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THE VALUE OF THE OXYGENATION INDEX IN THE PREDICTION OF POSTNATAL OUTCOME IN NEONATES WITH CONGENITAL DIAPHRAGMATIC HERNIA. PRELIMINARY REPORT

WSPÓŁCZYNNIK UTLENOWANIA JAKO PREDYKTOR WYNIKU LECZENIA NOWORODKÓW Z WRODZONĄ PRZEPUKLINĄ PRZEPONOWĄ. DONIESIENIE WSTĘPNE

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Abstract

The predicitive values of fetal ultrasonography and magnetic resonance imaging are well established as antenatal outcome predictors in neonates with congenital diaphragmatic hernia (CHD). Postnatal outcome predictors remain elusive.

The aim: *to evaluate the value of the oxygenation index (OI) as a predictor of postnatal survival.*

Material and methods: *58 newborns with congenital diaphragmatic hernia, treated in the same centre (a university hospital) between February 2006 and March 2014 were involved in the retrospective study. Standardized preoperative stabilization involved: sedation without muscle paralysis, high frequency oscillation ventilation (HFOV) and inhaled nitric oxide (iNO, used as required).*

Oxygenation index $OI = FiO_2 \cdot 100 \cdot M\ AP/PaO_2$, where FiO_2 is the fraction of inspired oxygen, MAP is the mean airway pressure, and PaO_2 is the partial pressure of oxygen in arterial blood, calculated at the end of the first day of standardized preoperative stabilization, and evaluated as a predictor of survival.

Results: *The overall survival rate on the hospital discharge was 74.1%. As far as the oxygenation index (OI) at the end of the first day of the preoperative stabilisation is concerned, in 40/43 survivors it was below or equal to 12, in one infant it equalled 12.7, and in two remaining survivors OI was much higher (18 and 56, respectively). The prognostic value of the oxygenation index was high, with the area under the curve (AUC) 0.943, sensitivity 0.930, and specificity 0.876.*

Conclusions: *The oxygenation index (OI) calculated at the end of the first day of standardized preoperative stabilization with high frequency oscillation ventilation (HFOV) and nitric oxide (iNO) is a simple and sensitive predictor of the survival of neonates with a congenital diaphragmatic hernia. It may be a valuable tool to select high-risk neonates who might require more invasive therapeutic modalities, i.e. extracorporeal membrane oxygenation (ECMO).*

Key words: hernias, diaphragmatic, congenital; high frequency oscillation ventilation; nitric oxide, newborn

Streszczenie

Wstęp: *Badanie ultrasonograficzne i badania metodą rezonansu magnetycznego w przypadku wrodzonej przepukliny przeponowej mają ustaloną pozycję w okresie prenatalnym jako predyktory przeżycia lub zgonu noworodka. Brakuje, jak dotąd, badania wykonywanego po urodzeniu dziecka, które pozwalałoby na ocenę rokowania w okresie stabilizacji poprzedzającej zabieg operacyjny.*

Celem prezentowanego badania była ocena wartości współczynnika utlenowania (OI) jako predyktora przeżycia noworodka.

Materiały i metody: *Badania retrospektywne objęły 58 noworodków z wrodzoną przepukliną przeponową, leczonych w okresie od lutego 2006 do marca 2014 w jednym ośrodku (w szpitalu uniwersyteckim). Stabilizacja przedoperacyjna obejmowała: sedację bez zwiotczenia mięśni, wentylację o wysokiej częstotliwości (HFOV) oraz stosowanie tlenku azotu, iNO (w razie potrzeby).*

Współczynnik utlenowania OI = $FiO_2 \cdot 100 \cdot MAP/PaO_2$, gdzie FiO_2 oznacza frakcję tlenu we wdychanym powietrzu, MAP- średnie ciśnienie w drogach oddechowych, a PaO2 – ciśnienie pacjalne tlenu we krwi tętniczej, obliczony pod koniec pierwszego dnia standardowej stabilizacji przedoperacyjnej, użyty został jako predyktor przeżycia noworodka.

Wyniki: *74,1% noworodków przeżyło do czasu wypisu ze szpitala. Spośród 43 noworodków z tej grupy, u 40 pod koniec pierwszego dnia standardowej stabilizacji przedoperacyjnej współczynnik utlenowania OI był mniejszy lub równy 12; u jednego OI wynosił 12,7, a u pozostałych dwóch pozostałych był on znacznie wyższy (odpowiednio: 18 i 56). Wartość predykcyjna współczynnika utlenowania była wysoka: pole pod krzywą (AUC) stanowiło 0,943, czułość testu wynosiła 0,930, swoistość - 0,876.*

Wnioski: Współczynnik utlenowania OI, obliczony pod koniec pierwszej doby stabilizacji noworodków z wrodzoną przepukliną przeponową za pomocą wentylacji o wysokiej częstotliwości (HFOV) i tlenku azotu (stosowanego w razie potrzeby) jest prostym i czułym predyktorem przeżycia dziecka. Może on być przydatny do wyłonienia grupy noworodków, u których należy rozważyć użycie bardziej inwazyjnych metod leczenia, w tym – zewnątrzustrojowego natleiania błonowego (ECMO).

Słowa kluczone: wrodzona przepuklina przeponowa, wentylacja oscylacyjna o wysokiej częstotliwości, tlenek azotu, noworodek

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INTRODUCTION

Newborns with congenital diaphragmatic hernia (CDH) may present with different clinical pictures ranging, from asymptomatic to severe respiratory distress. The overall risk of death is high [1, 2]; death immediately after birth or in the first days of life being due to lung hypoplasia and pulmonary hypertension.

The value of prenatal predictors of the outcome, such as fetal ultrasonography (USG) and magnetic resonance imaging (MRI), is well established. In fetal ultrasonography, the parameter most commonly used to predict postnatal outcome is the lung to head ratio (LHR), which provides indirect assessment of pulmonary hypoplasia based on the 2D measurement of the contralateral lung area and the head circumference. MR planimetry is used for the assessment of the fetal lung volume. Both ultrasonografic and NMR studies have suggested there is a critical lung volume below which survival is unlikely [3].

The treatment of infants with congenital diaphragmatic hernia showing respiratory distress at birth includes endotracheal intubation and ventilation, with manipulation of ventilator settings according to clinical criteria [4]. There are no randomized controlled trials showing that high frequency oscillation ventilation (HFOV), inspired nitrous oxide (iNO) and extracorporeal membrane oxygenation (ECMO) improve the outcome, but it seems that these new therapeutic methods have improved the overall survival in experienced centers [3, 5, 6]. Mortality in a subset of infants with severe CDH remains high.

Outcome prediction is very difficult. Up to date, there is no accurate method of predicting the clinical course of an individual infant. We have attempted to develop a clinical method for predicting the outcome of the infants with CDH, using data already present at the bedside and requiring minimal calculation. The oxygenation index $OI = FiO_2 \cdot 100 \cdot MAP/PaO_2$, where FiO_2 is the fraction of inspired oxygen, MAP is the mean airway pressure, and PaO_2 is the partial pressure of oxygen in arterial blood, is commonly used to predict the need for rescue ECMO therapy [7, 8].

The aim of our study was to assess the value of the oxygenation index (OI) calculated at the end of the first day of the standardized preoperative stabilization as a predictor of survival.

MATERIAL AND METHODS

We have reviewed the charts of all the 58 infants treated for congenital diaphragmatic hernia in our centre (a university hospital) between February 2006 and March 2014. There were no exclusions. The diagnosis was based either on their prenatal USG, or, if there was no prenatal diagnosis, on a postnatal chest X-ray and USG examination. The postnatal course was assessed in terms of survival on discharge from the hospital, or death.

PREOPERATIVE STABILIZATION

During the period of preoperative stabilization, all the newborns were placed on high frequency oscillation ventilation (HFOV), except for 1 infant who presented

breathing spontaneously, with minimal respiratory distress on arrival. The HFOV was configured with an average pressure Paw 9 – 16 cm H_2O (max. 21 cm H_2O, in 2 cases) to expand the lung contralateral to the defect to the 8th intercostal space, pressure difference ΔP= 35-45% of the peak pressure, frequency f=7-13 Hz, inspiratory time tin=33%, and FiO_2 adjusted as required to maintain the preductal SaO_2 between 90 and 99%. A nasogastric tube was placed and left open, with intermittent suctioning. A urinary catheter was placed. The preferred central venous access was the umbilical vein, with the catheter inserted immediately after birth. It was replaced before surgery by another means of central venous access (preferably – an epicutaneo-cava catheter, ECC). The right radial artery was cannulated, if possible. If this proved impossible, the arterial line was placed in the left radial, dorsalis pedis or tibialis posterior artery.

Medical treatment included sedation (sufentanil or fentanyl, 1-2μg·kg^{-1}·h^{-1} with midazolam 100-200 mg·kg^{-1}·h^{-1}) and cardiac inotropic support (dopamine and dobutamine 5-20 μg kg^{-1}·min^{-1}, noradrenaline, 0.01-1.0 μg kg^{-1}·min^{-1} , milrinone 0.3-0.7 μg kg^{-1}·min^{-1}, or adrenaline 0.01-1.0 μg kg^{-1}·min^{-1}), as required. Antibiotic prophylaxis included ampicyllin and an aminoglicosyde, unless otherwise indicated.

In the case of pulmonary hypertension in the echocardiographic examination, inhaled NO (iNO) was started. If the infant arrived in a critical condition, echocardiography was postponed, and iNO administration was started based on the preductal and postuctal SaO_2 difference >5%, at the initial dose of 10 ppm, and titrated to the patient's needs. The therapeutic goal was to give the minimum effective dose capable of raising preductal SaO_2 to at least 80%, and preferably above 90%. Continuous monitoring of NO and NO_2 concentration using an electrochemical scanner was performed. Methemoglobin concentration <5% and NO_2 below 2% were considered acceptable.

Such a protocol of preoperative stabilization may be considered a "maximal therapeutic intervention" in a centre without ECMO.

Surgical repair was delayed until the optimal values of blood gas analysis were reached, with FiO_2<0.4, no pulmonary hypertension "crisis" for at least 24 h, and urine output >0.5 ml·kg^{-1}·h^{-1}.

SURGICAL TREATMENT

Abdominal approach was used in all cases. Prosthetic material (a Gore-tex patch) was used in the case of a large defect or diaphragmatic agenesis. Conventional ventilation (intermittent positive pressure ventilation with positive end-expiratory pressure, IPPV+PEEP) was used during the surgery, except for the most severely ill infants, who were operated on while on HFOV. In all the infants HFOV was restarted after the surgery for at least 24 h, and followed for the weaning period by synchronized intermittent mandatory ventilation with positive end-expiratory pressure (SIMV+PEEP), and continuous positive pressure (CPAP) ventilation after the removal of the endotracheal tube.

OI CALCULATION

The oxygenation index (OI) was calculated using the FiO_2 (fraction of the inspired oxygen), MAP (airway pressure Paw) and arterial PO_2 (PaO_2) measured on the day following the admission to our hospital. Outcome was classified as survival or death on discharge from the hospital.

STATISTICS

The receiver operating characteristics (ROC) test was used to evaluate the cut-off point , the sensitivity and specificity of the oxygenation index as a predictor of survival. The 'pROC' package, version 1.7.3 was used.

RESULTS

Patient characteristics and outcome are summarized in table I.

Fifty eight newborn infants with CHD were analysed. The newborn who arrived breathing spontaneously with minimal respiratory distress was included in the analysis in spite of protocol violation. Fifty neonates underwent diaphragmatic hernia repair at a median age of 4 days (range 1-20). Eight died preoperatively, and 7 died in the postoperative period. Two critically ill infants had CDH surgery performed in the intensive care unit (ICU) while on HFOV; both of them died.

Forty three (74.1%) infants survived until discharge from the hospital. Forty of the 43 infants who had an oxygenation index of OI≤12 survived, while only 3 out of 18 infants with OI>12 survived until discharge (fig. 1).

The prognostic value of the oxygenation index calculated at the end of the first day of preoperative stabilization with HFOV and iNO (given if required) was high, with the cut-off point of 12. The area under the curve (AUC) was 0.943, SE 0.034, with 0.930 of sensitivity, and 0.876 of specificity (fig. 2).

Table I. Patients' characteristics and outcome.

Tabela I. Charakterystyka pacjentów i wynik leczenia.

Number of patients *Liczba noworodków*	58
Birth weight (g) *Urodzeniowa masa ciała (g)*	3015±555 [1300-3990]
Gestational age (weeks) *Wiek ciążowy (tyg.)*	37.5±2.1 [31-41]
Inhaled NO therapy *Leczenie tlenkiem azotu (iNO)*	75.8% (44/58)
Survival *Przeżycie*	74.1% (43/58)

*data are shown as mean ±SD and [range]/*dane przedstawiono jako średnią ±SD i [zakres]*

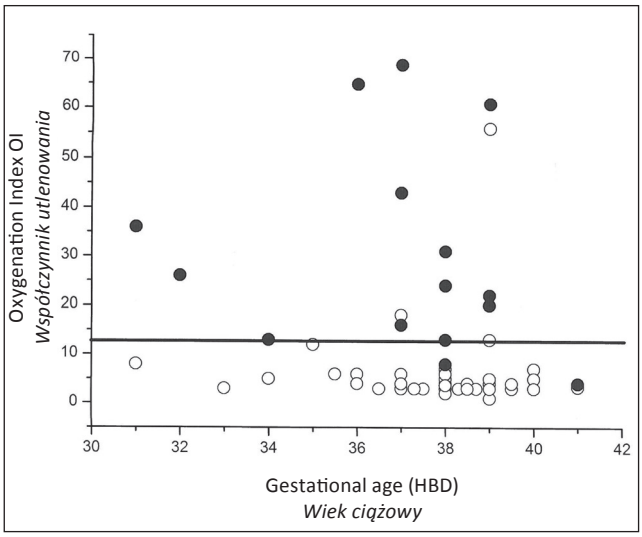

Fig. 1. Oxygenation index (OI) calculated at the end of the first day of the preoperative stabilization with HFOV and iNO (as required). Open circles – survivors, closed circle – nonsurvivors.

Ryc. 1. Współczynnik utlenowania obliczony pod koniec pierwszej doby stabilizacji przedoperacyjnej za pomocą wentylacji o wysokiej częstotliwości (HFOV) I tlenku azotu (w razie potrzeby). Białe kółka oznaczają noworodki, które przeżyły, czarne oznaczają zmarłe.

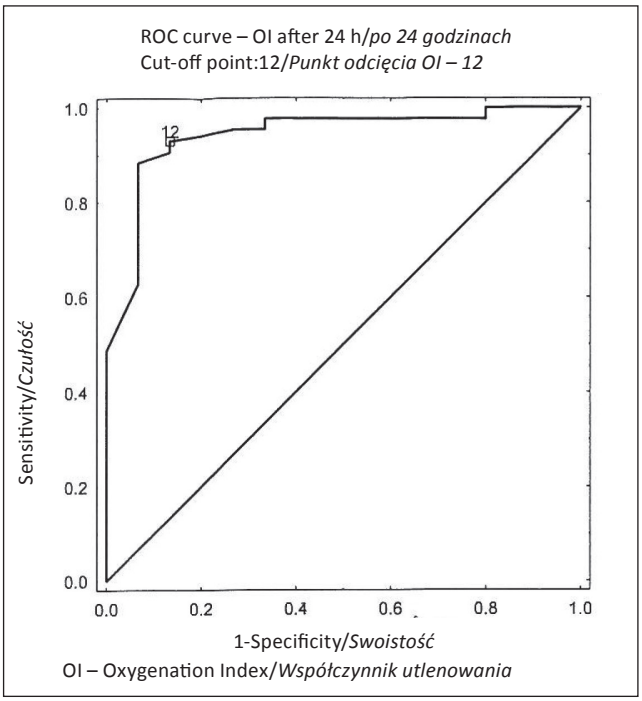

Fig. 2. Probability of the infants' survival based on the oxygenation index (OI) calculated at the end of the first day of the standardized preoperative stabilization. Area under curve (AUC) 0.943, sensitivity 0.930, specificity 0.876. Cut-off point – OI = 12.

Ryc. 2. Prawdopodobieństwo przeżycia noworodka oceniane na podstawie współczynnika utlenowania (OI) obliczonego pod koniec pierwszej doby stabilizacji przedoperacyjnej. Pole pod krzywą (area under curve, AUC) 0,943, czułość 0,930, swoistość 0,876. Punkt odcięcia OI = 12.

DISCUSSION

The death or survival of an infant with congenital diaphragmatic hernia immediately after birth or in the first days of life depends on the degree of pulmonary hypoplasia and pulmonary hypertension. Both clinical and postmortem studies have shown that there is a critical lung volume below which very high mortality is predicted [9, 10]. The total lung volume (TLV), and the functional residual capacity (FRC) can be measured at the bedside with a helium dilution computerized system [11], and infants with the smallest lung volume die. These findings are in line with fetal USG and MRI examinations. The assessment of pulmonary hypoplasia based on MRI-based fetal lung volume, MRI-based lung-to-head ratio and MRI-based total fetal lung volume is excellent in the prediction of neonatal survival, especially among fetuses with left-sided CDH [3, 6, 12, 13]. Their prognostic accuracy is slightly better than that of the sonographic lung-to-head ratio. Among fetuses with right-sided CDH, the prognostic value of all parameters is lower than among fetuses with a left-sided defect [3].

In spite of several attempts, a noninvasive bedside postnatal measurement that would predict survival with a congenital diaphragmatic hernia has been elusive. Using the oxygenation index (OI) as a predictor of the postnatal outcome is in line with the other attempts to correlate survival and the ability to establish oxygenation and CO_2 elimination. Inability to eliminate CO_2 was found to be a predictor of poor prognosis [14]. The Wilford Hall/Santa Rosa clinical prediction formula $WHSR_{PF}$=highest PaO_2 – highest $PaCO_2$ in arterial blood gas obtained during the initial 24 h of life was shown to have good predictive value [15].

It has been demonstrated that survival and nonsurvival of infants with congenital diaphragmatic hernia depends not only on pulmonary, but also on cardiovascular factors. Hypoplasia of the left ventricle and of pulmonary arteries not only mirrors the severity of pulmonary hypopasia, but may have an independent influence on the outcome [16, 17]. Springer et al. have calculated the left ventricular mass (LVMASS) and fractional shortening (SF) of the left ventricle from echocardiographic measurements and have shown that LVMASS $xFS^{1/2}$ <1.2 was associated with non-survival, despite maximal therapeutic intervention [18].

The reports presented in our study showed an overall 74.1% survival rate in a cohort of 58 "outborn" infants with CDH, with only 1 infant diagnosed late after birth, and presenting with minimal respiratory distress on admission. If compared with the results reported in the recently published multicenter VICI study [19], the survival rate was almost identical. The administration of iNO was considered necessary in 49.1% of the infants participating in the VICI study, and in 36.0% it was considered necessary to implement the rescue ECMO therapy.

The present study has several limitations. Firstly, the most severely affected "outborn" patients never reached the surgical centre, and they were not included in the survival analysis (hidden mortality). Secondly, the OI

depends on several reversible conditions that influence the total lung volume, and functional residual capacity, such as interstitial edema, atelectasis, intubating tube placement, and the compression of the lung by the stomach or bowel filled with gas, and finally, by the parameters of the mechanical ventilation itself. Thirdly, the blood sample used to calculate OI could be either preductal (from the right radial or right ulnar artery) or postductal (from the left radial or left ulnar artery, or from the arteries of the lower extremities), but the relatively small differences in PaO_2 estimated on the basis of the difference between preductal and postductal oxygen saturation (SaO2) suggest that the impact of the blood sample drawing site on the value of the oxygenation index was truly minor.

We did not attempt to find any correlation between the LHR, the oxygenation index and survival, because the LHR was assessed by ultrasound at different gestational ages. Since the lung to head ratio increases with gestational age in healthy fetuses [20], it seems essential to correct the LHR for the gestational age-related changes in the lung-to head ratio also in fetuses with CHD.

The present study has shown that the oxygenation index (OI) calculated at the end of the first day of standardized preoperative stabilization with HFOV (and iNO – as required), or "maximal therapeutic intervention" in a hospital without ECMO had a high predictive value of the outcome, with the cut-off point of 12.

CONCLUSION

The oxygenation index, OI, calculated at the end of the first day of the standardized preoperative stabilization of infants with congenital diaphragmatic hernia with high frequency oscillation ventilation (HFOV) and nitric oxide (iNO) is a simple and sensitive predictor of the infants' survival. It may be a valuable tool to select high-risk infants, for whom more invasive therapeutic modalities, i.e. ECMO may be considered.

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B W-G – Conception and design, anaysis and interpretation, drafting the manuscript/*Koncepcja pracy, analiza i interpretacja, przygotowanie manuskryptu*
SY – critical reviewing of the manuscript with important intellectual input/*istotny wkład intelektualny podczas przygotowywania manuskryptu*
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