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High frequency oscillatory ventilation and extracorporeal membrane oxygenation in severe persistent pulmonary hypertension of the newborn

V. Varnholt[1], P. Lasch[1], G. Suske[1], W. Kachel[1], and W. Brands[2]

Departments of [1]Paediatrics, [2]Paediatric Surgery, University Hospital of Mannheim, Theodor-Kutzer-Ufer, W-6800 Mannheim 1, Federal Republic of Germany

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Abstract. We report on 50 term and near-term neonates (birth weight > 1800 g, gestational age > 33 weeks) with severe persistent pulmonary hypertension of the newborn (PPHN), referred to us from January 1987 to July 1991 after failure of maximum conventional treatment. All infants had $paO_2 < 45$ mm Hg when ventilated with peak inspiratory pressure > 38 cm H_2O and $FiO_2 = 1.0$, hence meeting entry criteria for extracorporeal membrane oxygenation (ECMO). High frequency oscillatory ventilation (HFOV) was tried in all patients. If sufficient oxygenation could not be achieved ($paO_2 < 40$ mm Hg for at least 2 h), ECMO therapy was begun, which was the case in 25 children. Neonates responding to HFOV ($n = 25$) were of a slightly younger gestational age (37.0 weeks vs 38.8 weeks, $P < 0.05$), had higher Apgar scores and were less hypoxaemic before HFOV (paO_2 36.6 mm Hg vs 28.8 mm Hg, $P < 0.01$); during HFOV there was a significant rise in paO_2 (> 150 mm Hg; $P < 0.001$) and a fall in pCO_2 to 21.6 mm Hg ($P < 0.001$). Due to air leaks, which was the main complication of HFOV (52%), ECMO therapy had to be begun in two additional infants after an initial positive effect. HFOV tended to be successful in cases of primary PPHN, meconium aspiration and sepsis, but not in infants with lung hypoplasia as a result of diaphragmatic hernia or other reasons. Success or failure of HFOV could not be reliably predicted by any parameter. Mean duration of HFOV was 37.8 h vs 84.9 h of ECMO. PPHN could be overcome in 88% of the HFOV-treated and in 76% of the ECMO-treated infants; overall survival rate was 74% (predicted probability of survival using maximum conventional treatment < 10%). There were no significant differences between HFOV/ECMO groups with regard to duration of ventilation following HFOV/ECMO, total time in hospital, rate of bronchopulmonary dysplasia and neurological complications (intracranial haemorrhage, brain infarction). Among the survivors, the rate of mentally handicapped children was equal in both groups (overall 18.9%). Our analysis shows that about 50% of neonates with PPHN who fail to respond to conventional ventilatory support and maximum treatment can be treated successfully with HFOV, thus avoiding ECMO. By applying both forms of therapy, the survival rate of infants with severe PPHN can be increased from an estimated rate of < 10% up to 80%.

Key words: High frequency oscillatory ventilation – Extracorporeal membrane oxygenation – Persistent pulmonary hypertension of the newborn

Correspondence to: V. Varnholt

Abbreviations: $AaDO_2$ = alveolar-arterial O_2 difference (= 760 − 47 − pCO_2 − paO_2); BPD = bronchopulmonary dysplasia; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; HFOV = high frequency oscillatory ventilation; ICH = intracranial haemorrhage; MAP = mean airway pressure; NICU = neonatal intensive care unit; PEEP = positive end-expiratory pressure (cm H_2O); PIP = peak inspiratory pressure (cm H_2O); PPHN = persistent pulmonary hypertension of the newborn

Introduction

Clinical extracorporeal membrane oxygenation (ECMO) was introduced for treatment of severe persistent pulmonary hypertension of the newborn (PPHN) and associated illnesses 17 years ago [1]. Until 1989, more than 3500 children were treated, with a survival rate of more than 80% [23]. With maximum conventional treatment, the survival rate of these infants had been estimated to be less than 20%. In spite of this striking success of ECMO for neonates with life-threatening lung diseases, doubts and critical objectons still remain. There has been a lack of controlled studies [17] and the statistical analysis in the two randomized studies published so far [2, 18] has been criticized [17]. Furthermore, recently the prognosis of severe PPHN has considerably improved with conventional respiratory support [10]. Finally, ECMO therapy is a very invasive method carrying risks such as the ligation of major arteries and veins with changes in cerebral

blood flow [19], bleeding, thrombo-embolism and numerous technical complications. Moreover, ECMO implies an enormous expense and strain for a neonatal intensive care unit. Attempts have therefore been made to find alternative methods for treatment of infants with severe PPHN. The latter include high frequency oscillatory ventilation (HFOV) [15], which was first used in neonates about 12–15 years ago [16]. However, HFOV is – like ECMO – still considered an experimental therapy [4].

Here we report our experience with HFOV and ECMO in neonates with otherwise intractable lung disease. Criteria for the use of HFOV or/and ECMO will be discussed; mortality rates and neurological outcome in HFOV- or/and ECMO-treated infants will be analysed.

Material and methods

From January 1987 to July 1991 we treated 73 term and near term neonates (gestational age > 33 weeks, birth weight > 1800 g) with severe PPHN resulting from various underlying diseases. Of these, 26 children were primarily admitted to our hospital, the remaining 47 were referred from other neonatal intensive care units (NICU's). Out of the 73 babies, 52 had $paO_2 < 45$ mm Hg in spite of maximum ventilatory support and conventional treatment, evidence of PPHN in the absence of contra-indications for ECMO (intracranial haemorrhage (ICH), brain infarction, severe congenital heart disease, and congenital diaphragmatic hernia (CDH) group I). Two children died shortly after admission (one during cannulation for ECMO), the remaining 50 were included in our analysis.

All 50 infants were mechanically ventilated with a positive end-expiratory pressure (PEEP) of 3–6 cm H_2O, $t_i:t_e = 1:2$, $FiO_2 = 1.0$, rate 80–130/min (in our hospital). Rate, peak inspiratory pressure (PIP), PEEP, mean airway pressure (MAP) and $t_i:t_e$-ratio were adjusted in order to obtain $pCO_2 = 20$–25 mg Hg and paO_2 at least 50 mm Hg, if possible > 100 mm Hg. If hyperventilation failed, longer t_i and variations of PEEP were tried. In the referring hospitals numerous ventilator settings had already been tried (all with PIP > 38 cm H_2O and $FiO_2 = 1.0$) without achieving sufficient oxygenation.

All children were sedated with morphine or fentanyl and paralysed with vecuronium. Maximum conventional therapy consisted of circulatory support (catecholamines, substitution of fresh frozen plasma or packed red blood cells), vasodilators (prostacyclin, tolazolin) antibiotics, alkalisation by sodium bicarbonate (desired pH = 7.55–7.6) and surfactant instillation in cases of presumed respiratory distress syndrome (judged by radiological study).

The diagnosis of PPHN was established by echocardiography showing a right-to-left shunt through a patent foramen ovale or patent ductus arteriosus and by pre- and postductal pO_2 difference (simultaneously measured). In nearly all children arterial lines were available for continuous monitoring of blood pressure and repeated analysis of arterial blood samples. In addition pCO_2 (and in most cases also pO_2) were measured transcutaneously, O_2 saturation was monitored by pulse oximetry.

In all children HFOV was initially tried, i.e. in the inborn babies after failure of maximum ventilatory support with $paO_2 <$ 45 mm Hg. In all of the babies referred from other NICU's, HFOV was started within 1 h of arrival because of $paO_2 < 40$ mm Hg. The oscillatory ventilator used was a Stephan 300 (oscillation is induced by an electromagnetically-driven diaphragm), which can be combined with conventional mechanical support. Oscillatory frequency was about 1000/min (~ 16 Hz), $t_i:t_e$ ratio = 1:1, mostly superimposed by IMV (rate 5–15/ min, PIP 40–45 cm H_2O, $t_i = 1$ s) as described elsewhere [3]. Adjustments were possible by changing the amplitude of oscillation and by varying the flow of fresh gas (leading to changes in PEEP and MAP). HFOV was started with a MAP between 15 and 20 cm H_2O. If the application of HFOV was successful (increase of $paO_2 > 50$ mm Hg), HFOV was continued and in the following hours the FiO_2 was lowered gradually to 0.5, before the children were switched back to conventional ventilatory support (with MAP < 13 cm H_2O). ECMO therapy was begun if HFOV failed as defined by a $paO_2 < 40$ mm Hg for at least 2 h. A veno-arterial bypass as described elsewhere [14] was used (ECMO-machine, tube systems, cannulas: Jostra Medizintechnik (Hirrlingen, Germany); membrane oxygenator: Scimed Life Systems, Inc. (Minneapolis, Minnesota, USA) 0.6 or 0.8 m^2).

The initial flow rate was about 80% of the cardiac output; controlling and reduction of the ECMO-flow depended on the mixed venous O_2 saturation, which was considered adequate between 65% and 70%. The children were decannulated when $paO_2 = 50$–70 mm Hg could by obtained by conventional ventilatory support (PIP < 30 cm H_2O, MAP < 13 cm H_2O, $FiO_2 < 0.5$). Since 1990 carotid arteries were reconstructed.

Bronchopulmonary dysplasia (BPD) was defined as the need for intubation (and ventilation) and/or supplemental O_2 after the age of 4 weeks. All children were controlled neurologically during and after HFOV or ECMO by regular cranial ultrasound, EEG and somato-sensory evoked potentials. Before discharging the children from hospital a CT scan or MRI of the brain was performed. A neurological follow up was carried out either in our department or in the referring hospital.

Statistical anaylsis was done by either the χ^2-test (for dichotomous variables) or Wilcoxon test (for unpaired continuous variables).

Results

In 25/50 children ECMO support was begun after a short trial of HFOV (a few minutes in 14 and 0.25–3 h in 11 infants) because of further deterioration: paO_2 remained or dropped below 40 mm Hg. However, 25 children showed a considerable and continuous rise in paO_2 during oscillation and were kept on HFOV for a longer period of time.

The characteristics of the two groups are shown in Table 1: babies who responded to HFOV were about 1.8 weeks younger and had slightly higher Apgar scores.

Table 1. Characteristics of study patients

	ECMO	HFOV	*P*-value
Number	25	25	–
Male/female	16/9	17/8	NS
Birth modus (spontaneous/ caesarian section)	17/8	12/13	NS
Transferred/inborn	18/7	16/9	NS
GA[a] (weeks)	38.8 (35–42)	37.0 (34–41)	0.01
Birth weight[b] (g)	2965 ± 626	2942 ± 564	NS
Age at transfer[b] (days)	2.2 ± 2.0	3.8 ± 3.9	NS
1 min Apgar[b]	5.1 ± 2.7	6.0 ± 2.5	NS
5 min Apgar[b]	6.5 ± 2.2	7.4 ± 2.4	NS
10 min Apgar[b]	7.1 ± 1.9	8.6 ± 1.1	< 0.01

GA, Gestational age; NS, non significant

[a] Mean value (range)

[b] Mean ± SD

Table 2. Pre-ECMO/HFOV course

	ECMO ($n=25$)	HFOV ($n=25$)	P-value
Conventional therapy:			
Sodium bicarbonate	23	24	NS
Vasodilatators	21	13	<0.05
Catecholamines	24	22	NS
Blood exchange transfusion	3	5	NS
Surfactant instillation	2	9	<0.05
Barotraumatic complications (before HFOV)	7	5	NS
MAP[a] (cm H_2O)	19.1 ± 3.6	17.9 ± 2.9	NS
PIP[a] (cm H_2O)	44.8 ± 5.6	42.3 ± 3.7	NS
OI[a]	69.9 ± 30.8	51.4 ± 20.7	<0.01
paO_2/pAO_2[a]	0.041 ± 0.013	0.053 ± 0.015	<0.01
$AaDO_2$[a] (mm Hg)	634.4 ± 36.5	644.1 ± 15.6	NS

OI, Oxygenation index

[a] Mean ± SD

The pre-ECMO/HFOV course is shown in Table 2: there were no significant differences between the two groups with regard to conventional medical therapy (exception: surfactant application; no child improved) or ventilatory support (PIP, MAP). Before starting HFOV there was no difference in alveolar-arterial O_2 difference ($AaDO_2$). However, the oxygenation index and paO_2/pAO_2 were higher in the ECMO-babies.

Infants in whom HFOV failed had a lower paO_2 than children who responded to HFOV; their pCO_2 was also higher (Table 3). Under HFOV-trial the ECMO-babies showed almost no change in arterial blood gases in comparison to previous conventional ventilatory support. In the HFOV-responders, there was a further reduction of pCO_2 and rise in paO_2 to well over 100 mm Hg (range 80–400 mm Hg). The mean time until improvement occurred in the latter children ($paO_2 > 50$ mm Hg) was 1.8 h (0.2–5 h).

Table 4 shows that children with so-called primary PPHN (PPHN existing without underlying disease), meconium aspiration syndrome and sepsis reacted reasonably well to HFOV. In contrast, ECMO was necessary in all cases of CDH and lung hypoplasia; one patient with CDH who initially improved under HFOV died shortly after surgery from sudden barotraumatic complications.

Complications and outcome (Table 5)

The main complication under HFOV was air leaks (52%). Seven cases of pneumothorax were seen; after thoracocentesis, however, lung function improved and no death from pneumothorax occurred. In six other infants the barotraumatic complications were more severe: in two of these children respiratory insufficiency could be overcome by re-installing conventional ventilatory support. Two further babies had to be treated with ECMO, and two infants died (Table 6, numbers 10 and 11). Another complication of HFOV was necrotizing tracheitis ($n=1$) followed by cicatricial tracheal stenosis (tracheal bougienage was necessary).

Major complications of ECMO including thrombosis of the arterial cannula ($n=1$), haemothorax ($n=1$), renal failure with the need for haemofiltration ($n=3$) and air embolism ($n=1$), which led to brain infarction and ICH (number 7 in Table 6).

With regard to cerebral complications (ICH, brain infarction) there were no differences between the two groups. ICH (> grade II) in ECMO babies led to termination of ECMO, thereafter one out of two affected children died (number 2 in Table 6); the second baby with a moderate ICH had to undergo shunt implantation later on because of posthaemorrhagic hydrocephalus. There were three cases of ICH among the HFOV-babies with one death (number 12 in Table 6).

The mean duration of ECMO was 85 h, whereas the mean time on HFOV before a successful switch back to conventional ventilatory support was about 38 h.

Out of 25 HFOV-responders 4 (16%) died (Table 6). The mortality rate in the ECMO group was 36% (9 out of 25). Of these 9 babies, 6 died during or shortly after ECMO. Three other children could be successfully weaned at first, but in two cases relapse of PPHN occurred, the third died at the age of 6 months due to BPD (number 4, 5 and 9 in Table 6).

Time on conventional ventilation and total time in hospital after termination of ECMO or HFOV were very

Table 3. Analysis of arterial blood gases

	ECMO ($n=25$)		HFOV ($n=25$)		P-value (ECMO/HFOV)
Before HFOV:					
paO_2[a] (mm Hg)	28.8 ± 9.0		36.3 ± 10.0		<0.01
pCO_2[a] (mm Hg)	49.8 ± 38.3		32.4 ± 13.6		<0.05
	NS		$P<0.001$		
Under HFOV:		NS		$P<0.001$	
paO_2[a] (mm Hg)	33.7 ± 11.6[b]		179.3 ± 89.2		<0.001
pCO_2[a] (mm Hg)	46.7 ± 21.4[b]		21.5 ± 9.3		<0.001

[a] Mean ± SD

[b] $n=11$, in the other infants no arterial blood samples under HFOV were available

Table 4. Diagnosis of study patients

	ECMO ($n=25$)	HFOV ($n=25$)	*P*-value
PPHN (primary)	7	15	<0.05
MAS	3	4	NS
CDH	7	1	<0.025
Lung hypoplasia (hydrops, oligohydramnion)	4	0	<0.025
Sepsis:			
B-Streptococcus	3	3	NS
Gram-negative sepsis	1	1	
Gram-positive sepsis	0	1	

similar among the surviving patients. The rates of BPD were equal in both groups, as well as the rates of neurological damage (Table 5).

Discussion

We were able to demonstrate a beneficial effect of HFOV in 25 out of 50 infants with PPHN who failed to respond to optimized conventional ventilatory support and maximum conservative treatment and therefore met generally accepted ECMO entry criteria [21, 23]. This is in line with the results of others [5, 8], who also stressed that children of younger gestational age [5], with higher Apgar scores [8], less extensive hypoxaemia [5] and lower pCO_2 during conventional respirator therapy [5] seemed to respond more favourably to HFOV. In contrast, in another study [15] nearly all patients (37 out of 41 with 34 survivors) responded to HFOV. This positive response may be due to earlier institution of HFOV at the average age of 29 h, whereas our children referred from other hospitals arrived between the 2nd and 15th day (mean: 4th day).

The success of failure of HFOV could be predicted neither from the blood gas analysis nor from the clinical diagnosis: there were cases of primary PPHN, of meconium aspiration and of sepsis syndrome in both our HFOV- and ECMO-groups. Infants with lung hypoplasia (because of CDH or other diseases) did not respond to HFOV. This is consistent with the results of other studies [5, 15].

Because the prognosis of severe PPHN has considerably improved due to progress in conventional treatment [10], indications for alternative therapeutic strategies are, at present, difficult to evaluate.

Many authors use $AaDO_2$ as an entry criterion for ECMO; the probability of mortality is estimated to be above 80%, when the value is >620 mm Hg for 8 h [18, 21]. $AaDO_2$, however, also depends on the pCO_2. Furthermore, exact information about the duration of hypoxaemia is often not available in children referred from other NICU's (in our study population we estimated in the HFOV-group an $AaDO_2>620$ mm Hg for at least 15 h in all infants and in the ECMO-group an $AaDO_2>625$ mm Hg for at least 17 h in 23 infants, the two remaining infants had lower values because of excessively high pCO_2). In the study by Carter et al. $AaDO_2$ was >600 mm Hg for 11 h or 15 h [5].

Kohelet et al. [15] used $paO_2/pAO_2<0.1$ as a definition of hypoxaemia, O'Rourke et al. [18] $paO_2/pAO_2<$

Table 5. Complications and outcome (under and after ECMO/HFOV)

	ECMO ($n=25$)	HFOV ($n=25$)	*P*-value
Air leaks:	–		–
Pneumothorax		7	
Other (pneumomediastinum, PIE, pneumopericardium, pneumoperitoneum)		2 → Death 6 − 2 → ECMO 2 → Conventional ventilatory support	
ICH *(n)*	2	3	NS
Brain infarction *(n)*	3	3	NS
Time on HFOV/ECMO[a] (h)	84.9 ± 37.4	37.9 ± 14.4	<0.001
Recovery from PPHN *(n)*	19	22	NS
Total survival *(n)*	16	21	NS
Ventilator days after ECMO/HFOV[a]	10.6 ± 7.2	12.6 ± 21.3	NS
Total time in hospital[a] (days)	55.1 ± 23.7	52.5 ± 43.3	NS
BPD[b]	5	5	NS
Neurological damage[b] *(n)*	3	4	NS

[a] Mean ± SD, only surviving patients
[b] Only surviving patients (number 9 in Table 6 is included)

Table 6. Causes of death

	Patient	Therapy	Diagnosis and cause of death
1.	♂, 2100 g, GA 38	ECMO	B-streptococcus, sepsis, perinatal asphyxia, fetal endocarditis → subtotal stenosis of tricuspid and pulmonary valve
2.	♂, 2500 g, GA 36	ECMO	Lung hypoplasia because of hydrops, withdrawn from ECMO because of ICH
3.	♂, 2450 g, GA 41	ECMO	CDH, no weaning possible
4.	♂, 1800 g, GA 37	ECMO	Lung hypoplasia because of oligohydramnion, successful weaning from ECMO, relapsing PPHN and death 16 days later
5.	♀, 3450 g, GA 39	ECMO	PPHN, successful weaning from ECMO, relapsing PPHN and death 20 days later; anomal off-spring of left subclavian artery from the pulmonary artery
6.	♀, 2800 g, GA 38	ECMO	CDH, no weaning possible
7.	♂, 2880 g, GA 40	ECMO	CDH, air embolism → brain infarction and severe ICH → withdrawn from ECMO
8.	♂, 4200 g, GA 42	ECMO	PPHN, no weaning possible (12 d ECMO)
9.	♂, 3720 g, GA 41	ECMO	PPHN, successful waening from ECMO, death 5.5 months later because of BPD
10.	♂, 2300 g, GA 34	HFOV	PPHN, severe barotrauma under HFOV, missing parental consent for ECMO
11.	♀, 2700 g, GA 36	HFOV	CDH, after surgical repair severe air leaks without time for installing ECMO
12.	♀, 2800 g, GA 34	HFOV	Sepsis, ICH = contra-indication for ECMO
13.	♀, 2230 g, GA 37	HFOV	Birth asphyxia (1 min Apgar = 0), PPHN (improved under HFOV), withdrawn from intensive care because of severe haemorrhagic brain infarction

0.15 and postductal $paO_2 < 80$ mm Hg; in our group paO_2/pAO_2 ranged between 0.018–0.09, and in all infants paO_2 was < 45 mm Hg.

From the parameters $AaDO_2$, paO_2/pAO_2, paO_2 and oxygenation index we presume that the degree and duration of hypoxaemia in most of our children before starting HFOV/ECMO was more severe than in other study populations [5, 15, 18], thus resulting in a higher mortality rate (26%). On the other hand, the predicted mortality rate with conventional therapy, as calculated from our own results in the years before ECMO [13] and from the literature [18, 21], had to be estimated at least as high as 90%.

Although the difference in mortality in the ECMO- and HFOV-groups (36% versus 16%) was not statistically significant, we think that this difference results from the more severe underlying diseases such as sepsis or CDH in conjunction with prolonged hypoxaemia in the ECMO-group compared to the HFOV-patients.

The rate of air leaks (52%) under HFOV was higher than in other studies [15], although it was found to be similar [3], when HFOV was combined with IMV (rate up to 60/min). Again we suspect the high percentage of air leaks in our patients was due to poor general condition before HFOV. As a consequence a high MAP was necessary to ventilate enough alveoli for adequate gas exchange, resulting in an increased risk of air leaks. Severe barotraumatic complications (pneumopericardium, pneumomediastinum, pulmonary interstitial emphysema) as well as decreased cardiac output with systemic hypotension induced by increased functional residual capacity [6] may lead to the necessity to start ECMO after an initially successful trial of HFOV. Moreover, necrotizing tracheobronchitis with consequently delayed extubation can occur after HFOV [7].

The rate of ICH under HFOV-patients was relatively high with no difference in the ECMO-patients, corroborated by the findings of Carter and coworkers [5]. A possible reason is low pCO_2-value (necessary for overcoming PPHN), resulting in decreased cerebral blood flow and increased vulnerability of blood vessels [4]. Bleeding complications other than ICH under ECMO were of minor importance and did not influence our mortality rate.

Brain infarction, which is considered to be a typical complication of ECMO because of ligation of blood vessels, also occurred in the HFOV-group and may be related to hypoxaemia, hypotension or low pCO_2. After ECMO therapy the risk of brain infarction may be reduced by reconstruction of the carotid artery [9], which was started in our hospital in 1990.

Our BPD-rate in surviving ECMO-babies was higher than that given by other authors [11], again possibly resulting from the mostly delayed start of ECMO-therapy because of late transfer to our unit.

The neurological outcome was in agreement with the results given by other authors [11, 12, 20]. In the HFOV-group, the rate of BPD and neurological sequelae was equal to that in the ECMO-group – in contrast to other study populations [24]. Most cerebral damage seems to be induced by hypoxaemia before overcoming PPHN by means of either ECMO or HFOV.

Conclusions

With the application of HFOV and ECMO, a survival rate in term and near-term infants with severe PPHN (estimated mortality rate > 90%) of nearly 80% can be achieved. This results in a decrease of about 1.4% in overall neonatal mortality [22]. By HFOV-treatment of all children suffering from PPHN (without additional lung hypoplasia) and hypoxaemia with $paO_2 < 45$ mm Hg, 50% of these infants will survive with HFOV alone. Prolonged and extensive hypoxaemia seems to lower the

chances of successful treatment; in some children it takes several hours (usually 1–3 h) and repeated trials of HFOV before sufficient oxygenation is achieved [15]. If HFOV fails ($paO_2 < 40$ mm Hg for > 2 h), ECMO therapy has to be begun, which is also the therapy of choice in cases of severe barotraumatic complications. Before a trial of HFOV a prediction of success or failure of HFOV is impossible. Failure of HFOV and need for ECMO probably implies a higher mortality rate in comparison to children successfully treated with HFOV; the overall survival rate is not affected by HFOV-trial before ECMO-therapy. The neurological outcome of the surviving children (treated with ECMO or HFOV) is identical. HFOV may also be helpful for transfer of an infant who cannot be oxygenated by other forms of respiratory support, to the next ECMO centre.

HFOV and ECMO both have their justification in the treatment of severe PPHN. The decision about the best treatment with the lowest risk of mortality and neurological damage can be difficult and must be made individually in each case, reserving ECMO for the sickest children after failure of HFOV. In a further prospective study, randomizing infants with severe PPHN to either HFOV or ECMO, more information could be obtained about the risk and benefit ratio of HFOV vs. ECMO.

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