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Diagnosis-related deterioration of lung function after extracorporeal membrane oxygenation

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ABSTRACT

Objective: To assess lung function longitudinally after neonatal ECMO, and to identify any effects of diagnosis and perinatal characteristics.

Patients and methods: 121 neonatal ECMO-treated children (70 meconium aspiration syndrome, 20 congenital diaphragmatic hernia, 31 other diagnoses) performed altogether 191 lung function measurements at 5, 8 and/or 12 years. We assessed dynamic and static lung volumes, reversibility of airway obstruction and diffusion capacity.

Results: Mean SDS FEV_1 at 5 years before and after bronchodilation (-0.51 and 0.07) was significantly higher than at 8 (-0.79 and -0.4, $p<0.04$) and 12 years (-1.10 and -0.52, $p<0.003$). Mean SDS for all spirometric parameters before and after bronchodilation were significantly lower in the congenital diaphragmatic hernia group compared the other diagnostic groups (all $p≤0.025$). A significant volume of trapped air was observed in 86% patients with congenital diaphragmatic hernia, 50% with meconium aspiration syndrome and 58% with other diagnoses. After bronchodilation mean SDS FEV_1 and FVC were negatively influenced by duration of ventilation (both $p<0.001$) and duration of ECMO ($p=0.003$ and $p=0.02$ respectively).

Conclusion: Long-term pulmonary sequelae after neonatal ECMO-treatment mainly occur in congenital diaphragmatic hernia patients and tend to deteriorate over time.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique providing life support when conventional treatment for severe respiratory failure is not enough. Underlying diagnoses include meconium aspiration syndrome, congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension of the newborn (PPHN), sepsis and pneumonia. Ventilator settings are low during ECMO so the lungs can rest. Lung healing is promoted by reducing barotrauma and hyperoxia [1]. The collaborative UK ECMO trial showed improved survival of term infants with severe respiratory failure who were treated with ECMO [2-5]. The long-term pulmonary sequelae of neonatal ECMO have hardly been studied. Cross-sectional studies during or shortly after ECMO all reported reduced lung function, perhaps due to severity of the underlying respiratory disease [6-10].

We report a study in which we longitudinally evaluated residual lung function in neonatal ECMO-treated children now between 5 and 12 years of age, distinguished by underlying diagnosis. Furthermore we related perinatal characteristics to lung function.

METHODS

Participants

A prospective longitudinal follow-up study was conducted in children who received veno-arterial (VA) ECMO support within the first week of life between February 1991 and August 2004 at the Intensive Care Unit of the Erasmus MC-Sophia Children's Hospital. The cohort was supplemented with 5 children who received VA ECMO in two other ECMO centers (Nijmegen, The Netherlands: n=4 and Leuven, Belgium: n=1). Inclusion criteria and treatment protocols in those centers were the same as ours. ECMO was initiated in case of reversible severe respiratory failure and an estimated mortality risk of higher than 80% using the entry criteria of Stolar et al [11]. We reported our Eentry criteria and exclusion criteria earlier [10] and these did not change during the study period. The study was embedded in a structured prospective post-ECMO follow-up program initiated in 2001 that provides for regular assessments of lung function, growth and developmental parameters until 18 years of age [12]. Based on the national consensus on neonatal follow-up and the Dutch Ministry of Health's requirement to provide relevant data, the assessment protocol is the standard of care in the Netherlands following ECMO. As a consequence IRB approval was waived. The parents received information about the study and gave written informed consent for analysis of data collected during routine care. Background data were obtained from the charts, including diagnosis, gestational age, birth weight, age at onset of ECMO, duration of ECMO support, duration of mechanical ventilation, highest mean airway pressure (MAP) and highest oxygenation index (OI) prior to ECMO, total duration of mechanical ventilation (including ECMO), and duration of oxygen dependency.

Following Jobe and Bancalari, we defined chronic lung disease (CLD) as oxygen dependency at day 28 and classified it as as mild, moderate or severe, based on the amount of oxygen needed at day 56 or at discharge, whichever comes first [13].

Lung function

Pulmonary function tests were performed at 5, 8, and 12 years if children were in a clinically stable condition.

We obtained flow-volume curves; forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), and maximum midexpiratory phase (FEF_{25-75}) were determined from the best of three reproducible maneuvers. At 8 and 12 years we also determined total lung volume, functional residual capacity, and residual volume by helium dilution spirometry (TLC_{spiro} , FRC_{spiro} and RV_{spiro}, respectively) and by bodyplethysmography (TLC_{pleth}, FRC_{pleth} and RV_{pleth}), and carbon monoxide diffusion capacity (D_{LCO}) corrected for alveolar volume (K_{CO}) using a single breath method (all equipment: Jaeger Masterlab, Viasys, Hoechberg, Germany). Equipment and procedures were all according to European Respiratory Society (ERS) criteria [14].

Respiratory morbidity

At 5, 8, and 12 years a medical history was taken including the presence of atopic and respiratory symptoms, and prescription of prophylactic antibiotics, bronchodilators and inhaled corticosteroids medication for pulmonary disease.

Analysis

The OI was calculated as: [(Mean airway pressure x FiO_2)/PaO_2] x 100 [11]. FEV_1, FVC, FEV_1/FVC, and FEF_{25-75} were expressed as SDS calculated from the reference values of Stanojevic [15]. Volume of trapped air is considered significant when the ratio of plethysmographic to spirometric FRC is larger than 1.10 [16]. Post bronchodilator changes of FEV_1 were calculated as a simple percentage of the prebronchodilator value: 100x (post-pre)/post. A >11% bronchodilator change in FEV_1 was considered significant, reflecting reversible airflow obstruction [17].

The null hypothesis that the SDS of lung function parameters did not differ from those of the reference population (SDS=0) was tested with the one sample Student's T-test.

Mixed-model ANOVA, which allows for missing data, was applied for the longitudinal evaluation of the spirometric SDS at 5, 8 and 12 years and RV/TLC ratios, and the ratio of FRC_{pleth} to FRC_{spiro} and SDS of D_{LCO} at 8 and 12 years [18].

Values for the two largest diagnostic subgroups (CDH and MAS) were analyzed separately. The other subgroups were but small and we grouped these as "other diagnoses". Correlation coefficients between lung function parameters and gestational age, birth weight and duration of ventilation, supplemental oxygen and ECMO were established with Spearman's correlation test.

Possible associations between lung function parameters and CLD were explored by univariate analyses. All results are expressed as mean (SD) or median. P-values of <0.05 were considered significant. Statistical analysis was performed using SPSS 17.0.

RESULTS

238 children received ECMO support within the first week of life between February 1991 and August 2004 in the Erasmus MC - Sophia Children's Hospital; 166 survived (70%) (Figure 1). Twenty children could not perform reproducible lung function tests. Five children could not be traced, 4 were followed in another ECMO center, parents of 15 children gave no consent, and 6 children had not been tested for logistic reasons. Hence, the study population included 121 ECMO survivors (including the aforementioned 5 from other centers) who altogether performed 191 pulmonary function tests between February 2002 and March 2011 in Erasmus MC Rotterdam. Seventy children (58%) had been diagnosed with MAS; 20 (17%) with CDH. Smaller subgroups received ECMO for: persistent pulmonary hypertension of the newborn (PPHN; n=17), sepsis (n=8), pneumonia (n=4) and cardio respiratory failure (n=2). The characteristics at birth are shown in Table 1. The tested children did not differ from the non-tested children in gestational age, birth weight, underlying diagnosis, highest MAP, highest OI, age at onset of ECMO or duration of ECMO (data not shown). Atopic symptoms were reported in 7 (9.7%), 9 (11.7%) and 9 (21.4%) children at 5, 8 and 12 years respectively. One child at age 5 (1.4%) and 1 child at age 8 years (1.3%) took antibiotic prophylaxis to prevent recurrent airway infections. At 5 years, 10 children (13.9%) used bronchodilators (4 with additional inhaled steroids). At 8 years, 8 children (10.4%) used bronchodilators (5 with additional inhaled steroids). At 12 years, 4 children (9.8%) used bronchodilators (2 with additional inhaled steroids).

Lung function

Spirometry

The results of spirometry after bronchodilation (BD) are shown in Table 2. Significant differences from the norm (SDS=0) are indicated in the table. Significant reversibility of FEV_1 was observed in 34 measurements (18%). The median change in FEV_1 after BD was 5% (IQR 1 to 10%).

Mean SDS FEV_1 before and after BD significantly changed within time: at 5 years it was significantly higher than at 8 years (p=0.039 before and p=0.001 after BD) and at 12 years (p=0.003 before and p=0.001 after BD). It did not significantly change between 8 and 12 years.

Mean SDS FVC before and after BD did not change significantly within time (p-values not shown).

Mean SDS FEV_1/FVC at 5 years was higher than at 8 and 12 years, both before and after BD (all p-values < 0.001). After BD mean SDS FEV_1/FVC did not change significantly between 8 and 12 years; before BD it was higher at 8 years (p=0.033).

Mean SDS FEF_{25-75} after BD was higher at 5 years than at 8 years (p=0.02); it did not change significantly before BD or from 8 to 12 years before and after BD.

Figures 2 and 3 show the SDS FEV_1 at 5, 8, and 12 years for the three subgroups and the whole group, before and after BD. Initial diagnosis was a significant determinant in the mixed model: all spirometric parameters before BD in the CDH group were significantly lower than those in the other two subgroups. The parameters did not significantly differ between the MAS group and the other diagnoses group (data not shown). Individual measurements of FEV_1, before and after BD, in CDH patients are shown in Figures 3 and 4.

We analysed spirometric values in children with repeated measurements separately. After bronchodilation, SDS FEV_1 was significantly higher at 5 year compared with 8 and 12 years (p=0.002 and p=0.005

respectively). FEV_1/FVC was significantly higher at 5 years compared with 8 and 12 years (both p<0.001). FEF_{25-75} was significantly higher at 5 years compared with 8 years (p=0.028), there was no significant difference with 12 years. This is similar to the analysis of the whole group, including children with only one measurement. For all lung function parameters, differences between the different subgroups were independent of age.

Helium dilution spirometry, bodyplethysmography, and diffusion capacity at 8 and 12 years.
The mean (SD) $RV\%TLC_{spiro}$ at 8 years was 22.1 (8.3); at 12 years it was 21.1 (7.0). The mean (SD) $RV\%TLC_{pleth}$ at 8 years was 29.4 (8.2); at 12 years it was 26.5 (6.8) (Table 3).
The mean $FRC_{pleth/spiro}$ was 1.22 (0.22) at 8 years and 1.09 (0.11) at 12 years. A significant volume trapped air (defined as $FRC_{pleth/spiro}$>1.10)[16] was observed in 32 (64%) and 13 (46%) of children at 8 and 12 years, respectively. This concerned 12/14 measurements in the CDH group (86%), 26/52 in the MAS group (50%), and 7/12 in the other diagnoses group (58%).
Total diffusion capacity did not differ from the norm population at 8 and 12 years (p=0.286 and p=0.392 respectively). However, after correction for alveolar volume the diffusion capacity was significantly below the norm at the age of 8 (p<0.001) but not at 12 years (p=0.172).

Other determinants of lung function parameters
Beside the effects of age and initial diagnosis we evaluated the influence of other determinants on spirometric parameters. Before BD, mean SDS FEV_1 and SDS FVC were negatively influenced by duration of ventilation (both parameters p<0.001), duration of ECMO support (p≤0.001 for both parameters), and the presence of CLD (both p≤0.001). Both parameters were positively correlated to birth weight (both p≤0.001); SDS FEV_1 only was positively correlated to gestational age (p=0.001). After BD, mean SDS FEV_1, SDS FVC and SDS FEF_{25-75} were negatively influenced by duration of ventilation (all parameters p<0.001), duration of ECMO support (all p<0.03), and the presence of CLD (all p≤0.001). Mean SDS FEV_1, SDS FVC, SDS FEV_1/FVC and SDS FEF_{25-75} were positively influenced by birth weight (all p<0.05); mean SDS FEV_1 and SDS FEF_{25-75} were also positively influenced by gestational age (both p<0.01). In univariate analysis doubling of the logarithm ventilation time resulted in a mean decrease of -0.415 SDS FEV_1 at 5 years, -0.782 SDS FEV_1 at 8 years, and -1.35 SDS FEV_1 at 12 years (all p≤0.001).
$RV\%TLC_{pleth}$ and $FRC_{pleth/spiro}$ were positively correlated to duration of ventilation (p<0.001), duration of ECMO support (p<0.02), and birth weight (p<0.04). Highest MAP and OI before ECMO did not correlate with any of the lung function parameters.

DISCUSSION

Residual lung function of the studied 121 children – in terms of mean SDS FEV_1 and SDS FEF_{25-75} before BD – had significantly decreased between 5 and 12 years of age. CDH was associated with significantly lower spirometric values and higher frequency of a significant volume of trapped air compared to other diagnoses. Mean SDS FEV_1,FVC, and FEF_{25-75} were negatively influenced by duration of ventilation, and the presence of CLD.

Long-term pulmonary function abnormalities such as hyperinflation and airway obstruction are well recognized after neonatal respiratory failure secondary to lung injury from MAS, CDH and neonatal pneumonia [10, 19-20]. Treatment modalities such as supplemental oxygen and mechanical ventilation contribute to the pathogenesis of CLD [21]. Avoiding continued exposure to high inspired oxygen concentration and barotrauma during the course of ECMO has reduced mortality and encouraged lung healing and recovery. To our knowledge this is the first longitudinal study on the impact of neonatal ECMO on lung function in children between 5 and 12 years of age.

Beardsmore et al. in 2000 cross-sectionally studied 51 ECMO patients at age 1 year and found few differences in lung function compared with conventionally ventilated controls. This provided reassurance that in addition to decreased mortality respiratory function following ECMO was no worse [6]. In addition, another study by Beardsmore et al. showed that when children were categorized according to the underlying reason for ECMO, those treated for RDS and those treated beyond the first 3 weeks for bronchiolitis or pneumonia had poorer pulmonary function 12 months later. However, only few CDH patients were included in this studied population of 106 subjects [22]. Hofhuis and colleagues found below-average but normal lung volumes and stable forced expiratory flows during the first year of life in 64 infants following ECMO. At 12 months, only the CDH patients showed signs of hyperinflation with plethysmographic FRC significantly above normal [10]. In an earlier study we found significantly impaired expiratory flows and increased FRC levels in 12 ECMO and 31 non-ECMO treated CDH patients during the first year of life. The ECMO-treated CDH patients had significantly higher FRC levels, thus reflecting more hyperinflation [20]. In a cross-sectional study in 54 eight-year-old patients after severe neonatal respiratory failure, Majaesic and coworkers found a poorer pulmonary outcome in the subgroup of ECMO treated CDH patients [23]. In 2004 Hamutcu and coworkers cross-sectionally studied 50 children after neonatal ECMO treatment. At a mean age of 11 years they had significantly lower FEV_1 and FEF_{25-75} and hyperinflation with higher RV compared to healthy matched controls. Single breath diffusion capacity for carbon monoxide was within the normal range [19]. When children with congenital heart disease (8%) and CDH (12%) were excluded from analysis, no significant differences in lung function were observed. Boykin and coworkers reported signs of air trapping and mild lower airway obstruction in 17 ECMO-treated MAS patients [7].

The strength of the present study is the longitudinal aspect, as most other studies were performed cross-sectionally. A potential weakness is the lack of appropriate reference values for longitudinal spirometric measurements and the lack of a healthy control group in our study. Up-to-date reference data are needed to reflect evolving measurement techniques and equipment and changes in population characteristics. In 2008, Quanjer and co-workers compared 5 commonly used reference equation sets to serial measurements and found that Stanojevic's equations performed best and are suitable for longitudinal

data analysis as they cover a wide age range and account for a gradual transition from childhood into adulthood. In another study they compared 30 spirometry datasets and concluded that the use of local controls to validate reference equations will rarely be practical due to the numbers required and that the use of reference equations derived from large or collected datasets is recommended [24]. Therefore we computed SDS of spirometric values using those equations, which distinguish between the effects of disease and those of growth and development [25]. As treatment protocols improve over time, results from earlier studies may not just be applicable to patients treated with ECMO today. This is, albeit to a lower extent, also a limitation of our study. Not all patients were tested at all 3 time points, which created an unfavorable but unavoidable heterogeneity in the age distribution. Our ventilation strategies and ECMO treatment protocols have indeed been adjusted over the past decade, resulting in better survival in CDH patients [26]. Recent protocols based on meta-analysis of retrospective studies provide guidelines for the use of ECMO in CDH patients [27]. These could well lead to better long-term pulmonary outcome and lung function.

In our study, the SDS for all spirometric parameters in the CDH group were significantly lower than those in the MAS or other diagnoses patients. This finding is in line with findings from other studies. While infants with MAS have normal lung development, CDH is associated with lung hypoplasia and PPHN. The severity of lung hypoplasia and PPHN in CDH patients covers a wide range. ECMO-treated CDH patients are regarded as the most severe cases [20, 26]. Their improved survival might be counterbalanced by increased morbidity. Maldevelopment of the alveoli and pulmonary vessels with disturbed lung growth may be responsible for the deterioration of lung function. Also, prolonged ventilatory support and supplemental oxygen after ECMO treatment may result in CLD. Recurrent respiratory tract infections can further compromise lung function over time.

Our group has recently reported a significant decline of exercise capacity in a cohort of ECMO survivors which overlaps with the population described in the present study. [28]. Interestingly, this decline was irrespective of the underlying diagnosis and we were unable to show an association between maximal exercise capacity and SDS of FEV_1 and FEV_1/FVC. For all patients, we advocate an active lifestyle and healthy eating pattern as sports participation interacts positively and BMI negatively with exercise capacity [29].

Adequate treatment of recurrent respiratory tract infections, close monitoring and treatment of asthma could perhaps halt deterioration of exercise capacity and lung function, especially in CDH patients. The use of prophylactic bronchodilators, e.g. during exercise, should not be advised routinely.

From our results it can be concluded that lung function is compromised after neonatal ECMO treatment and seems to deteriorate over time in CDH patients only. Airway patency in patients with all other diagnoses was within the normal range and remained stable over time. Therefore we assume that the underlying condition and not ECMO itself is responsible for the compromised lung function post-ECMO. ECMO may even reduce the harmful effects of high pressure ventilation and high doses of oxygen. Although the severity of pulmonary hypertension diminishes during ECMO and later in CDH patients, sequelae of abnormal lung development will still be present as reflected by compromised lung function in this patient group.

We recommend prolonged follow-up, especially of patients with CDH, to further elucidate the increased respiratory morbidity that occurs with better survival and changing treatment protocols.

TABLES

Table 1. Clinical perinatal characteristics of neonatal ECMO-treated patients

	All participants	MAS	CDH	Other
N (male)	121 (65)	70 (33)	20 (15)	31 (17)
Gestational age (wk)	40 (34.7-43.3)	40.6 (36.6-43.3)	39 (36-40.9)	38.5 (34.7-42.3)
Birth weight (g)	3380 (2160-4980)	3400 (2300-4980)	3500 (2160-3810)	3280 (2375-4880)
Age at onset ECMO (hours)	25 (5-168)	23 (6-73)	16 (5-168)	40 (15-152)
Duration of ECMO (hours)	132 (24-369)	126 (24-345)	192 (68-369)	122 (53-288)
Duration of ventilation (days)	10 (1-70)	10 (1-34)	28 (11-70)	9.5 (2-30)
Highest MAP prior to ECMO (cm H_2O)	20 (12-45)	20 (14-30)	19 (12-45)	19 (13-26)
Highest OI prior to ECMO,	43 (15-143)	44 (27-143)	44 (15-130)	40 (21-106)
NO treated newborns, n (%)	80 (66)	42 (60)	13 (65)	25 (81)
CLD, n (%)	22 (18.2)	12 (17.2)	10 (50.0)	-
Mild CLD	11 (9.1)	10 (14.3)	1 (5.0)	-
Moderate CLD	1 (0.8)	-	1 (5.0)	-
Severe CLD	10 (8.3)	2 (2.9)	8 (40.0)	-

Data are expressed as median (range) unless otherwise indicated. Shown are the total group and the subgroups of infants. ECMO: Extracorporeal membrane oxygenation. MAS: meconium aspiration syndrome. CDH: congenital diaphragmatic hernia. MAP: mean airway pressure. OI: oxygenation index. NO= nitric oxide therapy. CLD: chronic lung disease, classified according to Jobe and Bancalari [13]

Table 2: Longitudinal results of spirometry after neonatal ECMO, after bronchodilation.

		5 yrs (n=72)	8 yrs (n=77)	12 yrs (n=42)
SDS FEV_1	All participants	0.07 (0.14)	-0.40 (0.15)†	-0.52 (0.16)†
	MAS	0.49 (0.17)‡	0.12 (0.14)	0.01 (0.23)
	CDH	-0.71 (0.40)	-2.27 (0.36)*	-2.73 (0.61)†
	Other	0.01 (0.23)	0.08 (0.31)	-0.49 (0.25)
SDS FVC	All participants	-0.08 (0.15)	-0.22 (0.13)	-0.29 (0.16)
	MAS	0.40 (0.18)†	0.01 (0.15)	0.12 (0.27)
	CDH	-0.69 (0.43)	-1.48 (0.35)*	-1.28 (0.98)
	Other	-0.01 (0.29)	0.19 (0.25)	-0.17 (0.33)
SDS FEV_1/FVC	All participants	0.32 (0.15)	-0.53 (0.12)*	-0.63 (0.15)*
	MAS	0.22 (0.19)	-0.19 (0.11)	-0.32 (0.19)
	CDH	0.11 (0.35)	-1.47 (0.39)‡	-2.16 (0.30)‡
	Other	0.21 (0.35)	-0.37 (0.28)	-0.61 (0.34)
SDS FEF_{25-75}	All participants	-0.56 (0.19)‡	-1.02 (0.18)*	-0.97 (0.20)*
	MAS	-0.12 (0.25)	-0.34 (0.14)†	-0.67 (0.21)‡
	CDH	-1.76 (0.42) ‡	-3.07 (0.46)*	-3.28 (0.54)‡
	Other	-0.82 (0.38)	-0.71 (0.42)	-0.93 (0.30)†

ECMO: extracorporeal membrane oxygenation. CDH: congenital diaphragmatic hernia. Mean SDS (± SE) are shown for FEV_1, FVC, FEV_1/FVC, and FEF_{25-75}. Number of patients studied in each group: MAS: 35, 46 and 26 at 5, 8 and 12 years, CDH: 15, 14 and 5 at 5, 8 and 12 years. other: 22, 17 and 11 at 5, 8 and 12 years.

SDS significantly below normal (SDS=0; one-sample Student T-test): †: $p < 0.05$; ‡: $p < 0.01$;*: $p ≤ 0.001$

Table 3. Static lung volumes and diffusion capacity at 8 and 12 years

	8 years	n	12 years	n
RV%TLC$_{spiro}$	22.1 (8.3)	56	21.1 (7.0)	30
RV%TLC$_{pleth}$	29.4 (8.2)	40	26.5 (6.8)	25
FRC$_{pleth/spiro}$	1.22 (0.22)	50	1.09 (0.11)	28
VTA, n (%)	32 (64)		13 (46)	
DL$_{CO}$c (SDS)	0.32 (1.6)	29	-0.28 (1.5)	22
K$_{CO}$c (SDS)	-0.95 (1.1)*	22	-0.41 (1.2)	18

DL$_{CO}$c: diffusion capacity corrected for Hb. K$_{CO}$c: diffusion capacity corrected for alveolar volume and Hb.
RV%TLC$_{spiro}$, RV%TLC$_{pleth}$: mean (SD) %. FRC$_{pleth/spiro}$, Diffusion capacity: mean (SD).
VTA: volume trapped air; number (%) of patients with significant VTA (defined as FRC$_{pleth/spiro}$ > 1.10) is shown.
*: significantly below normal (SDS-score = 0) (p<0.001 at 8 years).

FIGURE LEGENDS

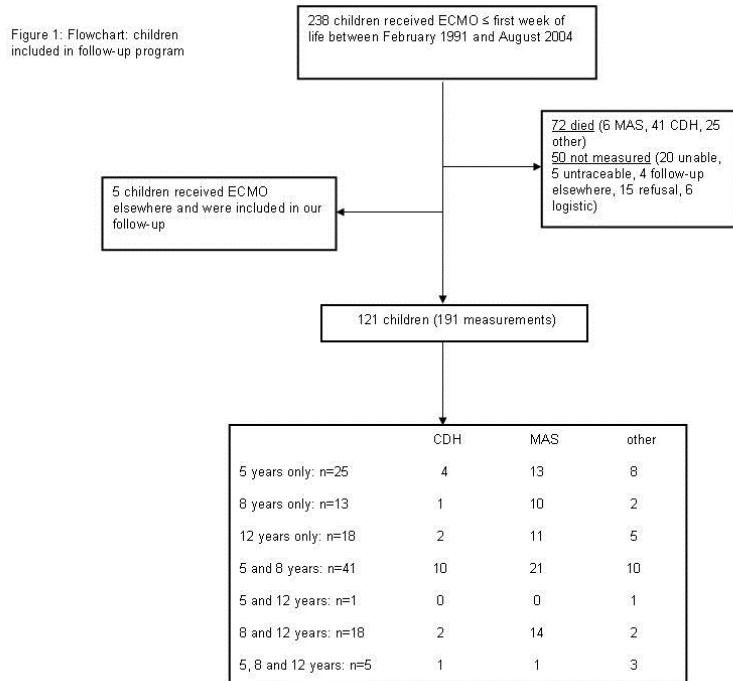Figure 1: Flowchart: children included in follow-up program.

Figure 1: Flowchart: children included in follow-up program

238 children received ECMO ≤ first week of life between February 1991 and August 2004

72 died (6 MAS, 41 CDH, 25 other)
50 not measured (20 unable, 5 untraceable, 4 follow-up elsewhere, 15 refusal, 6 logistic)

5 children received ECMO elsewhere and were included in our follow-up

121 children (191 measurements)

	CDH	MAS	other
5 years only: n=25	4	13	8
8 years only: n=13	1	10	2
12 years only: n=18	2	11	5
5 and 8 years: n=41	10	21	10
5 and 12 years: n=1	0	0	1
8 and 12 years: n=18	2	14	2
5, 8 and 12 years: n=5	1	1	3

Figure 2. SDS FEV_1 (mean, 95%CI) before bronchodilation at 5, 8 and 12 years for the different subgroups. Triangles represent CDH patients (n = 14, 13 and 5 at 5, 8, and 12 years respectively); circles represent children with MAS (n = 34, 46, and 24 at 5, 8, and 12 years respectively), squares represent children who underwent neonatal ECMO for other diagnoses (n = 22, 16 and 9 at 5, 8, and 12 years respectively). A summary of all cases is shown as diamond.

Figure 2. SDS FEV$_1$ (mean, 95%CI) before BD at 5, 8 and 12 years for the different subgroups.
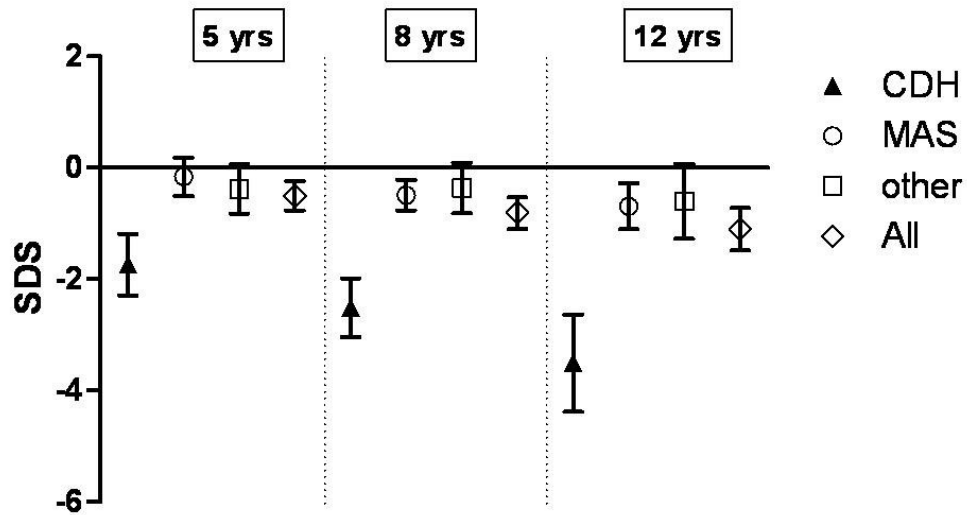

Figure 3. SDS FEV$_1$ (mean, 95%CI) after bronchodilation at 5, 8 and 12 years for the different subgroups. Triangles represent CDH patients (n= 10, 14 and 5 at 5, 8, and 12 years respectively); circles represent children with MAS (n=26, 46 and 23 at 5, 8, and 12 years respectively), squares represent children who underwent neonatal ECMO for other diagnoses (n= 16, 15 and 11 at 5, 8, and 12 years respectively). A summary of all cases is shown as diamond.

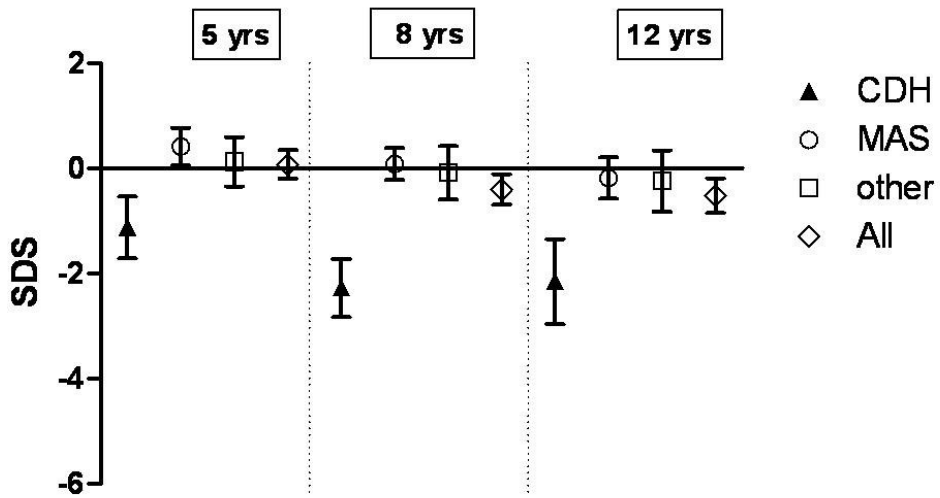Figure 3. SDS FEV$_1$ (mean, 95%CI) after BD at 5, 8 and 12 years for the different subgroups.

Figure 4. Change of SDS FEV$_1$ before bronchodilation in CDH patients from 5 to 12 years. Each dot respresents a measurement of an individual patient.

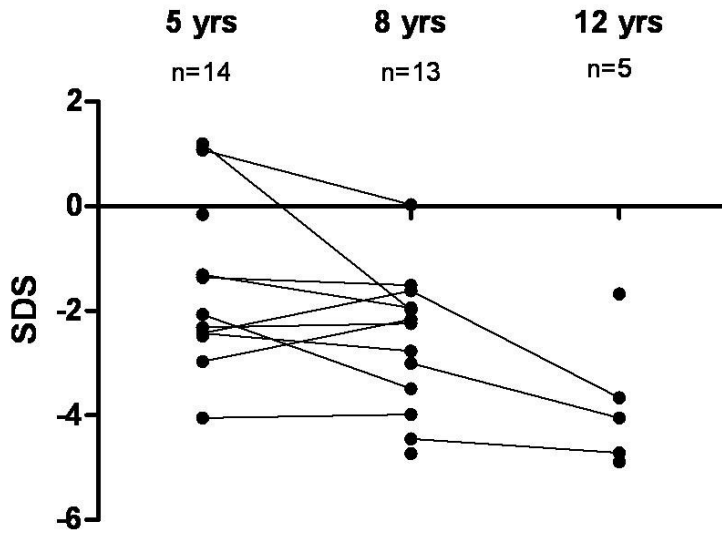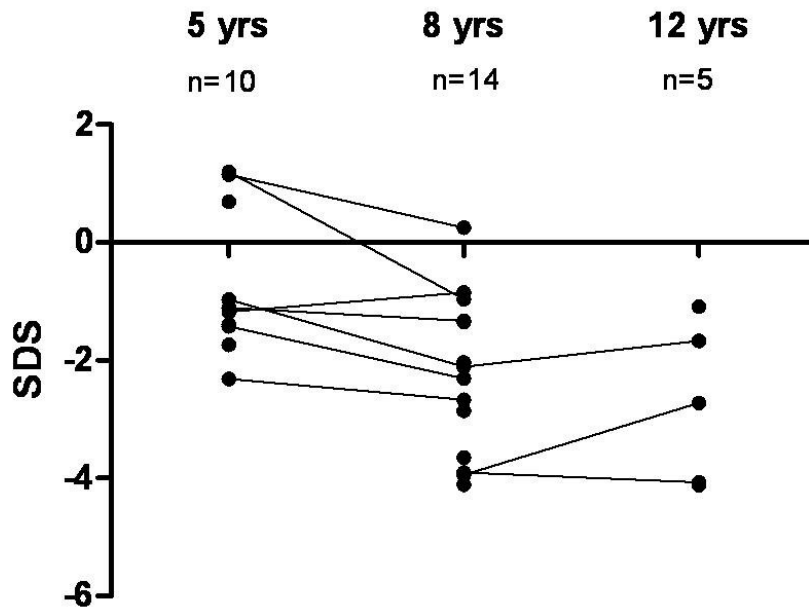Figure 4. SDS FEV$_1$ before BD in CDH patients

Figure 5. Change of SDS FEV_1 after bronchodilation in CDH patients from 5 to 12 years. Each dot respresents a measurement of an individual patient.

Figure 5. SDS FEV_1 after BD in CDH patients

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