Abnormalities in pulmonary function in infants with high-risk congenital diaphragmatic hernia

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Aims. The aim of the study was to analyze lung growth and abnormality of infant pulmonary function tests (IPFT) in congenital diaphragmatic hernia (CDH) survivors younger than three years of age with respect to unfavorable prognostic factors.

Methods. Thirty high-risk CDH survivors at the age of 1.32±0.54 years, body weight 9.76±1.25 kg were examined using IPFT: tidal breathing analysis, baby resistance/compliance, whole baby body plethysmography and rapid thoraco-abdominal compression. Gore-Tex patch was used in 13% of patients (GORE group). Pulmonary hypertension was diagnosed and managed in 13% (iNO group). Standard protocols and appropriate reference values were used and obtained data were statistically analysed.

Results. High incidence of peripheral airway obstruction (70%), increased value of functional residual capacity (FRC_p) 191.3±24.5 mL (126.5±36.9 % predicted; $P < 0.0005$), increased value of effective airway resistance (R_{eff}) 1.71±0.93 kPa.L^{-1}.s (144.4±80.1 % predicted; $P < 0.01$) and decreased specific compliance of the respiratory system (C_{rs}/kg) 14.1±2.3 mL.kPa.kg^{-1} (i.e., 76.1±20.1 % predicted, $P < 0.0005$) was noted in infants with CDH in comparison with reference values. Increased value of FRC_p was found in GORE group (165.7±51.9 versus 120.4±31.2, $P < 0.02$) and in iNO group (183.1±52.6 versus 117.8±25.7 mL; $P < 0.0005$).

Conclusion. A high incidence of peripheral airway obstruction, an increased value of FRC_p and decreased specific compliance of the respiratory system was noted in infants with CDH. Unfavorable prognostic factors (Gore-Tex patch, pulmonary hypertension) correlate with more severe alteration of pulmonary function in infants.

Key words: congenital diaphragmatic hernia, infant pulmonary function testing, lung dysfunction, chronic lung morbidity

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INTRODUCTION

Infants born with congenital diaphragmatic hernia (CDH) demonstrate a wide variability in lung hypoplasia and postnatal catch-up lung growth. In the past only newborns with less severe diaphragmatic hernia and favorable perinatal history survived. Today, these adults are largely free of clinical problems[1]. With improving neonatal intensive care mortality from CDH decreases and in comparison to the past even severely ill neonates with CDH survive[2,3]. Large diaphragmatic defect, lung hypoplasia, pulmonary hypertension, associated anomalies, FETO and ECMO therapy are determining factors of overall survival and long term morbidity[4-6]. These subpopulations of CDH survivors are identifiable groups[7], clearly at risk, and thus require long-term follow-up.

Prospective follow-up of CDH patients aims at identifying respiratory problems that have the potential to influence the quality of life of CDH survivors into adulthood. To prevent long term remodeling of the airways and improve prognosis, early diagnosis and treatment are necessary. Expansion of newer methods of early lung function testing to clinical practice could contribute to a better understanding of postnatal lung growth and prevention of chronic lung morbidity in children with CDH (ref.[8,9]). The aim of the present study was to analyse lung growth and functional abnormalities detected by infant pulmonary function testing (IPFT) prior to three years of age with respect to unfavorable prognostic factors in CDH survivors. As far as we are aware, the complex analysis of lung function using the four methods of IPFT (whole body plethysmography, tidal breathing analysis, baby resistance/compliance, and rapid thoraco-abdominal compression method – the "squeeze" method) simultaneously in CDH children under 13 kg and prior to three years of age, has not yet been published.

MATERIALS AND METHODS

During the study period (2006 to 2010), 73 consecutive neonates were treated for high-risk CDH (presenting with respiratory distress within 24 h of life or diagnosed prenatally). The management protocol has been described previously[10] and was identical for all patients. Extracorporeal membrane oxygenation (ECMO) was not used in any of the patients. Preoperative stabilization was achieved in 62 neonates who underwent surgical repair (85%), 11 patients died without any surgical intervention (15%). Six patients out of the 62 operated patients died during the early postoperative period. Total survival rate in the studied group was 77% and the survival rate of the operated patients was 90.3%. The repair of the diaphragmatic defect was performed via transverse laparotomy with interrupted non-absorbable sutures in one layer. In cases of aplasia of the posterior diaphragmatic rim, the patch was anchored with interrupted sutures around the ribs. Patches (1 mm Dual Gore-Tex patch) were only used when primary closure was not possible according to the decision of the attending surgeon. Inhaled nitric oxide (iNO) therapy was initiated based on the detection of pulmonary hypertension using echocardiography. Echocardiographic diagnosis of pulmonary hypertension was based on the presence of right-left blood shunting through the ductus arteriosus and foramen ovale, the measurement of tricuspidal valve insufficiency and estimation of pressure gradient on tricuspidal valve. The criteria for inhalation of iNO therapy were alveolo-arterial oxygen difference ($AaDO_2$) ≥ 550 mmHg on FiO_2 = 1,0; pre- and postductal differences of SaO_2 more than 5% and/or PaO_2 greater than 10 mmHg.

The study included patients whose parents signed a written consent to participate in the study. The study was approved by the institutional ethics committee.

Study design

Infant pulmonary function tests were performed in 30 infants and toddlers (53.6% of all survivors, 16 male, 14 female) after CDH repair whose body weight (BW) had not exceeded 13 kg. Demographic data and population characteristics are summarized in Table 1. Diaphragmatic reconstruction with a Gore-Tex patch and pulmonary hypertension were considered unfavorable prognostic factors. A Gore-Tex patch was used in 4 of 30 patients (13%, GORE group). Pulmonary hypertension was diagnosed and managed with iNO in 4 patients (13%, iNO group). Age at testing was 1.32±0.54 (median 1.07) years; body weight 9.76±1.25 kg (z-score -0,777) and body length 78.8±6.7 cm (z-score -0,024). After measurement of body weight and body length, each infant was sedated with chloral hydrate (80 mg/kg orally). When asleep, the patients were placed in a supine position in the whole-body plethysmograph with a neck roll for optimal airway patency. IPFT was not begun until the infant appeared to be in quiet sleep as has been recommended previously[11]. A special mask with a small amount of silicone putty was applied to ensure perfect seal. The tightness of the mask was verified by a test occlusion performed during the first measurement. Oxygen saturation was continuously monitored by pulse oximeter.

Infant pulmonary function tests

We used four IPFT methods in a series. The whole body plethysmography was performed first, followed by the other three methods in the following order: tidal breathing analysis, baby resistance/compliance and, finally, rapid thoraco-abdominal compression (the "squeeze" method). The total time period for the whole IPFT session did not exceed 20 min. All the above listed IPFT methods could be performed without altering the patient's position between the tests. A small mask (Rusch®, Silikomed size 1) was used. The occluded dead space of the mask and the system as a whole was 10 mL with the dead space of the mask equaling about 50% of the total dead space. No complications occurred during or after the IPFT.

Whole baby body plethysmography (BBP)

BBP was performed using the MS Baby Body system, ver. 4.6, VIASYS, Yorba Linda, U.S.A. To assess the effective flow resistance of the airways (R_{eff}) and the specific effective flow resistance of the airways (sR_{eff}), flow resistance was measured first. Second, occlusions for measurements of functional residual capacity (FRC_p) were performed at the end-inspiratory volume level. The resulting slope of the box pressure (P_{box}), assigned as volume–shift versus airway opening pressure (P_{ao}) during inspiratory/expiratory efforts, was used to calculate FRC_p. A minimum of five occlusions, each consisting of at least three inspiratory/expiratory movements, were analyzed[12]. The obtained FRC_p was corrected by deduction of the tidal volume (V_T).

Table 1. Characteristic of patients (n = 30).

Male : Female ratio	1.14 : 1
Mean birth weight	3097 g ± 540 g (range 2150-4320)
Mean gestational age	38.5 weeks ± 1,6 weeks (range 36-41)
Age at the time of IPFT	1.32 years ± 0,53 years (range 0.86-2.77)
Weight at the time of IPFT	9.76 kg ±1,24 kg (range 7.7-13)
Prenatally diagnosed	12/30 (40%)
Left-sided CDH	29/30 (97%)
iNO	4/30 (13%)
Gore-Tex patch	4/30 (13%)
Mean duration of mechanical ventilation	6.83 days (range 1-24)

Tidal breathing analysis (TBA)

Tidal breathing parameters were measured using the same setup as the BBP. The parameters of time to peak tidal expiratory flow (t_{PTEF}), total expiratory time (t_E) and its ratio (t_{PTEF}%t_E) were measured[9,13].

Baby resistance/compliance (BRC)

In order to assess passive respiratory mechanics the single occlusion technique (SOT) was performed. During SOT, the infant's airway was briefly occluded at the end-inspiratory part of the tidal breath. During the occlusion, Hering-Breuer reflex leads physiologically to relaxation of the respiratory system. During this relaxation, inspiration of the baby is inhibited and, following passive exhalation, is even prolonged[14]. We assessed compliance of the respiratory system (C_{rs}), specific C_{rs} (C_{rs}/kg) and the total respiratory system resistance (R_{rs}).

Rapid thoraco-abdominal compression (RTC)

RTC technique renders forced expiratory maneuvers possible even in infants. In spite of this technique operating in the tidal volume (V_T) range, it provides sensitive and reproducible data on airway patency. The RTC method was applied using the same technical setup (see above) with the addition of an inflatable jacket wrapped around the infant's chest and abdomen[15]. Compressed air from the external pressure source produced a rapid filling of the jacket. This movement generated a forced expiration from end-tidal inspiratory volume level (synchronously with the respiratory rate). We assessed both the qualitative and quantitative components of the RTC session. The difference between the shape of the preceding tidal breath and the forced partial expiratory flow-volume (PEFV) curve represented the qualitative aspect of the measurement (Fig. 1). The value of V'_{maxFRC} represented the quantitative component of the RTC method[15].

Reference values

The following reference values have been used: for the whole body BBP, the appropriate reference values reported by Hulskamp et al.[16] . For compliance of the respiratory system (C_{rs}) we used Tepper's reference values[17]. For the RTC we used the predicted values calculated using equations for V'_{maxFRC} allowing z-score transformation[18].

Statistical analysis

Descriptive statistics of the CDH study group are presented as means ± SD. Relative parameters (percent of

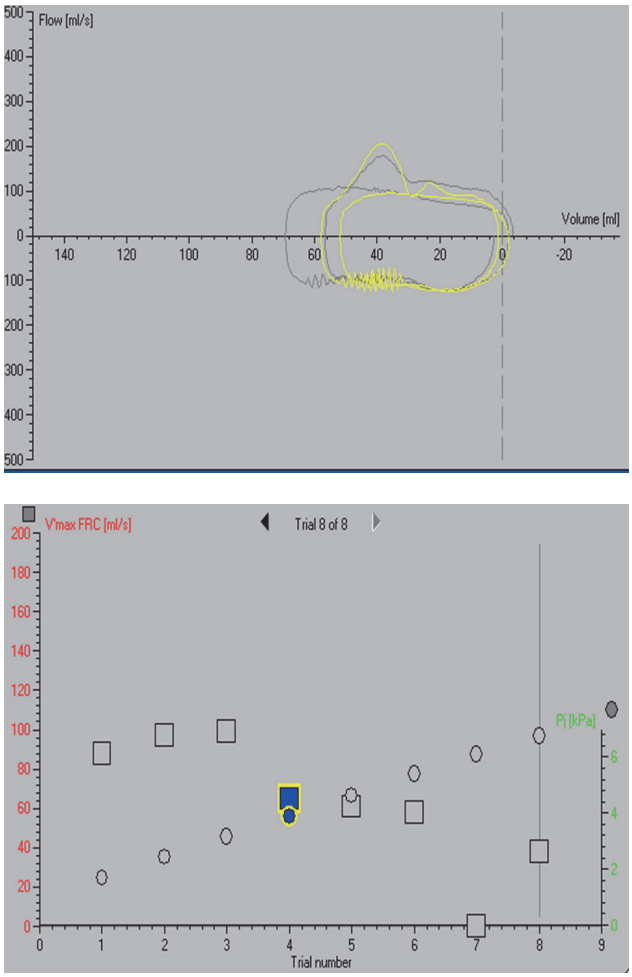

Fig. 1a,b. Rapid thoraco-abdominal compression method (RTC): severe airway obstruction in 13 months old boy after CDH repair.

1a. Apposition of the last two flow-volume curves (FVc) is shown. Note a very small differences between tidal (i.e. preceding) breaths and elicited (i.e., squeezed) FVc. A vertical dashes line on the right rim of the FVc represents the tidal end-expiratory volume level (FRC level).

1b. Preset driving pressure values (circles) are shown, there are 8 step-up values ranging from 3 to 10 kPa. There are also 8 step-up flow responses (defined as $V'max_{FRC}$ and shown as square). Note that values of $V'max_{FRC}$ did not increase which represent a severe airway obstruction.

Table 2. The results of pulmonary function testing in the whole study group in comparison with reference values.

Parameters	Actual value	% predicted *(z-score)	*P*
FRC_p [mL]	191.3±24.5	126.5±36.9	<0.0005
R_{eff} [kPa.L^{-1}.s]	1.71±0.93	144.4±80.1	<0.01
sR_{eff} [kPa.s^{-1}]	0.50±0.30	109.9±58.9	non significant
C_{rs}/kg [mL.kPa.kg^{-1}]	14.1±2.3	76.1±20.1	<0.0005
V'_{maxFRC} [mL.s^{-1}]	111.6±43.6	-2.387±0.833*	<0.00001

Results are presented as mean ± SD, except $V'_{max\ FRC}$ where z-score is used*

reference value and z-score, i.e. the difference between measured value and population mean relative to population standard deviation) were tested for difference of the CDH study group against reference values using one-sample t-test. An unpaired t-test was used for comparison of the two subgroups (GORE group, iNO group) to the rest of the CDH study group. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

We obtained technically acceptable IPFT data for the BBP, TBA and RTC methods in 30 infants; BRC data were completed in 16 infants. We have found a high incidence of peripheral airway obstruction (in 70% of patients tested), while the restrictive pattern was detected only in 6.7%. A typical finding of severe airway obstruction is presented in Figs. 1a,b. Increased values of functional residual capacity (FRC_p) ($P < 0.0005$), of effective airway resistance (R_{eff}) ($P < 0.01$), and decreased specific compliance of the respiratory system (C_{rs}/kg) ($P < 0.0005$) was noted in infants with CDH in comparison with reference values. The results of pulmonary function testing in the study group are shown in Table 2.

Functional residual capacity (FRC_p) equals 191.3±24.5 mL (126.5±36.9% predicted; $P < 0.0005$). The value of effective airway resistance (R_{eff}) reached 1.71±0.93 kPa.L^{-1}.s (144.4±80.1% predicted; $P < 0.01$), while specific effective airway resistance (sR_{eff}) was only 0.50±0.30 kPa.s^{-1} (109.9±58.9% predicted; n.s.). Specific compliance of the respiratory system (C_{rs}/kg) was 14.1±2.3 mL.kPa.kg^{-1} (i.e., 76.1±20.1% predicted, $P < 0.0005$). The following data reflect peripheral airway patency: a parameter of t_{PTEF}%t_E lowered to 22.2±8.5% predicted (not shown in Tab. 2), a parameter of V'_{maxFRC} reached only 111.6±43.6 mL.s^{-1} (z-score = -2.387±0.833).

An increased value of FRC_p at the time of testing (i.e., median 1.07 year) was found in the GORE group in comparison to the rest of the CDH study group (165.7±51.9 versus 120.4±31.2, $P<0.02$), while there were no significant differences in parameters Reff, $V'_{maxFRC,}$ C_{rs}/kg. Similarly, children in the iNO group revealed a higher value of FRC_p in comparison to the rest of the CDH study group (183.1±52.6 versus 117.8±25.7 mL; $P < 0.0005$).

DISCUSSION

The focus of attention of pediatric specialists has shifted from mere survival to decreasing long-term morbidity in high-risk CDH survivors. CDH survivors suffer from recurrent respiratory tract infections during their infancy and early childhood[19-21]. Trachsel et al.[21] has found a history of pneumonia in 35% and Okuyama et al.[19] in 26% of CDH survivors. Little is known about the etiology and natural course of these respiratory problems, which could have the potential to influence the quality of life of survivors of CDH into adulthood[22]. The etiology can be related to the embryology of the CDH, early postnatal therapy (ventilation, nutrition) and also the surgical treatment. Complex and precise tests are needed for a profound understanding of the main developmental events during both prenatal and postnatal periods in the hypoplastic lung in CDH.

For the assessment of pulmonary function, we used a complex of four IPFT methods; these methods revealed significant lung dysfunction in CDH survivors in comparison with population reference values (Table 2). We have found a high incidence of peripheral airway obstruction (in 70% of patients tested), while the restrictive pattern was detected only in 6.7%. We have found an increased value of FRCp, representing mild hyperinflation. We demonstrated slightly reduced specific compliance and a relatively significant increased total resistance of the respiratory system.

Our study investigated the influence of unfavourable prognostic factors (defect size = Gore-Tex patch, pulmonary hypertension = iNO treatment) on the development of lung function. Comparing patients with a Gore-Tex patch and patients with a primary suture, we found a significantly higher value FRC_p in the GORE group. Similarly, children in the iNO group revealed a higher value of FRC_p in comparison to the rest of the study group. Increased FRC_p reflects a moderate degree of hyperinflation. Our limited study could not reliably document whether the hyperinflation is due to the use of the synthetic patch or to the size of the defect itself. The adverse (iatrogenic) effect of aggressive artificial ventilation on lung hyperinflation cannot be excluded either. Nevertheless, the objective findings on IPFT may support early bronchodilator and anti-inflammatory therapy in cases of borderline clinical symptomatology. The results of the single center study presented here are not flawed by case selection bias and different therapeutic approaches. One team of attending neonatologists and pediatric surgeons directed the management and CDH patients presenting with respiratory distress within 24 h of life or diagnosed prenatally were included in the statistical analysis only. Regrettably, we were not able to collect a representative series of PFT from other age groups and the absence of serial IPFT information is the main weakness of our limited single center study.

The data on pulmonary function in CDH in early infancy are based on retrospective reviews from centers with limited numbers of patients[23-26]. The various degrees of pulmonary hypoplasia, the variety of postnatal management and differing testing techniques are the key factors which complicate the interpretation and comparison of studies. There are only a few papers that have been focused on the same patients and yielded at least a similar spectrum of pulmonary functional data.

Other unfavorable predictive factors were revealed by Wright et al. They used raised volume rapid thoracoabdominal compression technique and plethysmography to identify the factors that predict lung function in the first three years of life in 29 children with CDH (ref.[23]). Fourteen infants (48%) required extracorporeal membrane oxygenation (ECMO). The mean age at IPFT was 85.1±5weeks. Airflow obstruction was the most common

abnormality, seen in 14 subjects. Twelve subjects had air trapping, and 9 demonstrated restrictive disease. ECMO ($P = 0.002$), days on the ventilator ($P = 0.028$), and days on oxygen ($P = 0.023$) were associated with restrictive lung disease. They found mild deficits of lung function in the first three years of life. Clinical markers of increased severity (ECMO, ventilator days, and prolonged oxygen use) correlated with reduced lung function.

Panitch et al. analysed serial IFPT of 98 infants with CDH on 1-5 occasions using the raised volume rapid thoracic compression technique[22]. Forced expiratory flows were below normal. Total lung capacity was normal, but residual volume and functional residual capacity were elevated. Regrettably, they did not use the method of tidal breathing analysis (TBA) with measurement of time to peak tidal expiratory flow, total expiratory time and its ratio ($t_{PTEF}\%t_E$), which analyses active expiratory efforts and can detect participating obstructions. As in our study, their children requiring patch closure, pulmonary vasodilators, or ECMO had lower lung functions at follow up. They speculated that the presence of any of those markers of disease severity reflected more severe pulmonary hypoplasia, and this in turn resulted in greater overexpansion of airspaces with growth and diminished ability of the lung to undergo compensatory alveolarization.

Roehr et al.[24] found decreased C_{rs} with normal R_{rs} (compared to the control group) in infants after surgery for CDH at 44 weeks (range from 36-58) of postconceptional age. They also found a normal FRC value (measured by body-plethysmography at the time of testing). They suggested that the lungs of children after surgery for CDH were appropriately inflated. The breathing pattern differed considerably: CDH infants showed rapid, shallow breathing, i.e., significantly higher respiratory rate (RR) with significantly lower tidal volume, V_T ($P < 0.005$ and $P < 0.001$, respectively). The authors suggested that this different breathing pattern might be caused by the reduced C_{rs} in the CDH group. They considered the possibility of a growth in size of the existing (i.e., original or prenatally originated) alveoli along with the fact of a neoalveolarization, which contributes to a ("pathologically performed") restoration of the lung volume[27].

Kombourlis et al.[25] showed in their serial study (four assessments between 2.6±0.5 and 19.2±3.0 months of age) successive improvement and even normalization of lung function after repair of CDH. They found that all indices of lung function were abnormal during the first 6 months of life, but were almost normalized by the age of 24 months. A parameter of V'_{maxFRC} significantly improved over time (up to z-score 0.09±0.94), which means almost complete normalization of peripheral airway patency. According to our experience, such a result occurs more typically in infants and toddlers with chronic lung disease/bronchopulmonary dysplasia[28]. Kombourlis and co-workers also found a progressive increase of functional residual capacity (FRC_{N2}) from subnormal to significantly increased value, i.e., FRC_{N2} had actually increased above the predicted normal levels (z-score equals even 3.26±2.07). As FRC increased in parallel with an increase in C_{rs} the authors considered compensatory hyperinflation rather than true lung growth as being the causal mechanism. Increase of the respiratory system compliance (C_{rs}) was different from our results.

Recently, another study from Valfre et al.[26] presented a serial (longitudinal prospective) study on 61 CDH survivors within 24 months after CDH repair. The differences in lung function between patch- and non-patch-repaired CDH infants were found only at the age of 6 months, but after one year of age no differences were found between the groups. Authors measured just two IPFT parameters: R_{rs} and $t_{PTEF}\%t_E$. Their data showing persistent impairment in peripheral airway patency in toddlers after CDH repair were in agreement with our results in this study.

In the last couple of years, several studies looking at lung function outcomes in older children surviving congenital diaphragmatic hernia have been published[21]. Trachsel et al.[21] reported a cohort study of 26 adolescent survivors (mean age 13.2 years). Pulmonary function testing included standard spirometry (FEV_1, FVC and FRC determined by the nitrogen washout method) and body pletysmography. They found a high prevalence (48%) of airway responsiveness to bronchodilators (bronchial hyperresponsiveness) and mild to moderate airway obstruction as a long-term respiratory outcome in CDH patients. This correlates with the high occurrence of airway obstruction in our study. This increased incidence of obstructive findings in children with CDH may be partly a consequence of congenital abnormality in the formation of the respiratory tract in the prenatal period[29] and partly due to lung damage from the artificial pulmonary ventilation in the postnatal period[30]. By contrast, Stefanutti et al.[31] investigated 24 children aged 8.2 years by pulmonary perfusion scintigraphy (^{99m}Tc-MAA), static volume measurement, and spirometry. Pulmonary function appeared to be impaired in 45%, restrictive pattern was detected in 6 children (27.3%), an obstructive pattern in only 3 (13.6%) and mixed obstructive and restrictive impairment in 1 patient. They found a negative correlation between FEV_1 and the duration of ventilation at presentation. They suggested that this may be the consequence of lung hypoplasia, but initial ventilatory management may have contributed to increased pulmonary morbidity, as previously described by Ijsselstijn et al.[32].

Considering our results and the above mentioned published data, we presume that lung dysfunction, particularly in high-risk CDH infants, can be detected in early infancy. Application of new methods of early lung function testing into clinical practice will contribute to a better understanding of postnatal lung growth and prevention of chronic lung morbidity. Its usefulness as an individual decision making criterion for early bronchodilator and anti-inflammatory therapy is doubtful at present, as this will certainly continue to be a subjective decision by the attending team in years to come. Further studies are needed to define whether the early treatment may modify pulmonary function and morbidity in the future.

CONCLUSION

A high incidence of peripheral airway obstruction, an increased value of FRC_p and decreased specific compliance of the respiratory system was noted in infants with CDH. Neonates who required treatment of pulmonary hypertension or patch repair are burdened with a higher alteration of pulmonary function in childhood.

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