PULMONARY FUNCTION IMPAIRMENT AFTER TRACHEA-ESOPHAGEAL FISTULA: A MINOR ROLE FOR GASTRO-ESOPHAGEAL REFLUX DISEASE.

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PULMONARY FUNCTION IMPAIRMENT AFTER TRACHEA-ESOPHAGEAL FISTULA: A MINOR ROLE FOR GASTRO-ESOPHAGEAL REFLUX DISEASE.

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Running title: Cardiopulmonary function after trachea-esophageal fistula

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ABSTRACT

Background

Long term impairment of pulmonary function in trachea-esophageal fistula (TEF) patients is, at least in part, commonly ascribed to gastro-esophageal reflux disease (GERD). The objective of this study was to examine the independent effects of the underlying condition and GERD on cardiopulmonary function.

Methods

Cardiopulmonary function of TEF patients, who had (severe) GERD (s-GERD) requiring antireflux surgery (TEF+GERD, n = 11) and TEF patients who did not have s-GERD (group TEF-GERD, n =20) were compared with control patients who had isolated s-GERD requiring antireflux surgery (group GERD, n = 13).

All patients performed spirometry, lung volume measurements, measurement of diffusion capacity and maximal cardiopulmonary exercise testing (CPET).

Results

Mean age of the participants was 13.8 ± 2.7 (group TEF+GERD). 13.2 ± 2.9 (group TEF-GERD), and 14.7 ± 1.5 years (group GERD).FVC and TLC were significantly lower in patients with TEF (with and without s-GERD) when compared to patients with isolated s-GERD. Most pulmonary function parameters were similarly affected in both TEF groups , but FEV_1 was lower in the TEF+GERD group than in the TEF-GERD group. Cardiopulmonary exercise parameters were similar in all groups.

Conclusions

TEF patients had restrictive lung function impairment when compared to patients with isolated s-GERD. This difference may be due to several causes, including thoracotomy. FEV_1 was lower in TEF+GERD when compared to TEF-GERD indicating that GERD may affect large airway function in TEF patients. Other differences between TEF patients with and without s-GERD were not significant, suggesting only a minor role for GERD.

INTRODUCTION

Trachea-esophageal fistula (TEF) is a congenital anomaly affecting 1 in 2400 to 4500 newborns.(1;2) The most common variant is esophageal atresia (EA) with a distal fistula (type C). Other types are isolated EA without a fistula (type A) and EA with a proximal fistula (type B).(3) Many patients with TEF have associated congenital malformations. Since the first successful primary repair in 1941 by Haight and Towsley, there has been a dramatic improvement of survival,(4) due to improved neonatal care, which has resulted in an increased awareness of long term complications of TEF. Many TEF patients experience respiratory problems due to recurrent pneumonia, EA associated tracheomalacia (TM) and gastro-esophageal reflux disease (GERD).(5) Pulmonary function studies have shown obstructive impairment in 10-70% of the patients (6-9), while 18-36% had restrictive impairment.(7;8) It has been suggested that prolonged micro-aspiration of gastric contents in the first years of life may cause chronic pulmonary inflammation and fibrosis.(7) Surgical complications such as pleural scarring from empyema after anastomotic rupture and multiple thoracotomies may lead to restrictive lung disease.(7)

Data concerning maximal exercise capacity in TEF patients are lacking. Only one study including 8 TEF patients has been published, in which a reduced level of physical fitness, expressed in exercise duration and $V'O_2$max, was found.(10)

TEF patients with a history of GERD were more likely to have pulmonary function abnormalities and many authors have suggested that GERD in the first years after TEF repair may play a major role in TEF-associated pulmonary pathology.(7;8;11-13) The purpose of this study was to assess the influence of GERD on pulmonary function and exercise capacity in a group of patients aged 8-18 years, who had undergone neonatal surgical repair of TEF. We categorized TEF in two groups: those who had undergone anti-reflux surgery (and consequently were considered to have had severe GERD (s-GERD)) and those who had not ~~(considering to have had mild GERD).~~

In order to examine the effect of TEF and its surgical treatment on cardiopulmonary function we compared these two groups to a control group consisting of otherwise healthy patients who had undergone an antireflux procedure because of isolated s-GERD. We hypothesized that pulmonary function of TEF patients with s-GERD is comparable to control patients with s-GERD who did not have TEF. TEF patients without s-GERD were expected to have better lung function than TEF patients with s-GERD.

METHODS

Patients

All patients born with TEF who underwent thoracotomy at the Pediatric Surgical Centre of Amsterdam between 1988 and 1997 were considered eligible, if their age was over 8 year at the time of the study, i.e. the minimum needed to adequately perform lung function tests and CPET.
TEF patients were divided in 2 groups: TEF patients who had s-GERD requiring antireflux surgery (group TEF+GERD), and TEF patients who had not undergone antireflux surgery (group TEF-GERD.
The control group consisted of patients, born between 1988 and 1997, without TEF but with isolated s-GERD requiring antireflux surgery. All children underwent a Boerema anterior gastropexy, which was the standard antireflux procedure at that time. The following exclusion criteria were used: incapable of following instructions, physically not able to perform the tests, (partial) pneumonectomy, severe non-TEF related disease (e.g. bronchopulmonary dysplasia, cystic fibrosis etc), cardiac surgery, chromosomal anomaly, prematurity (≤ 34 weeks).
Indications for antireflux surgery were based on clinical findings in combination with results of diagnostic studies (upper gastrointestinal series, pH-studies and/or endoscopy). The patient's history was reviewed with specific attention to birth weight, gestational age, type of atresia, associated malformations, length of stay in the hospital (LOS), duration of ventilation, (GERD) and surgical complications including pleural injury (as reported by the surgeon in the operative report) .

The local Ethics Committee approved the study protocol. Written informed consent was obtained from each patient and their parent(s) prior to participation.

Study design

Patients who provided informed consent, then received a detailed medical history including information concerning respiratory complaints and physical performance was obtained. Pulmonary function testing included spirometry, lung volume measurements and measurement of diffusion capacity followed by cardiopulmonary exercise testing (CPET). All measurements were performed by experienced respiratory lab technicians according to the guidelines of the European Respiratory Society.(14)

Pulmonary function

Subjects performed standard spirometry and lung volume measurements.(14) All medication was discontinued 24 hours prior to testing. Forced expiratory volume (FEV_1), forced vital capacity (FVC), maximum midexpiratory flow (MMEF) and peak expiratory flow (PEF) were determined from the largest of three reproducible manoeuvres using a mass flow sensor (Vmax 229, Sensormedics, Yorba Linda, CA, USA). Spirometry was repeated after inhalation of 4x100 µg of salbutamol dose aerosol by metered dose inhaler to evaluate reversibility of potential bronchial obstruction and in order to prevent exercise-induced bronchoconstriction. A change of the $FEV_1 \geq 12\%$, expressed as percentage of the predicted value, was considered as a significant response.(14)

Lung volume measurements were carried out after bronchodilation. Functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV) were determined by whole body plethysmography. The mean of three reproducible manoeuvres was used for analysis.

Diffusion capacity for carbon monoxide (*D*L,CO) was measured by the single breath method using a multigasanalazyer (Sensor Medics) in combination with the mass flow sensor (Vmax 229,

Sensormedics, Yorba Linda, CA, USA). Mean value of two measurements was used to determine *D*L,CO, alveolar volume (*V*a) and *D*L,CO corrected for *V*a (KCO).

Results of the spirometry and the lung volume measurements were expressed as z-scores calculated as the difference between the observed and the predicted value divided by the standard deviation for normal reference values.(15-17) RV/TLC ratio was expressed as a percentage.

Cardiopulmonary exercise testing

Maximal exercise capacity was assessed using the Bruce treadmill test. Briefly summarized, the Bruce test protocol comprises three minute stages of increasing belt speed and percent grade on a treadmill (Marquette, 2000 treadmill).(18)

Children were always tested in the presence of their parent(s). Each patient was allowed to familiarise with the mouth piece and the treadmill, ~~enabled~~ by starting every test with 3 minutes of rest. Each child was urged to continue to the point of severe fatigue. Heart rate and oxygen saturation were monitored by finger pulse oximetry.

Parameters measured during CPET were minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$max), oxygen pulse (O_2-pulse; i.e. oxygen uptake divided by the heart rate), respiratory quotient (RQ), ratio of ventilation to CO_2 output ($\dot{V}E,CO_2$), respiratory rate and duration of the exercise test.

Respiratory gases were monitored on a breath-by-breath basis using a flow sensor (Vmax 229, Sensormedics, Yorba Linda, CA, USA).

The CPET was considered adequate if one or more of the following conditions were achieved: at least 80% of the maximal predicted heart rate (determined as 220 minus age in years) , RQ >1.0 for one minute or exhaustion of the subject.(19)

The $\dot{V}O_2$max and the $\dot{V}O_2$max/kg were expressed as z-scores calculated from reference values. (20)

Statistical analysis

Statistical analysis was performed using the unpaired t-test for normally distributed continuous data. Non parametric tests were used for non normally distributed continuous data. The Fisher exact test or the Chi-square were used for comparing categorical data.

To compare the three groups of patients, linear regression analysis was used with pulmonary function parameters and CPET results as dependent variables. The following variables were added as potential confounders to the model for pulmonary function parameters: atopy (defined as having eczema and/or allergic rhinitis), parental smoking and family history of asthma (1st degree relatives). For the CPET results we corrected for the frequency of participating in sports besides the other variables mentioned above. Statistical significance was defined as $p < 0.05$. SPSS 15.0 was used for data analysis.

RESULTS

Patient characteristics

Trachea-esophageal fistula

Eighty-four patients were treated for TEF in the Pediatric Surgical Centre of Amsterdam between 1988 and 1997. One patient died at the age of three years. Twenty-nine patients were excluded for the following reasons: prematurity (n = 18), type E atresia (n = 4), severe mental retardation (n = 1), cardiac surgery (n = 3), spinal tethered cord (n = 1), severe pulmonary infections (n =1) and paralysis of the recurrent laryngeal nerve (n =1).

Of the 54 eligible TEF patients 33 agreed to participate. Ten patients refused, nine patients could not be contacted and two patients had emigrated. Two of the 33 patients gave consent but did not show up (figure 1).

A comparison of the basic characteristics of 31 participating patients with those who were did not participate did not show significant differences (table 1).

One patient (3%) had EA without TEF. All patients underwent thoracotomy for TEF repair.

Fourteen participants (45%) had at least one congenital anomaly including a cardiac anomaly (5 patients), imperforate anus (5 patients), limb anomalies (2 patients) and renal anomalies (2 patients). Participants with a cardiac anomaly had a patent ductus arteriosus with an atrial septal defect (n = 3) or without an atrial septal defect (n = 2). Since their cardiac situation had been stable for years, none of them were being followed by a pediatric cardiologist.

Clinically relevant tracheomalacia was diagnosed in 4 participants (13%) by bronchoscopy. Two of them underwent aortopexy.

In 14 participants (45%) GERD had been demonstrated in the first four years after TEF repair by upper gastro- intestinal series (UGI), pH-metry and/or endoscopy (table 2). Eleven patients (35%) underwent a Boerema anterior gastropexy (TEF+GERD group) 18 ± 15 months after birth (range 1-70 months) (table 3). These children underwent antireflux surgery because of an ALTE (apparently life-threatening event) (n=3) growth restriction (n=3) or a combination. All patients had had recurrent respiratory infections in the first years of life.

At the time of the study none of these patients was treated for current GERD.

TEF participants (with and without s-GERD) who had current symptoms of tracheomalacia had significantly more respiratory infections (1.3 vs 2.8x/yr; p = 0.002) and episodes of bronchitis (0.0 vs 1.4x/yr; p = 0.001) than TEF patients who did not have current symptoms of tracheomalacia. Six TEF patients (27% in TEF+GERD group vs 14% in TEF-GERD group; p = 0.41) had current gastrointestinal symptoms such as heartburn and regurgitation. None of the patients used antireflux medication. At follow-up none of the patients had a scoliosis.

Control group

An age matched control group was recruited from 46 GERD patients who were operated in the Pediatric Surgical Centre of Amsterdam for isolated s-GERD.

Of these, 16 could not be located and of the 30 remaining patients 17 refused to participate. Hence 13 otherwise healthy controls were included. Reasons for surgery in the GERD group were ALTE (n

=2), growth restriction (n=8), recurrent respiratory tract infections (n=2) or a combination. None of the patients had current gastrointestinal symptoms.

Pulmonary function

In one TEF patient pulmonary function was not assessed because of a serious respiratory infection at follow-up visit. Spirometry and lung volume measurements of four patients (three with TEF) could not be reproduced despite detailed instructions and were therefore excluded from analysis.

All pulmonary function results were normally distributed. Five patients (1 group TEF-GERD; 4 group GERD) had an obstructive impairment (z-score $FEV_1/FVC < -1.64$), none of the patients responded adequately to bronchodilation (i.e. improvement of $FEV_1 \geq 12\%$) (table 4).

FVC was significantly lower in patient with TEF (with and without s-GERD) when compared to patients with isolated s-GERD (z-score FVC TEF+GERD -1.57±0.92; TEF-GERD -1.09±0.92; GERD 0.05±1.00).TLC was also significantly lower in patients with TEF (with and without s-GERD) when compared to group GERD (z-score TLC TEF+GERD -0.88±0.85, TEF-GERD -0.68±0.47; GERD 0.01±0.77) (table 4).

Among all TEF patients, TLC was similar in those with or without a history of pleural injury (TLC z-score -0.73 vs -0.70; p = 0.91). Similarly, among all TEF patients, TLC was similar in those with or without a history of post-operative pneumonia (TLC z-score -0.79 vs -0.34; p = 0.35).

TEF patients with and without current gastrointestinal symptoms had similar lung function.

The differences we found remained significant after adjustment for potential confounders in regression analysis.

Exercise Capacity

Three patients did not perform CPET because of serious respiratory infection at time of follow-up (n = 1, group TEF-GERD) and technical problems (n = 2; group TEF+GERD) respectively. Forty-one patients

underwent CPET, 38 patients achieved maximal exercise defined as a predicted heart rate > 80% and/or RQ > 1.00 during one minute. Results of three patients were excluded from analysis, because they had to stop early and did therefore not reach the level of maximal exercise: in two patients (both group TEF-GERD) this was due to painful legs and in one patient (group TEF+GERD) this was due to shortness of breath. FEV_1/FVC before and after BD and MMEF before and after BD were significantly lower in the six patients that did not perform or not complete the CPET. None of the children desaturated during exercise.

Reliable exercise data could be obtained in 38 patients and showed that only one patient (group TEF-GERD) had an abnormally low $\dot{V}O_2$max score (< -1.96), probably because of airway obstruction (FEV_1/FVC z-score -2.14). $\dot{V}O_2$max and $\dot{V}O_2$max/kg were similar in group TEF+GERD, TEF-GERD and GERD (table 5) when corrected for atopy, asthma family (1st grade), parental smoking habits and frequency of sport practise.

DISCUSSION

We found mild to moderate, mainly restrictive, pulmonary function abnormalities in TEF patients, years after surgical correction. Results of the CPET were normal and similar for all groups after correction for potential confounders (e.g. atopy, parental smoking and family history of asthma). Previous studies of lung function in TEF patients have demonstrated obstructive impairment in 10-70% of the TEF patients and many studies document a relation between obstructive impairment and GERD in the early years after TEF repair.(6;8;9;21) The largest study, from Chetcuti et al, described 154 patients born with TEF, and found a significantly lower FEV_1 and FEF50% in TEF patients with early radiologically proven GERD in comparison to TEF patients without GERD 6-37 years after TEF repair.(7) In contrast we did not find obstructive impairment in TEF patients with s-GERD. The lower values for FEV_1 and MMEF we found, were most likely due to relative restrictive impairment since the reduction in FVC was proportionally greater than that in FEV_1.

Almost all patients had a TLC within normal range, but mean TLC was significantly lower in TEF patients (with and without s GERD) when compared to isolated GERD controls. In the literature in 18-36% of the TEF patients restrictive pulmonary function was seen, especially when TEF patients had GERD.(7;8) In our study, differences between TEF patients with and without surgically treated GERD were not significant, suggesting a minor role for GERD. In addition antireflux surgery could have a protective effect if it avoids long-term damage from GERD.

There are several possible explanation for relative restrictive lung function impairment in TEF. First of all, it could result from suboptimal lung growth in the early years of life due to recurrent infection.(6) This might be due to an ineffective cough technique due to tracheomalacia resulting in recurrent pneumonia.(22) Furthermore recurrent (micro-)aspiration due to GERD in the first years after TEF repair may contribute to early epithelial damage and consequently increased risk for infection. Together this may result in impaired or altered lung growth. Since isolated GERD patients have less episodes of bronchitis and normal pulmonary function parameters, TEF-associated factors such as tracheomalacia may play a more prominent role than GERD itself. Secondly, it has been suggested

that pleural scarring from empyema after anastomotic rupture may lead to mild restrictive disease.(7;23) In our group of TEF patients we did not find a relation between postoperative pneumonia and restrictive impairment. Thirdly, previous research has suggested a correlation between scoliosis, which is more common in TEF,(24) and pulmonary function impairment.(25) However in our study none of the patients had a scoliosis. Fourthly, thoracotomy itself may also result in restrictive impairment. In adolescents with scoliosis it has been demonstrated that thoracoscopic approach leads to a smaller decline in pulmonary function one year after surgery in comparison to the more invasive technique of open thoracotomy.(26) Thoracoscopic approach to treatment of TEF is becoming increasingly accepted. Long term effects on pulmonary function are not yet available, but are expected to be less with the open thoracotomy technique.(27)

We hypothesized that patients with TEF and s-GERD would have a reduced diffusion capacity and $V'O_{2,}$max when compared to TEF patients without s-GERD, since prolonged micro-aspiration of gastric acid in the airways and potentially into the alveoli may cause chronic pulmonary inflammation and pulmonary fibrosis.(28) It has been documented that adult patients with severe GERD have a reduced level of *D*L,CO and *K*'CO compared to patients without GERD.(28) We did not find evidence for damage of the alveolar membrane and subsequent gas exchange impairment reflected by the normal diffusion capacity, since almost all patients achieved maximal exercise and $V'O_{2,}$max was similar for all groups after correction for confounders. Mean z-scores for $V'O_{2,}$max, *D*L,CO and KCO were approximately 0, indicating that our patients are probably comparable to the healthy population. Our results therefore do not concord with Zaccara et al who reported a reduced exercise capacity in TEF patients. This could probably be attributed to a lower degree of physical fitness since almost all patients in the study of Zaccara et al reported reduced level of physical activity ~~generally~~ because of parental anxiety and a strict Italian law that regulates sports activities.

The respiratory symptoms we observed are common after TEF repair.(5;6) Daily functioning does not seem affected since frequency of sport practise and exercise-related symptoms did not differ between TEF patients and GERD patients. Except for three TEF patients, all patients practised sports

at the same level as their peers. This might be due to the willingness of TEF patients to accept symptoms that they assume are due to the congenital abnormality as well as the fact that many patients have been living with airway pathology since birth and might therefore not fully appreciate their respiratory limitations.

We are aware that a major limitation of this study is the small sample size. This could result in the inability to demonstrate differences between groups e.g. in pulmonary function. It was expected that many GERD controls could not be traced because the majority of these patients did not receive medical treatment for many years. Despite a clear informed consent letter the willingness of GERD controls to participate was low, probably because most GERD controls felt healthy for many years and therefore ~~might~~ lack motivation. Another limitation is the possible positive selection of CPET participants, since non-CPET participants had reduced pulmonary function parameters. Another limitation is the definition of severe GERD. We choose to define severe GERD as GERD which needed antireflux surgery. Patients with severe GERD eventually responding to medication are not included in this group. We assumed that patients with most severe GERD (i.e. many symptoms and/or prolonged duration of symptoms) will eventually undergo surgery, increasing the likelihood of finding of long-term damage of GERD in these patients. It was expected that if GERD has an effect on pulmonary function, it will be most pronounced in these patients. We ~~agree~~ realize that, on the other hand, patients with severe GERD eventually responding to medication are not included in the GERD group.

This is the first study that compares lung function of TEF patients with patients who had isolated s-GERD. TEF patients with and without s-GERD had mild relative restrictive impairment when compared to GERD controls. TEF patients with s-GERD had a significantly lower FEV_1 when compared to TEF patients without s-GERD suggesting that GERD may affect large airway function in TEF patients. Diffusion capacity and exercise capacity were normal in nearly all patients. Since GERD controls did not have any pulmonary function impairment, other factors such as tracheomalacia or thoracotomy might play a more important role. We speculate that TEF patients undergoing

thoracoscopic repair of TEF will have reduced restrictive pulmonary function impairment in comparison to patients undergoing a thoracotomy. To improve pulmonary outcome in TEF patients further research comparing both treatment modalities is recommended.

LIST OF ABBREVIATIONS

CO_2	Carbon dioxide
CPET	Cardiopulmonary exercise testiing
*D*L,CO	Diffusion capacity carbon monoxide
EA	Esophageal atresia
FEV_1	Forced expiratory volume in one second
FRC	Forced residual volume
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
KCO	Diffusion capacity corrected for alveolar volume
LOS	Length of stay in hospital
MMEF	Maximum midexpiratory flow
PEF	Peak expiratory flow
RQ	Respiratory quotient
RV	Residual volume
SD	Standard deviation
SPSS	Statistical package social siences

Sp,O_2	Transcutaneous oxygen saturation
TEF	Tracheo-esophageal fistula
TLC	Total lung capacity
TM	Tracheomalacia
Va	Alveolar volume
VC	Vital capacity
*V'*E	Minute ventilation
*V'*E,CO	Ratio of ventilation to carbon dioxide output
V'O_2	Maximal oxygen uptake

REFERENCES

1. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. Chest 2004;126: 915-925.
2. Sillen U, Hagberg S, Rubenson A, Werkmaster K. Management of esophageal atresia: review of 16 years' experience. J.Pediatr.Surg. 1988;23:805-809.
3. Gross R. The surgery of infancy and childhood. Philadelphia, PA: WB Saunders; 1957.
4. Haight C, Towsley HA. congenital atresia of the esophagus and tracheoesophageal fistula. Extrapleural ligation of fistula and end to end anastomosis of esophageal segments. Surg Gynecol Obstet 1943;76:672-688.
5. Chetcuti P, Phelan PD. Respiratory morbidity after repair of oesophageal atresia and tracheo-oesophageal fistula. Arch.Dis.Child 1993;68:167-170.
6. Agrawal L, Beardsmore CS, MacFadyen UM. Respiratory function in childhood following repair of oesophageal atresia and tracheoesophageal fistula. Arch.Dis.Child 1999;81:404-408.
7. Chetcuti P, Phelan PD, Greenwood R. Lung function abnormalities in repaired oesophageal atresia and tracheo-oesophageal fistula. Thorax 1992;47:1030-1034.
8. Robertson DF, Mobaireek K, Davis GM, Coates AL. Late pulmonary function following repair of tracheoesophageal fistula or esophageal atresia. Pediatr.Pulmonol. 1995;20:21-26.
9. Somppi E, Tammela O, Ruuska T, Rahnasto J, Laitinen J, Turjanmaa V et al. Outcome of patients operated on for esophageal atresia: 30 years' experience. J.Pediatr.Surg 1998;33:1341-1346.
10. Zaccara A, Felici F, Turchetta A, Calzolari A, Lucchetti MC, Rivosecchi M et al. Physical fitness testing in children operated on for tracheoesophageal fistula. J.Pediatr.Surg. 1995;30:1334-1337.
11. Biller JA, Allen JL, Schuster SR, Treves ST, Winter HS. Long-term evaluation of esophageal and pulmonary function in patients with repaired esophageal atresia and tracheoesophageal fistula. Dig.Dis.Sci. 1987;32:985-990.

12. Chetcuti P, Myers NA, Phelan PD, Beasley SW. Adults who survived repair of congenital oesophageal atresia and tracheo-oesophageal fistula. BMJ 1988;297:344-346.
13. Milligan DW, Levison H. Lung function in children following repair of tracheoesophageal fistula. J.Pediatr. 1979;95:24-27.
14. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur.Respir.J.Suppl 1993;16:5-40.
15. Zapletal A, Samanek M, Paul T. Lung function in children and adolescents, Methods, Reference values. Basel: Karger; 1987.
16. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H et al. Reference ranges for spirometry across all ages: a new approach. Am.J.Respir.Crit Care Med. 2008;177:253-260.
17. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur.Respir.J. 1995;8:492-506.
18. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am.Heart J. 1973;85:546-562.
19. ATS/ACCP Statement on cardiopulmonary exercise testing. Am.J.Respir.Crit Care Med. 2003;167:211-277.
20. Binkhorst R, Hof van 't M, Saris W. maximale inspanning door kinderen; referentiewaarden voor 6-18 jarige meisjes en jongens. Den Haag: Nederlandse Hart Stichting; 1982.
21. Beardsmore CS, MacFadyen UM, Johnstone MS, Williams A, Simpson H. Clinical findings and respiratory function in infants following repair of oesophageal atresia and tracheo-oesophageal fistula. Eur.Respir.J. 1994;7:1039-1047.
22. Benjamin B, Cohen D, Glasson M. Tracheomalacia in association with congenital tracheoesophageal fistula. Surgery 1976;79:504-508.
23. Chetcuti P, Myers NA, Phelan PD, Beasley SW, Dickens DR. Chest wall deformity in patients with repaired esophageal atresia. J.Pediatr.Surg. 1989;24:244-247.
24. Luzzatto C, Ronconi M, Turra S, Guglielmi M, Zanardo V. Long-term follow-up results after surgical repair of esophageal atresia. Padiatr Padol. 1990;25: 313-20.

25. Newton PO, Faro FD, Gollogly S, Betz RR, Lenke LG, Lowe TG. Results of preoperative pulmonary function testing of adolescents with idiopathic scoliosis. A study of six hundred and thirty-one patients. J Bone Joint Surg Am. 2005;87:1937-1946.

26 Faro FD, Marks MC, Newton PO, Blanke K, Lenke LG. Perioperative changes in pulmonary function after anterior scoliosis instrumentation: thoracoscopic versus open approaches. Spine 2005;30:1058-1063.

27. van der Zee D, Bax KN. Thoracoscopic treatment of esophageal atresia with distal fistula and of tracheomalacia. Semin.Pediatr.Surg. 2007;16:224-230.

28. Schachter LM, Dixon J, Pierce RJ, O'Brien P. Severe gastroesophageal reflux is associated with reduced carbon monoxide diffusing capacity. Chest 2003;123:1932-1938.

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Long term impairment of pulmonary function in trachea-esophageal fistula (TEF) patients is, at least in part, commonly ascribed to gastro-esophageal reflux disease (GERD). The objective of this study was to examine the independent effects of the underlying condition and GERD on cardiopulmonary function.

Methods

Cardiopulmonary function of TEF patients, who had (severe) GERD (s-GERD) requiring antireflux surgery (TEF+GERD, n = 11) and TEF patients who did not have s-GERD (group TEF-GERD, n =20) were compared with control patients who had isolated s-GERD requiring antireflux surgery (group GERD, n = 13).

All patients performed spirometry, lung volume measurements, measurement of diffusion capacity and maximal cardiopulmonary exercise testing (CPET).

Results

Mean age of the participants was 13.8 ± 2.7 (group TEF+GERD). 13.2 ± 2.9 (group TEF-GERD), and 14.7 ± 1.5 years (group GERD).FVC and TLC were significantly lower in patients with TEF (with and without s-GERD) when compared to patients with isolated s-GERD. Most pulmonary function parameters were similarly affected in both TEF groups , but FEV_1 was lower in the TEF+GERD group than in the TEF-GERD group. Cardiopulmonary exercise parameters were similar in all groups.

Conclusions

TEF patients had restrictive lung function impairment when compared to patients with isolated s-GERD. This difference may be due to several causes, including thoracotomy. FEV_1 was lower in TEF+GERD when compared to TEF-GERD indicating that GERD may affect large airway function in TEF patients. Other differences between TEF patients with and without s-GERD were not significant, suggesting only a minor role for GERD.

INTRODUCTION

Trachea-esophageal fistula (TEF) is a congenital anomaly affecting 1 in 2400 to 4500 newborns.(1;2) The most common variant is esophageal atresia (EA) with a distal fistula (type C). Other types are isolated EA without a fistula (type A) and EA with a proximal fistula (type B).(3) Many patients with TEF have associated congenital malformations. Since the first successful primary repair in 1941 by Haight and Towsley, there has been a dramatic improvement of survival,(4) due to improved neonatal care, which has resulted in an increased awareness of long term complications of TEF. Many TEF patients experience respiratory problems due to recurrent pneumonia, EA associated tracheomalacia (TM) and gastro-esophageal reflux disease (GERD).(5) Pulmonary function studies have shown obstructive impairment in 10-70% of the patients (6-9), while 18-36% had restrictive impairment.(7;8) It has been suggested that prolonged micro-aspiration of gastric contents in the first years of life may cause chronic pulmonary inflammation and fibrosis.(7) Surgical complications such as pleural scarring from empyema after anastomotic rupture and multiple thoracotomies may lead to restrictive lung disease.(7)

Data concerning maximal exercise capacity in TEF patients are lacking. Only one study including 8 TEF patients has been published, in which a reduced level of physical fitness, expressed in exercise duration and $V'O_2$max, was found.(10)

TEF patients with a history of GERD were more likely to have pulmonary function abnormalities and many authors have suggested that GERD in the first years after TEF repair may play a major role in TEF-associated pulmonary pathology.(7;8;11-13) The purpose of this study was to assess the influence of GERD on pulmonary function and exercise capacity in a group of patients aged 8-18 years, who had undergone neonatal surgical repair of TEF. We categorized TEF in two groups: those who had undergone anti-reflux surgery (and consequently were considered to have had severe GERD (s-GERD)) and those who had not ~~(considering to have had mild GERD).~~

In order to examine the effect of TEF and its surgical treatment on cardiopulmonary function we compared these two groups to a control group consisting of otherwise healthy patients who had undergone an antireflux procedure because of isolated s-GERD. We hypothesized that pulmonary function of TEF patients with s-GERD is comparable to control patients with s-GERD who did not have TEF. TEF patients without s-GERD were expected to have better lung function than TEF patients with s-GERD.

METHODS

Patients

All patients born with TEF who underwent thoracotomy at the Pediatric Surgical Centre of Amsterdam between 1988 and 1997 were considered eligible, if their age was over 8 year at the time of the study, i.e. the minimum needed to adequately perform lung function tests and CPET.

TEF patients were divided in 2 groups: TEF patients who had s-GERD requiring antireflux surgery (group TEF+GERD), and TEF patients who had not undergone antireflux surgery (group TEF-GERD.

The control group consisted of patients, born between 1988 and 1997, without TEF but with isolated s-GERD requiring antireflux surgery. All children underwent a Boerema anterior gastropexy, which was the standard antireflux procedure at that time. The following exclusion criteria were used: incapable of following instructions, physically not able to perform the tests, (partial) pneumonectomy, severe non-TEF related disease (e.g. bronchopulmonary dysplasia, cystic fibrosis etc), cardiac surgery, chromosomal anomaly, prematurity (≤ 34 weeks).

Indications for antireflux surgery were based on clinical findings in combination with results of diagnostic studies (upper gastrointestinal series, pH-studies and/or endoscopy). The patient's history was reviewed with specific attention to birth weight, gestational age, type of atresia, associated malformations, length of stay in the hospital (LOS), duration of ventilation, (GERD) and surgical complications including pleural injury (as reported by the surgeon in the operative report) .

The local Ethics Committee approved the study protocol. Written informed consent was obtained from each patient and their parent(s) prior to participation.

Study design

Patients who provided informed consent, then received a detailed medical history including information concerning respiratory complaints and physical performance was obtained. Pulmonary function testing included spirometry, lung volume measurements and measurement of diffusion capacity followed by cardiopulmonary exercise testing (CPET). All measurements were performed by experienced respiratory lab technicians according to the guidelines of the European Respiratory Society.(14)

Pulmonary function

Subjects performed standard spirometry and lung volume measurements.(14) All medication was discontinued 24 hours prior to testing. Forced expiratory volume (FEV_1), forced vital capacity (FVC), maximum midexpiratory flow (MMEF) and peak expiratory flow (PEF) were determined from the largest of three reproducible manoeuvres using a mass flow sensor (Vmax 229, Sensormedics, Yorba Linda, CA, USA). Spirometry was repeated after inhalation of 4x100 µg of salbutamol dose aerosol by metered dose inhaler to evaluate reversibility of potential bronchial obstruction and in order to prevent exercise-induced bronchoconstriction. A change of the $FEV_1 \geq 12\%$, expressed as percentage of the predicted value, was considered as a significant response.(14)

Lung volume measurements were carried out after bronchodilation. Functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV) were determined by whole body plethysmography. The mean of three reproducible manoeuvres was used for analysis.

Diffusion capacity for carbon monoxide (DL,CO) was measured by the single breath method using a multigasanalazyer (Sensor Medics) in combination with the mass flow sensor (Vmax 229,

Sensormedics, Yorba Linda, CA, USA). Mean value of two measurements was used to determine *D*L,CO, alveolar volume (*V*a) and *D*L,CO corrected for *V*a (KCO).

Results of the spirometry and the lung volume measurements were expressed as z-scores calculated as the difference between the observed and the predicted value divided by the standard deviation for normal reference values.(15-17) RV/TLC ratio was expressed as a percentage.

Cardiopulmonary exercise testing

Maximal exercise capacity was assessed using the Bruce treadmill test. Briefly summarized, the Bruce test protocol comprises three minute stages of increasing belt speed and percent grade on a treadmill (Marquette, 2000 treadmill).(18)

Children were always tested in the presence of their parent(s). Each patient was allowed to familiarise with the mouth piece and the treadmill, ~~enabled~~ by starting every test with 3 minutes of rest. Each child was urged to continue to the point of severe fatigue. Heart rate and oxygen saturation were monitored by finger pulse oximetry.

Parameters measured during CPET were minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$max), oxygen pulse (O_2-pulse; i.e. oxygen uptake divided by the heart rate), respiratory quotient (RQ), ratio of ventilation to CO_2 output ($\dot{V}E,CO_2$), respiratory rate and duration of the exercise test.

Respiratory gases were monitored on a breath-by-breath basis using a flow sensor (Vmax 229, Sensormedics, Yorba Linda, CA, USA).

The CPET was considered adequate if one or more of the following conditions were achieved: at least 80% of the maximal predicted heart rate (determined as 220 minus age in years) , RQ >1.0 for one minute or exhaustion of the subject.(19)

The $\dot{V}O_2$max and the $\dot{V}O_2$max/kg were expressed as z-scores calculated from reference values. (20)

Statistical analysis

Statistical analysis was performed using the unpaired t-test for normally distributed continuous data. Non parametric tests were used for non normally distributed continuous data. The Fisher exact test or the Chi-square were used for comparing categorical data.

To compare the three groups of patients, linear regression analysis was used with pulmonary function parameters and CPET results as dependent variables. The following variables were added as potential confounders to the model for pulmonary function parameters: atopy (defined as having eczema and/or allergic rhinitis), parental smoking and family history of asthma (1st degree relatives). For the CPET results we corrected for the frequency of participating in sports besides the other variables mentioned above. Statistical significance was defined as $p < 0.05$. SPSS 15.0 was used for data analysis.

RESULTS

Patient characteristics

Trachea-esophageal fistula

Eighty-four patients were treated for TEF in the Pediatric Surgical Centre of Amsterdam between 1988 and 1997. One patient died at the age of three years. Twenty-nine patients were excluded for the following reasons: prematurity (n = 18), type E atresia (n = 4), severe mental retardation (n = 1), cardiac surgery (n = 3), spinal tethered cord (n = 1), severe pulmonary infections (n =1) and paralysis of the recurrent laryngeal nerve (n =1).

Of the 54 eligible TEF patients 33 agreed to participate. Ten patients refused, nine patients could not be contacted and two patients had emigrated. Two of the 33 patients gave consent but did not show up (figure 1).

A comparison of the basic characteristics of 31 participating patients with those who were did not participate did not show significant differences (table 1).

One patient (3%) had EA without TEF. All patients underwent thoracotomy for TEF repair.

Fourteen participants (45%) had at least one congenital anomaly including a cardiac anomaly (5 patients), imperforate anus (5 patients), limb anomalies (2 patients) and renal anomalies (2 patients). Participants with a cardiac anomaly had a patent ductus arteriosus with an atrial septal defect (n = 3) or without an atrial septal defect (n = 2). Since their cardiac situation had been stable for years, none of them were being followed by a pediatric cardiologist.

Clinically relevant tracheomalacia was diagnosed in 4 participants (13%) by bronchoscopy. Two of them underwent aortopexy.

In 14 participants (45%) GERD had been demonstrated in the first four years after TEF repair by upper gastro- intestinal series (UGI), pH-metry and/or endoscopy (table 2). Eleven patients (35%) underwent a Boerema anterior gastropexy (TEF+GERD group) 18 ± 15 months after birth (range 1-70 months) (table 3). These children underwent antireflux surgery because of an ALTE (apparently life-threatening event) (n=3) growth restriction (n=3) or a combination. All patients had had recurrent respiratory infections in the first years of life.

At the time of the study none of these patients was treated for current GERD.

TEF participants (with and without s-GERD) who had current symptoms of tracheomalacia had significantly more respiratory infections (1.3 vs 2.8x/yr; p = 0.002) and episodes of bronchitis (0.0 vs 1.4x/yr; p = 0.001) than TEF patients who did not have current symptoms of tracheomalacia. Six TEF patients (27% in TEF+GERD group vs 14% in TEF-GERD group; p = 0.41) had current gastrointestinal symptoms such as heartburn and regurgitation. None of the patients used antireflux medication. At follow-up none of the patients had a scoliosis.

Control group

An age matched control group was recruited from 46 GERD patients who were operated in the Pediatric Surgical Centre of Amsterdam for isolated s-GERD.

Of these, 16 could not be located and of the 30 remaining patients 17 refused to participate. Hence 13 otherwise healthy controls were included. Reasons for surgery in the GERD group were ALTE (n

=2), growth restriction (n=8), recurrent respiratory tract infections (n=2) or a combination. None of the patients had current gastrointestinal symptoms.

Pulmonary function

In one TEF patient pulmonary function was not assessed because of a serious respiratory infection at follow-up visit. Spirometry and lung volume measurements of four patients (three with TEF) could not be reproduced despite detailed instructions and were therefore excluded from analysis.

All pulmonary function results were normally distributed. Five patients (1 group TEF-GERD; 4 group GERD) had an obstructive impairment (z-score $FEV_1/FVC < -1.64$), none of the patients responded adequately to bronchodilation (i.e. improvement of $FEV_1 \geq 12\%$) (table 4).

FVC was significantly lower in patient with TEF (with and without s-GERD) when compared to patients with isolated s-GERD (z-score FVC TEF+GERD -1.57±0.92; TEF-GERD -1.09±0.92; GERD 0.05±1.00).TLC was also significantly lower in patients with TEF (with and without s-GERD) when compared to group GERD (z-score TLC TEF+GERD -0.88±0.85, TEF-GERD -0.68±0.47; GERD 0.01±0.77) (table 4).

Among all TEF patients, TLC was similar in those with or without a history of pleural injury (TLC z-score -0.73 vs -0.70; p = 0.91). Similarly, among all TEF patients, TLC was similar in those with or without a history of post-operative pneumonia (TLC z-score -0.79 vs -0.34; p = 0.35).

TEF patients with and without current gastrointestinal symptoms had similar lung function.

The differences we found remained significant after adjustment for potential confounders in regression analysis.

Exercise Capacity

Three patients did not perform CPET because of serious respiratory infection at time of follow-up (n = 1, group TEF-GERD) and technical problems (n = 2; group TEF+GERD) respectively. Forty-one patients

underwent CPET, 38 patients achieved maximal exercise defined as a predicted heart rate > 80% and/or RQ > 1.00 during one minute. Results of three patients were excluded from analysis, because they had to stop early and did therefore not reach the level of maximal exercise: in two patients (both group TEF-GERD) this was due to painful legs and in one patient (group TEF+GERD) this was due to shortness of breath. FEV_1/FVC before and after BD and MMEF before and after BD were significantly lower in the six patients that did not perform or not complete the CPET. None of the children desaturated during exercise.

Reliable exercise data could be obtained in 38 patients and showed that only one patient (group TEF-GERD) had an abnormally low $\dot{V}O_2$max score (< -1.96), probably because of airway obstruction (FEV_1/FVC z-score -2.14). $\dot{V}O_2$max and $\dot{V}O_2$max/kg were similar in group TEF+GERD, TEF-GERD and GERD (table 5) when corrected for atopy, asthma family (1st grade), parental smoking habits and frequency of sport practise.

DISCUSSION

We found mild to moderate, mainly restrictive, pulmonary function abnormalities in TEF patients, years after surgical correction. Results of the CPET were normal and similar for all groups after correction for potential confounders (e.g. atopy, parental smoking and family history of asthma). Previous studies of lung function in TEF patients have demonstrated obstructive impairment in 10-70% of the TEF patients and many studies document a relation between obstructive impairment and GERD in the early years after TEF repair.(6;8;9;21) The largest study, from Chetcuti et al, described 154 patients born with TEF, and found a significantly lower FEV_1 and FEF50% in TEF patients with early radiologically proven GERD in comparison to TEF patients without GERD 6-37 years after TEF repair.(7) In contrast we did not find obstructive impairment in TEF patients with s-GERD. The lower values for FEV_1 and MMEF we found, were most likely due to relative restrictive impairment since the reduction in FVC was proportionally greater than that in FEV_1.

Almost all patients had a TLC within normal range, but mean TLC was significantly lower in TEF patients (with and without s GERD) when compared to isolated GERD controls. In the literature in 18-36% of the TEF patients restrictive pulmonary function was seen, especially when TEF patients had GERD.(7;8) In our study, differences between TEF patients with and without surgically treated GERD were not significant, suggesting a minor role for GERD. In addition antireflux surgery could have a protective effect if it avoids long-term damage from GERD.

There are several possible explanation for relative restrictive lung function impairment in TEF. First of all, it could result from suboptimal lung growth in the early years of life due to recurrent infection.(6) This might be due to an ineffective cough technique due to tracheomalacia resulting in recurrent pneumonia.(22) Furthermore recurrent (micro-)aspiration due to GERD in the first years after TEF repair may contribute to early epithelial damage and consequently increased risk for infection. Together this may result in impaired or altered lung growth. Since isolated GERD patients have less episodes of bronchitis and normal pulmonary function parameters, TEF-associated factors such as tracheomalacia may play a more prominent role than GERD itself. Secondly, it has been suggested

that pleural scarring from empyema after anastomotic rupture may lead to mild restrictive disease.(7;23) In our group of TEF patients we did not find a relation between postoperative pneumonia and restrictive impairment. Thirdly, previous research has suggested a correlation between scoliosis, which is more common in TEF,(24) and pulmonary function impairment.(25) However in our study none of the patients had a scoliosis. Fourthly, thoracotomy itself may also result in restrictive impairment. In adolescents with scoliosis it has been demonstrated that thoracoscopic approach leads to a smaller decline in pulmonary function one year after surgery in comparison to the more invasive technique of open thoracotomy.(26) Thoracoscopic approach to treatment of TEF is becoming increasingly accepted. Long term effects on pulmonary function are not yet available, but are expected to be less with the open thoracotomy technique.(27)

We hypothesized that patients with TEF and s-GERD would have a reduced diffusion capacity and $V'O_{2,}$max when compared to TEF patients without s-GERD, since prolonged micro-aspiration of gastric acid in the airways and potentially into the alveoli may cause chronic pulmonary inflammation and pulmonary fibrosis.(28) It has been documented that adult patients with severe GERD have a reduced level of *D*L,CO and *K*'CO compared to patients without GERD.(28) We did not find evidence for damage of the alveolar membrane and subsequent gas exchange impairment reflected by the normal diffusion capacity, since almost all patients achieved maximal exercise and $V'O_{2,}$max was similar for all groups after correction for confounders. Mean z-scores for $V'O_{2,}$max, *D*L,CO and KCO were approximately 0, indicating that our patients are probably comparable to the healthy population. Our results therefore do not concord with Zaccara et al who reported a reduced exercise capacity in TEF patients. This could probably be attributed to a lower degree of physical fitness since almost all patients in the study of Zaccara et al reported reduced level of physical activity ~~generally~~ because of parental anxiety and a strict Italian law that regulates sports activities.

The respiratory symptoms we observed are common after TEF repair.(5;6) Daily functioning does not seem affected since frequency of sport practise and exercise-related symptoms did not differ between TEF patients and GERD patients. Except for three TEF patients, all patients practised sports

at the same level as their peers. This might be due to the willingness of TEF patients to accept symptoms that they assume are due to the congenital abnormality as well as the fact that many patients have been living with airway pathology since birth and might therefore not fully appreciate their respiratory limitations.

We are aware that a major limitation of this study is the small sample size. This could result in the inability to demonstrate differences between groups e.g. in pulmonary function. It was expected that many GERD controls could not be traced because the majority of these patients did not receive medical treatment for many years. Despite a clear informed consent letter the willingness of GERD controls to participate was low, probably because most GERD controls felt healthy for many years and therefore ~~might~~ lack motivation. Another limitation is the possible positive selection of CPET participants, since non-CPET participants had reduced pulmonary function parameters. Another limitation is the definition of severe GERD. We choose to define severe GERD as GERD which needed antireflux surgery. Patients with severe GERD eventually responding to medication are not included in this group. We assumed that patients with most severe GERD (i.e. many symptoms and/or prolonged duration of symptoms) will eventually undergo surgery, increasing the likelihood of finding of long-term damage of GERD in these patients. It was expected that if GERD has an effect on pulmonary function, it will be most pronounced in these patients. We ~~agree~~ realize that, on the other hand, patients with severe GERD eventually responding to medication are not included in the GERD group.

This is the first study that compares lung function of TEF patients with patients who had isolated s-GERD. TEF patients with and without s-GERD had mild relative restrictive impairment when compared to GERD controls. TEF patients with s-GERD had a significantly lower FEV_1 when compared to TEF patients without s-GERD suggesting that GERD may affect large airway function in TEF patients. Diffusion capacity and exercise capacity were normal in nearly all patients. Since GERD controls did not have any pulmonary function impairment, other factors such as tracheomalacia or thoracotomy might play a more important role. We speculate that TEF patients undergoing

thoracoscopic repair of TEF will have reduced restrictive pulmonary function impairment in comparison to patients undergoing a thoracotomy. To improve pulmonary outcome in TEF patients further research comparing both treatment modalities is recommended.

LIST OF ABBREVIATIONS

CO_2	Carbon dioxide
CPET	Cardiopulmonary exercise testiing
*D*L,CO	Diffusion capacity carbon monoxide
EA	Esophageal atresia
FEV_1	Forced expiratory volume in one second
FRC	Forced residual volume
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
KCO	Diffusion capacity corrected for alveolar volume
LOS	Length of stay in hospital
MMEF	Maximum midexpiratory flow
PEF	Peak expiratory flow
RQ	Respiratory quotient
RV	Residual volume
SD	Standard deviation
SPSS	Statistical package social siences

Sp,O_2	Transcutaneous oxygen saturation
TEF	Tracheo-esophageal fistula
TLC	Total lung capacity
TM	Tracheomalacia
Va	Alveolar volume
VC	Vital capacity
*V'*E	Minute ventilation
*V'*E,CO	Ratio of ventilation to carbon dioxide output
V'O_2	Maximal oxygen uptake

REFERENCES

1. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. Chest 2004;126: 915-925.
2. Sillen U, Hagberg S, Rubenson A, Werkmaster K. Management of esophageal atresia: review of 16 years' experience. J.Pediatr.Surg. 1988;23:805-809.
3. Gross R. The surgery of infancy and childhood. Philadelphia, PA: WB Saunders; 1957.
4. Haight C, Towsley HA. congenital atresia of the esophagus and tracheoesophageal fistula. Extrapleural ligation of fistula and end to end anastomosis of esophageal segments. Surg Gynecol Obstet 1943;76:672-688.
5. Chetcuti P, Phelan PD. Respiratory morbidity after repair of oesophageal atresia and tracheo-oesophageal fistula. Arch.Dis.Child 1993;68:167-170.
6. Agrawal L, Beardsmore CS, MacFadyen UM. Respiratory function in childhood following repair of oesophageal atresia and tracheoesophageal fistula. Arch.Dis.Child 1999;81:404-408.
7. Chetcuti P, Phelan PD, Greenwood R. Lung function abnormalities in repaired oesophageal atresia and tracheo-oesophageal fistula. Thorax 1992;47:1030-1034.
8. Robertson DF, Mobaireek K, Davis GM, Coates AL. Late pulmonary function following repair of tracheoesophageal fistula or esophageal atresia. Pediatr.Pulmonol. 1995;20:21-26.
9. Somppi E, Tammela O, Ruuska T, Rahnasto J, Laitinen J, Turjanmaa V et al. Outcome of patients operated on for esophageal atresia: 30 years' experience. J.Pediatr.Surg 1998;33:1341-1346.
10. Zaccara A, Felici F, Turchetta A, Calzolari A, Lucchetti MC, Rivosecchi M et al. Physical fitness testing in children operated on for tracheoesophageal fistula. J.Pediatr.Surg. 1995;30:1334-1337.
11. Biller JA, Allen JL, Schuster SR, Treves ST, Winter HS. Long-term evaluation of esophageal and pulmonary function in patients with repaired esophageal atresia and tracheoesophageal fistula. Dig.Dis.Sci. 1987;32:985-990.

12. Chetcuti P, Myers NA, Phelan PD, Beasley SW. Adults who survived repair of congenital oesophageal atresia and tracheo-oesophageal fistula. BMJ 1988;297:344-346.
13. Milligan DW, Levison H. Lung function in children following repair of tracheoesophageal fistula. J.Pediatr. 1979;95:24-27.
14. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur.Respir.J.Suppl 1993;16:5-40.
15. Zapletal A, Samanek M, Paul T. Lung function in children and adolescents, Methods, Reference values. Basel: Karger; 1987.
16. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H et al. Reference ranges for spirometry across all ages: a new approach. Am.J.Respir.Crit Care Med. 2008;177:253-260.
17. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur.Respir.J. 1995;8:492-506.
18. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am.Heart J. 1973;85:546-562.
19. ATS/ACCP Statement on cardiopulmonary exercise testing. Am.J.Respir.Crit Care Med. 2003;167:211-277.
20. Binkhorst R, Hof van 't M, Saris W. maximale inspanning door kinderen; referentiewaarden voor 6-18 jarige meisjes en jongens. Den Haag: Nederlandse Hart Stichting; 1982.
21. Beardsmore CS, MacFadyen UM, Johnstone MS, Williams A, Simpson H. Clinical findings and respiratory function in infants following repair of oesophageal atresia and tracheo-oesophageal fistula. Eur.Respir.J. 1994;7:1039-1047.
22. Benjamin B, Cohen D, Glasson M. Tracheomalacia in association with congenital tracheoesophageal fistula. Surgery 1976;79:504-508.
23. Chetcuti P, Myers NA, Phelan PD, Beasley SW, Dickens DR. Chest wall deformity in patients with repaired esophageal atresia. J.Pediatr.Surg. 1989;24:244-247.
24. Luzzatto C, Ronconi M, Turra S, Guglielmi M, Zanardo V. Long-term follow-up results after surgical repair of esophageal atresia. Padiatr Padol. 1990;25: 313-20.

25. Newton PO, Faro FD, Gollogly S, Betz RR, Lenke LG, Lowe TG. Results of preoperative pulmonary function testing of adolescents with idiopathic scoliosis. A study of six hundred and thirty-one patients. J Bone Joint Surg Am. 2005;87:1937-1946.

26 Faro FD, Marks MC, Newton PO, Blanke K, Lenke LG. Perioperative changes in pulmonary function after anterior scoliosis instrumentation: thoracoscopic versus open approaches. Spine 2005;30:1058-1063.

27. van der Zee D, Bax KN. Thoracoscopic treatment of esophageal atresia with distal fistula and of tracheomalacia. Semin.Pediatr.Surg. 2007;16:224-230.

28. Schachter LM, Dixon J, Pierce RJ, O'Brien P. Severe gastroesophageal reflux is associated with reduced carbon monoxide diffusing capacity. Chest 2003;123:1932-1938.

Table 1. Comparison of basic characteristics of participants and non-participants with trachea-esophageal fistula.

	Participants **n = 31**	**Non-participants** **n = 23**	**p-value**
Male	14 (45%)	13 (57%)	0.58
Birth weight (mean ± SD)	2910 ± 455	2824 ± 591	0.55
Gestational age (median weeks)	39.5	40	0.46
LOS (median days)	15	21	0.11
Congenital anomalies	14 (45%)	9 (39%)	0.59
Pleural injury	9 (29%)	9 (39%)	0.38
Antireflux surgery	11 (35%)	7 (30%)	0.78
Tracheomalacia	4 (13%)	1 (4%)	0.59
Respiratory illness (5 yrs)	13 (42%)	8 (35%)	0.78

LOS: Length of stay hospital

Table 2. Diagnosis of GERD in all 3 patient groups. Numbers indicate number of patients. With regard to pH-metry patients were considered to have pathologic acid GERD when the reflux index was ≥10% or with nocturnal episodes of acid reflux. Esophagitis was histologically graded according to the ESPGHAN-criteria[21].

Diagnosis	Group TEF-GERD (n = 20)	Group TEF+GERD (n =11)	Group GERD (n =13)
pH-metry	3/19	8/11	11/12 (1 unknown)
Histology (esophagitis)	1/1	5/9	12/13
UGIS		5/8	6/9

Table 3. Patient characteristics and results of the follow-up visit.

Group TEF+GERD (I): TEF patients with surgically treated GERD; Group TEF-GERD (II): TEF patients without surgically treated GERD; Group GERD (III): GERD patients who had antireflux surgery. Bronchitis was defined as a an episode of productive cough lasting for more than 5 days. Tracheamalacia was defined as persistent barking cough.

	Group TEF+GERD (I) n = 11	Group TEF-GERD (II) n = 20	Group GERD (III) n = 13	p-value		
				I vs II	I vs III	II vs III
Age at follow-up (mean years ± SD)	13.8 ± 2.7	13.2 ± 2.9	14.7 ± 1.5	0.55	0.33	0.051
Male	7 (64%)	7 (35%)	11 (85%)	0.15	0.36	0.10
LOS (median days)	18	15	12	0.03	0.001	0.002
Pleural injury	3 (30%)	6 (30%)	-	1.00	-	-
Postoperative leakage	0	0	-	1.00	-	-
Recurrent fistula	0	0	-	1.00	-	-
Tracheomalacia	7 (64%)	14 (70%)	-	0.12	-	-
Congenital anomalies	7 (64%)	8 (40%)	-	0.27	-	-
Age at antireflux surgery (median months)	7	-	11	-	0.19	-
Pulmonary medication	2 (18%)	5 (25%)	2 (15%)	1.0	1.00	0.68
Poor exercise tolerance	0 (0%)	2 (10%)	1 (8%)	0.53	1.00	1.00
Dyspnea during exercise	1 (9%)	5 (25%)	2 (15%)	0.38	1.00	0.68
Sport practise x/ wk	2.5 ± 1.6	2.4 ± 1.7	2.5 ± 1.3	0.90	0.65	0.19

(mean ± SD)						
Daily coughing	1 (9%)	2 (10%)	0 (0%)	1.0	0.46	0.51
Wheezing	2 (18%)	7 (35%)	2 (15%)	0.43	1.00	0.26
Respiratory infections/year (mean ± SD	2.5 ± 1.9	2.2 ± 1.3	1.5 ± 1.9	0.74	0.25	0.21
Bronchitis/year (mean ± SD)	1.6 ± 2.0	0.6 ± 1.0	0.2 ± 0.6	0.15	0.06	0.31

Table 4. Baseline pulmonary function results of TEF patients with surgically treated GERD (group TEF+GERD (I)), TEF patients without surgically treated GERD (group TEF-GERD (II)) and surgically treated GERD controls (group GERD (III)). Results are expressed as z-scores (SD) calculated from a reference population according to Stanojevic et al (FEV_1, FVC, FEV_1/FVC and MMEF),(16) Stocks et al (FRC, RV, TLC and RV/TLC) (17) and Zapletal (PEF, VC, *D*L,CO and *D*L,CO/*V'*a).(15) * $p < 0.05$

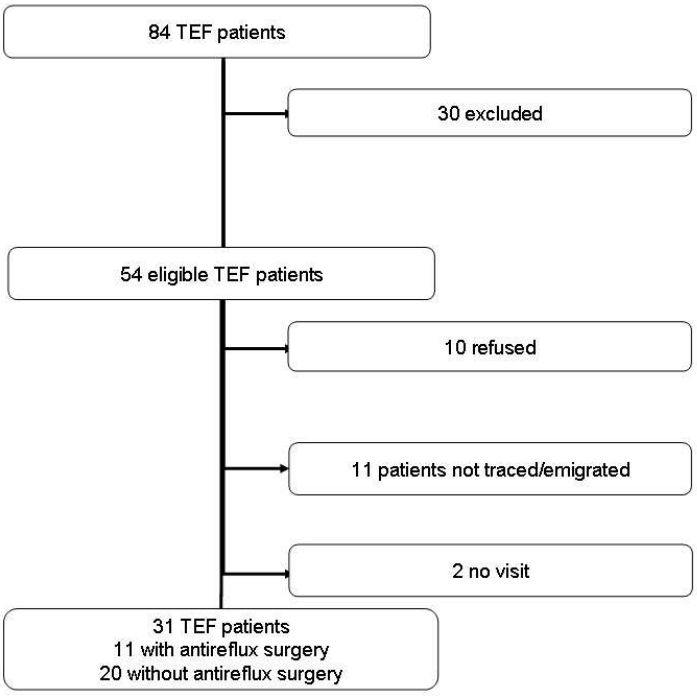
		Group TEF+GERD (I) N = 11	Group TEF-GERD (II) N =16	Group GERD (III) N = 12	CI of the difference I vs II	I vs III	II vs III
FEV_1	**Before BD**	-1.67 (1.04)	-0.89 (0.82)	0.18 (1.22)	-0.52 – -0.05*	0.86 – 2.83*	0.28 – 1.86*
	After BD	-1.22 (1.07)	-0.81 (0.76)	0.65 (1.21)	-1.14 – 0.31	0.88 – 2.86*	0.69– 2.22*
FVC	**Before BD**	-1.57 (0.92)	-1.09 (0.92)	0.05 (1.00)	-1.21 – 0.27	0.79 – 2.46*	0.40 – 1.90*
	After BD	-1.39 (0.95)	-1.01 (0.92)	0.16 (1.09)	-1.13 – 0.37	0.66 – 2.44*	0.39 – 1.95*
FEV_1/FVC	**Before BD**	-0.39 (0.97)	-0.22 (1.25)	0.10 (0.80)	-1.09 – 0.75	-0.28 – 1.25	-0.54 – 1.16
	After BD	0.07 (0.66)	0.17 (1.18)	0.67 (0.64)	-0.84 – 0.64	0.04 – 1.17*	-0.27 – 1.28
MMEF	**Before BD**	-1.23 (1.04)	-0.87 (0.93)	0.04 (0.99)	-1.15 – 0.43	0.38 – 2.14*	0.16 – 1.66*
	After BD	-0.71 (0.87)	-0.42 (0.97)	0.71 (0.82)	-1.03 – 0.47	0.68 – 2.15*	0.42 –1.85*
PEF	**Before BD**	-1.41 (1.58)	-1.28 (1.12)	-0.10 (1.12)	-1.20 – 0.93	0.09 – 2.52*	0.27 – 2.07*
	After BD	-1.06 (1.36)	-1.18 (1.26)	0.32 (1.10)	-0.93 – 1.17	0.31 – 2.44*	0.56 – 2.43*
VC	**Before BD**	-1.99 (1.48)	-1.28 (0.99)	0.54 (1.43)	-1.67 – 0.27	1.26 – 3.79*	0.88 – 2.76*
	After BD	-1.83 (1.82)	-1.11 (0.91)	0.66 (1.58)	-1.80 – 0.38	1.01 – 3.96*	0.69 – 2.85*
FRC		-0.90 (0.93)	-0.82 (0.82)	-0.66 (0.50)	-0.87 – 0.61	-0.43 – 0.90	-.42 – 0.72
TLC		-0.88 (0.85)	-0.68 (0.47)	0.01 (0.77)	-0.81 – 0.40	0.18 – 1.62*	0.20 – 1.18*
RV/TLC (%)		23.6 (2.8)	22.6 (5.9)	18.0 (4.5)	-2.60 – 4.55	-9.06 - - 2.14*	-8.97 – - 0.28*

***D*L,CO**	-0.80 (1.05)	-0.62 (0.71)	-0.21 (0.75)	-0.90 – 0.54	-0.26 – 1.43	-0.17 – 0.99
***D*L,CO /*V*'a**	0.03 (0.21)	0.04 (0.15)	-0.04 (0.19)	-0.15 – 0.14	-0.24 – 0.11	-0.21 – 0.06

BD: bronchodilation; CI : confidence interval.

Table 5. Results of the CPET. Numbers are expressed as mean ± SD. Group TEF+GERD (I): TEF patients with surgically treated GERD; Group TEF-GERD (II): TEF patients without surgically treated GERD; Group GERD (III): GERD patients who had antireflux surgery.

Parameter	Group TEF+GERD (I) n = 8	Group TEF-GERD (II) n= 17	Group GERD (III) n = 13	p-value		
	Mean ± SD	Mean ± SD	Mean ± SD	I vs II	I vs III	II vs III
Heart rate max (% predicted)	95.4 ± 4.3	94.1 ± 4.5	94.0 ± 5.0	0.51	0.53	0.99
Respiratory rate (x/min)	48.1 ± 10.4	48.6 ± 7.7	47.8 ± 7.6	0.90	0.94	0.30
Respiratory Quotient	1.09 ± 0.07	1.11 ± 0.08	1.12 ± 0.05	0.56	0.33	0.66
***V'*e max (L/min)**	76.5 ± 24.7	65.3 ± 16.1**	92.6 ± 15.3**	0.20	0.08	<0.001
z-score $V'O_2$,max	0.46 ± 1.86	-0.27 ± 1.60**	0.73 ± 1.14**	0.34	0.68	0.05
z-score $V'O_2$,max/kg	0.54 ± 0.96	-0.08 ± 1.68	-0.07 ± 1.32	0.34	0.70	0.96
O_2-pulse (% predicted)	116.3 ± 19.2	109.9 ± 18.1	114.4 ± 13.6	0.44	0.81	0.42
***V'*E,CO_2**	26.9 ± 3.3	28.9 ± 2.3	27.9 ± 3.0	0.09	0.46	0.22
***Sp*O_2 (%)**	95.8 ± 2.7	96.7 ± 1.9	96.0 ± 1.7	0.33	0.80	0.40



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