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Adapted ECMO criteria for newborns with persistent pulmonary hypertension after inhaled nitric oxide and/or high-frequency oscillatory ventilation

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Abstract Purpose: Early prediction of extracorporeal membrane oxygenation (ECMO) requirement in term newborns with persistent pulmonary hypertension (PPHN), partially responding to inhaled nitric oxide (iNO) and/or high-frequency oscillatory ventilation (HFOV), based on oxygenation parameters. **Methods:** This was a retrospective cohort study in 53 partial responders from among 133 term newborns with PPHN born between 2002 and 2007. Alveolar-to-arterial oxygen gradient (AaDO₂) values were determined in these 53 partial responders during the initial 72 h of iNO and/or HFOV treatment and compared between newborns who ultimately did ($n = 11$) and did not ($n = 42$) need ECMO. **Results:** Over 72 h, partial responders not requiring ECMO showed a more profound AaDO₂ decrease than those who needed ECMO (median decline 242.5 mmHg, IQR 144 to 353 mmHg, vs. 35 mmHg, IQR -15 to 123 mmHg; $p = 0.0007$). A decline of <123 mmHg over 72 h predicted the need for ECMO (sensitivity 82 %, specificity 79 %). At

72 h, AaDO₂ was significantly lower in partial responders without the need for ECMO than in those who did need ECMO (median 369 mmHg, IQR 258 to 478 mmHg, vs. 570 mmHg IQR 455 to 590 mmHg; $p = 0.0008$). An AaDO₂ >561 mmHg at 72 h predicted the need for ECMO (sensitivity 64 %, specificity 95 %, positive predictive value 78 %).

Conclusions: In term newborns with PPHN partially responding to iNO and/or HFOV, oxygenation-based prediction of the need for ECMO appears to be possible after 72 h. ECMO centers are encouraged to develop their own prediction model in order to prevent both lung damage and unnecessary ECMO runs.

Keywords High-frequency oscillation ventilation · Nitric oxide · Extracorporeal membrane oxygenation · Persistent pulmonary hypertension of newborn · Selection criteria · Newborn

Introduction

Newborns with persistent pulmonary hypertension (PPHN) have traditionally been treated with conventional mechanical ventilation, oxygen, sedation, nonselective

vasodilators, inotropic and vasopressor support, muscle relaxants, and interventions to reverse acidosis. Extracorporeal membrane oxygenation (ECMO) has been used as rescue treatment whenever conservative management fails. Although new treatment modalities, such as high-

frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO), have become available, traditional ECMO entry criteria—an oxygenation index (OI) of >40 or an alveolar-to-arterial oxygen gradient (AaDO₂) of >600 – 610 mmHg for several hours—are still used [1–4]. Several studies have shown that iNO, especially in combination with HFOV, can significantly ameliorate oxygenation and reduce the need for ECMO treatment [5–17]. However, their use sometimes causes a delay in the initiation of ECMO. In newborns treated in this way, prolongation of iNO and/or HFOV with high oxygen levels may induce chronic lung disease (CLD) and extend the intensive care stay with all its associated risks [18]. On the other hand, initiating ECMO too early unnecessarily exposes newborns to harmful procedures (e.g. major vessel cannulation, systemic anticoagulation), while they could have been successfully managed with iNO, HFOV, and other noninvasive therapies [1].

Current ECMO entry criteria (Table 1) are suitable for situations in which newborns with PPHN respond well or not at all to iNO and/or HFOV treatment [1]. In newborns with a partial response to iNO and/or HFOV, adequate oxygenation can usually be maintained, but (short-term) reversal of PPHN does not occur. Because current ECMO criteria are never met in these latter newborns, they may develop lung damage and even die due to prolonged treatment with iNO and/or HFOV. Therefore, adapted ECMO entry criteria are needed for partial responders. So

far, only Kössel et al. [19] have established guidelines that help predict whether a response to iNO and/or HFOV is temporary or persistent. These authors concluded that an OI of ≥ 25 after 72 h of iNO and/or HFOV predicts the need for ECMO in newborns with acute respiratory failure and signs of PPHN. We sought to determine whether the need for ECMO can be predicted in a timely manner in PPHN patients with an intermediate response to iNO and/or HFOV, using AaDO₂ as oxygenation parameter.

Materials and methods

Patient selection and treatment

Newborns with a gestational age ≥ 37 weeks and a birth weight $\geq 2,000$ g, born between 1 January 2002 and 31 December 2007, admitted to our department for treatment of PPHN using iNO and/or HFOV, with an AaDO₂ ≥ 500 mmHg at the start of iNO and/or HFOV, were selected for this study. An AaDO₂ ≥ 500 mmHg can be regarded as an indicator of severe PPHN [20]. The clinical diagnosis of PPHN was confirmed echocardiographically (tricuspid valve regurgitation, right-to-left or bidirectional shunt at the atrial or ductal level) in all patients. Newborns with (congenital) heart disease, pulmonary anomalies (including congenital diaphragmatic hernia, CDH), severe hypoxic-ischemic encephalopathy, major intracranial hemorrhage, and those that died ≤ 72 h after birth, were excluded (Fig. 1).

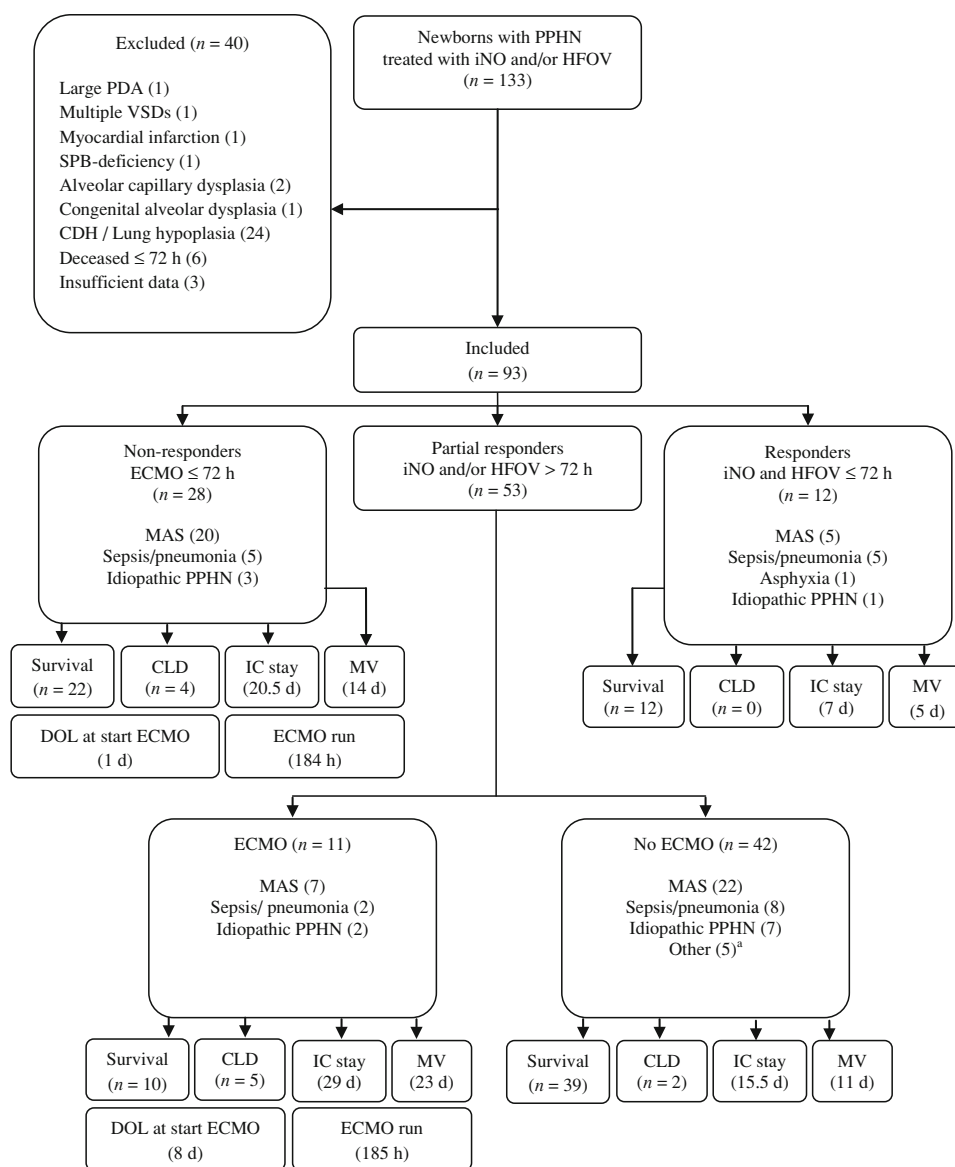
Treatment of PPHN was started with conventional ventilation (Babylog 8000; Dräger, Lübeck, Germany) with high fractions of inspired oxygen (FiO₂) to maintain postductal arterial oxygen saturation ≥ 95 % and partial arterial oxygen pressure (paO₂) >80 mmHg (10.6 kPa). Patients were sedated with morphine and/or midazolam and, if needed, given a muscle relaxant. If PPHN persisted, iNO (Solmix 1000; Dutch Technical Gas Company, Tilburg, The Netherlands) was added to a maximum of 20 ppm. In newborns with systemic hypotension, cardiovascular support consisted of dopamine (maximum 20 $\mu\text{g}/\text{kg}/\text{min}$), dobutamine (maximum 20 $\mu\text{g}/\text{kg}/\text{min}$), norepinephrine (maximum 1 $\mu\text{g}/\text{kg}/\text{min}$), corticosteroids, and/or epinephrine (maximum 1 $\mu\text{g}/\text{kg}/\text{min}$). Surfactant (beractant, Survanta; Ross Laboratories, Columbus, OH; one dose = 100 mg/kg) was administered to newborns with meconium aspiration syndrome (MAS). HFOV (Loudspeaker type, 3100A; SensorMedics Corporation, Yorba Linda, CA) was used when conventional ventilation failed to improve oxygenation and/or in the presence of severe hypercarbia or barotrauma.

Patients with PPHN resolution were gradually weaned from iNO and/or HFOV on the condition that paO₂ remained >80 mmHg. In those without PPHN resolution, venovenous or venoarterial ECMO was started once they

Table 1 Current ECMO entry and exclusion criteria in Radboud University Nijmegen Medical Centre

	Criterion
Entry criteria	FiO ₂ 1.0 and iNO 20 ppm and one of the following: AaDO ₂ >600 mmHg for 8 consecutive hours AaDO ₂ >605 mmHg and peak inspiratory pressure ≥ 38 cmH ₂ O or mean airway pressure ≥ 20 cmH ₂ O for 4 consecutive hours paO ₂ <40 mmHg and pH <7.15 during an acute deterioration of 2 h paO ₂ <55 mmHg for 3 consecutive hours Multiple manifestations of barotrauma In congenital diaphragmatic hernia: in addition to the above at least one preductal paO ₂ ≥ 80 mmHg
Exclusion criteria	Gestational age <34 weeks Birth weight $<2,000$ g Significant coagulopathy or uncontrolled bleeding Major intracranial hemorrhage Hypoxic-ischemic encephalopathy (Sarnat stage 2 or 3) Complex congenital heart disease or other lethal congenital anomalies Irreversible lung pathology Mechanical ventilation >10 days

Fig. 1 Flow chart. *PDA* patent ductus arteriosus, *VSD* ventricular septal defect, *SPB-deficiency* surfactant protein-B deficiency, *CDH* congenital diaphragmatic hernia, *MAS* meconium aspiration syndrome, *CLD* chronic lung disease, *IC* intensive care, *MV* mechanical ventilation, *DOL* day of life; ^aSevere allo-immune hemolytic anemia (2), pulmonary hemorrhage (1), asphyxia (1), respiratory distress syndrome (1); IC stay, MV and DOL are denoted as median days; ECMO run is in median hours



fulfilled current ECMO entry criteria (for conciseness referred to as 'ECMO need') and did not meet the exclusion criteria (Table 1).

Data collection and processing

The medical records of all newborns were reviewed. Sex, gestational age, birth weight, Apgar score after 1 and 5 min, and primary diagnosis were recorded. The following data were collected for 72 after the initiation of iNO and/or HFOV: ventilation mode, ventilator settings, mean doses of iNO, inotropic and vasopressor agents, and use of corticosteroids and surfactant. For each newborn, all arterial blood gases determined over 72 h were recorded. The FiO_2 value at the time of each blood gas

determination was retrieved from the patient's record and, using the mean barometric pressure in the vicinity of our hospital on the day in question (www.knmi.nl/climatology/daily_data), the corresponding AaDO_2 was calculated using the formula $\text{AaDO}_2 = (\text{p}_{\text{atm}} - 47) \times \text{FiO}_2 - (\text{paO}_2 + \text{paCO}_2)$. Because a high paCO_2 falsely lowers AaDO_2 , a paCO_2 of 37.5 mmHg (= 5 kPa) was used to calculate AaDO_2 in patients with hypercarbia ($\text{paCO}_2 > 6.5$ kPa). Each patient had at least 6, but usually 12 to 24 blood gas determinations per day. Mean daily AaDO_2 was determined for the first 72 h of iNO and/or HFOV or until ECMO was initiated. Outcome parameters were: days on mechanical ventilation, ECMO need, hours on ECMO, day of life on which ECMO was initiated, days on the NICU, CLD ($\text{FiO}_2 > 0.21$ beyond day 28), and survival.

We defined the following groups (Fig. 1): (1) responders (successfully managed with iNO and/or HFOV and both modalities ceased at ≤ 72 h); (2) nonresponders (failed to improve on iNO and/or HFOV and ECMO initiated at ≤ 72 h); (3) partial responders (improved to a certain extent, but iNO and/or HFOV still needed beyond 72 h). Partial responders were subdivided into two groups: one that did and one that did not eventually need ECMO. We determined whether AaDO₂ at 24, 48 or 72 h after the start of iNO and/or HFOV could predict ECMO need in partial responders. Since paO₂ and paCO₂, and therefore AaDO₂, can fluctuate from one hour to another, we also assessed whether prediction based on mean daily AaDO₂ was more accurate. Finally, we determined whether the course of AaDO₂ during 72 h of iNO and/or HFOV treatment was indicative of ECMO need.

Statistical analysis

Nominal data are presented as number with percentage, ordinal and continuous variables as median with interquartile range (IQR). Background characteristics, survival and CLD were compared using Fisher's exact test. The Mann-Whitney *U* test was used for comparison of AaDO₂ values, time on mechanical ventilation and days on the

NICU. Receiver operating characteristic (ROC) curves were created to determine whether AaDO₂ at $t = 24$, $t = 48$, or $t = 72$ h (or mean AaDO₂ on day 1, 2 or 3) could be used as predictor of ECMO. Logistic regression analysis was used to identify cut-off values for AaDO₂ that best distinguished partial responders who needed ECMO from those who did not. The statistical significance level was set at $p < 0.05$. All statistical analyses were performed using SPSS Software (SPSS, Chicago, IL).

Results

Between 2002 and 2007, 133 term newborns were treated at our center for PPHN with iNO and/or HFOV. After excluding 40 newborns, 93 were eligible for further analysis. Of these, 12 were classified as responders and 28 as nonresponders. The remaining 53 were partial responders, of whom 11 did and 42 did not need ECMO. Patient numbers, primary diagnoses, and outcomes for all groups are shown in Fig. 1. Background characteristics are shown in Table 2.

AaDO₂ just before initiation of iNO and/or HFOV was significantly higher in partial responders who did not

Table 2 Background characteristics

	Responders ($n = 12$)	Partial responders No ECMO ($n = 42$)	Partial responders ECMO ($n = 11$)	Non-responders ($n = 28$)
Male	5 (42 %)	27 (64 %)	5 (45 %)	16 (57 %)
Gestational age (days)	287 (278–291)	284 (274–290)	288 (278–293)	289 (280–294)
Birth weight (g)	3,500 (3,331–3,835)	3,563 (3,130–4,100)	3,585 (3,285–3,800)	3,593 (3,303–4,000)
Apgar score				
At 1 min	2.5 (2–6)	5 (3–7)	7 (4–8)	5 (2–7)
At 5 min	7 (4–7.5)	7 (5–8)	7 (5–8)	6 (4–7)
Primary diagnosis				
Meconium aspiration syndrome	5 (42 %)	22 (52 %)	7 (64 %)	20 (71 %)
Sepsis/pneumonia	5 (42 %)	8 (19 %)	2 (18 %)	5 (18 %)
Idiopathic PPHN	1 (8 %)	7 (17 %)	2 (18 %)	3 (11 %)
Other	1 (8 %)	5 (12 %)	0 (0 %)	0 (0 %)
Ventilation mode				
SIMV	9 (75 %)	12 (29 %)	3 (27 %)	9 (32 %)
HFOV	1 (8 %)	11 (26 %)	4 (36 %)	11 (39 %)
SIMV and HFOV	2 (17 %)	19 (45 %)	4 (36 %)	8 (29 %)
Baseline AaDO ₂ (mmHg)	607 (583–636)	618 (604–632)*	595 (567–623)	629 (618–638)
Mean airway pressure (cmH ₂ O)	9.5 (8.6–10.9)	16.7 (13.2–18.7)	17.9 (12.8–21.2)	18.7 (16.6–19.4)
iNO (ppm)	6.7 (4.4–9.0) ^a	20 (17.5–20.0)	20 (18.3–20.0)	20 (18.5–20.0)
Surfactant	0 (0 %)	24 (57 %)	10 (91 %)*	19 (68 %)
Surfactant doses	0	1 (0–1)	1 (1–1.5)	1 (0–1)
Dopamine + dobutamine ($\mu\text{g}/\text{kg}/\text{min}$)	14.7 (9.8–22.5)	22.0 (13.5–30.0)	20.0 (14.0–30.0)	21.3 (14.5–30.0)
Norepinephrine + epinephrine ($\mu\text{g}/\text{kg}/\text{min}$)	0.0 (0.0–0.04)	0.04 (0.0–0.17)	0.02 (0.0–0.10)	0.0 (0.0–0.15)
Corticosteroids	4 (33 %)	21 (50 %)	8 (73 %)	12 (43 %)

Data are presented as number (percentage) or median (interquartile range)

SIMV synchronized intermittent mandatory ventilation

* $p < 0.05$ between the two partial responder groups

^a One newborn in this group did not receive iNO

require ECMO than in those who did need ECMO (618 mmHg, IQR 604 to 632 mmHg vs. 595 mmHg, IQR 567 to 623 mmHg; $p = 0.02$). Partial responders needing ECMO received significantly more surfactant. All remaining background characteristics were comparable between the two partial responder groups, including the level of cardiovascular and ventilator support (Table 2). Only one patient (responder group) did not receive iNO.

In partial responders without ECMO need, AaDO₂ showed a persistent decline from the initiation of iNO and/or HFOV onwards (Fig. 2). In this group, a median decrease of 242.5 mmHg (IQR 144 to 353 mmHg) occurred over 72 h. In partial responders with ECMO need, AaDO₂ decreased in the first 48 h, but showed an increase thereafter. This group showed an overall decrease of only 35 mmHg (IQR -15 to 123 mmHg). This difference in decline over 72 h was significant ($p = 0.0007$). At $t = 24$ h and $t = 48$ h, median AaDO₂ was not significantly different between the two partial responder groups. At $t = 72$ h, median AaDO₂ was significantly lower in partial responders without ECMO need (369 mmHg, IQR 258 to 478 mmHg) than in partial responders requiring ECMO (570 mmHg, IQR 455 to 590 mmHg; $p = 0.0008$).

A ROC curve was plotted (not shown) for the median decline in AaDO₂ over 72 h as a predictor of ECMO need. The area under this curve (AUC) was 0.83. Sensitivity and specificity combined were maximal (82 % and 79 %, respectively) at a median AaDO₂ decline of 123 mmHg over 72 h.

Figure 3 shows that the ability of AaDO₂ to predict ECMO need increased with time elapsed from the start of iNO and/or HFOV. At $t = 72$ h, the AUC was 0.83. An AaDO₂ of >561 mmHg at 72 h had a sensitivity, specificity and positive predictive value (PPV) of 64 %, 95 %, and 78 %, respectively, for the prediction of ECMO need in partial responders.

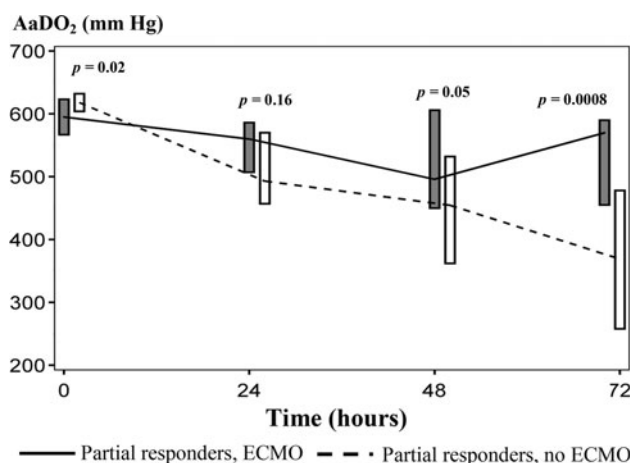


Fig. 2 AaDO₂ course after initiating iNO and/or HFOV (medians with IQR)

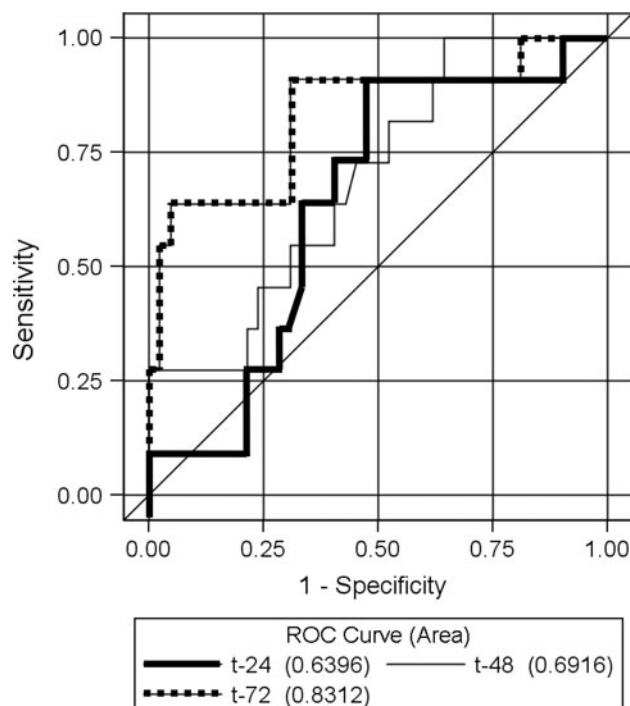


Fig. 3 ROC curves for the AaDO₂ after 24, 48 and 72 h of iNO and/or HFOV as predictors of ECMO need

In none of the statistical analyses did the use of mean daily AaDO₂, instead of AaDO₂ at $t = 24$, 48 and 72 h, result in more significant outcomes (results not shown). Survival was comparable between the two partial responder groups. Mortality was directly related to PPHN. CLD incidence was higher and time on mechanical ventilation and time on the NICU were significantly longer in partial responders with ECMO need (Fig. 1).

Discussion

Newborns with PPHN are commonly managed with iNO, HFOV and/or surfactant, only followed by ECMO when these modalities fail. Difficulty arises when newborns are partially responsive to iNO and/or HFOV to the extent that current ECMO criteria are not met, though aggressive respiratory and cardiovascular support remains necessary, which may result in death or the development of CLD. There is a need for adapted ECMO criteria that appropriately address this situation.

Several studies have attempted to predict ECMO need based on the initial response of newborns to either iNO or high-frequency ventilation. However, none of these studies specifically addressed the group of partial responders. Baumgart et al. [21] demonstrated that a significant decrease in OI (i.e. 15) after 6 h of high-frequency jet ventilation renders the need for ECMO

unlikely. A similar conclusion was drawn by Paranka et al. [22], who found that an arterial-to-alveolar (a/A) oxygen ratio of ≤ 0.08 following 6 h of HFOV predicts ECMO need in newborns with acute respiratory failure and without CDH or lung hypoplasia with a sensitivity of 77 % and specificity of 92 %. These authors also ascertained that the a/A ratio just before initiation of HFOV and a diagnosis of CDH/lung hypoplasia are independent predictors of ECMO need.

Amongst the studies that used the short-term response to iNO as a predictor of ECMO need is that of Biban et al., who found that newborns showing a significant improvement in oxygenation parameters within 1 to 6 h from the start of iNO can usually be successfully managed with iNO in combination with conventional mechanical ventilation. Newborns showing no improvement in oxygenation during the first hours of iNO administration should be treated with ECMO immediately [12]. Fakioglu et al. [20] recommend initiating ECMO if OI or AaDO₂ have not significantly decreased after 4 h of iNO. According to these authors, an OI of >20 or an AaDO₂ of >600 mmHg after 4 h of iNO is associated with a relative risk for ECMO of 7 and 4.5, respectively. Since the response to iNO at 4 h was not indicative of 'late ECMO requirement' (i.e. ECMO after 2–4 days of iNO), these results do not apply to partial responders. A substitute marker for 'late ECMO' was nevertheless identified: OI at the start of iNO was significantly higher in patients who needed ECMO compared to those who could be managed with iNO alone (63.0 ± 27.0 vs. 31.4 ± 7.7 , respectively). In newborns with MAS, Friedlich et al. [23] found that the OI after 6 h of iNO was significantly higher in those who required ECMO compared to those who did not (55.9 ± 40.1 vs. 29.9 ± 13.7 , respectively). In contrast to the aforementioned studies, Goldman et al. [24] stressed that an early response to iNO does not guarantee a sustained effect, nor does it guarantee that ECMO can be avoided. The main disadvantage of all these studies is that none of them investigated the response to the combination of iNO and HFOV to develop a prediction model, despite the availability of evidence demonstrating that HFOV enhances alveolar recruitment and thereby favors iNO delivery, rendering the simultaneous use of these two modalities more effective than either alone [9, 13]. In addition, whereas short-term responses to either iNO or HFOV can be used to determine the need for early ECMO, they cannot be used to predict whether ECMO will be required after several days of iNO and/or HFOV.

The only study that has looked at the possibility of predicting ECMO need in newborns with PPHN after a longer period of iNO and/or HFOV is that of Kössel et al. [19]. In this well-designed, prospective trial, the OI after 24, 48 and 72 h of iNO and/or HFOV was used to predict whether a response would be temporary or sustained. All newborns who did not require ECMO showed a persistent decline in OI during the initial 72 h of iNO and/or HFOV

treatment. The authors concluded that an OI of ≥ 25 is a useful entry criterion for ECMO in newborns with respiratory failure pretreated with iNO and/or HFOV for 72 h. An important shortcoming of this study is that its conclusions are based on small patient numbers. We therefore endeavored to confirm the findings of Kössel et al. in a larger group of patients. Furthermore, the group of patients having a 'sustained response' in the study of Kössel et al. included both responders and partial responders. We left responders out of our analysis to develop adapted ECMO criteria specifically addressing the group of newborns in which a decision regarding ECMO has to be made after 72 h of iNO and/or HFOV.

We found that a decline in AaDO₂ of <123 mmHg during 72 h of iNO and/or HFOV treatment predicted ECMO need with a sensitivity and specificity of 82 % and 79 %, respectively. Although desirable, reasonably accurate prediction of ECMO need was not feasible before 72 h after the start of iNO and/or HFOV. An AaDO₂ of >561 mmHg at 72 h predicted ECMO need with a sensitivity of 64 %, a specificity of 95 %, and a PPV of 78 %. Contrary to the results reported by Fakioglu et al. [20] and Paranka et al. [22], oxygenation parameters at baseline were not indicative of ultimate ECMO need in our study. Baseline AaDO₂ was significantly higher in partial responders not requiring ECMO than in those ending up on ECMO. We do not have a clear explanation for this observation.

The results of our study are comparable to those of Kössel et al. [19]. We therefore believe that it is possible to predict ECMO need based on either OI or AaDO₂ after 72 h of iNO and/or HFOV treatment. Although our overall survival was good (89 %), the high incidence of CLD (45 %) in partial responders started on ECMO after 8 days of iNO and/or HFOV supports our belief that morbidity may be reduced by earlier recognition of ECMO need. Due to limited patient numbers, it was impossible to perform subgroup analysis and develop adapted ECMO entry criteria for specific primary diagnoses. In general, newborns with respiratory distress syndrome are most likely to show a sustained response to iNO and HFOV, whereas patients with MAS or sepsis/pneumonia usually respond to a lesser extent [12, 19, 22]. The use of iNO in structural PPHN (e.g. CDH) is controversial [17] and the usefulness of HFOV in this situation is currently under investigation in a prospective trial [25].

Limitations

Our study has limitations inherent to retrospective cohort studies. Data were not gathered according to a predetermined study protocol, but acquired during everyday clinical practice. The facts that PPHN treatment is highly protocolized and ECMO criteria are strictly used in our

center, render this limitation a little less restrictive. It should be noted, however, that we do not have specific criteria to initiate HFOV. We generally switch to HFOV in patients with severe hypercarbia or barotrauma or when conventional ventilation fails. In our center, we use AaDO₂ as the oxygenation parameter instead of OI, because we want to avoid the high airway pressures required to achieve an OI of >40 [15, 26]. AaDO₂ does not, however, reflect the intensity of ventilator support. In order to provide some insight into the intensity of mechanical ventilation, we determined the median mean airway pressure during the 72 h of iNO and/or HFOV treatment in all groups. Mean airway pressure was not significantly different between partial responders with and without ECMO need. Furthermore, the PPV of our adapted ECMO criteria was 78 %, which implies that one in every five newborns will be put on ECMO unnecessarily. However, one should bear in mind that the original ECMO entry criteria (AaDO₂ >600 mmHg) have been used with a similar level of accuracy [4]. Finally, we acknowledge that the adapted ECMO criteria provided in this report can only be applied to newborns with PPHN

treated in our own center and in centers with an approach very similar to ours.

Conclusions

In our population of term newborns with PPHN, an AaDO₂ of >561 mmHg after 72 h of iNO and/or HFOV predicted eventual ECMO need. We recommend that other centers develop their own adapted ECMO criteria. Prospective studies should then be performed to validate these criteria and test their ability to prevent lung damage due to prolonged aggressive ventilation on the one hand and unnecessary ECMO runs on the other.

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Conflicts of interest The authors have no financial or ethical conflicts of interest.

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