Respiratory and esophageal morbidity in adults with repaired esophageal atresia

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Cover picture: Vladimir Gatzinsky

To my family

Abstract

Background: Esophageal atresia (EA) often leads to persistent esophageal and respiratory symptoms, as well as impaired esophageal and lung function in adulthood. The reasons for this, and the connections between symptoms and documented abnormalities, are not fully understood.
Purpose: We wanted to investigate a cohort of adults previously operated on for EA in order to describe the prevalence of symptoms and functional abnormalities, as well as to investigate whether, and if so how, they are connected.
Methods: Seventy-three of 79 patients operated on for EA in Gothenburg in 1968-1983 agreed to participate in the first part of the study involving questionnaires relating to symptoms from the esophagus and respiratory tract. Twenty-nine patients agreed to undergo further investigations of pulmonary and esophageal function.
Results: From the questionnaire studies, we found that, even though the overall quality of life was good, a considerable number of patients had troublesome symptoms. Both esophageal and respiratory symptoms were frequent. Fifty-seven percent experienced swallowing disturbances (dysphagia) which appeared to be associated with regurgitation, which was in turn noted in 40%. Thirty-two percent experienced heartburn. Different respiratory symptoms, such as wheeze and long-standing cough (44% and 30% respectively), were much more common in this cohort than in the general population. Asthma was reported by 30%, even though no predisposing factors were noted. Impaired respiratory function, either obstructive and/or restrictive, was noted in 22/28 (79%). The obstruction was mainly in the peripheral airways, 17/28 (61%) subjects (measured by multiple-breath inert gas washout, MBW), while only six (21%) subjects displayed values indicating central obstruction. Nine patients had restrictive disease. Airway hyper-responsiveness was frequent and associated with atopy and airway inflammation. However, respiratory symptoms or doctor-diagnosed asthma (DDA) did not correlate with any specific lung function test abnormality. There was a high prevalence of gastro-esophageal reflux (GER) measured by pH multichannel intraluminal impedance (pH-MII) involving both pathological reflux episodes with a pH of < 4 and of > 4 (5/15 and 10/15 subjects respectively). Dysphagia correlated to the number of weakly acidic reflux episodes, while esophageal mucosal damage (14/24 subjects with esophagitis, two of whom had Barrett's esophagus) correlated to the reflux index (RI) and the number of episodes of weakly acidic reflux. Lower esophageal sphincter incompetence to any extent was frequent (21/24 subjects) and correlated to the number of acid reflux episodes and RI.
Conclusion: A high prevalence of both respiratory and esophageal symptoms remains in adulthood. The impaired pulmonary function appears to be more pronounced than previously described. Even non-acidic reflux episodes appear to contribute to the esophageal morbidity. New investigative modalities such as MBW and pH-MII have helped us in further describing and understanding the late sequelae of EA. Classical asthma appears to be difficult to diagnose in this patient group. Given

the high prevalence of both respiratory and esophageal morbidity, further studies and long-term follow-up, including MBW and pH-MII, are warranted.

Keywords: esophageal atresia, long-term outcome, pulmonary function, gastro-esophageal reflux, dysphagia

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Contents

List of publications

The thesis is based on the following articles:

I. **Gatzinsky V, Jönsson L, Johansson C, Göthberg G, Sillén U, Friberg LG**
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Eur J Pediatr Surg. 2011 Mar;21(2):94-8.

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Long-term respiratory symptoms following oesophageal atresia.
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III. **Gatzinsky V, Wennergren G, Jönsson L, Ekerljung L, Houltz B, Redfors S, Sillén U, Gustafsson P**
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IV. **Gatzinsky V, Andersson O, Eriksson A, Jönsson L, Abrahamsson K, Sillén U**
pH multichannel intraluminal impedance in adults operated for esophageal atresia - what can it tell us?
In manuscript

List of Abbreviations

AHR	Airway hyper-responsiveness
ATS	American Thoracic Society
DDA	Doctor-diagnosed asthma
EA	Esophageal atresia
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GER	Gastro-esophageal reflux
GERD	Gastro-esophageal reflux disease
GerdQ	Gastro-esophageal reflux disease questionnaire
LCI	Lung clearance index
LES	Lower esophageal sphincter
FENO	Fractional exhaled nitric oxide
MBW	Multiple-breath inert gas washout
OR	Odds ratio
PFT	Pulmonary function test
pH-MII	pH multichannel intraluminal impedance
PPI	Proton pump inhibitors
QoL	Quality of life
SCC	Squamous cell carcinoma
TEF	Tracheo-esophageal fistula
TLC	Total lung capacity
VACTERL	Vertebral, anorectal, cardiac, trachea-esophageal, renal, limb

Introduction

Esophageal atresia (EA) is a congenital malformation which was first described in the 17th century, but it took almost 300 years before it could be corrected. Initially, the postoperative mortality was high, but, due to advances in pediatric and cardiac surgery, as well as improved intensive care, the overall survival rates nowadays exceed 90% (1, 2). Today, interest focuses on the long-term outcome, with special emphasis on esophageal and respiratory symptoms, as they have been shown to follow the patients into adulthood (3). The main esophageal symptoms are gastro-esophageal reflux (GER) and dysphagia (4, 5), while the respiratory problems are due to pulmonary impairment leading to both restrictive and obstructive patterns (6, 7, 8). The reasons for both the esophageal and pulmonary impairments are multifactorial and not fully understood, but they appear to affect the quality of life (4, 8). The correlation between symptoms and the results of clinical investigations, when it comes to both the esophagus and the lungs, has not been consistent. There are probably many reasons for this. One of them, at least when it comes to dysphagia, might be the lack of a uniform definition.

For unknown reasons, there also appears to be an over-representation of doctor-diagnosed asthma within this patient group (7, 8, 9). Taken together, the above-mentioned reasons might contribute to the fact that there are no clear guidelines on how these patients should be monitored through life. Further studies designed to produce a better understanding of the symptoms and clinical findings are needed to answer this question.

Background data Esophageal atresia

History

The first description of esophageal atresia was given in 1670, when, in a paper entitled *Description of A Monstrous Birth in Plymouth*, William Durston described how he was called to the delivery of conjoined twins, one of whom had esophageal atresia. In 1697, Thomas Gibson was the first to describe esophageal atresia with a distal fistula, which is the most common type (10).

It would take almost two and a half centuries, 1939, before the first survivors were recorded, using a staged approach performed independently by Dr William Ladd (11) in Boston and Dr Logan Leven (12) in Minnesota. Two years later, Dr Cameron Haight performed the first successful primary repair (13) and, in 1947, Dr Philip Sandblom performed the first operation in Sweden (14).

Embryology and etiology

The differentiation of the early foregut into the esophagus and trachea takes place in the fourth week of gestation. There is still controversy about how this is done, but there are two main theories (15). The first theory proposes that the formation of a tracheal diverticulum takes place from the primitive digestive tube, which then grows rapidly in the caudal direction, resulting in the separation of the trachea and esophagus. In the second theory, the trachea-esophageal foregut tube is separated by the formation of lateral epithelial ridges which meet and fuse in the midline in a cranial direction. The exact pathway is not known, but failure to make this separation complete results in EA.

Following the introduction of an experimental model, which induces EA and the same spectrum of associated malformations in rodents, there is now a way to look for possible etiological mechanisms (16). This model has helped demonstrate an inherent abnormality of the neurological supply of the esophagus, as well as a delay in the innervation of the respiratory tract (17, 18). It has also been shown that experimentally induced EA is accompanied by tracheobronchial malformations, including tracheomalacia, and also by delayed tracheobronchial branching, indicating a close relationship between EA and affected pulmonary function (19, 20, 21). The current opinion is that the etiology of EA malformation is multifactorial and probably involves both genetic and/or environmental factors (22, 23).

Epidemiology

EA, which is the most common congenital malformation of the esophagus, has been described as having an incidence of between 3-4/10,000 newborns (24, 25). A slight male predominance and a higher frequency of twinning have been shown in the EA group. The malformation is also more common among Caucasians and with increased maternal age (26, 27, 28).

Anatomy and classification

There have been different classifications over the years. The first classification was made by a radiologist named Vogt in 1929 (29). In 1953, Gross made his classification, which is probably the most used worldwide nowadays (30). Kluth presented the most detailed classification in 1976 (31).
The five main types and incidences according to Gross are presented below (Figure 1).

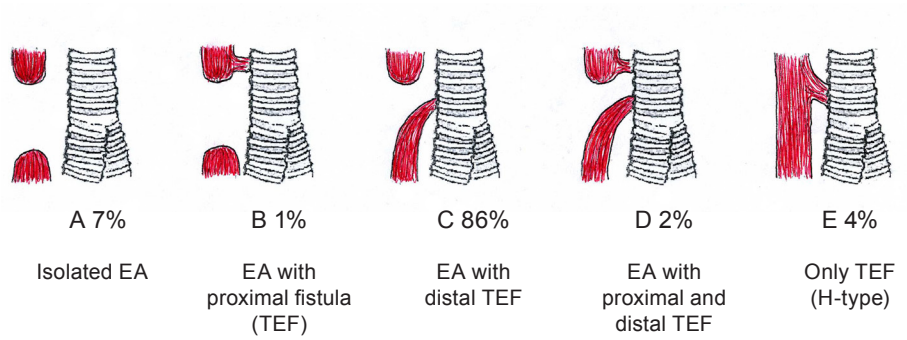

Figure 1. Classification according to Gross.

In addition to the above-mentioned anatomical classification, patients with EA can also be divided into different risk classification groups. In 1962, Waterston made the first classification, which took account of birth weight, pneumonia and associated malformations (32). Different risk classifications have followed (33, 34, 35) and the one proposed by Spitz, involving birth weight and cardiac anomaly, is probably the most commonly used nowadays. Despite recent contributions, Waterston's classification has still been shown to have prognostic relevance (36).

Associated anomalies

Associated anomalies occur in 40-50% of cases, where the majority involve one or more of the VACTERL (vertebral, anorectal, cardiac, tracheo-esophageal, renal and limb) associations (25, 37). VACTERL (38) is an acronym which is used when two or more of the previously mentioned malformations are present in association with the esophageal atresia. The most commonly associated malformations are in the cardiovascular system, 22-32% (2, 39), followed by the genitourinary, anorectal and gastrointestinal system, each of which is seen in about 15% (2, 37). Associated chromosomal abnormalities occur in about 5% of EA children (25, 38). Associated anomalies are most common in cases of EA without TEF and least common in cases with isolated TEF (H-type) (37).

Diagnosis

EA is difficult to diagnose prenatally and, as a result, most of the cases that are born are undiagnosed. The absence of a stomach bubble together with polyhydramniosis are two non-specific prenatal signs which might arouse suspicion (40, 41), but the positive predictive value has unfortunately been shown to be 56% at best (40). How-

ever, some authors propose that these signs should lead to the further identification of chest and neck anatomy by ultrasound in order to look for the upper esophageal pouch, which, if found, has been shown to have a positive predictive value of 100% (42).

Once born, the diagnosis might be suspected if the child has excessive salivation and regurgitates or chokes and coughs in conjunction with the first feed. The inability to pass a catheter into the stomach strongly suggests the diagnosis and, by performing a plain X-ray with the catheter in place, the diagnosis is often confirmed.

It is desirable to determine the type of atresia before surgery, since this determines the initial surgical approach. Air in the stomach and abdomen confirms the presence of a distal fistula, while the absence of air in the gastrointestinal tract raises the suspicion of an isolated esophageal atresia. In the event of a fistula between the trachea and esophagus, without any atresia, so-called H-type, the diagnosis is often delayed and suspected after recurrent respiratory infections and/or coughing and choking during feeding. Bronchoscopy, together with esophagoscopy, are often required to confirm the diagnosis of this latter type.

Preoperative treatment

The patient should be placed in the supine position with the head elevated, while a suction catheter should be placed in the upper esophageal pouch in order to prevent aspiration.

Even though there is no consensus on preoperative medication, both antibiotics and acid suppression could be used in order to reduce the risk of preoperative complications.

Preoperative screening for associated anomalies with special emphasis on renal and cardiac anomalies, including the determination of the side of the aortic arch, is nowadays performed at most centers (43, 44).

Many centers also perform a preoperative bronchoscopy in order to localize the fistula or any other structural abnormality which might influence the planning or outcome of surgery (43, 45, 46).

Surgery

The exact surgical approach depends on the type of EA. The most common type, i.e. EA with a distal fistula, is operated on using a right-sided thoracotomy.

Even though thoracoscopy made its appearance in 1999 (47) and has attracted increasing interest during the last decade, there is still a lack of convincing data to indicate whether this actually benefits the patient more than conventional thoracotomy, which must still be regarded as the gold standard (48, 49).

If the aortic arch is right-sided, as seen in around 3%, (50, 51), some authors recommend considering a left-sided thoracotomy (50, 52). Others state that a conventional right-sided thoracotomy should be performed, when possible, irrespective of the site of the aortic arch (51, 53). In order to preserve muscle and innervation, some alternative skin incisions have been proposed (54, 55). The entrance into the thoracic cage is between the fourth and fifth ribs and an extra-pleural approach is often made to obtain access to the atresia. In most cases, it is feasible to perform a primary anastomosis between the two ends (Figure 2), even though some lengthen-

ing of the proximal pouch might be considered in some cases in order to reduce tension (56, 57). The long- or wide-gap esophageal atresia poses a greater challenge for the pediatric surgeon. Even though there is no consensus on the exact definition of long-gap EA, or how to measure the length between the two ends, the main problem is that the distance between the two ends is too long to make a primary anastomosis. In the event of an isolated esophageal atresia, this can be suspected and prepared for by initiating the surgery through the abdomen in order to measure the gap. A fistula must always be closed, but, if for any reason, the primary anastomosis cannot be performed, the patients should be given a gastrostomy for feeding while the two esophageal ends are left in place. This "wait-and-see" staged repair is preferred by most surgeons, even though some advocate a staged esophageal lengthening by traction during the process (58), a technique which has, however, been questioned due to reproduction difficulties (59).

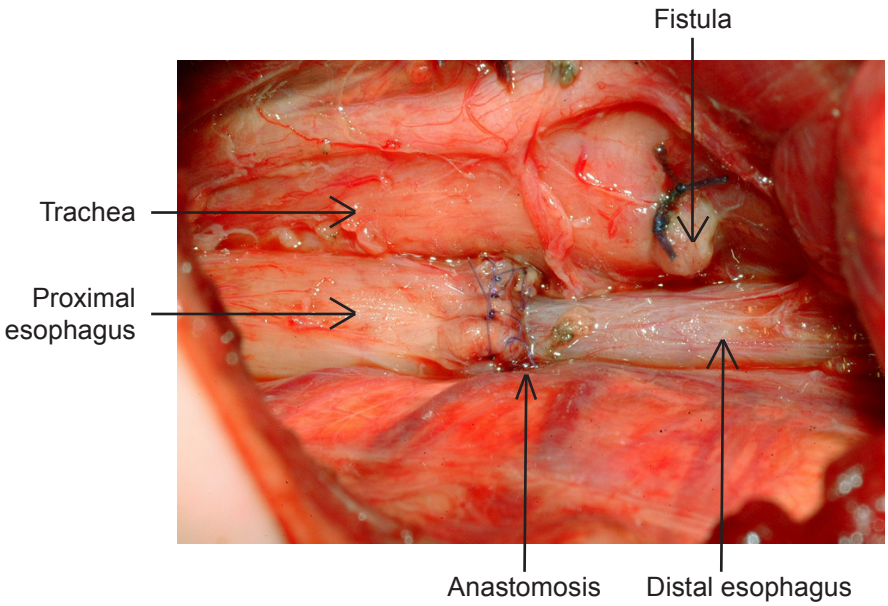

Figure 2. Esophageal primary anastomosis.

During the wait, the distance between the two gaps is measured radiologically at regular intervals and a delayed primary anastomosis might be attempted when the gap has narrowed sufficiently. It has been suggested that, if the gap persists after 12 weeks, the need for an esophageal replacement should be considered (60). Whenever delayed primary repair is not successful, there are different options regarding esophageal replacement, such as jejunal or colonic interposition (61, 62), gastric transposition (63) or different types of gastroplasty (64, 65, 66). As all techniques have their pros and cons, there is no consensus on which is to be preferred (59, 67) and the procedure of choice is often linked to what the surgeon is comfortable with.

The isolated H-type fistula is often operated on through the neck using a cervical approach, even though some cases require a right-sided thoracotomy.

Outcome

Survival

Overall survival nowadays is more than 90% (1, 2). In the past, mortality was mostly associated with cardiac malformations, prematurity, respiratory complications and infections. Advanced intensive care and cardiac surgery are the main reasons for this progress. One recent study illustrates this in a clear way by comparing two adjacent time periods. Despite a higher frequency of low birth weight and major cardiac defects in the latter group, the overall survival rate increased (1).

Early morbidity

The most common reported early complications are anastomotic leak, stricture and recurrent fistula.

An esophageal anastomotic leak is the earliest complication reported in 7-25% (1, 2, 68). The leak is usually due to anastomotic tension, but the surgical procedure may also be responsible (68). Minor leaks can usually be managed conservatively with a chest drain, the suspension of oral feeding and antibiotics, while major leaks, which usually occur within 48 hours (37), often require surgical intervention.

The incidence of anastomotic strictures varies widely, due to the lack of a uniform definition, but a need for dilatation has been noted in up to 80% (1, 2). Nowadays, dilatation is often performed using endoscopic balloon dilatation and anastomotic stricture resection is only needed in a few percent (2, 43, 69).

In recent studies, a recurrent fistula is reported in 2-8% (1, 2, 43, 69) and is often present with respiratory symptoms during feeding. The fistula can be closed either by surgery or using different endoscopic techniques (70, 71).

Late morbidity

Esophageal morbidity is mainly due to gastro-esophageal reflux and dysphagia. Dysphagia is reported in up to 85% of survivors (5, 72, 73, 74). The main cause can probably be attributed to disturbed esophageal motility, innate or iatrogenic, but gastro-esophageal reflux and esophageal stricture must also be ruled out.

Gastro-esophageal reflux is almost as common and is reported in up to 63% of patients operated on for EA (5, 75, 76). Esophageal dysmotility, together with changes in the anatomy of the gastro-esophageal junction, are regarded as the main causes (77). Conservative treatment is quite often not sufficient, due to the complex nature of GER in this patient group, and the proportion of patients requiring fundoplication ranges from 10% to 50% (77).

The high prevalence of GER in turn leads to a high prevalence of esophagitis. This might lead to metaplasia in the esophagus, Barrett's esophagus, which has been reported in up to 36% of EA survivors (78). The difference in the way Barrett's is defined might explain the fairly wide prevalence range and there is still no universally accepted consensus on this matter (79). Barrett's is in turn a well-known risk factor for adenocarcinoma (80), which has so far been reported in three patients undergo-

ing surgery for EA. Seven cases of squamous cell carcinoma (SCC) have also been reported in this patient group, all at an age around 40, which raises the question of whether the risk increases further with age (81). The pathogenesis of SCC in patients with EA is uncertain. However, the association between EA and the risk of esophageal cancer has been questioned (25, 82), but a longer follow-up is warranted before such a correlation can be ruled out or definitely established.

Respiratory morbidity is fairly common following EA repair. Both respiratory symptoms and pulmonary function test abnormalities are more common than in the general population. The cause is probably multifactorial, including both congenital causes, such as pulmonary hypoplasia and tracheomalacia, and acquired causes, such as GER, leading to recurrent aspiration and the postoperative restriction of the thoracic cage (83). Long-term follow-up studies have reported both restrictive and obstructive abnormalities (6, 7, 8). Symptoms including wheeze, long-standing cough and repeated respiratory infections are common and, even though it has been stated that there is an improvement over time, many patients have symptoms persisting into adulthood (8, 76, 84). A higher incidence of doctor-diagnosed asthma (DDA) has also been reported compared with the general population (8). The reason for this is not known, but there is perhaps a tendency to over-diagnose asthma in this population, because respiratory symptoms mimicking asthma in EA patients may be due to other causes (6).

General background data regarding the esophagus and the lungs

Esophagus

The esophagus is a hollow organ which transports food to the stomach, mainly by peristalsis mediated by both intrinsic and extrinsic innervation. The distal part has a valvular function which prevents food and liquid from re-entering the esophagus once they reach the stomach. It may also, as a result of relaxation, serve as a safety valve in order to evacuate excessive swallowed air.

The lower esophageal sphincter (LES), together with the crural diaphragm and the anatomical flap valve, serve as this anti-reflux barrier, protecting the esophagus from prolonged exposure to acidic content from the ventricle. Moreover, esophageal peristalsis is an important factor when it comes to protection from GER. Mechanisms or events that affect these defensive mechanisms, such as an increased gastro-esophageal pressure gradient, can exacerbate the reflux. Obesity, male gender and increasing age have all been associated with both GER and Barrett´s esophagus. The action when it comes to the way GER induces epithelial injury is complex and not fully understood.

Gastro-esophageal reflux

GER is common in the general population. Episodes of the reflux of gastric content to the esophagus may occur in healthy subjects, in relation to the transient relaxation of the lower esophageal sphincter after meals to release swallowed air, for example, and can thus be regarded as a physiological event. Gastro-esophageal reflux disease (GERD), on the other hand, is defined as reflux that causes troublesome symptoms, mucosal injury to the esophagus or both (85). The main symptoms are heartburn and regurgitation. In the western world, an approximate prevalence of 10-20% of GERD, defined by at least weekly heartburn and/or acid regurgitation, has been observed (86). In addition to the effect on the esophagus, which can lead to severe esophagitis and intestinal metaplasia (Barrett's esophagus), GERD might also cause extra-esophageal problems such as hoarseness, coughing and asthma. Since the diagnosis is based on symptoms and/or histological findings, there is no universal diagnostic method, even though endoscopy with biopsies, proton-pump inhibitor tests and ambulatory pH monitoring are often used in order to evaluate the presence of GER.

The treatment of gastro-esophageal reflux is often conservative, including lifestyle and dietary modifications. Medication with antacids or acid inhibition (PPI) might help, even though they do not provide any definite solution. If troublesome symptoms persist in patients with proven GERD, or if patients are reluctant to use PPI for the rest of their lives, surgery could be considered as a last option.

Barrett's esophagus

Barrett's esophagus is a condition in which metaplastic columnar epithelium, which predisposes to cancer development, replaces the stratified squamous epithelium that

normally lines the distal esophagus (87). It is not known why columnar epithelium replaces the squamous epithelium. There is no consensus on whether or not any type of columnar epithelium, i.e. gastric fundic-, cardia- or intestinal type, sampled from the tubular esophagus should be recognized as Barrett's esophagus. The British and US guidelines disagree on whether or not the histological diagnosis must include intestinal metaplasia (87, 88) The prevalence of Barrett's esophagus in the general population has been reported to be 1.3-1.6% in two population-based studies (89, 90). The association between Barrett's esophagus and adenocarcinoma has been established since the 1970s and it is believed to develop through the metaplasia-dysplasia-carcinoma sequence.

Dysphagia

Dysphagia is also a symptom that occurs in the general population. It involves difficulty swallowing and is a condition which increases with age and is reported by 5-8% of the general population aged 50 years and over (91). Typically, the patient describes food being "held up" retrosternally or in the neck, but atypical symptoms, such as meal-related regurgitations and a sense of fullness retrosternally, can also be reported. One of the main questions is whether the patient actually has dysphagia, as a globus sensation and odynophagia (pain on swallowing), for example, can sometimes be misinterpreted as dysphagia. Dysphagia can be caused by a variety of disorders (neuromyogenic, structural or motility based), from the oropharyngeal region all the way down to the lower esophageal sphincter. When it comes to suspected esophageal dysphagia, the most valuable and commonly used investigations are endoscopy, esophageal manometry and a barium-swallow study. The treatment strategy depends on the cause.

Lungs

To understand the information that is received from different lung investigations, a knowledge of the structure and development of the airway system is mandatory. Lung development begins in the fourth week of gestation, as a ventral diverticulum from the foregut, and starts branching dichotomously with each airway dividing into smaller airways. In this way, the cross-sectional area of the airways in total is successively increased against the periphery, which means a reduction in airway resistance. This leads to the peripheral airways, less than 2 mm in diameter, which represent about 90% of the total lung volume, only contributing to about 10% of the total airway resistance (92). Alveolarization continues to the age of three at least, after which further lung growth occurs as a result of increasing alveolar size. The respiratory system is divided into elements of air conduction and air exchange. The conductive part (airway generation 0-16) leads the oxygen to the acinar part (airway generation 17-23) where the gas exchange takes place (Figure 3). Development of the lung is controlled genetically, but it can be influenced by both pre- and postnatal factors.

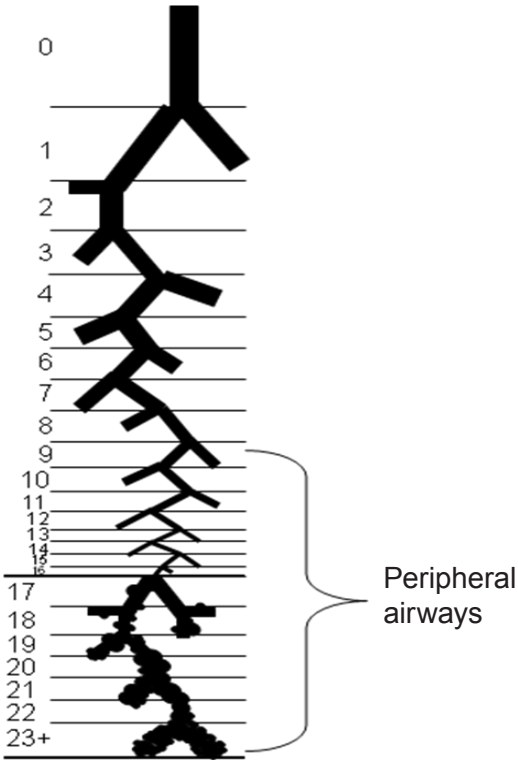

Figure 3. Schematic presentation of the dichotomic dividing structure of the airway tree.

Asthma

Asthma is the most common chronic disease among children and young adults. Even though there is no clear consensus on how to define asthma, it includes a heterogeneous group of conditions that are characterized by recurrent episodes of airway obstruction, which reverse either spontaneously or after using medication. The etiology is complex, involving both genetic and environmental factors. The symptoms include wheeze, chest tightness, breathlessness and cough. Asthma is usually connected with bronchial hyper-responsiveness and evidence of chronic airway inflammation. In young adults, asthma is often associated with the presence of allergic sensitization or eczema. This means that asthmatic individuals often have positive allergy screening test, fractional exhaled nitric oxide (FENO) and bronchial hyper-responsiveness tests.

The prevalence globally of doctor-diagnosed asthma in an adult population aged 18-45 has been estimated to be 4.3%, but with a range between 0.2-21% (93). A recent Swedish study found that the overall prevalence of doctor-diagnosed asthma in a population aged 16-75 years was 8.3% (94). In the age groups of 26-35 years and 36-45 years, the prevalence of doctor-diagnosed asthma was 10.2% and 8.4%, respectively. The first symptoms usually occur during the preschool years, but many of these children do not develop chronic asthma. There is currently no established

strategy for the primary prevention of asthma and the two most important aspects of asthma therapy are pharmacological therapy and environmental therapy. The cornerstones of asthma medication are bronchodilators (beta-2-agonists) and inhaled corticosteroids.

Aims

The aims of this study were:

- to describe the occurrence of respiratory symptoms in adulthood among patients who underwent surgery for EA, compared with the presence of the symptoms in the general population

- to investigate the prevalence of dysfunction of the peripheral airways, as indicated by a raised lung clearance index (LCI), and whether a raised LCI is associated with respiratory symptoms. In addition, the aim was to evaluate whether the asthma diagnosis is accurate

- to measure dysphagia following esophageal atresia quantitatively and, by doing so, investigate whether dysphagia correlates with early risk factors, symptoms of GER and quality of life (QoL)

- to introduce pH multichannel intraluminal impedance (pH-MII) to evaluate the prevalence of GER in an adult group of patients who underwent surgery for esophageal atresia as newborns and to evaluate the association between esophageal symptoms and the results of pH-MII. In addition, we aimed to investigate whether pH-MII could improve the identification of risk factors for changes in esophageal histology, i.e. esophagitis and Barrett's esophagus

Patients

Between 1968 and 1983, 110 patients underwent surgery for EA at the Children's Hospital in Gothenburg. Eighty (43 men and 37 women) of the 110 patients were still alive and 79 were located through the Swedish Population Register Center. The hospital records were reviewed for clinical data: gender, birth weight, type of atresia, associated malformations, anastomotic tension (as reported by the surgeon), post-operative complications including anastomotic stricture, re-operations and, finally, the need for anti-reflux surgery. Twenty-eight (35%) patients had associated malformations. A diagnosis of VACTERL (vertebral, anorectal, cardiac, tracheo-esophageal, renal and limb), defined as the presence of three or more associated malformations, was made in seven patients. The clinical characteristics are shown in Table 1.

Table 1. Clinical characteristics of survivors undergoing surgery for esophageal atresia in Gothenburg 1968-1983 (n=79).

	Gross type A (n=3)	Gross type B (n=1)	Gross type C (n=69)	Gross type D (n=1)	Gross type E (n=5)
Surgical procedure					
Primary anastomosis	1		69	1	5
Delayed primary anastomosis	1	1			
Colonic interposition	1				
Associated anomalies					
Congenital heart disease			6	1	
Gastrointestinal			9		
Urogenital			5		
Musculoskeletal			8		
Chromosomal	1				
CNS†			2		
Complications					
Stricture	3		16		
Recurrent TEF‡			2		
Leak	2	1	7		
Re-operation due to stricture, leakage or re-fistulation	1		11		

†CNS, central nervous system ‡TEF, trachea-esophageal fistula

In the spring of 2008, the located 79 patients were contacted with a letter describing the studies. Of the 79 patients, 73 (92%) completed the questionnaires on esophageal (Paper 1) and respiratory (Paper 2) symptoms. In order to make the study group in the esophageal questionnaires (Paper 1) as homogeneous as possible, we chose to focus the further analysis in this paper on those patients representing the vast majority: Gross type C (63 patients). Twenty-nine of these sixty-three (46%) patients agreed to undergo further testing of their respiratory (Paper 3) and esophageal (Paper 4) function (Figure 4).

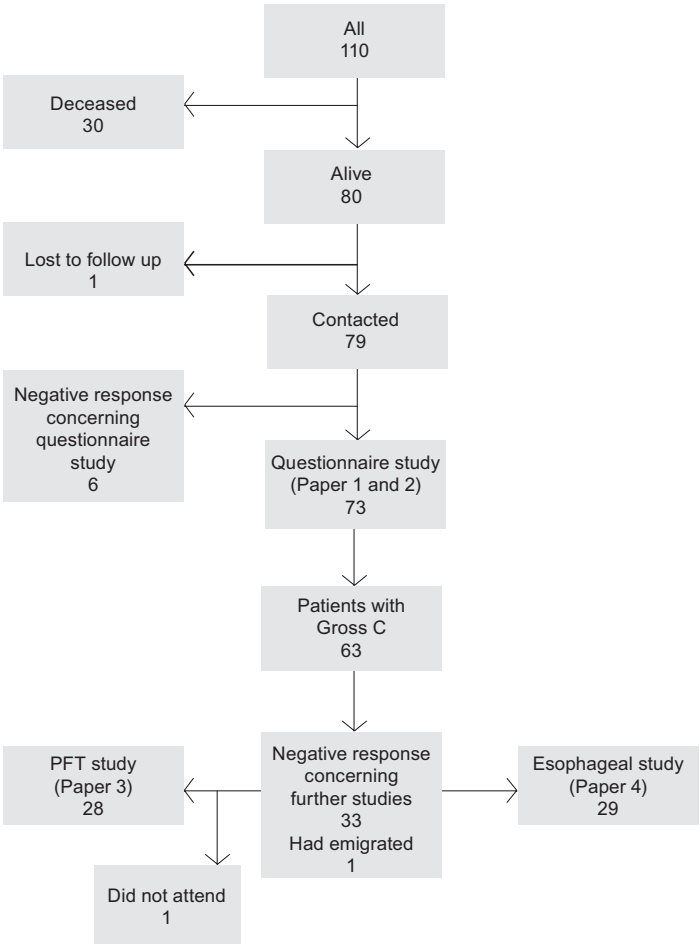

Figure 4. Flow chart of patients operated for esophageal atresia in Gothenburg between 1968 and 1983.

Methods

Questionnaires

Dysphagia score (Papers 1 and 4)

The numerical dysphagia score is composed of 9 items of food with different viscosities and solidities. The score was originally constructed by Dakkak et al. as an instrument transforming symptoms of dysphagia into a numerical score, with obvious advantages regarding its use in the evaluation of clinical trials, and also to be used as a convenient tool in clinical practice (95). Initially, a score of 45 was regarded as no difficulty swallowing. The score has since been reversed by Watson et al., so that the numerical score increases with the severity of the dysphagia. As a result, score 45 now means severe dysphagia (96), which is the score used in our study (Table 2).

Table 2. Dysphagia score.

Dysphagia score

Due to swallowing difficulties, I have problems:

	Never	Sometimes	Always
Drinking water	☐	☐	☐
Drinking milk	☐	☐	☐
Eating yoghurt	☐	☐	☐
Eating jam or jelly	☐	☐	☐
Eating mashed potatoes or scrambled eggs	☐	☐	☐
Eating boiled vegetables or fish	☐	☐	☐
Eating bread	☐	☐	☐
Eating fresh fruit	☐	☐	☐
Eating meat	☐	☐	☐

Gastro-esophageal reflux score (Papers 1 and 4)

The gastro-esophageal reflux disease questionnaire (GerdQ) was developed as a tool

for the diagnosis and management of gastro-esophageal reflux disease in primary care. It has a seven-day time frame and the questions are derived from previously validated instruments (97). Two of the questions, regurgitation and heartburn, were used in our calculations, as they have been shown to have the strongest correlation to GER.

Quality of Life (QoL)(Paper 1)

The SF-36v2™ measures 8 components of health and also yields two summary component scores describing physical and mental health. In this study, we used the Swedish version of the SF-36v2™ (QualityMetric Inc., Lincoln RI, USA). The Swedish version has been shown to have good reliability and validity (98). For comparison with patient data, an age- and gender-matched reference sample was randomly selected from the Swedish SF-36v2 population database (98).

Respiratory symptoms (Papers 2 and 3)

These questions were based on the Swedish OLIN (Obstruktiv Lungsjukdom i Norrbotten, Obstructive Lung Disease in Northern Sweden) questionnaire that has been used in several studies of obstructive lung disease in Northern Europe (99). The questionnaire contained questions on obstructive respiratory disease, respiratory symptoms, rhinitis and possible risk factors for disease, such as smoking and a family history of asthma or allergy (Appendix 1). As controls, 4,979 gender- and age-matched subjects from the same geographical region were used (Paper 2).

All patients were also asked about weight, height, medication and other diseases.

Pulmonary function tests (PFTs) (Paper 3)

SF_6 multiple-breath inert gas washout (SF_6 MBW)

The presence of impaired peripheral airway function was measured by SF_6 multiple-breath inert gas washout (SF_6MBW). This was performed in triplicate and according to existing recommendations (100, 101)(Figures 5 and 6).

During the wash-in phase, a dry gas mixture containing 4% SF_6, 4% helium (He), 21% oxygen (O_2) and balance nitrogen (N_2) was administered. Wash-in continued until inspiratory and expiratory SF_6 concentrations were stable and equal, including an additional 30 seconds, after which washout was initiated. Washout continued until the end-tidal SF_6 concentration was below 1/40th of the starting concentration. The lung clear index (LCI), a marker of ventilation distribution inhomogeneity, was calculated as the number of lung volume turnovers required to reduce the end-tidal SF_6 concentration to less than 1/40th of the initial concentration. The mean value of three LCI recordings in each subject was reported and expressed as z-scores, which were derived from the predicted LCI values and residual standard deviations (RSD) from a matched group of 33 healthy controls. If the intra-session variability of LCI values was large (coefficient of variation > 5%), the most deviant value was excluded and the mean LCI was based on the two remaining recordings.

Figure 5. Subject performing a washout. The supply of wash-in gas is provided by the cylinder in the background. A gas analyser is used to measure flow and SF_6 concentration and expiratory volume is displayed to the subject on a separate screen.

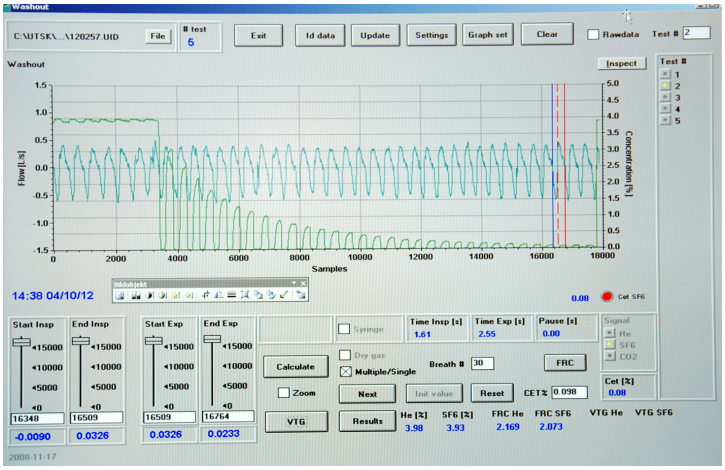

Figure 6. Wash-out phase as displayed on the monitor during the investigation.

Spirometry

Spirometry was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards (102). The results were compared with predicted values using the new global "all ages" reference values presented by Stanojevic et al. (103). FEV_1, FVC and FEV_1/FVC ratios were recorded. A low FEV_1/FVC (z-score <-1.96) was interpreted as evidence of an obstructive ventilatory defect.

Whole-body plethysmography

Total lung capacity (TLC) was measured by whole-body plethysmography according to current ATS/ERS standards (104). TLC z-scores of < -1.96 were interpreted as

evidence of a restrictive ventilatory defect. For whole-body plethysmography, Swedish reference values were used (105, 106).

All the subjects inhaled 400 mcg of salbutamol following the pulmonary function tests and an increase in FEV_1 of at least 12% above the initial value, following bronchodilation medication, was taken as evidence of reversible airway obstruction.
Findings of an abnormally reduced FEV_1/FVC ratio in combination with TLC and LCI within normal limits were used to indicate the presence of an isolated central airway obstruction, while the finding of an abnormally raised LCI in combination with an FEV_1/FVC ratio and TLC within normal limits was used to classify the defect as an isolated peripheral airway obstruction.

Allergy test, FENO and bronchoreactivity (Paper 3)

Allergy test

The UniCAP-Phadiatop™ assay was used to determine the presence of allergic sensitisation. This test is a qualitative serological test that reveals the presence of serum IgE antibodies to the most common allergens in Scandinavia: birch, timothy and mugwort pollens; cat, dog and horse dander; house-dust mites and mould allergen. A positive Phadiatop™ result was used to indicate the presence of an atopic phenotype.

Fractional exhaled nitric oxide (FENO)

As a marker of airway inflammation, FENO was measured in accordance with the ATS recommendations (107). Reported values are the mean concentrations calculated from three measurements that agree within 10%. Previously reported FENO reference values were used, taking age and height into account (108).

Methacholine challenge

The presence and severity of airway hyper-responsiveness (AHR) was determined by a direct bronchial methacholine challenge, which was performed using a tidal volume-triggered dosimetric method. It was performed in all subjects whose baseline FEV_1 was above 60% of predicted values. Medication which could potentially affect AHR assessment was discontinued and patients were asked to refrain from tea, coffee or Coca-Cola within four hours prior to investigation. The subjects were to be free of any viral respiratory infection or asthma exacerbation requiring oral steroids during the two-week period preceding the test. Methacholine was inhaled in subsequently increasing doses at intervals of at least one minute until FEV_1 had decreased by 20% or more compared with baseline, or when a cumulative dose of 5.825 mg had been given. The provocative dose of methacholine resulting in a 20% fall in FEV_1 ($PD_{20}FEV_1$) was calculated by linear interpolation. The subjects were divided into four AHR severity groups based on the challenge results: $PD_{20}FEV_1 < 100$ mcg was regarded as evidence of severe AHR, 100-500 mcg as moderate, 500-2,000 mcg as mild AHR and > 2,000 mcg as the absence of AHR.

Esophageal examinations (Paper 4)

pH multichannel intraluminal impedance (pH-MII)

pH-MII was used to detect GER episodes, irrespective of pH. During the time of registration, the study subjects were instructed to record the time of meals, the time spent in the supine position and symptoms as they occurred. They were also instructed to maintain normal daily living but to avoid alcohol, carbonated beverages, food with a low pH and previously mentioned medications.
A six-segment impedance catheter was used and the pH electrode within the catheter was positioned 5 cm above the manometrically determined lower esophageal sphincter. The data were recorded for 24 hours and then transferred to a computer for analysis. The result was also reviewed and edited manually by one independent investigator for bolus events.

Reflux events were characterised by impedance, while their acidity was characterised by simultaneous pH monitoring. A reflux episode was defined as retrograde bolus movement in at least two consecutive recording channels. The evaluated variables were as follows.

1. Number of acid (pH<4), weakly acidic (pH 4-7) and weakly alkaline (pH>7) reflux episodes. The number of acid reflux >55, weakly acidic reflux >26 or weakly alkaline reflux >1 episodes were regarded as pathological (109).
2. The reflux index (RI) was defined as the percentage of investigated time with esophageal pH of < 4. An RI of > 4.2% was regarded as pathological (110).
3. Bolus exposure (BE) was defined as the percentage of investigated time with reflux, irrespective of the pH level. A BE of > 1.4% was defined as pathological (109).

Esophageal manometry

Esophageal manometry was carried out with a transnasally placed 8-lumen manometer catheter perfused with water at a constant rate of 0.5 ml/minute with a low-compliance perfusion system. Esophageal pressure characteristics were transferred to a polygraph and transformed to a computer for graphic calculation and analysis.
The location of the gastro-esophageal junction was determined using stepwise withdrawal through the high-pressure zone. The basal pressure of the lower esophageal sphincter (LES) was measured during end expiration using the stationary pull-through technique (111).
The subjects performed 10 wet swallows with 5 ml of room-tempered tap water with an interval of at least 20 seconds between each swallow. The mean amplitude of the contraction waves was calculated. The occurrence of simultaneous contractions, failed peristalsis or non-propagating contractions was then compiled.
An LES basal tonus of < 10 mm Hg was regarded as hypotonic, while < 30 mm Hg in the distal esophagus, calculated as the average pressure of 10 wet swallows, was regarded as a low-pressured esophagus (112).
All the manometric examinations were performed and analyzed by one investigator.

Upper gastrointestinal endoscopy

The patients were prepared with an overnight fast and the procedure was performed

under locally applied mucosal anesthetics, without sedation, with the patient placed in a left lateral position.
During the investigation, special emphasis was placed on the following findings: macroscopic esophageal strictures, function of the lower esophageal sphincter, identification of the esophago-gastric junction and presence of mucosal lesions in the esophagus and in the vicinity of the cardia region.
Biopsies were retrieved from predefined locations and additional biopsies were taken if other mucosal lesions were seen. Biopsy specimens were fixed in 10% buffered formalin. All cases with macroscopic esophageal inflammatory lesions (esophagitis) were classified in accordance with the LA classification (A-D) (113). Barrett's esophagus was suspected endoscopically if a columnar lined esophageal epithelium occurred above the esophago-gastric junction. All endoscopies were performed by the same experienced adult gastroenterologist.

Histology
For histology, eosin and alcian blue periodic acid-Schiff double staining were used. Esophagitis was graded according to Ismail-Beigi et al. (114). Barrett's esophagus was defined as intestinal metaplasia with goblet cells in the tubular esophagus. All samples were analyzed by a single pathologist specializing in the gastrointestinal tract.

Statistical methods
Continuous variables were described using the mean, standard deviation (SD), median and range, while categorical variables were described with n and %.
For comparisons between two groups, Fisher's exact test was used for dichotomous variables and the Mann-Whitney U-test for continuous variables. Mantel-Haenszel's exact test was used for ordered categorical variables, while the chi-square exact test was used for non-ordered categorical variables.
Correlations between the dysphagia score and SF-36 scales and continuous variables were calculated using Spearman's correlation (Paper 1). Gastro-esophageal reflux symptoms which could predict dysphagia were investigated using multiple stepwise regression analysis and the association was described by odds ratios and 95% confidence intervals (Paper 1).
Odds ratios (OR) with 95% confidence intervals (CI) were calculated from 2x2 contingency tables using standard methods (Paper 2).
For comparisons involving more than two groups, the Mantel-Haenszel chi^2 test was used for ordered categorical variables, while Spearman´s rank correlation test was used for continuous variables (Paper 3).
For comparisons involving more than two groups, the Mantel-Haenszel chi^2 test was used for ordered categorical variables, while the Jonckheere-Terpstra test was used for continuous variables (Paper 4).
All significance tests were two-tailed and conducted at the 0.05 significance level.

Ethical approval
The studies were approved by the ethics committee at the University of Gothenburg.

Results

Respiratory symptoms and airway function (Papers 2 and 3)

Seventy-three of 79 patients (92%) completed the questionnaire on respiratory symptoms (Paper 2). Respiratory symptoms were consistently more common among EA patients than controls (Table 3).

Table 3. Respiratory symptoms among 73 adult subjects operated on for esophageal atresia.

Variable	EA n (%)	Controls n (%)	p-value
Doctor-diagnosed asthma	22 (30.1%)	477 (9.6%)	<0.0001
Asthma medication	17 (23.9%)	432 (8.7%)	0.0002
Cough with sputum production	25 (34.2%)	633 (12.7%)	<0.0001
Long-standing cough	22 (30.1%)	573 (11.5%)	<0.0001
Wheezing last 12 months	32 (44.4%)	825 (16.6%)	<0.0001
Recurrent wheeze	21 (28.8%)	275 (5.5%)	<0.0001

The OR for physician-diagnosed asthma among the subjects with repaired EA compared with the control group was 4.1. Similarly, the OR for using asthma medication was 3.3, while the OR for recurrent wheeze was 6.9. However, when it came to allergic rhinitis or a family history of asthma, there was no statistically significant difference between the EA and control groups. Nor was there any statistically significant difference in the prevalence of smokers or ex-smokers between the groups.

To make the study group as homogeneous as possible, the 63 subjects with the most common EA malformation (EA Gross type C, i. e. esophageal atresia with a distal tracheal fistula) were selected for further pulmonary investigations (Paper 3). Twenty-eight of the sixty-three (44%) eligible subjects agreed to undergo pulmonary functional testing and also completed the original questionnaire used in the previous study (Paper 2) to provide a current symptom assessment.

Only six of the 28 subjects tested (21%) had normal FEV_1/FVC ratio, LCI and TLC results. The most common abnormality, found in 17 subjects (61%), was a raised LCI, indicating a peripheral airway obstruction. The second most common abnormality was a reduced FEV_1, seen in 14 subjects (50%). However, only six subjects demonstrated an abnormally reduced FEV_1/FVC ratio, which indicates a central airway obstruction (Table 4).

Table 4. Pulmonary function abnormalities among 28 adult EA subjects.

Abnormal pulmonary function	Number of patients (%)
Raised LCI	17 (61)
Reduced FEV_1	14 (50)
Reduced FEV_1/FVC	6 (21)
Reduced TLC	9 (32)

No consistent relationships were found between a history of respiratory symptoms and lung function abnormalities, probably due to the fact that the respiratory symptoms in our subjects were also common in the group of six patients with normal PFTs.
The Phadiatop was positive in 11 subjects, three of whom also had a positive bronchodilator response. FENO was elevated in six subjects, five of whom had a positive Phadiatop, but there was no statistically significant relationship between FENO and/or any lung function abnormality.
The methacholine challenge test was positive in 17/22 (77%) of the investigated subjects and correlated to a positive Phadiatop as well as raised FENO.
The subjects with doctor-diagnosed asthma, 8/28 (29%), did not differ from the remainder in terms of symptoms, pulmonary function tests (Figure 7), Phadiatop, FENO or AHR.

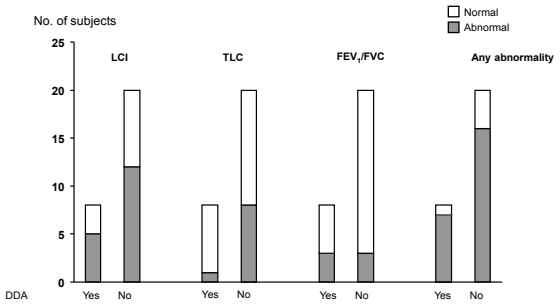

Figure 7. Number of subjects with normal or abnormal lung function findings in relation to a history of doctor-diagnosed asthma (DDA).

Esophageal symptoms and function (Papers 1 and 4)

The 69/79 (87%) subjects with the most common type of EA, Gross type C, were chosen for further esophageal investigations and 63/69 (91%) of them agreed to participate in the questionnaire study (Paper 1).
As many as 36/63 (57%) had swallowing difficulties to various degrees and, the higher the viscosity and solidity of the food, the more subjects reported symptoms of dysphagia. Data from previous hospital charts, or current smoking habits, weight, height or BMI were not able to give any explanation why these patients had dysphagia. Twenty patients (32%) reported heartburn and 25 (40%) had various degrees of

regurgitation. Multiple stepwise regression analysis showed an association between the dysphagia score and regurgitation, yielding an OR of 2.8 (95% CI: 1.2-6.6), but no such connection to heartburn was found.
There was no difference in QoL between the EA patients and the control group and the dysphagia score did not correlate statistically to the QoL.

Twenty-nine of the 63 (46%) subjects agreed to enter the study protocol which would evaluate their esophageal function (Paper 4). pH-MII was performed in 15/29, manometry was performed by 19/29 and 24/29 (83%) subjects were investigated with upper gastrointestinal endoscopy.
Eleven subjects (73%) displayed any pathological reflux variable measured by pH-MII. The distribution between the different parameters is presented in Table 5.

Table 5. pH multichannel intraluminal impedance results in 15 adult subjects previously operated on for esophageal atresia.

pH/impedance monitoring, n=15	Results (median, range)	Normal value	Number abnormal (%)
pH < 4 variables			
Acid reflux episodes, number	18 (1-81)	≤ 55	4 (27)
Acid exposure time (%)			
– Total (RI)	0.7 (0-19.2)	≤ 4.2	2 (13)
– Upright	1 (0-7.3)	≤ 6.3	1 (7)
– Supine	0 (0-32.3)	≤ 1.2	4 (27)
Total number any abnormality pH < 4			5 (33)
pH > 4 variables			
Weakly acidic reflux episodes, number	25 (5-80)	≤ 26	7 (47)
Weakly alkaline reflux episodes, number	1 (0-5)	≤ 1.0	6 (40)
Total number any abnormality pH > 4			10 (66)
Bolus exposure time (%)	0.6 (0-2.6)	≤1.4	3 (20)

There was a correlation between the number of weakly acidic reflux episodes and the numeric dysphagia score (p=0.023), while the other pH-MII parameters did not correlate to the score.
Neither heartburn nor regurgitation correlated statistically to pH-MII variables.

Manometry showed that most of the subjects, 14/19 (74%), had hypotonic wave amplitude in the distal esophagus. This finding correlated to non-propagating peristalsis, which was registered in nine subjects (p=0.032) (Figures 8 and 9).

Both upper and lower esophageal sphincter pressure were normal in the majority of the subjects (18/19 and 16/19 respectively). There was no correlation between dysphagia and esophageal motility.

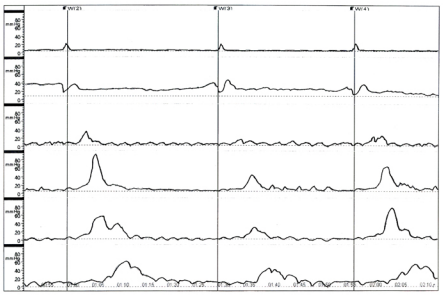

Figure 8. Manometry showing propagating peristalsis.

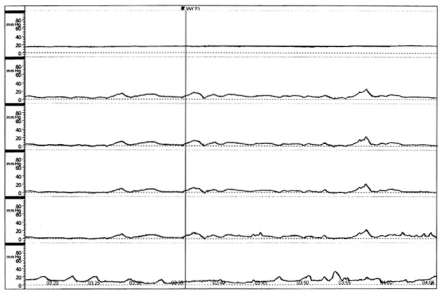

Figure 9. Manometry showing non-propagating peristalsis.

Upper gastrointestinal endoscopy revealed 10/24 (42%) subjects with esophagitis, according to the LA classification. Histological esophagitis, according to Ismail-Beigi classification, was present in 14/24 (58%), two of whom also had Barrett's esophagus.(Figures 10 and 11). Esophagitis was associated with a raised RI and number of episodes of weakly acidic reflux ((p=0.028 and p=0.040 respectively) and tended to be related to the dysphagia score (p=0.052).
The majority of the subjects had partial or complete LES incompetence (14 and 7 respectively), which correlated to an increased number of acid reflux episodes and pathological RI (p=0.012 and 0.050 respectively).

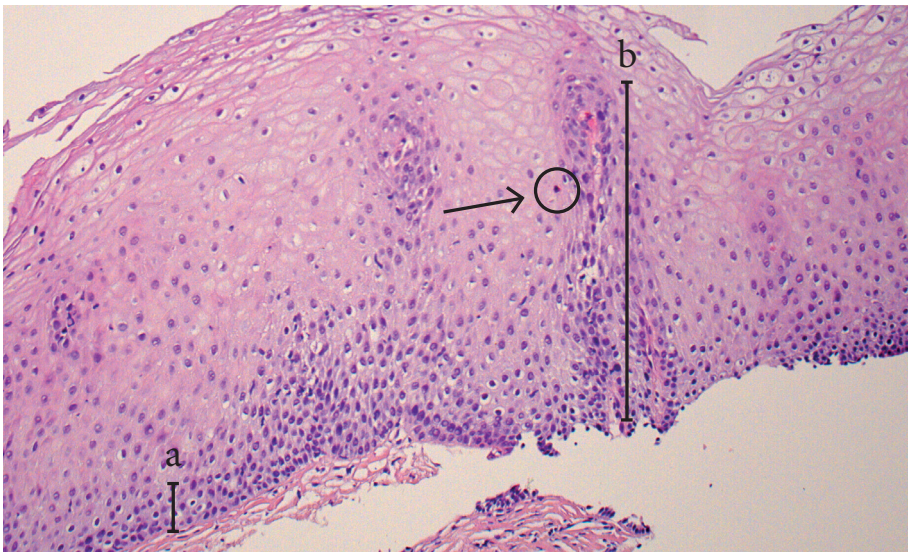

Figure 10. Esophageal squamous epithelium with thicker basal cell layer (a) and elongated papillae (b) which is characteristic for esophagitis. Arrow pointing at intraepithelial eosinophilic granulocyte.

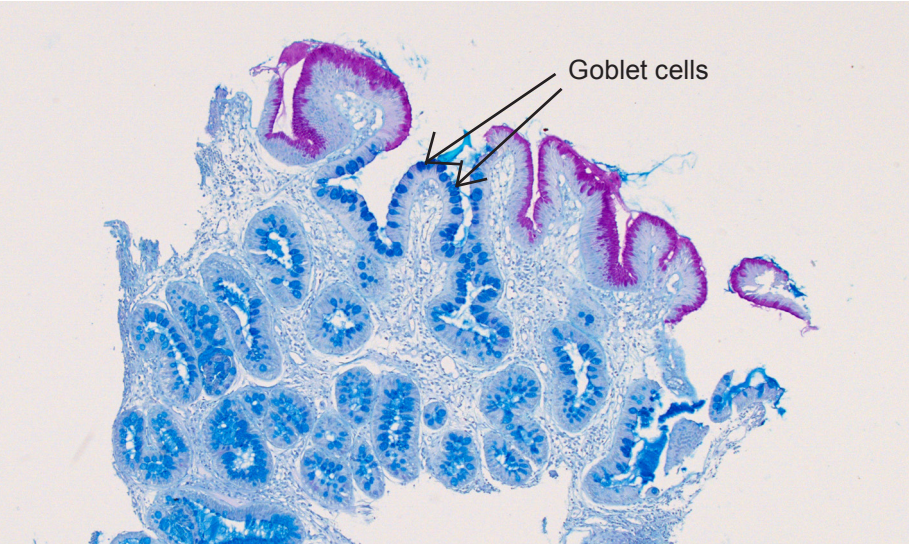

Figure 11. Esophageal biopsy with columnar lined epithelium including intestinal metaplasia with goblet cells (Barrett's esophagus).

General discussion

Since the first successful repair of a patient with EA, we currently have a high survival rate and a growing number of patients are reaching adulthood.
This study was mainly made up of two parts. In the first part (Papers 2 and 3), we based our results on symptoms and functional aspects of the lungs. The second part (Papers 1 and 4) was structured in the same way but with respect to the esophagus.

We found a high prevalence of respiratory symptoms in our EA group compared with controls, including a diagnosis of asthma and the use of asthma medication. Our results are consistent with the largest population-based study of respiratory morbidity in adults with repaired EA (8). Even though we did not have data on the previous prevalence of respiratory symptoms in our EA cohort, our follow-up data did not indicate a reduction in prevalence with age, which has been stated by other investigators (8, 84). Twenty-eight subjects performed the pulmonary function tests (PFTs) and, even though only one had no reported symptom, we were unable to find a correlation between pulmonary function and respiratory symptoms. This has been noted before, even though previous studies have reported conflicting results (8, 115). The reason for this in our material was probably that respiratory symptoms were common, irrespective of normal or pathological pulmonary function tests. The pulmonary function tests revealed that as many as 22/28 (79%) of the subjects had pulmonary function test abnormality indicating an obstructive and/or restrictive disease. What was striking was that the majority of the subjects, 17/28, had abnormal lung function, which was caused by peripheral airway obstruction. This has never been described before and would have been missed if only conventional spirometry had been used. The reason for the pulmonary impairment is not known, but it is probably multifactorial, including both congenital (tracheomalacia, abnormal airway epithelium, defective vagal nerve) and acquired (gastro-esophageal reflux, postoperative restriction of the thorax) causes.
In the literature, the prevalence of asthma among patients with EA varies between 12% and 29%. We found a prevalence of 30% with doctor-diagnosed asthma (DDA), even though we did not see an over-representation of rhinitis or a family history of asthma, which is usually the case in subjects with asthma. Asthma-like symptoms, such as wheeze, attacks of breathlessness and long-standing cough, were very common among the EA subjects, which might make the asthma diagnosis difficult. Among the subjects who performed the PFTs, we did not notice any difference between those with or without doctor-diagnosed asthma with respect to symptoms or PFT results, even though elevated FENO, positive Phadiatop and airway hyperresponsiveness, typical in allergic asthma, were also common in our cohort (21%, 39% and 77% respectively). However, the prevalence was similar in terms of the numbers of subjects in the groups with or without DDA. Taken together, these findings raise the question of whether the diagnostic term “asthma” is correctly used in this patient group. Perhaps a diagnostic term such as “EA asthma” could prove use-

ful in EA patients with asthma-like symptoms not fulfilling the criteria for classical asthma.

Dysphagia was seen to some extent in 57% of our patients, which is in accordance with most previous reports (3, 72). The definition when it comes to dysphagia varies in different studies and a comparison between studies and correlations to corresponding factors might therefore be difficult. In an attempt to solve this problem, we used a numeric scoring system (96). The prevalence of heartburn and regurgitation in our patient cohort was 32% and 40% respectively, which is in line with previous observations of the symptoms of GER (72, 74). By scoring dysphagia, we were able to find an association between dysphagia and regurgitation. Even though we focused on patients with Gross type C, using the dysphagia score enabled us to see a clear difference regarding dysphagia when we made a comparison with the often more complicated Gross type A. Twenty-nine subjects agreed to undergo further esophageal investigations with pH-MII, esophageal manometry and upper gastrointestinal endoscopy (15/29, 19/29 and 24/29 subjects respectively completed the investigations). To our knowledge, this is the first investigation in adults with repaired EA which has used pH-MII. Interestingly, our data showed that the number of weakly acidic reflux episodes was related to dysphagia, which in turn tended to be more severe among patients with more severe mucosal injury. This correlation would have been missed if we had only used regular pH monitoring. However, even though esophageal dysmotility, which predisposes for dysphagia, was noted in the majority of patients, we did not find a correlation to the dysphagia score. Eleven subjects (73%) displayed any pathological reflux variable measured with pH-MII, but neither heartburn nor regurgitation correlated statistically to pH-MII parameters, even though the subjects with regurgitation had a tendency to have more weakly acidic reflux episodes and increased bolus exposure time. This shows that merely symptomatology might not be enough to find those subjects with pathological GER. Among the patients with histologically proven esophagitis, 14/24 (58%), two of whom had Barrett's esophagus, we found that there was a correlation with both increased RI and the number of episodes of weakly acidic reflux. The increased RI, as well as an increased number of acid reflux episodes, was also noted among those with an incompetence of the lower esophageal sphincter. This is an interesting finding, since most studies of EA, including ours, have shown normal LES pressure in the majority of subjects. Our findings show that endoscopy, as well as pH-MII, appear to be important in the follow-up of EA patients.

Conclusion and future considerations

Both esophageal and respiratory morbidity extends into adulthood to a considerable degree among adults with repaired EA.
The pulmonary impairment appears to be greater than previously believed, especially in the peripheral lung. This stresses the importance of a close follow-up of lung function while the subjects are growing up. Since symptoms do not appear to predict the severity, the screening of lung function, including MBW, should be performed regularly, even though we are at present unable to say to which extent. The reason for pulmonary impairment is probably multifactorial, but early detection might help us properly to investigate and rule out, or treat, subclinical causes, such as micro-aspiration or infections which can be treated. Future studies, which we plan, of both children and adults, might tell us whether there is a connection between a raised LCI and pathological pH-MII findings. When it comes to the asthma diagnosis, this must perhaps be reconsidered and instead referred to as "EA asthma" or some other suitable name.

Even though most pediatric surgeons agree that surveillance endoscopies should be performed in adults operated on for EA, there is no consensus on when or how often. This is especially true if the patient has no complaints. It is easy to understand that individuals with signs of GER require further surveillance, but we also noted that dysphagia tended to be correlated to the number of weakly acidic reflux episodes, which was in turn a factor predisposing for esophageal mucosal injury. This implies that not only those with signs of GER but also those with dysphagia should receive attention. Perhaps all the children leaving the pediatric community should perform both pH-MII and endoscopy in order to serve as an aid when it comes to planning future surveillance.

Future studies are desirable in order to verify our results and establish guidelines for the surveillance of adults operated on for EA.

Sammanfattning på svenska

Esofagusatresi (EA) eller avbruten matstrupe är en medfödd missbildning som drabbar 1:3000 nyfödda barn. Orsaken är okänd och behandlingen är kirurgisk med en rekonstruktion av matstrupen. Missbildningen bidrar till att en hel del av patienterna besväras av problem som relateras till både matstrupen och luftvägarna. Dessa besvär följer ofta med upp i vuxen ålder.

Syftet med denna studie var att ta reda på hur mycket besvär som förekommer i vuxen ålder samt hur lung- och matstrupsfunktionen ter sig i olika mätningar samt om dessa mätningsresultat kan förklara besvären.

Sjuttiotre av 80 överlevande patienter opererade i Göteborg mellan 1968-1983 för EA gick med på att delta i den första delen av studien som bestod av att svara på frågeformulär som handlade om symptom från luftvägarna och matstrupen. Tjugonio av dessa patienter gick därefter med på att genomföra andra delen av studien vilken innefattade funktionsundersökningar av lungorna och matstrupen.

I frågeformulären framkom att dessa patienter överlag har en god livskvalité. Vi noterade dock att symptom både från luftvägarna och matstrupe var mycket vanligt förekommande. Femtiosju procent upplevde att de hade sväljningssvårigheter i varierande grad och detta verkade vara kopplat till besvär med uppstötningar, vilket noterades hos 40 %. Trettiotvå procent besvärades av halsbränna. Olika luftvägssymptom såsom väsningar och långvarig hosta var överrepresenterat när man jämförde med allmänheten. Detta gällde även diagnosen astma, trots att inga kända riskfaktorer var överrepresenterade i patientgruppen jämfört med allmänheten.

Lungfunktionsundersökningarna visade att så många som 79 % av de patienter som undersöktes hade en påverkad lungfunktion och att denna påverkan framförallt satt i de perifera delarna av lungan. Vi noterade även att överkänsliga luftvägar var mycket vanligt förekommande och förknippat med allergi och tecken på inflammation i luftvägarna. Trots detta så fann vi inget samband mellan symptomen och lungundersökningarna. Vi kunde inte heller påvisa en skillnad mellan de som fått diagnosen astma och övriga, vare sig i undersökningsresultat eller i symptom.

Matstrupsundersökningarna, pH och impedans, visade på en sjukligt ökad förekomst av uppstötningar från magsäcken. Tack vare impedansmätningen så kunde vi även registrera de uppstötningar som var svagt sura eller basiska (pH > 4), vilka dominerade (noterades hos 66 % av patienterna). Denna typ av uppstötning korrelerade till sväljnings-svårigheter men även till skada på matstrupens slemhinna. Inte oväntat fanns också ett samband mellan skada på matstrupens slemhinna och sura uppstötningar (pH < 4). Skada på matstrupens slemhinna noterades via gastroskopi hos 14/24 patienter varav 2 stycken även hade en annan typ av slemhinna som normalt ses i tarmen, talande för en allvarlig slemhinneskada.

Både luftvägs- och matstrupssymptom är mycket vanligt hos vuxna individer opererade för EA. Lungfunktionen tycks mer påverkad än vad som tidigare varit känt och uppstötningar med pH värden både över och under 4 verkar kunna bidra till matstrupsbesvär samt slemhinneskada. Astma verkar vara svårt att diagnostisera i denna patientgrupp eftersom symptomen är svårtolkade. Sammantaget visar denna studie på vikten av fortsatt uppföljning av denna patientgrupp även i vuxen ålder.

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