Long-term Pulmonary Sequelae in Children with Congenital Diaphragmatic Hernia

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Neonates with congenital diaphragmatic hernia (CDH) often suffer from respiratory insufficiency due to lung hypoplasia and pulmonary hypertension. Artificial ventilation is frequently required, and this leads to a high incidence of bronchopulmonary dysplasia. Long-term follow-up studies have shown persisting airway obstruction. To evaluate the long-term pulmonary sequelae in CDH, we studied 40 CDH patients of age 7 to 18 yr (median 11.7 yr) and 65 age-matched controls without CDH and lung hypoplasia who underwent similar neonatal treatment. Mild airway obstruction was found in both groups with more peripheral airway obstruction in CDH patients than in control subjects. Both groups had normal TLC and single-breath carbon monoxide diffusion capacity (DLCO). CDH patients had increased residual volume (RV) and RV/TLC compared with controls. Increased airway responsiveness to methacholine (MCH) was common but bronchoconstriction to inhaled metabisulfite (MBS) was rare both in CDH and control subjects. We conclude that this group of CDH patients has minor residual lung function impairment. Mild airway obstruction and increased airway responsiveness to inhaled MCH but not to MBS suggest that structural changes in distal airways are involved and not autonomic nerve dysfunction. Both artificial ventilation in the neonatal period and residual lung hypoplasia seem important determinants of persistent lung function abnormalities in CDH patients.

METHODS

Patients

A group of 45 children survived neonatal operative repair of CDH in our Department of Pediatric Surgery between 1975 and 1986. Forty could be traced and were willing to participate. Operative repair was performed immediately after diagnosis of CDH in all patients using an abdominal approach. Thirty-five children with left-sided CDH and one with right-sided CDH had surgery within the first day of life. All patients routinely received antimicrobial prophylaxis perioperatively. Thirty-one children suffered from severe respiratory insufficiency within the first 6 h...
after birth. We attempted to select two age-matched control patients with­
out CDH for each CDH patient. The controls were selected from files of
the Neonatal and Pediatric Intensive Care Units of the Sophia Child­
en’s Hospital in Rotterdam, and the Neonatal Intensive Care Units of the
Wilhelmina Children’s Hospital in Utrecht and the Free Univer­
sity Hospital in Amsterdam. These control patients were all matched
for age at follow-up, and further selected to obtain the best possible
match for gestational age, birth weight, duration of artificial ventila­
tion, duration of supplemental oxygen, and sex. To be included in this
study the following criteria had to be met by all patients: (1) ability to
perform lung function tests reproducibly, that is, coefficient of vari­
ation in three consecutive measurements of FEV₁, < 5%; (2) clinically
stable period of at least 3 wk prior to the lung function tests. Exclusion
criteria were: any previous thoracic surgery for other reasons than CDH;
(congenital) heart disease; lung hypoplasia following prolonged rupture
of membranes or renal anomalies with oligohydramnion, or other con­
genital or acquired disorders of the lungs or airways; inability to follow
study instructions; inability to inhale medication adequately. The study
was approved by the medical ethical committees of all hospitals involved.
Written informed consent was obtained from all parents.

Study Design
During a prestudy visit a detailed medical history, including personal
and family history of atopy and lung disease, was taken. Furthermore,
the parents were asked to fill out a standardized questionnaire referring
to respiratory symptoms, consultation of physicians, and smoking habits.
Physical examination was performed including pulse, blood pressure,
respiratory rate, and auscultation of heart and lungs. Two wk before
the lung function tests, daily peak flow measurements (Mini Wright Peak­
flowmeter; Airmed, Harlow, UK) were performed at home in the morn­
ing and evening (before taking medication if required), and recorded
on a daily record card. The highest value of three consecutive measure­
ments was used for further analysis. The symptoms cough, wheezing,
production of sputum, and dyspnea were recorded daily. For each symp­
tom a score from 0 (absent) to three (severe) was given. In this way a
maximum score of 96 could be obtained within an 8-d period. The mean
diurnal variation of peak flow (which is the absolute difference between
morning and evening value divided by the mean value of morning and
evening × 100%) (18) and the total cumulative symptom score from
Day 8 to Day 15 were evaluated.

Lung function tests were performed on two separate days within a
1-wk period. Any medication was discontinued 12 h prior to the tests.
To avoid diurnal variation in the measurements, all tests were done in
the morning. Spirometry was performed on the first day between 9:00
and 11:00 a.m., and followed by an inhalation provocation test with
methacholine (MCH) when the baseline ratio of forced expiratory vol­
ume in one second to vital capacity (FEV₁/VC) was at least 0.7. One
hour later, when the baseline FEV₁ had returned to at least 90% of the
initial baseline, an inhalation provocation test with methasulphite (MBS)
was performed. Methacholine is a bronchoconstrictor which acts directly
at airway smooth muscle, whereas MBS acts indirectly, probably via
neuronal pathways (19). On the second day, spirometry and volume-flow
curves were recorded before and after maximal bronchodi­lata­tion with terbutaline to study reversibility of airway obstruction. Helium dilution
spirometry, body plethysmography, and single-breath carbon mono­
xide diffusion capacity (DLCO) were carried out before bronchodi­lata­tion only.

Lung Function and Bronchial Provocation Tests
Spirometry was performed using a water-sealed spirometer (Volu­
test Model V13; Mijnhardt, Zeist, the Netherlands). FEV₁, VC, and PEFR were
determined as the best of three reproducible measurements. Flow-volume
curves were obtained with a heated Fleisch pneumotachograph (Num­
ber 3.1184; Godart Statham, Bilthoven, the Netherlands) connected to
a computer. FEV₁, FVC, peak expiratory flow (PEF), and maximal ex­
piratory flows at 25% of the FVC (MEF₂₅) were determined and the best of three consecutive measurements was recorded and expressed as
percentage of predicted values (20).

Spirometry and flow-volume curves were performed before and 15
min after 1 mg of terbutaline sulfate, delivered by turbuhaler (Astra Phar­
maceuticals, Lund, Sweden) as two inhalations of 500 µg. After each inhalation
the breath was held for 5 s. The change, expressed as percent­
age of predicted value, was calculated to evaluate reversibility of any
airflow obstruction.

A water-sealed spirometer (Expirograph; Godart Statham, Bilthoven,
the Netherlands) filled with a known concentration of helium was used
to determine TLCHe, residual volume of helium (RVHe), VCHe, tidal vol­
tume (TV), inspiratory reserve volume (IRV), and expiratory reserve vol­
ume (ERV). Helium was allowed to wash in for at least 5 min during
normal tidal breathing until a stable concentration was obtained. Volumes
were expressed as percentage of the actual TLC. Specific conductance
of airs (SGaw), TLCpleth, RVpleth, and RV/TLC were determined by
body plethysmography (Jaeger Masterlab, Würzburg, Germany), and
the best of three consecutive measurements was recorded. All values,
except RV/TLC, were expressed as a percentage of predicted values (20).
Carbon monoxide diffusion capacity (DLCO) was measured using a single­
breath method (Jaeger Masterlab, Würzburg, Germany). Reference values
for DLCO and DLCO corrected for alveolar volume (DLCO/Ns) were based
on a study performed in our laboratory in 103 healthy Dutch children (21).

Inhalation provocation was carried out with aerosolized methacho­
line bromide and sodium metabisulphite (Na₂SO₃, buffered to pH 7.4
by adding phosphate buffer). MCH was given in doubling concentra­
tions of 0.15 to 39.2 mg/ml, MBS in doubling concentrations of 2 to
256 mg/ml as described previously (22). The aerosols were generated
by a calibrated De Vilbiss 66 Nebulizer (De Vilbiss Co., Somerset, PA),
with closed vent, attached to a French-Rosenthal dosimeter (Labora­
tory for Applied Immunology, Baltimore, MD) driven by air at 138 kPa.
The children were instructed to inspire slowly and as deeply as possible.
During inspiration the dosimeter was triggered for 0.6 s. After full in­
spiration, breath was held for 5 s. A total of 20 µl of aerosol was deliv­
ered to the mouth in 4 consecutive breaths. Mouth doses were 3 to 784
µg for MCH, and 40 to 5,120 µg for MBS. Provocations with MCH
and MBS were preceded by inhalation of normal saline. The interval
between consecutive doses was 3 min. FEV₁ was measured in triplicate
after each dose-step until the best value had fallen from baseline by at
least 20%. The provocative dose that resulted in a 20% fall in FEV₁ (PD₂₀)
was calculated by interpolation of the dose–response curve on a log­
linear scale.

All lung function tests were performed with subjects in sitting posi­
tion. All volumes were corrected to BTPS conditions. The equipment
and procedures were in accordance with international recommendations (23,
24).

Data Analysis
Where two control patients were available for a CDH patient, the mean
value of two matched controls was used for paired analysis of the differ­
cences between CDH patients and controls. In the few cases where only
one control patient was available, the data of this control patient were
used. To exclude the influence of prematurity and atopy as confound­ing
factors, separate analysis of data was performed after excluding all
prematurely born infants, and after exclusion of all atopic children. Data
of CDH patients and controls were compared with paired t tests, or Wil­
coxon’s signed-rank test if appropriate. Paired comparisons of percen­
tages were done with the Mantel-Haenszel test. Logarithmic transforma­
tion was used in all analyses of PD₂₀/MCH to approximate a normal
distribution. To evaluate the effect of age on PD₂₀/MCH, logistic regres­
sion was performed. Because only few responded to MBS, these data
were described without further statistical analysis. The relation between
patient characteristics and lung function results was studied by least
squares regression. Multiple regression analysis for continuous outcomes
was used to study interaction between variables, i.e., whether the magni­
itude of the difference between both groups depended on certain other
parameters. Correlation coefficients given are Spearman’s. Data given
are mean ± SEM unless stated otherwise. Statistical significance was
accepted at 1% level for all tests.

RESULTS
Patient Characteristics, Questionnaire,
and Physical Examination
In the CDH group (n = 40), all patients except two had left­
sided CDH. Two patients were small for gestational age; three
children were born prematurely. Two CDH patients had only a
exercise endurance was mentioned by 18% of the CDH group.

Tory revealed lung symptoms within the last year in 11 of 40 CDH patients and 23% of control patients had a history of atopy (NS). The medical history of physical examination, and daily peak flow registrations were not significantly different after exclusion of prematurely born children, or after exclusion of atopic subjects.

### Lung Function

Analysis was performed on data from 35 CDH patients and 65 matched control patients. Spirometry showed a significantly lower FEV1/VC in CDH compared with controls before bronchodilatation (Table 2; p = 0.01). Flow-volume curves showed normal values for FVC and PEF before and after bronchodilatation in both groups (data not shown). FEV1 was significantly lower in CDH patients compared with controls before and after bronchodilatation (84 ± 3 versus 95 ± 2, and 92 ± 3 versus 101 ± 2% predicted, respectively). The percentage of patients with abnormally low FEV1 and MEF25 values (< 1.96 SD from predicted) was high in both groups: FEV1 was abnormal in 67% of CDH patients and 25% of controls before bronchodilatation, and in 47% of CDH patients and 22% of controls after bronchodilatation. MEF25 was abnormally low in CDH before and after bronchodilatation in 79% and 59% and in controls in 41% and 22% respectively. After 1 mg of inhaled terbutaline flow-volume curves showed a significant increase in FEV1 and MEF25 in both CDH and in controls (Table 2; p < 0.001). CDH patients and controls showed no significant differences in reversibility of airflow obstruction (Table 2).

Body plethysmography showed a significantly higher mean RVpleth and RV/TLCpleth in CDH than in control patients (Table 2; p = 0.001 and 0.006, respectively). SGaw was 181 ± 15% predicted in CDH and 156 ± 12% predicted in controls (NS). Air trapping was estimated from the difference between TLCpleth and TLCtHc: Mean trapped air was 5 ± 0.5% of TLCpleth in CDH and 3 ± 0.6% in controls (NS). RV/TLCtHc was 26 ± 1% in CDH and 23 ± 1% in controls (p = 0.006). No differences in ERV, TV, and IRV were found between the groups.

DlCO was measured in 17 matched couples and was 103 ± 3% predicted in CDH and 105 ± 2% predicted in control patients (NS). DLCO/Va was 93 ± 3% predicted in CDH and 101 ± 2% predicted in controls (NS).

Separate analysis of term born patients showed similar percentage of predicted values for all lung function tests. In controls spirometric FEV1/VC before and after bronchodilatation were significantly lower (differences of means both 5) in the atopic children than in nonatopic children. The same was true of MEF25 (difference of means before and after bronchodilatation, respectively, 14% and 24%). Abnormal MEF25 was observed in 22% of term born controls without an atopic history, irrespective of bronchodilatation.

### Airway Responsiveness

In four CDH patients and in four controls FEV1/VC was less...
Inhalation provocation with methacholine (MCH) in CDH and in control patients. The provocative dose that resulted in a 20% or more decrease in FEV₁ after inhalation of MCH was 784 μg. Nonrespondents are indicated in closed circles. After exclusion of premature-born children two CDH and four control respondents were left; after exclusion of atopic children only one respondent to inhalation of MBS was present in each group. No difference in the prevalence of increased responsiveness to MCH and MBS was found between CDH patients and controls with or without a history of atopy, and the same was true for PD₂₀MCH and PD₂₀MBS in respondents. No relation between positive challenge tests and a positive family history for lung disease or atopy was apparent in CDH and control patients.

**Correlation between Lung Function Results and Other Patient Characteristics**

This analysis was performed in 38 CDH patients and 65 controls. The results of the lung function tests and the prevalence of increased airway responsiveness on the one hand, and gestational age, birth weight, maximal FIO₂, or parental smoking habits on the other hand did not correlate for either group. In CDH the duration of artificial ventilation correlated negatively with spirometric FEV₁ before and after bronchodilatation (Figure 2), spirometric VC before and after bronchodilatation, FEV₁ and FVC in flow-volume curves after bronchodilatation, and VCpleth. All slopes resulting from linear regression analysis of lung function parameters against duration of ventilation in CDH patients were between -1.0 and -1.2% predicted per day of ventilation (p < 0.01 in all cases), whereas no significant slopes were found in control patients (slopes varied from -0.3 to 0.3). In addition, CDH patients and control were grouped according to whether or not they had been ventilated for at least 7 d. Controls who had been ventilated for less than 7 d had similar lung function results as those who had been ventilated for at least 7 d. However, CDH patients who had been ventilated for 7 d or more had significantly lower FEV₁ and VC (spirometry and flow-volume curves, before and after bronchodilatation), PEF before dilatation dilatation with 1 mg of inhaled terbutaline measured by spirometry in CDH (closed circles) and controls (open circles). The regression lines are indicated for both groups: solid line for CDH (y = 103.03 - 1.12 \* ventilation; p = 0.0001) and dashed line for controls (y = 103.14 - 0.02 \* ventilation; p = 0.97).

**Figure 1.** Inhalation provocation with methacholine (MCH) in CDH and in control patients. The provocative dose that resulted in a 20% decrease of FEV₁ is indicated for MCH on a logarithmic scale. CDH patients are shown as closed circles and controls as open circles. The highest dose of MCH was 784 μg. Nonrespondents are indicated in the box.

**Figure 2.** Relation between duration of artificial ventilation (days) and FEV₁ (expressed as percentage of predicted) after bronchodilatation with 1 mg of inhaled terbutaline measured by spirometry in CDH (closed circles) and controls (open circles). The regression lines are indicated for both groups: solid line for CDH (y = 103.03 - 1.12 \* ventilation; p = 0.0001) and dashed line for controls (y = 103.14 - 0.02 \* ventilation; p = 0.97).
bronchodilatation, and MEF$_{25}$ after bronchodilatation than CDH patients who had been ventilated for up to 7 d. CDH patients ventilated for at least 7 d had significantly lower TLC$_{He}$, TLC$_{plen}$, VC$_{plen}$, and higher RV/TLC$_{plen}$ than those who had been ventilated shorter (Table 3). DLCO was 93 ± 4% predicted in CDH patients ventilated for up to 7 d and 98 ± 4% in those who had been ventilated for 7 d or more (NS). Both for CDH and control patients a negative correlation was found between the duration of oxygen supply and FEV$_1$, and VC before and after bronchodilatation in spirometry, FVC before and after bronchodilatation, FEV$_1$ before bronchodilatation in flow-volume curves, TLC$_{plen}$, TLC$_{He}$, VC$_{plen}$, and RV/TLC$_{plen}$. Similar correlations were found after exclusion of children who were born prematurely and/or had a positive atopic history. Age at follow-up in CDH and in controls correlated positively with PEF before and after bronchodilatation. In CDH, the probability to have a positive response to inhalation of MCH, i.e., PD$_{20}$MCH < 784 µg, correlated negatively with age (p = 0.001; Figure 3). The same was true for the probability to have a PD$_{20}$MCH < 150 µg (p = 0.004; Figure 3). No significant relation between the presence and the magnitude of PD$_{20}$MCH and age could be shown for control patients. The relations of these parameters with age, however, did not differ significantly between the two groups. Children who had respiratory symptoms during the first 3 yr of life or within the last year had significantly lower FEV$_1$/VC, FEV$_1$, and MEF$_{25}$ before and after bronchodilatation compared with children without respiratory symptoms. Similar results were found after exclusion of prematures and atopic subjects.

DISCUSSION

We found mild obstructive lung function abnormalities and a high prevalence of increased airway responsiveness to methacholine both in children with neonatal repair of CDH and, to a lesser extent, in age-matched controls. The controls underwent similar neonatal treatment but had not been operated on for CDH and did not have lung hypoplasia. Both groups showed normal total lung capacity and normal diffusion capacity under resting conditions, suggesting that no important lung function impairment had resulted from CDH.

Interpretation of long-term pulmonary sequelae after neonatal repair of CDH has been difficult because of the lack of comparative long-term data on lung function abnormalities in ventilated term neonates without CDH. The present study is the first in which lung function data of CDH patients are compared with those of age-matched controls who were selected for the best possible match for gestational age, birth weight, duration of artificial ventilation and oxygen supply, and sex. Gestational age was slightly, but significantly lower in the control group and it could be argued that this may explain differences in lung function. However, mean gestational age was more than 37 wk in both groups (37.7 versus 39.6 wk), and similar results were found after separate analysis of term born children. Therefore differences in lung function between the two groups can not be attributed to differences in gestational age. The maximal F$_{O2}$ was significantly lower in CDH than in controls, but did not correlate with the measured lung function parameters. The groups were similar with respect to atopic history, positive family history for atopy or lung diseases, and smoking habits. Therefore, these potential confounding factors cannot explain differences in lung function between CDH and controls either.

We found more peripheral airway obstruction in CDH patients than in controls, as was apparent from decreased FEV$_1$/VC and MEF$_{25}$, high percentages of abnormal FEV$_1$, and abnormal FEV$_1$ and MEF$_{25}$ in more than 20% of cases after exclusion of the prematurely born and atopic children. Separate analysis of term born children without a history of atopy indicated that in controls FEV$_1$/VC and MEF$_{25}$ were higher in nonatopic children compared with atopic children. Such a difference could not be demonstrated for the CDH group (with only three children having a history of atopy). There was no difference in reversibility of airway obstruction between the groups. The mean reversibility of FEV$_1$ was within the normal range seen in healthy individuals (24). Mild airflow obstruction (13, 14, 26) or normal spirometry (17) were reported in school age children before 1976. A number of these children were operated on after the perinatal period at ages up to 2 yr. An unspecified number were ventilated postoperatively. It is likely that the number was small. In patients born subsequently, Falconer and coworkers (15) found evidence of re-

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&lt;7 d (n = 23)</th>
<th>&gt;7 d (n = 15)</th>
</tr>
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<tbody>
<tr>
<td>Duration of ventilation, median (range)</td>
<td>2 (0-6) d</td>
<td>16 (7-49) d</td>
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<tr>
<td>Spirometry</td>
<td></td>
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<tr>
<td>FEV$_1$ before BD</td>
<td>98 ± 3</td>
<td>74 ± 4</td>
</tr>
<tr>
<td>FEV$_1$ after BD</td>
<td>103 ± 3</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>VC before BD</td>
<td>103 ± 3</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>Flow-volume curves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF before BD</td>
<td>100 ± 4</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>MEF$_{25}$ after BD</td>
<td>76 ± 6</td>
<td>48 ± 7</td>
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<tr>
<td>Body plethysmography</td>
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<tr>
<td>TLC</td>
<td>108 ± 3</td>
<td>96 ± 3</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>27 ± 1</td>
<td>33 ± 2</td>
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*Values are mean ± SEM. All data are expressed as percentage of predicted, except RV/TLC. Significant differences were found for all parameters (p < 0.01).
duced expiratory flows at 50% VC. Seven of his 19 children had been ventilated for 4 d or more.

Airflow obstruction has been described in several follow-up studies of premature children with and without BPD (3–5, 9, 27), but normal spirometric results have also been reported (8). The airflow obstruction described in nonventilated CDH patients suggests residual hypoplasia of lungs or airways. Abnormal tracheal or bronchial cartilage has been described in CDH (28). This may enhance airflow obstruction as a result of inadequate support, and, hence, dynamic compression of the intrathoracic airway during forced expiration. In addition, functional impairment may have resulted from airway damage due to artificial ventilation and oxygen treatment in ventilated CDH patients.

TLC and VC were normal in our study, consistent with the observations of others (13, 14), although restrictive defects have also been observed (29). Residual volume was marginally elevated in our study in that of Reid and Hutcherson (29).

Normal TLC and VC in CDH suggest that absence of residual lung hypoplasia and it may well be that the compensatory lung growth takes place during the first year of life (30). However, the number of alveoli may still be reduced. Therefore we also measured diffusion capacity, which is a measure of the diffusion surface and consequently of the alveolar surface. DlCO and DLCO corrected for alveolar volume were normal in CDH and in control patients. This suggests the presence of a normal diffusion surface area under resting conditions at long-term follow-up in CDH, as described previously (14). Exercise stress testing with measurement of DlCO would be necessary to reveal the functional significance of a possible residual lung hypoplasia. In favor of residual lung hypoplasia are mild airflow obstruction, decreased lung perfusion on the ipsilateral side of the diaphragmatic defect (14, 16, 29), the observation that anatomic formation of further generations of airways and conducting vessels does not develop after 16 wk gestation (31), and findings of long-term lung morphology after neonatal repair of CDH: Normal total lung volume, but an abnormal lung structure, has been described in three cases of CDH at autopsy after 2.5 to 64 mo (32, 33). Whereas the total number of alveoli was either decreased (32, 33) or normal (33), the alveolar size was increased in all cases, especially on the ipsilateral side. The lower DLCO/VA in our CDH patients compared with controls may indicate persistence of such morphologic abnormalities. The normal DLCO in CDH patients and in age-matched ventilated controls suggests that diffusion capacity is not severely affected by lung damage caused by artificial ventilation.

There are no data on airway responsiveness at long-term follow-up in children with CDH. We found a high prevalence of MCH responsiveness both in CDH (56%) and in control patients (38%), irrespective of an atopic history or a positive family history for atopy or lung disease. Several investigators have described increased airway responsiveness to inhalation of MCH or histamine in premature infants following artificial ventilation (5, 6, 27). A high prevalence of exercise-induced bronchospasm was found in a group of term born children with meconium aspiration syndrome following a short period of artificial ventilation (34). The high prevalence of increased airway responsiveness to MCH, together with the smaller number of positive responders after inhalation of MBS, suggests that the mechanism of airway narrowing in our patients is different from that in asthmatic subjects where both challenges correlate well (35). Residual structural narrowing of distal airways or airway smooth muscle hypertrophy may explain our findings, because these abnormalities would lead to increased airway responsiveness only as a result of the altered airway geometry (36). Because no differences were found between CDH patients and controls, it can be assumed that artificial ventilation during the neonatal period is a more likely cause of these abnormalities than lung or airway hypoplasia in CDH. We found that the prevalence of airway responsiveness to MCH was significantly lower in older CDH patients. This may reflect the natural history of airway responsiveness following artificial ventilation in the neonatal period, although our cross-sectional data do not allow for this assumption. Another possible explanation is that older patients had been artificially ventilated for a shorter period of time because of the restricted intensive care treatment in those days. Therefore CDH patients born earlier, e.g., between 1975 and 1980, and who survived their neonatal period, may have had less severe lung hypoplasia with less structural small airway abnormalities than the children who were born later.

We found a negative correlation between the duration of ventilation and FEV1 at follow-up in CDH. A negative correlation between FEV1 and duration of ventilation has been described in follow-up studies of premature as well (4, 9). Previous studies in ventilated premature infants without BPD suggest that the effect of artificial ventilation is independent of gestational age (8, 9). However, most premature infants with very low birth weight will require artificial ventilation for a longer period of time and are more likely to develop BPD (2). A high incidence of BPD in CDH patients has been reported by Bos and coworkers (12) who studied a group of CDH survivors born between 1980 and 1989 with respiratory insufficiency within the first 6 h after birth. The children in our study group were born between 1975 and 1986 when extracorporeal membrane oxygenation and high-frequency oscillatory ventilation were not available. It can be assumed that especially CDH patients with less severe lung hypoplasia survived at that time, whereas the children with severe lung hypoplasia and severe persistent pulmonary hypertension may have died even before reaching the Pediatric Surgical Intensive Care Unit. This assumption is supported by the fact that our group of CDH patients had a median duration of ventilation of only 4 d with a mean maximal FiO2 of 0.5. That we found lung function abnormalities especially in CDH patients who were ventilated for at least 7 d suggests that respiratory morbidity may well increase in those children with more severe lung hypoplasia, who will require artificial ventilation for longer periods of time and who presently survive CDH (3, 8, 9).

In conclusion, we found mild obstructive lung function abnormalities in CDH and also, but to a lesser extent, in carefully matched control patients. The difference between CDH patients and controls could not be explained by differences in patient characteristics and could therefore be due to residual lung hypoplasia and/or to anatomic and functional changes of the thoracic wall, the diaphragm, or the airway cartilage in the CDH patients. CDH patients showed no important reduction of lung volume and diffusion capacity under resting conditions. Airway responsiveness to MCH, but not to MBS, was increased in both groups, suggesting that the mechanism of airway narrowing was different from that in asthmatics. We speculate that structural abnormalities in distal airways are responsible for the high incidence of increased airway responsiveness. Our data suggest that not only residual lung hypoplasia, but also neonatal intensive care treatment contribute to the persisting airway obstruction and increased airway responsiveness in CDH patients.

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