Risk Factors for Chronic Lung Disease and Mortality in Newborns with Congenital Diaphragmatic Hernia

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Abstract
Background: Congenital diaphragmatic hernia (CDH) is associated with a mortality rate of 10–35% in live-born infants. Moreover, CDH survivors have a substantial risk of developing long-term pulmonary sequelae, such as bronchopulmonary dysplasia (BPD). **Objectives:** This study aims to evaluate risk factors associated with BPD and mortality in neonates with CDH, with particular focus on the initial ventilation mode. **Methods:** Eligible for inclusion were live-born infants with CDH born from 2001 through 2006 at the centers participating in the CDH Study Group. BPD (defined as oxygen dependency at day 30) and/or mortality by day 30 served as the primary endpoint. **Results:** A total of 2,078 neonates were included in the analysis. At day 30, 56% of the patients had either died or met the criteria for BPD. In infants who survived until day 30, the prevalence of BPD was 41%. The overall mortality rate was 31%. High-frequency oscillatory ventilation as initial ventilation mode, a right-sided defect, a prenatal diagnosis, a lower Apgar score at 5 min, a cardiac anomaly, a chromosomal anomaly and a lower gestational age were all associated with BPD and/or mortality by day 30. **Conclusions:** Despite improvements in neonatal care, the rates of BPD and early mortality in newborns with CDH are still considerable. Several important risk factors for a worse outcome are reported in this nonrandomized prospective observational study.

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Introduction

Congenital diaphragmatic hernia (CDH) is a rare congenital anomaly which occurs in approximately 1 in every 2,500 live births [1]. It is associated with severe pulmonary hypoplasia and pulmonary hypertension. Mortality rates ranging from 10 to 35% have been reported, depending on case selection [1–5]. Survival rates have increased with improvements in neonatal care, including

See Appendix for the members of the writing committee of the Congenital Diaphragmatic Hernia Study Group as well as a full list of the centers that contributed to the Congenital Diaphragmatic Hernia Registry.

'gentle' ventilation strategies, delayed surgery and extra-corporeal membrane oxygenation (ECMO) in selected cases [4–8]. However, survivors of CDH remain at high risk of developing secondary morbidity. Long-term pulmonary sequelae, such as chronic lung disease, persistent pulmonary hypertension, asthmatic symptoms and recurrent respiratory tract infections have been reported in 30–50% of cases [9–14]. Alarmed by this information, the American Academy of Pediatrics developed official guidelines for structural and interdisciplinary follow-up [15].

Bronchopulmonary dysplasia (BPD) is a chronic respiratory disorder presenting early after birth. It mostly occurs in premature infants or term infants who have acute pulmonary disease. Ventilator-induced lung injury and high concentrations of oxygen predispose newborns to develop BPD [16, 17]. In newborns with CDH, the severity of lung hypoplasia may also be predictive for the development of BPD [13, 14, 18].

Research efforts have been directed at optimizing ventilation strategies for newborns with CDH. The 'permissive hypercapnia' approach, for example, led to higher survival rates and less pulmonary morbidity [5, 19]. Around the world, newborns with CDH typically receive conventional ventilation, with high-frequency oscillatory ventilation (HFO) as rescue therapy. However, in certain cases HFO will serve as the initial ventilation mode [20]. Observational and retrospective studies have reported that HFO as an initial ventilation mode may be an effective method to reduce mortality and chronic lung disease in children with CDH [7, 21–24]. So far, no prospective trials have been carried out to determine if initial ventilation treatment with HFO may reduce long-term pulmonary sequelae. Moreover, most studies so far have focused on mortality and the need for ECMO rather than on chronic lung disease as outcome measures [9, 18, 25].

The aim of this study is to describe possible risk factors for BPD and early mortality in infants with CDH. More specifically, this study aimed to determine if the initial ventilation mode, either conventional ventilation or HFO, has some bearing on outcome.

Methods

Patients
We retrieved data from the large multi-institutional database of the CDH Study Group. This cooperative network of over 50 centers was established in 1995 to compile data on live-born children with CDH. Data on prenatal evaluation, mode of delivery, neonatal care, surgery and clinical outcome until hospital dis-charge or death are prospectively recorded on standardized registry forms and entered into a central database [26].

In the CDH Registry database, data on the mode and duration of ventilation were available from the year 2001 until the year 2006. Therefore, we only included children born between January 2001 and December 2006. The large majority had been treated with conventional ventilation or HFO as initial ventilation mode. The few newborns treated with high-frequency jet ventilation were excluded from the analysis. Newborns with central or bilateral CDH were excluded as well because their clinical course differs from that of those with more common left- or right-sided CDH [27].

For the purpose of this article, data from 64 centers were collected. Centers are arbitrarily coded in the CDH Registry database as 'high-volume' or 'low-volume' centers. High-volume centers are those that admit more than 10 newborns with CDH per year. Furthermore, centers were coded as ECMO centers or non-ECMO centers.

The primary outcome measure in this study was BPD and/or mortality by day 30. In addition, separate analyses were performed for mortality by day 30 and BPD. Jobe and Bancalari [28] have defined BPD as oxygen dependency at day 28 or at 36 weeks postmenstrual age, depending on the gestational age at birth. However, the CDH Registry database holds data on oxygen dependency at day 30 instead of day 28. This is why we used oxygen dependency at day 30 as the criterion for BPD. The severity of BPD is determined at day 56 or at discharge, whichever comes first [28]. However, this could not be determined since data on oxygen dependency at day 56 were not recorded in the CDH Registry. Data on oxygen dependency at discharge or transfer are presented in a descriptive way.

Statistical Analysis
To test associations between individual putative risk factors and outcome measures, univariate analyses were performed, using χ^2 and Mann-Whitney U tests where appropriate. Baseline variables that showed a significant effect in univariate analysis were entered into multiple logistic regression analyses for BPD and/or mortality by day 30 and BPD and mortality by day 30 separately using a stepwise backward elimination method. p values for trend over the study years for all 3 outcome measures were also calculated using logistic regression. As many data on medication for pulmonary hypertension and the position of the liver were missing, we did not use these variables in the statistical analysis. Results of the regression analyses are given as odds ratios with the 95% confidence interval. Data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, Ill., USA). A two-sided p value less than 0.05 was considered statistically significant.

Results

The CDH database held data on 4,466 patients born from 1995 onwards. Eligible subjects were those born between 2001 and 2006, a total of 2,134 children. Of these, 56 were excluded based on our exclusion criteria or incorrect data, leaving 2,078 subjects (fig. 1). Analysis revealed no significant differences in baseline patient characteris-
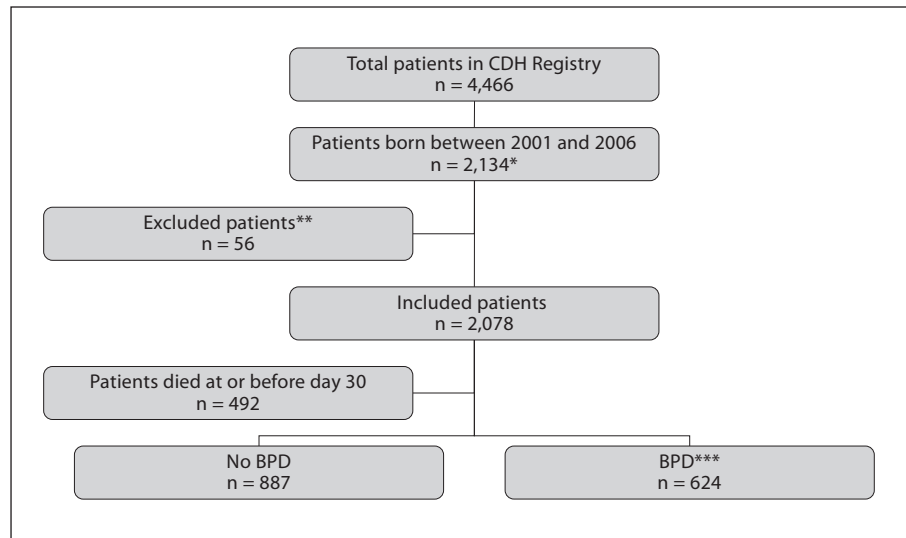
Fig. 1. Flowchart of patient inclusion and exclusion in the present study. * 2,120 patients were born before 2001; 212 patients were born after 2006. ** Due to bilateral CDH (n = 13), central CDH (n = 4), high-frequency jet ventilation (n = 13) or incorrect data on survival (n = 26). *** Data on BPD were missing for 75 patients.

tics, the prevalence of BPD (p = 0.762) or the survival rate (p = 0.122) between the patients included in the study and patients who were born before 2001 (n = 2,120). BPD and/or mortality by day 30 was present in 56% (n = 1,116/2,003, missing data = 75) of the included patients and 58% (n = 1,162/2,012, missing data = 8) of the nonincluded patients who were born before 2001 (p = 0.144). Patient characteristics are shown in table 1.

BPD and Mortality by Day 30

By day 30, 56% of all the study infants (n = 1,116/2,003, missing data = 75) had either died or met the criteria for BPD. Mortality by day 30 was 24% (n = 492/2,078). Overall mortality until hospital discharge for all 2,078 newborns was 31% (n = 634/2,078). Of the newborns that survived until day 30, 41% (n = 624/1,511, missing data = 75) met the criteria for BPD. Of these infants, 56% (n = 344/612, missing data = 12) had mechanical ventilation, 9% (n = 57/612) had continuous positive airway pressure and 34% (n = 211/612) had a nasal cannula at day 30. Of the infants that survived, 21% (n = 304/1,423, missing data = 21) were oxygen dependent at discharge or transfer. Of these, 17% (n = 51/295, missing data = 11) were mechanically ventilated at discharge or transfer, 2% (n = 6/295) received continuous positive airway pressure and 81% (n = 238/295) had a nasal cannula.

The prevalence of BPD and/or death by day 30 did not change over the study period (p for trend = 0.251). The prevalences of mortality by day 30 and BPD separately also did not change significantly over the study period (p for trend = 0.625 and 0.317, respectively).

Table 1. Baseline characteristics for all live-born patients with CDH (n = 2,078) born between 2001 and 2006

Variable	Number of patients	%
Males	1,235/2,076	59
Birth in high-volume center	1,132/2,078	54
Birth in ECMO center	1,910/2,078	92
Inborn	837/2,076	40
Vaginal delivery	1,021/1,855	55
Prenatal diagnosis	1,246/2,073	60
Cardiac abnormality	322/2,077	16
Chromosomal abnormality	89/2,077	4
Other abnormality[1]	176/2,078	8
Left-sided defect	1,735/2,060	84

Continuous variables	Median	Range
Gestational age at birth, weeks	38	23–42
Birth weight, kg	3.03	0.57–4.90
Apgar score at 5 min	7	0–10

Numbers do not always add up to 2,078 because of missing data.

[1] Other abnormality is classified as a congenital anomaly other than congenital heart disease or a chromosomal abnormality.

Extracorporeal Membrane Oxygenation

A total of 1,910 infants were born in an ECMO center. Overall, an ECMO procedure was performed in 29% of the patients (n = 595/2,078). The median day on which ECMO was started was the second day of life (range

Table 2. Baseline patient characteristics for patients with CDH who received initial ventilatory treatment with HFO (n = 674) or CMV (n = 1,261)

Variable	HFO	%	CMV	%	p value
Males	391/674	58	753/1,260	60	0.485
Birth in high-volume center	398/674	59	708/1,262	56	0.230
Birth in ECMO center	651/674	96	1,144/1,262	91	<0.001
Inborn	360/674	53	422/1,260	33	<0.001
Vaginal delivery	312/588	53	665/1,161	57	0.104
Prenatal diagnosis	480/674	71	673/1,261	53	<0.001
Cardiac abnormality	93/674	14	203/1,261	16	0.203
Chromosomal abnormality	33/673	5	46/1,262	4	0.226
Other abnormality[1]	69/674	10	92/1,262	7	0.031
Left-sided defect	562/673	84	1,057/1,258	84	0.819

Continuous variables	Median	Range	Median	Range	p value
Gestational age at birth, weeks	38	26–42	38	26–42	0.126
Birth weight, kg	3.0	0.6–4.9	3.1	0.7–4.8	<0.001
Apgar score at 5 min	7	1–9	7	0–10	<0.001

Numbers do not always add up to 1,935 because of missing data. CMV = Conventional mechanical ventilation.

[1] Other abnormality is classified as a congenital anomaly other than congenital heart disease or a chromosomal abnormality.

0–129). The median duration of the ECMO treatment was 10 days (range 0–42). A total of 283 patients (48%) had surgical correction of the diaphragmatic defect during the ECMO treatment.

A total of 93% infants (n = 523/564, missing data = 31) who underwent an ECMO procedure had either died by day 30 or met the criteria for BPD, compared with 41% of the infants (n = 591/1,439, missing data = 44) who did not undergo an ECMO procedure (p < 0.001). By day 30, 38% of the patients who underwent an ECMO procedure had died (n = 212/564, missing data = 31), compared to 19% (n = 280/1,483) of the patients who did not undergo an ECMO procedure (p < 0.001). Overall mortality after an ECMO procedure was 51% (n = 285/564, missing data = 31). BPD was present in 88% of the patients who underwent an ECMO procedure and survived until day 30 (n = 311/352), compared to 27% of the patients who did not undergo an ECMO procedure and survived until day 30 (n = 313/1,159; p < 0.001).

Surgical Repair

A surgical repair was performed in 83% of all patients (n = 1,729/2,078). The median day of surgical repair was the fourth day of life (range 0–112). A patch repair, as opposed to primary repair, was performed in 49% of the cases (n = 837/1,725, missing data = 4).

Seventy-five percent of the infants (n = 599/801, missing data = 36) who underwent a patch repair had either died by day 30 or met the criteria for BPD, compared with 20% of the infants (n = 171/854, missing data = 34) who did not undergo a patch repair (p < 0.001). Of the patients who underwent a patch repair, 16% (n = 132/837) had died by day 30, compared to 2% (n = 18/888) of the patients who underwent a primary repair (p < 0.001). BPD was present in 70% of the patients who underwent a patch repair and survived until day 30 (n = 467/669, missing data = 36), compared to 18% of the patients who underwent a primary repair and survived until day 30 (n = 153/852, missing data = 34; p < 0.001).

Initial Ventilation Mode

Of all patients, 35% received HFO (n = 674/1,936) and 65% received conventional ventilation (n = 1,262/1,936, missing data = 142) as initial ventilation mode. The median duration of ventilation in children initially treated with HFO was 17 days (range 1–199), compared to 11 days (range 0–741) in children treated with conventional ventilation (p < 0.001).

Table 3. Univariate analyses of baseline variables for patients born between 2001 and 2006 who had BPD and/or had died by day 30 (n = 1,116, missing data = 75)

Variable	BPD and/or death by day 30	%	p value
Gender			0.160
Male	649/1,192	58	
Female	467/809	58	
Volume of center			0.085
High	521/900	58	
Low	595/1,103	54	
Birth in ECMO center			0.006
Yes	1,040/1,836	57	
No	76/167	46	
Birth location			<0.001
Inborn	534/812	66	
Outborn	582/1,189	49	
Method of delivery			<0.001
Cesarean section	496/807	61	
Vaginal delivery	499/985	51	
Prenatal diagnosis			<0.001
Yes	802/1,204	67	
No	310/794	39	
Cardiac abnormality			<0.001
Yes	242/312	78	
No	874/1,690	52	
Chromosomal abnormality			<0.001
Yes	78/87	90	
No	1,037/1,915	54	
Other abnormality[1]			1.000
Yes	94/169	56	
No	1,022/1,834	56	
Side of defect			<0.001
Left	879/1,667	53	
Right	229/328	70	
Initial ventilation mode			<0.001
HFO	460/632	73	
CMV	564/1,233	46	

Continuous variables	Median (range)	p value
Gestational age, weeks	6 (0–10)	<0.001
Birth weight, kg	2.93 (0.57–4.80)	<0.001
Apgar score at 5 min	38 (23–42)	<0.001

Numbers do not always add up to 1,116 because of missing data. CMV = Conventional mechanical ventilation.
[1] Other abnormality is classified as a congenital anomaly other than congenital heart disease or a chromosomal abnormality.

Differences in baseline patient characteristics between patients who initially received HFO or conventional ventilation are presented in table 2. Patients who received HFO as the initial ventilation mode were significantly more often prenatally diagnosed (p < 0.001), inborn (i.e. born in a tertiary clinic; p < 0.001) and born in an ECMO center (p < 0.001), had significantly more other abnormalities (p = 0.031) and had a significantly lower median birth weight (p < 0.001) and Apgar score at 5 min (p < 0.001).

Patients who received initial treatment with HFO had BPD and/or died by day 30 significantly more often than patients who received initial treatment with conventional ventilation (p < 0.001; data shown in tables 3 and 4).

Of the infants who initially received HFO, 39% (n = 260/674) underwent an ECMO procedure, compared with 23% (n = 296/1,262) of the infants who initially received conventional ventilation (p < 0.001). In total, 526 patients who initially received HFO and 1,100 patients who initially received conventional ventilation underwent a surgical repair. Of those patients, 64% of the patients who were initially treated with HFO (n = 336/524, missing data = 2) underwent a patch repair, as opposed to primary closure, compared with 40% (n = 441/1,098, missing data = 2) of patients treated with conventional ventilation as initial ventilation mode (p < 0.001).

Multivariate Analysis

The univariate analyses of baseline variables for BPD and/or mortality by day 30 are presented in table 3. Separate univariate analyses for BPD and mortality by day 30 are presented in table 4. Baseline variables that were significant were entered into multiple logistic regression analyses for all 3 outcome measures. Variables regarding surgical repair and ECMO therapy were not entered into the multivariate analyses, because we only included those variables that were known at baseline.

As data on the method of delivery were missing for 223 patients, we excluded this variable from the multivariate analyses. Birth weight and gestational age were both significant in the univariate analyses, but due to their high correlation with each other, only gestational age was added to the multivariate analysis.

The baseline variables location of birth (in- or outborn, i.e. not in a tertiary clinic), birth in an ECMO center (yes or no), prenatal diagnosis, cardiac abnormality, chromosomal abnormality, side of the defect (left or right side), Apgar score at 5 min, the initial mode of ventilation and gestational age were all entered in the multivariate analyses for early mortality and BPD.

The results of the final multivariate analyses are shown in tables 5, 6 and 7. A lower gestational age, a cardiac anomaly, a chromosomal anomaly, a prenatal diagnosis, a right-sided defect, a lower Apgar score at 5 min and

Table 4. Univariate analyses of baseline variables for patients born between 2001 and 2006 who had BPD (n = 624) or who had died by day 30 (n = 492)

Variable	BPD	%	p value	Death by day 30	%	p value
Gender			0.420			0.150
Male	370/913	41		279/1,235	23	
Female	254/596	43		213/841	25	
Volume of center			0.071			0.398
High	303/690	44		276/1,132	24	
Low	321/821	39		236/946	25	
Birth in ECMO center			<0.001			0.016
Yes	601/1,397	43		439/1,910	23	
No	23/114	20		53/168	32	
Birth location			<0.001			<0.001
Inborn	260/538	48		274/837	33	
Outborn	364/971	37		218/1,239	18	
Method of delivery			0.007			<0.001
Cesarean section	255/566	45		241/834	29	
Vaginal delivery	294/780	38		205/1,021	20	
Prenatal diagnosis			<0.001			<0.001
Yes	434/836	52		368/1,246	30	
No	188/672	28		122/827	15	
Cardiac abnormality			<0.001			<0.001
Yes	127/197	64		115/322	36	
No	497/1,313	38		377/1,755	21	
Chromosomal abnormality			<0.001			<0.001
Yes	23/32	72		55/89	62	
No	601/1,479	41		436/1,988	22	
Other abnormality[1]			0.445			0.241
Yes	46/121	38		48/176	27	
No	578/1,390	42		444/1,902	23	
Side of defect			<0.001			0.001
Left	497/1,285	39		382/1,735	22	
Right	127/226	56		102/335	30	
Initial ventilation mode			<0.001			<0.001
HFO	229/401	57		231/674	34	
CMV	346/1,015	34		218/1,262	17	

Continuous variables	Median (range)			Median (range)		
Gestational age, weeks	38 (23–42)		<0.001	38 (26–42)		<0.001
Birth weight, kg	3.00 (0.64–4.8)		<0.001	2.79 (0.57–4.48)		<0.001
Apgar score at 5 min	7 (0–10)		<0.001	6 (0–9)		<0.001

Numbers do not always add up to 624 and 492 because of missing data. CMV = Conventional mechanical ventilation.

[1] Other abnormality is classified as a congenital anomaly other than congenital heart disease or a chromosomal abnormality.

HFO as initial ventilation mode were associated with a higher risk of BPD and/or death by day 30. Having a chromosomal anomaly was also associated with early mortality, but not with BPD. Additionally, being inborn was associated with a higher risk of mortality by day 30, and being outborn was associated with a higher risk of BPD.

Although we did not include variables that were not known at baseline, we did test for various interactions between these variables and the baseline variables. In this regard, we found an interaction between the need for ECMO treatment and the initial mode of ventilation in the multivariate analyses for BPD and/or death by day 30

Table 5. Multivariate logistic regression analysis of BPD and/or death by day 30 (n = 1,686)

Variable	OR	95% CI	p value
Gestational age in weeks	0.84	0.81–0.90	<0.001
Cardiac abnormality	2.62	1.85–3.72	<0.001
Chromosomal abnormality	3.04	1.42–6.51	0.004
Prenatal diagnosis	3.90	3.00–5.00	<0.001
Right-sided defect	2.76	1.96–3.89	<0.001
Apgar score at 5 min	0.61	0.57–0.65	<0.001
HFO as initial ventilation mode	2.53	1.95–3.27	<0.001

Nonsignificant variables in the multivariate analysis: birth in ECMO center (odds ratio 1.39, 95% confidence interval 0.80–2.44; p = 0.244) and location of birth (odds ratio 1.1, 95% confidence interval 0.83–1.46; p = 0.487). OR = Odds ratio; CI = confidence interval.

Table 6. Multivariate logistic regression analysis for BPD (n = 1,293)

Variable	OR	95% CI	p value
Gestational age in weeks	0.87	0.82–0.92	<0.001
Cardiac abnormality	2.42	1.85–3.67	<0.001
Inborn	0.70	0.52–0.95	0.023
Prenatal diagnosis	4.27	3.05–5.80	<0.001
Right-sided defect	2.51	1.73–3.64	<0.001
Apgar score at 5 min	0.66	0.61–0.71	<0.001
HFO as initial ventilation mode	2.29	1.73–3.04	<0.001

Nonsignificant variables in the multivariate analysis: birth in ECMO center (odds ratio 1.81, 95% confidence interval 0.94–3.48; p = 0.074) and having a chromosomal abnormality (odds ratio 1.37, 95% confidence interval 0.57–3.26; p = 0.480). OR = Odds ratio; CI = confidence interval.

Table 7. Multivariate logistic regression analysis for mortality by day 30 (n = 1,749)

Variable	OR	95% CI	p value
Gestational age in weeks	0.87	0.83–0.92	<0.001
Cardiac abnormality	1.54	1.11–2.14	0.010
Chromosomal abnormality	4.49	2.63–7.67	<0.001
Inborn	1.76	1.30–2.38	<0.001
Prenatal diagnosis	1.80	1.28–2.02	<0.001
Right-sided defect	1.88	1.35–2.63	<0.001
Apgar score at 5 min	0.68	0.64–0.73	<0.001
HFO as initial ventilation mode	1.85	1.42–2.41	<0.001

Nonsignificant variable in the multivariate analysis: birth in ECMO center (odds ratio 0.71, 95% confidence interval 0.37–1.34; p = 0.286). OR = Odds ratio; CI = confidence interval.

and BPD alone. This revealed that in patients who underwent an ECMO procedure, the initial mode of ventilation was no longer associated with these outcome measures.

Also, we found an interaction between the location of birth and HFO as initial ventilation mode. In patients who were born outside a tertiary clinic, HFO was still associated with a higher risk of BPD and/or death by day 30 and BPD alone. In patients who were born in a tertiary clinic, HFO gave a slightly higher risk of BPD and/or death by day 30 and BPD alone. However, this was not significant because the confidence intervals overlapped.

We did not find any interactions between birth in an ECMO center, the volume of the center and the initial ventilation mode. Also, we did not find any variables that modified the effect of HFO in the analysis for early mortality.

Discussion

In this study, 56% of all the infants included had either died or met the criteria for BPD at day 30. In survivors of CDH, BPD, with a prevalence of 41%, remains an important clinical issue. Moreover, the prevalence of BPD and/or early mortality remained constant over the years of the study period, despite promising advances in neonatal care and urgent reports from centers around the world. Unexpectedly, this study showed that initial ventilatory treatment with HFO was associated with worse postnatal outcome.

We can propose several causes for the high prevalence of BPD. Firstly, these children's hypoplastic lungs may be more susceptible to oxygen toxicity than the lungs of other newborns with respiratory distress [12]. Moreover, maldevelopment of the pulmonary vasculature may contribute to pulmonary hypertension, which in itself increases morbidity and mortality in BPD [29]. Thirdly, the asymmetry of the lungs may result in areas of differential compliance and the subsequent risk of overexpansion of the alveoli [12, 13]. Fourthly, although centers mostly use gentle ventilation strategies nowadays, aggressive ventilation strategies with high peak inspiratory pressures cannot always be avoided. Subsequent volutrauma, barotrauma and atelectrauma may contribute to significant

pulmonary injury, including diffuse alveolar damage, hyaline membrane formation and intra-alveolar hemorrhage [23, 30].

This study suggests that HFO as the initial ventilation mode is a risk factor for BPD and/or mortality by day 30 and for BPD and mortality separately. This was a somewhat surprising finding because previous retrospective and observational studies indicated that HFO as the initial ventilation mode might be an effective method to increase survival and reduce BPD in newborns with CDH [21, 22, 24]. It was thought to ameliorate ventilation-induced lung injury by promoting uniform lung inflation, reducing barotrauma and suppressing inflammatory mediators [23, 30–33]. On the other hand, HFO might well cause lung hyperinflation. The resultant higher alveolar and mean airway pressures would then raise the risk of pulmonary barotrauma and hemodynamic instability, due to adverse effects on venous return and pulmonary vascular resistance [23].

A possible explanation for the association between HFO as the initial ventilation mode and BPD as well as early mortality might be that the infants who initially received HFO were more severely ill from the start. Compared with those patients who received conventional ventilation initially, patients who received HFO as initial treatment had a significantly lower Apgar score at 5 min and a lower birth weight. Patients who received HFO were more often inborn and prenatally diagnosed compared with infants who received conventional ventilation. HFO was also associated with a significantly longer duration of ventilation compared with conventional ventilation. Furthermore, patients who received initial treatment with HFO underwent an ECMO procedure more often. Moreover, they more often had a patch repair, which might be associated with a larger defect size and more severe pulmonary hypoplasia. Therefore, we may speculate that these infants' condition was worse than that of infants on conventional ventilation from the start.

In this regard, it is unfortunate that some variables that might have given an indication of the severity of disease could not be included in the multivariate analyses because they were not known at baseline. However, we did test for various interactions between variables. In this regard, we found that in patients who underwent an ECMO procedure, the initial mode of ventilation was no longer associated with BPD and/or death by day 30 and BPD alone. Also, HFO gave only a slightly higher risk of BPD and/or death by day 30 and BPD alone in patients who were born in a tertiary clinic. Moreover, we did not find any variables that modified the effect of HFO in the analysis for early mortality. Baseline data on prenatal predictors of outcome, such as the lung-to-head ratio, were not available. It may, for example, be speculated that fetuses with a lower lung-to-head ratio and a possible worse outcome may have been treated initially with HFO.

A right-sided defect was associated with a higher risk of BPD and/or early mortality and BPD and early mortality separately. This is in line with previous studies, which reported a higher risk of mortality and worse outcome in patients with right-sided defects [34, 35].

Furthermore, a prenatal diagnosis was another important risk factor for BPD and/or early mortality and BPD and early mortality separately. Infants who are diagnosed prenatally are more likely to have more obvious anomalies and a more severe herniation visible on ultrasound, which may explain this higher risk of a worse outcome. However, prenatal detection of the diaphragmatic defect in infants with CDH may be dependent on the quality of obstetric care and prenatal screening.

A low Apgar score at 5 min of life was also associated with a higher risk of a worse outcome. This is in line with a previous study by the CDH Study Group, which reported that the Apgar score at 5 min predicted mortality in newborns with CDH [36]. Furthermore, a cardiac abnormality, a chromosomal anomaly and a lower gestational age were also associated with worse outcome.

Being inborn, i.e. in a tertiary clinic, was a risk factor for early mortality in this study. This may be explained by the fact that mortality is not always reported in pregnancy terminations, stillbirths and outborn children who die shortly after birth [37]. As a consequence, the mortality rate for inborn children with CDH may be relatively higher. However, it must be taken into account that the study centers in the CDH Registry use different referral policies.

This study did not show an association between the volume of the center and postnatal outcome. However, a previous study reported higher survival rates in high-volume centers, defined as more than 6 patients with CDH admitted per year [38]. This difference may be explained by the fact that we used a different cutoff to define the volume of the center. Also, no association was found between postnatal outcome and birth in an ECMO center. In the multivariate analysis, no associations were found between birth in an ECMO center, birth in a high-volume center and the initial ventilation mode. More specific data on the type of center and the treatment protocols they used are lacking, since all centers are anonymously coded in the CDH Registry. Differences between the var-

ious centers may therefore still play a role in outcome in infants with CDH, although we were not able to find such an association in this study.

This study showed that gender was not a risk factor for worse outcome in newborns with CDH. Studies in preterm infants reported boys to be at higher risk for BPD and mortality in general [39, 40]. As newborns with CDH are usually born at term, the above-mentioned association reported for premature infants may not be fully applicable to them.

Although ECMO could not be included in the multivariate analysis, because it is not a baseline characteristic, ECMO was associated with a higher risk of BPD and early mortality in univariate analyses. Patients with CDH who need ECMO therapy are likely to have severe pulmonary hypoplasia and pulmonary hypertension, resulting in a higher risk of worse outcome. Mortality after an ECMO procedure was 51%, which is comparable to previous studies and data from the Extracorporeal Life Support Organization registry [41, 42]. The role of ECMO in the treatment of infants with CDH is still unclear [43]. However, in nonrandomized trials, ECMO has been reported to improve survival in infants with CDH [44, 45].

This is the first study to describe chronic lung disease and its risk factors in a large number of patients with CDH. However, its possible limitations should not go unmentioned. For one, some important data could not be determined, such as disease severity, pulmonary hypertension, the position of the liver, the severity of BPD and prenatal predictors of outcome. Therefore, additional research should be performed taking into account the full spectrum of the disease. Moreover, patients who received HFO underwent an ECMO procedure more often, and the association between BPD and/or death by day 30 and BPD alone and the initial ventilation mode was not shown in infants who received ECMO therapy. Therefore, confounding by indication may have biased our results. Furthermore, selection bias could have occurred because only data from hospitals participating in the CDH Study Group were retrieved. In addition, these hospitals used different treatment protocols and referral policies, which may have influenced outcomes. In this regard, oxygen dependency was not defined according to standard practice in our study centers. A previous study by Walsh et al. [46] reported a lower incidence of BPD if oxygen dependency was confirmed by a room air challenge test. Since data on room air challenge tests were not available in our study, our results may have been biased.

Conclusion

BPD and mortality in newborns with CDH remain important problems, despite improvements in neonatal care. Moreover, BPD may lead to long-term pulmonary morbidity. HFO has been heralded as a promising ventilation treatment to reduce mortality and pulmonary morbidity in CDH newborns. However, in the present study, initial ventilation treatment with HFO was associated with a higher risk of a worse outcome. Nonetheless, the results of this study must be interpreted with caution, because selection bias and confounding by indication may have occurred. Therefore, further prospective studies are needed to study risk factors and optimal ventilation strategies in children with CDH. In addition, standardized treatment protocols and follow-up guidelines, such as those developed by the American Academy of Pediatrics in 2008, should be implemented as crucial ways to improve healthcare in children with CDH [15]. This calls for extensive collaboration between centers with expertise in the treatment of newborns with CDH, such as the CDH Euro-Consortium, which recently initiated the VICI trial, a randomized controlled trial on ventilation strategies in infants with CDH (www.vicitrial.com).

Appendix

Writing Committee
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