuchenie* [Neonatology: news, opinions, training], 2017, no. 1, pp. 58–71 (in Russian).

3. Mintzer J. P., Parvez B., La Gamma E. F. Regional tissue oxygen extraction and severity of anemia in very low birth weight neonates: a pilot NIRS analysis. *American Journal of Perinatology*, 2018, vol. 35, no. 14, pp. 1411–1418. https://doi.org/10.1055/s-0038-1660458

4. Wong F. Y., Barfield C. P., Campbell L., Brodecky V. A., Walker A. M. Validation of cerebral venous oxygenation measured using near-infrared spectroscopy and partial jugular venous occlusion in the newborn lamb. *Journal of Cerebral Blood Flow and Metabolism*, 2008, vol. 28, no. 1, pp. 74–80. https://doi.org/10.1038/sj.jcbfm.9600507

5. Watzman H. M., Kurth C. D., Montenegro L. M., Rome J., Steven J. M., Nicolson S. C. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology*, 2000, vol. 93, no. 4, pp. 947–953. https://doi.org/10.1097/00000542-200010000-00012

6. Naulaers G., Meyns B., Miserez M., Leunens V., Van Huffel S., Casaer P., Weindling M., Devlieger H. Use of tissue oxygenation index and fractional tissue oxygen extraction as non-invasive parameters for cerebral oxygenation. A validation study in piglets. *Neonatology*, 2007, vol. 92, no. 2, pp. 120–126. https://doi.org/10.1159/000101063

7. Mebius M. J., van der Laan M. E., Verhagen E. A., Roofthooft M. T., Bos A. F., Kooi E. M. Cerebral oxygen saturation during the first 72h after birth in infants diagnosed prenatally with congenital heart disease. *Early Human Development*, 2016, vol. 103, pp. 199–203. https://doi.org/10.1016/j.earlhumdev.2016.10.001

8. Lemmers P. M. A. *The clinical use of near infrared spectroscopy-monitored cerebral oxygen saturation and extraction in the preterm infant. Utrecht University Repository*. 2010. 144 p. Available at: http://dspace.library.uu.nl/handle/1874/40574 (accessed 10 October 2014).

9. Sankovets D. N., Gned'ko T. V., Svirskaya O. Ya. Reference values of abdominal and cerebral oxygenation in term infants: a pilot study. *Reproduktivnoe zdorov'e. Vostochnaya Evropa* [Reproductive health. Eastern Europe], 2018, vol. 8, no. 2, pp. 209–218 (in Russian).

10. Kleinman C. S., Seri I. *Hemodynamics and cardiology: neonatology questions and controversies*. 2nd ed. Philadelphia, Elsevier, 2012. 576 p.

11. Sankovets D. N., Vitushko A. N. Correlation of regional oxygenation with red blood parameters and arterial blood gas in neonates]. *Reproduktivnoe zdorov'e. Vostochnaya Evropa* [Reproductive health. Eastern Europe], 2020, vol. 10, no. 1, pp. 69–82 (in Russian).

12. Sankovets D., Gned'ko T. Use of splanchnic-cerebral oxygenation ratio as noninvasive marker for tissue hypoperfusion [Electronic resource]. *AAP National Conference and Exhibition: abstr., San Francisco, 22–25 Oct. 2016*. Available at: https://www.researchgate.net/publication/341909215_Use_of_Splanchnic-cerebral_Oxygenation_Ratio_as_Noninvasive_Marker_for_Tissue_Hypoperfusion (accessed 28.12.2018).

13. Singh Y. Echocardiographic evaluation of hemodynamics in neonates and children. *Frontiers in Pediatrics*, 2017, vol. 5, art. 201. https://doi.org/10.3389/fped.2017.00201

14. Pellicer A., Gayá F., Madero R., Quero J., Cabañas F. Noninvasive continuous monitoring of the effects of head position on brain hemodynamics in ventilated infants. *Pediatrics*, 2002, vol. 109, no. 3, pp. 434–440. https://doi.org/10.1542/peds.109.3.434

15. Sankovets D. N., Vitushko A. N. Cardiorespiratory status and cerebral oxygenation in neonates with respiratory disorders. *Neonatologiya: novosti, mneniya, obuchenie* [Neonatology: news, opinions, training], 2020, vol. 8, no. 2, pp. 13–20 (in Russian).

16. Sankovets D. N., Gned'ko T. V. Cerebral effects of epinephrine and norepinephrine in newborns with distributive shock. *Materialy IX Vserossiiskogo obrazovatel'nogo kongressa «Anesteziya i reanimatsiya v akusherstve i neonatologii» (Moskva, 23–25 noyabrya 2016 goda)* [Materials of the IX All-Russian Educational Congress "Anesthesia and resuscitation in obstetrics and neonatology" (Moscow, November 23–25, 2016)]. Moscow, 2016, pp. 43–44 (in Russian).

17. Sankovets D. N., Gned'ko T. V. Regional oxygenation in neonates with anemia. *Pediatriya. Vostochnaya Evropa* [Pediatry. Eastern Europe], 2020, vol. 8, no. 2, pp. 184–196 (in Russian).

18. Sankovets D. N., Svirskaya O. Ya., Gned'ko T. V. Effect of exchange blood transfusion on regional oxygenation in newborns with haemolytic disease. *Voprosy prakticheskoi pediatrii* [Questions of practical pediatrics], 2015, vol. 10, no. 1, pp. 75–78 (in Russian).

19. Vanderhaegen J., Naulaers G., Vanhole C., de Smet D., van Huffel S., Vanhaesebrouck S., Devlieger H. The effect of changes in $tPCO_2$ on the fractional tissue oxygen extraction – as measured by near-infrared spectroscopy – in neonates during the first days of life. *European Journal of Paediatric Neurology*, 2009, vol. 13, no. 2, pp. 128–134. https://doi.org/10.1016/j.ejpn.2008.02.012

20. Milan A., Freato F., Vanzo V., Chiandetti L., Zaramella P. Influence of ventilation mode on neonatal cerebral blood flow and volume. *Early Human Development*, 2009, vol. 85, no. 7, pp. 415–419. https://doi.org/10.1016/j.earlhumdev.2009.01.008

21. Baerts W., Lemmers P. M., van Bel F. Cerebral oxygenation and oxygen extraction in the preterm infant during desaturation: effects of increasing FiO(2) to assist recovery. *Neonatology*, 2011, vol. 99, no. 1, pp. 65–72. https://doi.org/10.1159/000302717

22. Hunter C. L., Oei J. L., Lui K., Schindler T. Cerebral oxygenation as measured by near-infrared spectroscopy in neonatal intensive care: correlation with arterial oxygenation. *Acta Paediatrica*, 2017, vol. 106, no. 7, pp. 1073–1078. https://doi.org/10.1111/apa.13848

23. Sankovets D. N. Cerebral oximetry: applications in neonatology. *Pediatriya. Vostochnaya Evropa* [Pediatry. Eastern Europe], 2015, no. 4, pp. 108–117 (in Russian).

24. van Bel F., Lemmers P., Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. *Neonatology*, 2008, vol. 94, no. 4, pp. 237–244. https://doi.org/10.1159/000151642

25. Toet M. C., Flinterman A., Laar I., Vries J. W., Bennink G. B., Uiterwaal C. S., Bel F. Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 hours after arterial switch procedure in neonates without pre-existing brain damage: its relationship to neurodevelopmental outcome. *Experimental Brain Research*, 2005, vol. 165, no. 3, pp. 343–350. https://doi.org/10.1007/s00221-005-2300-3

26. Sood E. D., Benzaquen J. S., Davies R. R., Woodford E., Pizarro C. Predictive value of perioperative near-infrared spectroscopy for neurodevelopmental outcomes after cardiac surgery in infancy. *Journal of Thoracic and Cardiovascular Surgery*, 2013, vol. 145, no. 2, pp. 438–445e1. https://doi.org/10.1016/j.jtcvs.2012.10.033

27. Sankovets D. N. Differences in regional oxygen status and systemic hemodynamics among term and preterm neonates with respiratory disorders. *Reproduktivnoe zdorov'e. Vostochnaya Evropa* [Reproductive health. Eastern Europe], 2020, vol. 10, no. 3, pp. 357–368 (in Russian).

28. Hüning B. M., Horsch S., Roll C. Blood sampling via umbilical vein catheters decreases cerebral oxygenation and blood volume in preterm infants. *Acta Paediatrica*, 2007, vol. 96, no. 11, pp. 1617–1621. https://doi.org/10.1111/j.1651-2227.2007.00512.x

29. Limperopoulos C., Gauvreau K. K., O'Leary H., Moore M., Bassan H., Eichenwald E. C., Soul J. S., Ringer S. A., Di Salvo D. N., duPlessis A. J. Cerebral hemodynamic changes during intensive care of preterm infants. *Pediatrics*, 2008, vol. 122, no. 5, e1006–e1013. https://doi.org/10.1542/peds.2008-0768

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