

Respiratory morbidity and growth after thoracotomic or thoracoscopic repair of esophageal atresia

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Abstract

Background:

Respiratory morbidity has been described in patients who underwent repair of esophageal atresia at neonatal age. We compared the influence of thoracotomy or thoracoscopy on lung function, respiratory symptoms and growth.

Methods

Functional residual capacity (FRC_p), indicative of lung volume, and maximal expiratory flow at functional residual capacity ($V'_{max_{FRC}}$), indicative of airway patency, of 37 infants operated for esophageal atresia were measured with Masterscreen Babybody at 6 and 12 months. SD-scores were calculated for $V'_{max_{FRC}}$.

Results

Repair was by thoracotomy in 21 cases (57%) and by thoracoscopy in 16 cases (43%). Lung function parameters did not differ between types of surgery (FRC_p ; $p=0.384$ and $V_{max_{FRC}}$; $p=0.241$). FRC_p values were in the upper normal range and increased from 6 to 12 months (22.5 and 25.4 mL/kg respectively, $p=0.010$). Mean (SD) $V'_{max_{FRC}}$ was below the norm without significant change in SD-scores from 6 to 12 months (-1.9 and -2.3 respectively, $p=0.248$).

Lung function or type of repair were not associated with clinical evolution up to 2 years.

Conclusion

Lung function during the first year was similar in infants with thoracotomy or thoracoscopy. Ongoing follow-up including pulmonary function testing is needed to determine whether differences occur at later age in this cohort.

Introduction

Specialized centers with optimal anesthetic and neonatal support facilities and surgical experience have reported 92% survival rates in infants with esophageal atresia (EA) with tracheo-esophageal fistula (TEF) [1]. Mortality cases are mainly related to prematurity and associated anomalies. The focus of attention is shifting to morbidity, because persistent respiratory symptoms are increasingly recognized after repair of EA, especially in the type with TEF. Symptoms include respiratory tract infections (RTI), brassy cough, chronic cough, stridor, dyspnea and wheezing [2], and are thought to result from tracheomalacia, abnormal epithelial function and defective esophageal motility. Severe tracheomalacia can cause collapse with life-threatening cyanotic spells sometimes even resulting in death. These symptoms are most pronounced in the first years of life with a tendency to improve considerably after this age [3-4]. Lung function abnormalities with both mild obstructive and restrictive patterns were described in several cross-sectional studies in infancy (3 months) [5], childhood (6-19 years) [3,6-7] and adulthood (\leq 37 years) [6]. Restrictive lung function is supposed to result from reduced lung growth after surgery rather than being a concomitant feature of the EA [8]. Thoracotomy-induced rib-fusion and reflux-associated problems are considered major risk factors for the restrictive ventilatory defects in EA patients [8]. However, longitudinal studies - especially within the first years of life - are scarce. Therefore, the above mentioned assumption on restrictive lung function in EA remains speculative.

We report a study that evaluated lung function longitudinally at 6 and 12 months after thoracotomic or thoracoscopic repair of EA. We also inventoried respiratory symptoms, gastro-intestinal morbidity, and physical growth within the first two years of life, compared for the two types of surgery. Furthermore we evaluated whether lung function outcomes in the first year of life could predict respiratory symptoms at two years of age and studied possible associations between clinical characteristics, other factors contributing to respiratory morbidity and lung function parameters.

Methods

The children included in this study all participated in a longitudinal follow-up program for surviving patients with EA admitted to the intensive care unit of the Erasmus MC - Sophia Children's Hospital between January 2005 and March 2009. Five types of EA are distinguished depending on the presence or absence of a TEF and its location. Until 2006, surgical repair was always by thoracotomy. Then, in 2006 a pediatric surgeon broadly experienced in minimal invasive surgery introduced thoracoscopic procedures in our department [9-10]. As a consequence, learning curve was minimalised. After preoperative cardiac ultrasound showing a normal turning aorta a right-sided extrapleural posterolateral thoracotomy was performed under general anaesthesia. Right-sided transpleural thoracoscopy was performed by insertion of 3 cannulae (2x3 mm, 1x5 mm) and CO₂ insufflation at a pressure of 5 mm Hg and a flow of 0.5 L/min. No chest drainage tube was placed routinely, feeding and anti-reflux therapy by nasogastric tube was started at day 3. All patients received morphine intravenously as analgesic treatment with doses adjusted to validated pain assessment using the COMFORT-B scale as published before by our group [11].

Ventilatory support was provided by conventional ventilation (Babylog 8000, Dräger Medical, Lübeck, Germany).

We recorded gestational age, birth weight, sex, type of EA, additional congenital anomalies, duration of ventilation and supplemental oxygen and thoracotomy or thoracoscopic repair. Retrospectively we recorded the presence of rib fusions on a chest X-ray in the first year of life. Lung function tests and other examinations were performed as described below

The follow-up programme aims to regularly assess lung function, growth and developmental parameters until 18 years of age [4,12]. The assessment protocol is the standard of care in the Erasmus MC-Sophia Children's Hospital and is offered to all children with congenital anomalies. Lung function is performed routinely in all children with abnormal development of the respiratory system tract. The Erasmus MC Medical Ethical Review Board (IRB) ruled that the "Medical Research in Human Subjects Act" does not apply to this research proposal, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed". Therefore IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes. Lung function data were evaluated at the end of 2011.

Lung function

Lung function was measured at the ages of 6 and 12 months (corrected for prematurity), provided the infants showed no signs of infection, had no acute respiratory symptoms, were not mechanically ventilated and were not dependent of supplemental oxygen. Sedation consisted of chloral hydrate (50-75 mg/kg). Functional residual capacity (FRC_p) was measured by whole body plethysmography (Masterscreen Babybody, Viasys, Hochberg, Germany) as described previously [13]. The mean FRC_p (mL/kg) of 3 to 5 technically acceptable measurements was calculated. FRC_p was expressed in mL/kg as suggested by Hülkamp et al [14]. The normal range suggested by those authors is 13 to 26 mL/kg. Forced expiratory flow at FRC_p ($V'_{max_{FRC}}$), a measure of airway patency and compressibility, was determined by the end-tidal rapid thoracoabdominal compression technique (Masterscreen Babybody, Viasys, Hochberg, Germany). The mean $V'_{max_{FRC}}$ (mL/s) of 3 to 5 technically acceptable measurements, with reliable end tidal expiratory flow generation, was calculated. All equipment and procedures complied with the guidelines of the ERS/ATS Task force on standards for infant respiratory testing[15]. We used the $V'_{max_{FRC}}$ reference values provided by Hoo and colleagues[16]. Tidal flow limitation, which indicates that maximal expiratory flow is achieved during tidal breathing, was recorded during lung function measurement[17].

FRC_p (mL/kg) was the primary outcome measure. Standard deviation scores (SDS) $V'_{max_{FRC}}$, respiratory symptoms and anthropometric SDS were the secondary outcome measures.

Respiratory morbidity, gastro-intestinal morbidity and physical growth

Before lung function testing, infants were physically examined at both follow-up visits. Examination included height and weight measurements, pulmonary auscultation, and neurological examination. Respiratory rate (RR) was measured during lung function assessment. The following respiratory outcome variables were recorded: the occurrence of one or more respiratory tract infections (RTI)

necessitating therapeutic courses of antibiotic treatment over the last 6 months prior to assessment, use of prophylactic antibiotics, and the use of inhaled bronchodilators and/or corticosteroids. Gastro-esophageal reflux (GER) was evaluated by barium swallow X-ray and pH-metry as previously described by our team [18]. According to the criteria by Vandenplas [19-20], a gastro-esophageal reflux index of > 10% was considered pathological. Gastrointestinal symptoms, use of medication and surgical treatment for GER were recorded. Dutch population data served as reference values for physical growth [21]. Chest X-rays were examined retrospectively to evaluate the presence of rib fusions.

Data analysis

Patient characteristics are presented as number of patients (percentage) or median (range). Mann Whitney U tests served to test differences in perinatal characteristics between included and excluded patients and between patients with a thoracotomic (group 1) and thoracoscopic (group 2) surgical repair. In this longitudinal study, the data are composed of repeated lung function measurement values obtained in different individuals at two time points (6 and 12 months of age). Most infants were assessed at both time points; some, however, only once. Differences between the subgroup of patients measured both times, the subgroup measured only at 6, and the subgroup measured only at 12 months were explored with the Chi-square and Kruskal-Wallis tests. Anthropometric and lung function data are presented as mean (SD). $V'_{\max_{FRC}}$ SDS were calculated as the difference between observed and predicted value divided by the residual standard deviation from the reference values for $V'_{\max_{FRC}}$. Since repeated measurements ANOVA allows for missing data at one time point, FRC_p , $V'_{\max_{FRC}}$, SDS $V_{\max_{FRC}}$ and SDS for height and for weight for height were evaluated by this method [22-23]. Proportion of FRC_p values above the normal range and the prevalence of flow limitation between both groups were compared with the Chi-square test.

To set approximate normal distribution for FRC_p , data were log-transformed. Back transforming the resulting means resulted in geometric means, which are presented. We analyzed the following parameters as covariates in univariate Mixed Models to investigate if they had a significant influence on lung function parameters: gestational age, birth weight, duration of ventilation, duration of supplemental oxygen, age at surgery and type of surgery (thoracotomy or thoracoscopy). The duration of supplemental oxygen was transformed logarithmically in order to reduce the effect of outlying values. All results are expressed as mean (95% CI) or median (range, IQR). The significance level was set at $p < 0.05$. SPSS 17.0 (Chicago, Illinois) was used for the analyses.

Results

Between January 2005 and March 2009, 55 newborns with EA were admitted to the Intensive Care Unit of the Erasmus MC-Sophia Children's Hospital. Five children with severe other congenital and/or syndromal anomalies died during admission, from causes unrelated to EA (trisomy 18 in one, CHARGE syndrome in one, cardiac anomalies in three). Thirteen infants (24%) were not included for various reasons; upper airway obstruction ($n = 4$), parental refusal to join the follow-up program including lung function measurement ($n = 5$), failure to sleep during lung function measurement ($n =$

2), severe scoliosis (n = 1) and the presence of a nasogastric tube preventing lung function measurement (n = 1). Thus, 37 infants were included in this study (Figure 1).

None of the perinatal characteristics differed significantly between included and excluded patients (not shown). Infants were born after a median gestational age of 38.3 weeks (range 28.9-42.3 weeks) with a median birth weight of 2.70 kg (range 1.08-3.81 kg). Two patients had an esophageal atresia without a tracheo-esophageal fistula (type A), the other 35 patients had an esophageal atresia with a distal tracheo-esophageal fistula (type C). Twenty-one patients underwent thoracotomic and 16 patients thoracoscopic type of repair. All infants had been ventilated conventionally for a median of 2 days (range 1-7 days) and needed supplemental oxygen for a median of 2 days (range 1-35 days). Ten patients (27%) were born prematurely, one of them was born at 29 weeks and developed CLD according to the definition by Jobe and Bancalari [24]. Two suffered from tracheomalacia with life-threatening incidents requiring an aortopexia at the ages of 7 and 11 weeks, respectively. Five patients had additional cardiac anomalies, all without hemodynamic consequences. These anomalies spontaneously resolved in 2 cases and remained without consequences in 2 other cases. One other patient was operated on at the age of 2 weeks for coarctation of the aorta. Seventeen patients (46%) developed an anastomotic stricture for which a median of 3 (range 1-15) dilatation procedures were necessary. One patient in group 1 suffered from atopic eczema, and the family history of 8 patients was positive for atopic symptoms (4 in each group). Perinatal characteristics (gestational age, birth weight, type of EA, age at surgery, duration of ventilation and supplemental oxygen, incidence of additional anomalies and anastomotic strictures) did not differ significantly between patients undergoing a thoracotomic (group 1) and a thoracoscopic (group 2) type of repair.

Twenty-eight infants were measured both at 6 and 12 months of age (16 in group 1). Nine were seen only once (5 in group 1), either at 6 or at 12 months, for the following reasons: failure to sleep during one of the measurements (n = 5), respiratory tract infection at the time of measurement (n = 2), upper airway obstruction (n = 1), loss to follow-up (n = 1) and logistic reasons (n = 2). Thirty-five (95%) of all children were also seen at the age of 2 years. The other participants in this study have not reached that age yet.

The surgical procedure had been right-sided in all cases. In 1 patient, conversion to open thoracotomy was needed. Chest X-rays performed within the first 5 years of life (median 11, range 1.5-65 months) in 19/21 patients (90%) who underwent a thoracotomy revealed rib fusion at the ipsilateral side in 2/19 (10%). One other patient (5%) had a rib fusion at the contralateral side where formerly a thoracic drain had been placed. None of the 16 patients who underwent a thoracoscopic procedure showed rib fusions on chest X-rays within the first 3 years of life (median 8, range 1.5-36 months).

Lung function measurements and respiratory morbidity

The median postnatal age at the first lung function test was 32 weeks (range 24-43 weeks; n = 33); at the second it was 57 weeks (range 51-66 weeks; n = 30). The corresponding median ages corrected for prematurity were 30 weeks (range 24-39 weeks) and 54 weeks (range 49-66 weeks), respectively. Reliable $V'_{max_{FRC}}$ measurements were obtained in 25 patients at 6 months and in 27 patients at 12

months. Reliable FRC_p measurements were obtained in 31 patients at 6 months and in 30 patients at 12 months. Reliable FRC_p measurement with inability to measure SDS $V'_{max_{FRC}}$ was caused by failure to sleep in 4 cases where the infant woke up during rapid inflation of the jacket, in 2 cases a gastrostomy drain needed for a severe anastomotic stricture prevented the infant from wearing the jacket. Two infants had tidal flow limitation and one had an irregular breathing pattern.

FRC_p and SDS $V'_{max_{FRC}}$ were not associated with type of surgery ($p=0.384$ and $p=0.241$ respectively (Table 1). The mean FRC_p increased significantly from 6 to 12 months ($p=0.010$). SDS $V'_{max_{FRC}}$ did not change significantly over time ($p=0.248$). The results are presented in Table 1 and Figure 2. Results from analyses excluding the two patients with a long-gap-type EA (type A) were not significantly different (data not shown). FRC_p values ≤ 13 mL/kg were noted in neither group. Twenty-five percent of FRC_p measurements resulted in values > 26 mL/kg. Seven FRC_p measurements in 6 patients ($n=3$ in each group) resulted in values >30 mL/kg (Figure 2). These proportions did not differ significantly between groups ($p=0.366$ for $FRC_p >26$ mL/kg; $p=0.430$ for $FRC_p > 30$ mL/kg). All 6 patients with $FRC_p > 30$ mL/kg had airflow obstruction with SDS $V'_{max_{FRC}}$ between -2.24 and -3.57 . Tidal flow limitation was found in two of them (both group 2); two other patients (1 in group 1 and 1 in group 2) had clinical evidence of tracheomalacia. In the total study population tidal flow limitation was found in seven patients (six at 6 months and one at 12 months). Three patients with flow limitation underwent thoracotomy (14% of patients in group 1) and 4 underwent thoracoscopy (25% of patients in group 2). This proportion was not significantly different between both groups ($p=0.437$) None of the patients underwent a bronchoscopy as a routine pre- or postoperative diagnostic procedure to confirm the extent of tracheomalacia. At 6 months, 4/19 (21%) infants in group 1 and 2/14 (14%) infants in group 2 had a respiratory rate ≥ 40 breaths/. At 12 months, 4/18 (22%) infants in group 1 and 2/14 (14%) infants in group 2 had a respiratory rate ≥ 35 breaths/min (Table 2). These proportions did not differ significantly between group 1 and 2 (both $p\geq 0.672$) [25].

Respiratory morbidity data are shown in Table 2. In the first year of life, significantly more patients in group 1 than in group 2 used inhalation medication ($p=0.037$). Other parameters did not significantly differ between the groups.

FRC_p values and SDS $V'_{max_{FRC}}$ at 6 and 12 months were not associated with the occurrence of \geq RTI requiring therapeutic antibiotic treatment in the previous 6 months. Two infants at 6 months and three at 12 months (all underwent thoracotomy) were being treated with prophylactic antibiotics for urologic reasons (all had an anorectal malformation as well). FRC_p at 12 months was significantly higher in these five children ($p=0.006$, airway and urologic prophylaxis). At 12 months, the use of bronchodilators and inhaled corticosteroids was not associated with lower FRC_p or SDS $V'_{max_{FRC}}$. At 6 months, the use of bronchodilators and inhaled corticosteroids was associated with higher log FRC_p ($p=0.031$). At 24 months of age, neither number of RTI within the past 6 months nor the use of prophylactic antibiotics was associated with lung function parameters during the first year of life.

Associations between lung function parameters and clinical characteristics

A longer duration of the log supplemental oxygen days was associated with higher SDS $V'_{\max_{FRC}}$ only at 12 months ($p=0.020$). A two-fold longer duration of supplemental oxygen days resulted in a mean increase of 0.4 SDS $V'_{\max_{FRC}}$ at both time points. Other significant associations between clinical characteristics and FRC_p values or SDS $V'_{\max_{FRC}}$ were not found. When analyses were repeated after exclusion of the 2 patients with a long gap type EA (type A), results did not change significantly (not shown).

Gastro-intestinal morbidity

A barium swallow X-ray was performed in 36 infants (21 infants in group 1; 15 in group 2) at a median age of 10 (IQR 6-13) weeks. In group 1 1/21 (5%) had no signs of reflux; 3/21 (14%) had reflux on abdominal compression; and 17/21(80%) had spontaneous reflux. In group 2 7/15 (47%) had no reflux, whereas 8/15 (53%) had spontaneous reflux. pH-metry was performed in 35 infants at a median age of 9 (IQR 8-17) weeks. Two patients were only measured during 24 hours while receiving anti-reflux medication; pathological reflux was found in 1 of them. Thirty-three patients were measured during 24 hours without receiving anti-reflux medication; 27 of them were measured another 24 hours while receiving anti-reflux medication. Pathological GER was found in 3 of the former without therapy (3/33; 9.1%, 1 patient in group 1; 2 in group 2) and in 2 of the latter (2/27; 7.4%, 1 in each group). Four patients (2 in each group) who suffered from severe tracheomalacia with life-threatening events underwent a surgical anti-reflux procedure before the age of 6 months (normal pH-metry $n=2$, pathological GER $n=1$, no pH-metry available $n=1$).

Physical growth

For the total group. mean (95% CI) SDS height was -0.38 (-0.70 to -0.06), -0.46 (-0.80 to -0.12), and -0.54 (-0.85 to -0.24) at 6, 12, and 24 months respectively. Mean (95% CI) SDS weight for height was -0.57 (-0.94 to -0.20), -0.70 (-1.07 to -0.33) and -0.78 (-1.13 to -0.43) at 6, 12 and 24 months respectively. At all ages SDS height and weight for height were significantly below the norm (SDS=0, all $p \leq 0.023$). In Figures 3 and 4 SDS height and SDS weight for height are shown for each individual patient in group 1 and in group 2; height in group 2 was significantly lower than in group 1 (≤ 0.001 at 6, 12 and 24 months); weight for height in group 1 was significantly lower than in group 2 (≤ 0.001 at 6, 12 and 24 months).

Discussion

In this study we longitudinally evaluated lung function during the first year of life in 37 infants after thoracotomic or thoracoscopic repair of EA. Thirty-five patients had type C EA and 2 type A. Furthermore we evaluated possible relationships between lung function, perinatal characteristics and respiratory morbidity. Lung function did not differ by type of surgery. FRC_p values, referring to intrathoracic lung volume [26], were in the upper normal range and had significantly increased from 6 to 12 months. SDS $V'_{\max_{FRC}}$ was significantly below the norm without a significant change from 6 to

12 months. Flow limitation, which may reflect severe airway malacia, was found in 7 patients (19%) of whom 4 had undergone thoracoscopic type of repair (25% of all patients in this group).

Lung function abnormalities in patients with EA with obstructive as well as restrictive patterns have been described at different ages from infancy [3,5] and childhood [3,6-7] to adulthood [6,8,27]. Sistonen and colleagues reported restrictive lung function in 57% of 101 adult EA patients (aged 22-56 years), for which thoracotomy-induced rib fusion was a significant risk factor [27]. Thirty percent of these adult EA patients had rib fusions in the previous thoracotomy area [28]. In the present study only 3 patients show rib fusion in the first year of life, all after thoracotomy. A thoracoscopic repair might contribute to a reduction of rib fusion and later concomitant restrictive ventilatory defects but we did not find a significant difference in lung function yet in the first year of life. Maybe differences in lung function between the 2 types of repair may become manifest later in life. FRC_p corrected for body weight increased significantly from 6 to 12 months suggesting an increase in lung volume. There is no reason to assume that this is based on extensive lung growth during the first year of life after repair of EA. It might well be that persistent higher airway obstruction caused by tracheomalacia, together with recurrent RTI, caused a mild form of hyperinflation, reflected by FRC_p values in the upper normal range. Indeed, 4 patients with FRC_p values far above the normal range also had low SDS $V'_{max_{FRC}}$ values and 3 of them had clinical signs of substantial tracheomalacia with tidal flow limitation.

SDS $V'_{max_{FRC}}$ was significantly below the norm without a significant difference between thoracotomic and thoracoscopic type of repair and a change during the first year of life. Beardsmore et al. also found abnormal lung function at various time-points during the first year of life in 9 of 16 EA-TEF patients [5]. These patients' functional abnormalities were related with severity of persistent symptoms. Other studies have reported airway obstruction in 30- 41% of older EA patients [6-7]. A longer duration of log supplemental oxygen days was associated with higher $V'_{max_{FRC}}$. This may be a false positive, type 1 error, however, in view of the multiple tests performed.

Recurrent RTI were reported in 30-40% of our patients, in line with findings from other studies in EA patients [29-30]. Recurrent RTI, as seen in patients with cystic fibrosis and primary ciliary dyskinesia, are associated with significantly diminished flows [31-32] and hyperinflation and air trapping [31]. Recurrent RTI could therefore have contributed to the decreased SDS $V'_{max_{FRC}}$ and FRC_p values in the upper normal range. A thoracoscopic type of repair did not reduce the occurrence of RTI.

Tidal flow limitation was found in 7 patients (19%). Van der Wiel and colleagues showed that tidal flow limitation was 100% predictive of airway malacia, as diagnosed by bronchoscopy; although only half of 32 wheezy infants with airway malacia had tidal flow limitation [33]. Turner and colleagues found an association between tidal flow limitation early in the first year of life and reduced lung function later in life [34]. Thus, absence of tidal flow limitation does not rule out airway malacia but presence of tidal flow limitation may identify an at-risk group in these EA patients.

In the present study only 2 patients who were treated with anti-reflux medication showed pathological GER. We therefore assume that GER did not substantially affect lung function results in our study.

Like subjects in comparable studies, physical growth of our subjects was impaired [4,30]. As FRC_p in mL/kg and SDS $V_{max_{FRC}}$ are corrected for weight and length respectively, we assume this impaired growth did not influence the lung function results. On the other hand, impaired nutritional status can influence the prevalence of RTI.

Growth impairment was evident in EA patients. Height was significantly lower in patients with thoracoscopic repair, whereas weight for height was significantly lower in patients with thoracotomy repair. At this point, numbers of patients in each group are still small and only few patients who underwent thoracoscopic repair have reached the age of 5 years. Previously Gischler et al. found catch-up growth in patients with EA at 5 years of age [4]. We recommend ongoing follow-up to evaluate if these differences are consistent over time.

A potential limitation of our study was that we were not allowed to examine healthy controls, as sedation of healthy infants for research purposes is not permitted in the Netherlands. Therefore, we had to use reference values published by others. We expressed FRC_p values in mL/kg as described previously [23]. The normal range of FRC, suggested by Hülkamp et al, is 13-26 mL/kg, mean 19.6, SD 3.4 [14]. Regarding $V'_{max_{FRC}}$, we used the reference values provided by Hoo and colleagues. These reference values are based on a large representative population of healthy infants [16] and others have applied these as well in tests with the same equipment as we used [35].

Chest X-rays were performed post-operatively in all patients, but in only 13 patients a repeated chest X-ray was made after the age of 12 months. In patients with only a chest X-ray early in the first year of life, rib fusions may not have been diagnosed which is also a limitation of this study.

Another limitation is the lack of lung function measurements at older age. In a previous study we found that only few 5-year-old EA-patients could successfully perform flow-volume measurement testing [4]. In the present cohort we will therefore evaluate lung function, including measurement of airway patency, and static and dynamic lung volumes, at the age of 8 years. Agrawal and colleagues found that $V'_{max_{FRC}}$ scores obtained in infancy and SDS MEF_{50} and SDS MEF_{25} retested at school age did not correlate. They concluded that the observations and testing in infancy for medium term prediction of both clinical and laboratory based respiratory function were not reliable and that long term respiratory follow-up should be included in general pediatric care to assess suspected asthma and responses to bronchodilators [3].

In conclusion, there were no differences in lung function in the first year of life after thoracotomy or thoracoscopic type of repair of EA, and the influence of ribfusion was low. We did not find arguments to recommend one of these types of surgery. The results of lung function testing at 6 and 12 months were of limited predictive value for respiratory morbidity at older age. In view of these findings, our clinical experience and the recommendations reviewed by Frey [36] we suggest that lung function tests need not to be tested routinely in EA patients in the first year of life. Frey proposes that infant lung function testing may be useful in case of tracheomalacia to assess the overall effect of bronchodilator treatment – ultimately aimed at preventing increased flow limitation due to relaxation of

airway smooth muscle tone. [36]. For all EA patients, clinical care should especially consist of frequent monitoring focused on nutritional status and RTI prevention. Low-threshold use of antibiotics, prophylactic antibiotics and vaccination for respiratory syncytial and influenza virus is recommended in case of recurrent RTI. Those who underwent surgical repair should be followed until adulthood to establish long-term evolution of lung function.

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Figure legends

Figure 1: Flowchart

Figure 1

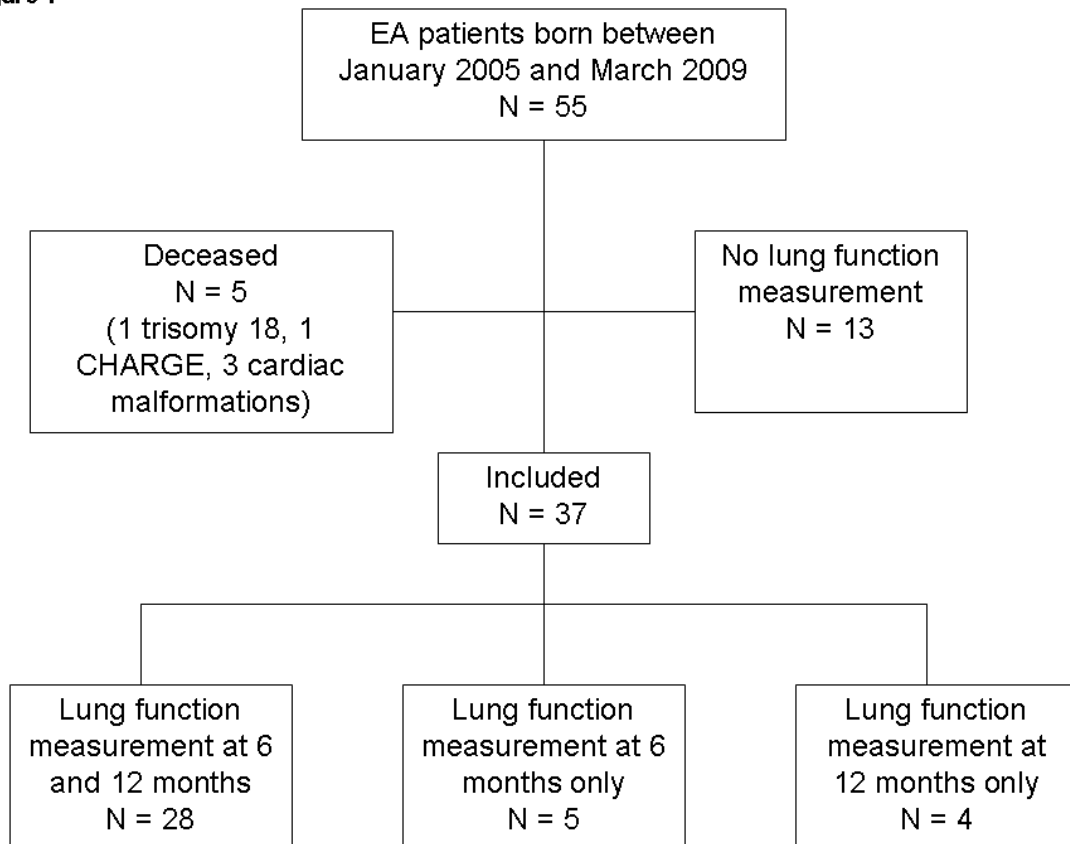


Figure 2a: FRC_p (mL/kg) at 6 and 12 months in group 1, patients with thoracotomic type of repair (group 1). Repeated measurements are indicated by closed dots and a connecting line. The range of normal values (between 13 and 26 mL/kg) is indicated by dotted horizontal lines.

2b: FRC_p (mL/kg) at 6 and 12 months in group 2, patients with thoracoscopic type of repair (group 2). Repeated measurements are indicated by open dots and a connecting line. The range of normal values (between 13 and 26 mL/kg) is indicated by dotted horizontal lines.

Figure 2a

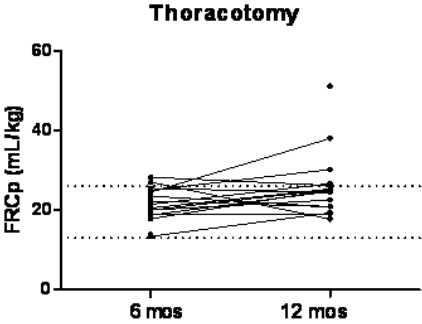


Figure 2b

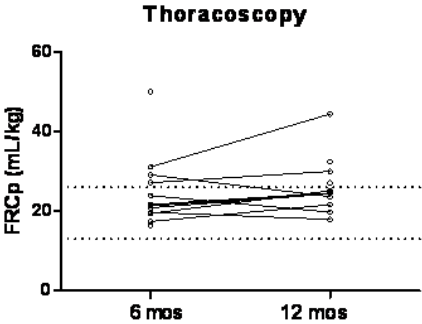


Figure 3a: SDS height at 6, 12 and 24 months in group 1 (thoracotomy group). Each dot represents a measurement of an individual patient. Repeated measurements are represented by a connecting line.

3b SDS height in group 2 (thoracoscopy group).

Figure 3a

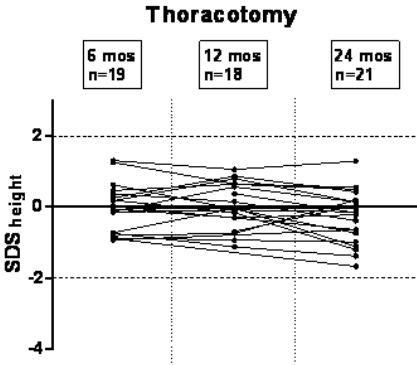


Figure 3b

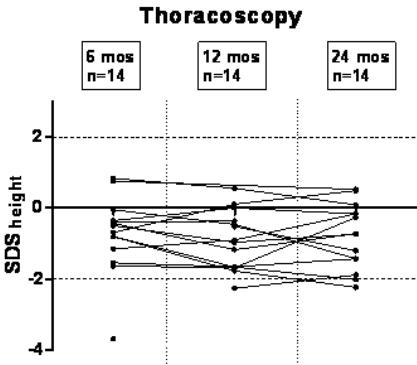


Figure 4a: SDS weight for height at 6, 12 and 24 months in group 1 (thoracotomy group). Each dot represents a measurement of an individual patient. Repeated measurements are represented by a connecting line.

4b SDS weight for height in group 2 (thoracoscopy group).

Figure 4a

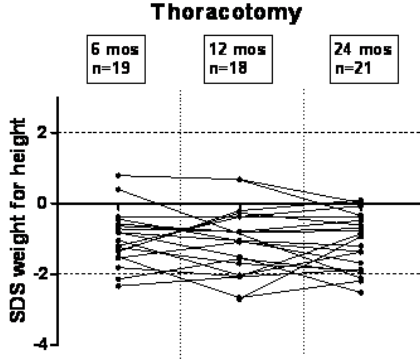
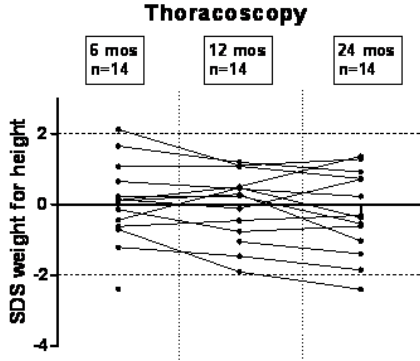


Figure 4b



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Table 1	Group 1 (n=21)		Group 2 (n=16)	
	6 mos (n=19)	12 mos (n=18)	6 mos (n=14)	12 mos (n=14)
FRC _p , mL/kg	21.1 (18.9-23.7)	25.2 (22.3-28.5)	23.7 (20.5-27.4)	25.5 (22.2-29.3)
Vmax _{FRC} , SDS	-1.4 (-2.2 to -0.6)	-2.3 (-2.8 to -1.7)	-2.4 (-3.3 to -1.5)	-2.2 (-2.9 to -1.5)
Vmax _{FRC} , mL/sec	94.9 (58.0-131.7)	111.8 (72.8-150.9)	70.2 (28.6-111.8)	116.4 (69.3-163.5)
RR, breaths/min	33.2 (30.3-36.2)	31.9 (27.8-36.1)	34.2 (30.6-37.7)	28.5 (23.6-33.4)

Table 1:

Group 1: patients underwent thoracotomy. Group 2: patients underwent thoracoscopy.

FRC_p: functional residual capacity. Vmax_{FRC}: maximal expiratory flow at functional residual capacity.

RR: respiratory rate. * $p < 0.001$ below the reference value (SDS = 0). Mean (95% CI) values from analysis of variance are shown.

FRC_p was significantly higher at 12 months compared with 6 months ($p=0.010$). Vmax_{FRC} mL/sec and RR were significantly lower at 12 months compared with 6 months ($p=0.023$ and $p=0.005$ respectively). SDS Vmax_{FRC} did not differ significantly between 6 and 12 months. All parameters were not significantly different between infants in group 1 and group 2.

Table 2

	Group 1			Group 2		
	6 mos (n=18)	12 mos (n=19)	2 yrs (n=21)	6 mos (n=16)	12 mos (n=16)	2 yrs (n=14)
RTI with AB treatment, n (%)	4 (22)	7 (37)	6 (29)	6 (38)	8 (50)	5 (36)
Profylactic AB						
Airway, n (%)	2 (11)	1 (5)	2 (10)	2 (13)	2 (13)	3 (21)
Urologic, n (%)	1(6)	3 (16)	3 (14)	1 (6)	0	2 (14)
Use of bronchodilators, n (%)	5 (28)	5 (26)	2 (10)	1 (6)	2 (13)	0
Use of inhaled steroids, n (%)	1 (6)	2 (11)	0	1 (6)	1 (6)	1(7)
Auscultatory abnormalities						
Wheezing	NA	NA	NA	NA	NA	NA
Mucus	3 (16)	4 (21)	3 (14)	4 (25)	2 (13)	1 (7)

Table 2:

Group 1: patients underwent thoracotomy. Group 2: patients underwent thoracoscopy.

RTI: ≥ 1 respiratory tract infection in the past 6 months requiring a therapeutic dose of AB; AB = antibiotics. NA=not applicable.