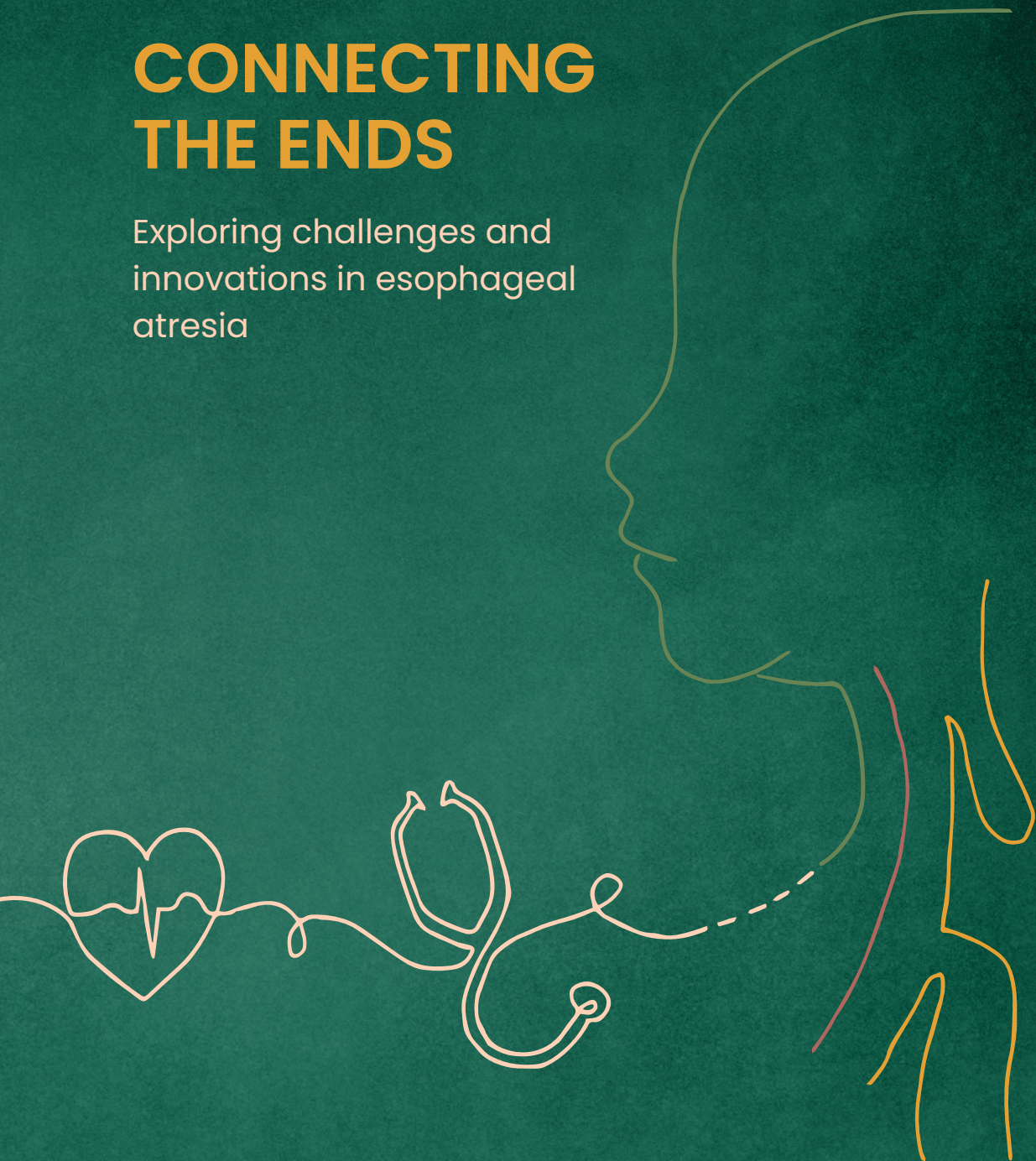


CONNECTING THE ENDS

Exploring challenges and
innovations in esophageal
atresia



E. SOFIE VAN TUYLL VAN SEROOSKERKEN

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EXPLORING CHALLENGES AND INNOVATIONS
IN ESOPHAGEAL ATRESIA

E.S. VAN TUYLL VAN SEROOSKERKEN

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Connecting the ends

Exploring challenges and innovations in esophageal atresia

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CONTENTS

Chapter 1	General introduction and thesis outline	7
Part I	Thoracoscopic repair of esophageal atresia	
Chapter 2	Thoracoscopic Repair Of Esophageal Atresia	27
Part II	Long-gap esophageal atresia	
Chapter 3	Graft dilatation and Barrett's esophagus in adults after gastric pull-up and jejunal interposition for long-gap esophageal atresia	43
Chapter 4	Quality of life after esophageal replacement in children	61
Chapter 5	Childhood outcome after correction of long-gap esophageal atresia by Thoracoscopic external Traction Technique	79
Part III	Respiratory effects	
Chapter 6	Thoracoscopic posterior tracheopexy during primary esophageal atresia repair: a new approach to prevent tracheomalacia complications	99
Chapter 7	Primary Posterior Tracheopexy In Esophageal Atresia Decreases Respiratory Tract Infections	111
Chapter 8	Primary posterior tracheopexy in esophageal atresia patients with concurrent tracheomalacia; a cost analysis study	127
Chapter 9	Airway Epithelial Cultures of Children with Esophageal Atresia as a Model to Study Respiratory Tract Disorders	141
Chapter 10	Bacterial colonization of the lower airways in children with esophageal atresia	155
Chapter 11	Summary and general discussion	167
Appendices	Nederlandse samenvatting	184
	List of publications	190
	Curriculum Vitae	193
	Dankwoord	194



CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

BACKGROUND

Esophageal atresia (EA) is a rare congenital malformation in which the proximal esophagus ends blindly and is therefore not connected to the stomach. The prevalence in Europe is 2.43 per 10,000 live births¹. This corresponds to around 40 newborns with EA per year in the Netherlands.

The first patient with EA was recorded in a conjoined twin, in 1670 by Durston². The first description of a patient with EA with a distal tracheoesophageal fistula was in 1697, by Gibson. In 1840, Thomas Hill described a patient with a combination of EA and anorectal malformation. There was no treatment for EA at that time and therefore, this malformation was fatal.

The first successful surgical repair of EA was performed by Cameron Haight in 1941³. Over the past 80 years, surgical techniques have improved significantly. In 1999, the first successful thoracoscopic repair of an EA was accomplished and a few years later the first successful thoracoscopic repair in the Netherlands was performed⁴. With improved surgical techniques together with enhanced perioperative care, survival rates now exceed 95%⁵. This has led to a change of focus from mortality to long-term morbidity and increased quality of life^{6,7}.

Classification

EA can be classified into six types, according to the Gross classification. Approximately 85% of the EA patients are classified as a type C, in which the atresia is accompanied by a distal tracheoesophageal fistula (TEF). In up to 10% of the cases, patients have a long-gap esophageal atresia (LGEA) without a TEF (Gross type A) or with only a proximal TEF (Gross type B)⁸. Even less common is type D, in which there is a proximal and distal fistula, and type E, in which there is a TEF without an atresia of the esophagus. In type F, EA entails a esophageal stenosis without a TEF (**Figure 1**).

In up to half of the cases, EA is accompanied by one or multiple associated anomalies. In 33% of EA patients the criteria for the VACTERL-association are met and three or more VACTERL-associated anomalies are present (vertebral, anorectal, cardiac, tracheoesophageal, renal, and limb)⁹⁻¹². Furthermore, EA can also be part of a syndrome, including CHARGE (coloboma, hearth defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities), Feingold or Down syndrome¹.

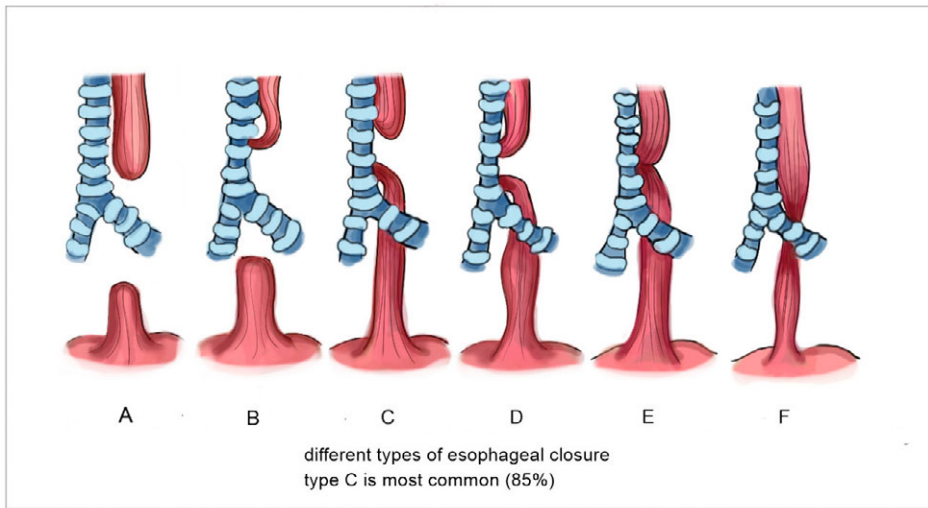


Figure 1. Gross classification for esophageal atresia

Diagnosis

Prenatal diagnosis of EA is possible, although it remains challenging. On ultrasound, certain signs raise suspicion of EA. These signs include polyhydramnios, small or absent stomach and a blind-ending dilated proximal esophageal pouch ("pouch sign"). Ultrasound has a sensitivity of 31.7% in detecting EA, therefore two thirds of the patients are identified after birth. If a fetal magnetic resonance imaging is performed following an abnormal ultrasound, sensitivity is 94.7% and specificity 89.3%¹³. If EA is suspected, delivery preferably takes place in a specialized tertiary center. However, most diagnoses are still made postpartum, when newborns present with blowing bubbles, or in some cases with respiratory distress due to aspiration or reflux through the TEF causing continues aspiration. A nasogastric tube will be placed and if it hampers, a thoracic and abdominal X-ray will be performed to confirm the diagnosis of EA. A curled up nasogastric tube is pathognomonic for EA. Only if the diagnosis remains unclear, a contrast study can be performed.

Surgical procedures for EA

Preoperative management

Newborns with EA require surgical intervention early in life, to take down the distal TEF and to restore the continuity of the esophagus and enable food passage.

In the Netherlands, healthcare professionals decided that EA treatment needs to be centralized in order to increase expertise and is therefore only performed in three specialized tertiary pediatric hospitals: the Wilhelmina Children's Hospital Utrecht, Sophia Children's Hospital Rotterdam and Emma Children's Hospital Amsterdam. As soon as the

diagnosis EA is suspected, patients will be transported to one of these hospitals. Surgical repair of the esophagus will preferably be performed within the first days of life.

Bronchoscopy

Prior to surgery, all EA patients undergo an examination of the airway by rigid and/or flexible bronchoscopy by the otorhinolaryngologist to evaluate tracheomalacia (TM) and the presence of laryngeal cleft and/or a proximal TEF. TM entails a collapse of the trachea while breathing. TM is assessed by a standardized scoring system at three different levels; the upper, middle and lower third of the trachea¹⁴. Tracheal collapse in tracheomalacia can be considered mild (0-33% collapse), moderate (34-66% collapse) or severe (67% collapse or more at any level)^{15,16}.

Primary EA repair (Gross type C)

EA repair can be performed by an open or thoracoscopic procedure. First, the distal esophagus is localized and the TEF is identified. When the TEF is localized and mobilized, a suture can be introduced and placed around the distal fistula and tied close to the trachea. Thereafter, the fistula can be transected at the esophageal side. Subsequently, the proximal pouch is identified. With a sliding knot, the esophageal ends can be anastomosed^{4,19}.

LGEA repair (Gross type A and B)

Primary EA repair is not feasible in the majority of patients with long-gap esophageal atresia (LGEA) due to a wider gap between the proximal and distal esophageal pouch. Several techniques have been advocated to restore the continuity of the esophagus, including esophageal replacement, delayed primary anastomosis and lengthening techniques²⁰. Preservation of the native esophagus is considered to be the best esophagus^{21,22}.

Esophageal replacement

Gastric pull-up

The gastric pull-up was the most commonly performed surgical approach for LGEA²³ as introduced by Spitz²⁴. This procedure is relatively easy to perform and requires only one anastomosis. The stomach is transposed into the thorax and anastomosed to the proximal esophageal pouch²⁴ (**Figure 2**). This transposition of the stomach causes an alteration of the position of the gastroesophageal junction and consequently a decrease of the angle of His²⁵. This results into loss of the anti-reflux barrier mechanisms and may lead to an increased prevalence of gastroesophageal reflux²⁶.

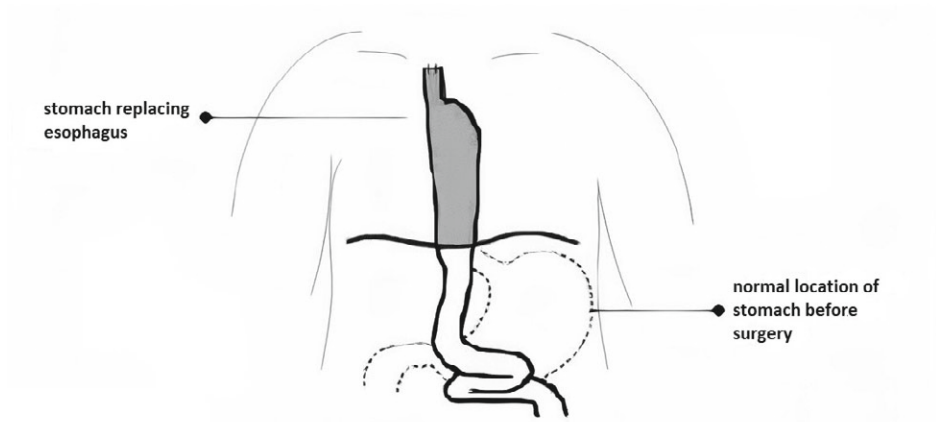


Figure 2. Gastric pull-up procedure

Jejunal interposition

Jejunal interposition is preferably performed at 8 to 12 weeks after birth. Via a thoracotomy the distance between the esophageal pouches is estimated. A laparotomy is performed and the jejunal graft is created. First, the stomach is mobilized and a tunnel from the abdomen into the right chest is created. The jejunum is transected close to the Treitz ligament and close to the third mesenteric branch. The upper part of the graft will be used to restore the esophageal continuity. The jejunal graft is transposed through the left mesocolon and the posterior hiatus into the right chest. An anastomosis is performed between the upper and lower esophageal pouches and the graft (**Figure 3**)²⁷. Jejunal interposition requires three anastomosis and is a technically complex procedure.

Colon interposition

The International Network on Esophageal Atresia (INoEA) has stated that colon interposition for esophageal replacement in LGEA is considered a last resort if other treatments are not applicable^{8,23}. A segment of the colon is mobilized to create a colonic graft. The colonic graft is transferred into the thorax and positioned between the proximal and distal esophageal pouches and can be used either in isoperistaltic or antiperistaltic direction. This procedure requires three anastomoses, two at the esophagus and one in the colon (**Figure 4**). An important disadvantage of this technique is elongation and dilatation of the colon graft over time²⁸⁻³⁰.

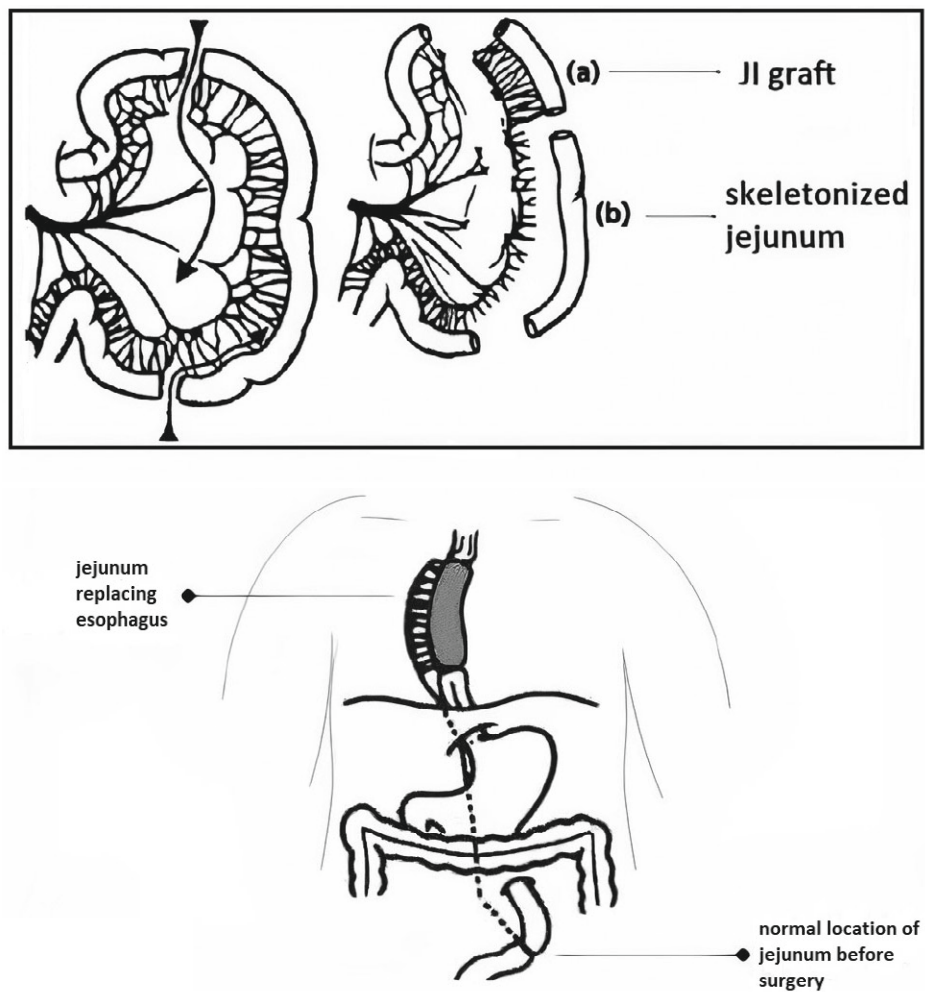


Figure 3. Division of the mesenteric artery branches of the jejunum
a) JI-graft with blood supply (a) and the skeletonized distal part of the upper jejunum that will be removed (b). b) the jejunal interposition procedure

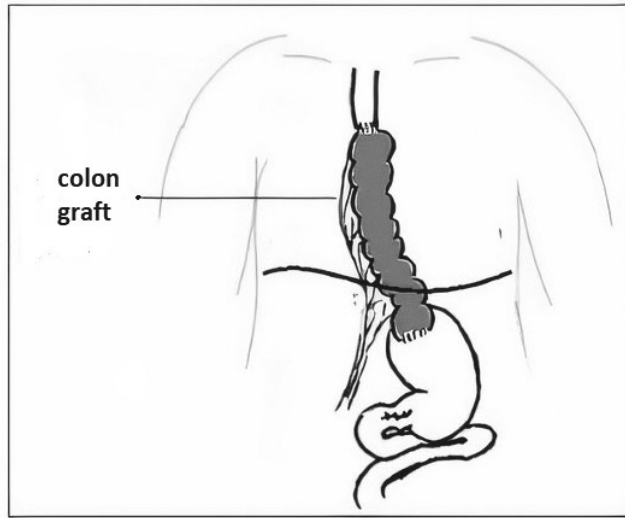


Figure 4. Colon interposition procedure

Esophageal atresia correction with the native esophagus

Delayed primary anastomosis

This technique assumes that the esophageal pouches will grow over time and a primary anastomosis can be performed³¹. When the esophageal pouches tend to grow longer, the gap will become small enough for esophageal repair and a primary anastomosis will be performed^{31,32}. Sometimes bougienage will be used to stretch the esophageal pouch while waiting. The time to achieve delayed primary anastomosis is usually three months. Until then, patients will be fed by gastrostomy³³.

Traction techniques

Foker technique

The open traction technique, as first described by Foker et al.^{34,35}, entails placement of traction sutures at the proximal and distal esophageal pouches, to achieve approximation. The sutures are externalized through the chest wall and external traction is performed to lengthen the proximal and distal esophageal segment within days to weeks. During this period, patients are mechanically ventilated and paralyzed. When the pouches have gained sufficient length, an anastomosis is performed during a final surgical procedure to restore esophageal continuity.

Thoracoscopic traction technique

The thoracoscopic traction technique (TTT)^{36,37}, developed by van der Zee, Tytgat et al., entails a similar operation technique as the Foker-technique however, the surgical procedure is performed thoracoscopically. Initially, a laparoscopic gastrostomy was

performed. Nowadays, before the traction is applied on both esophageal pouches, a gastropexy is performed to prevent the stomach from migrating into the thorax. Subsequently, traction sutures are positioned at the esophageal pouches and the sutures are led out through the chest wall. Clips are positioned at the ends of the esophageal pouches to assess pouch approximation through chest X-rays. After a few days, once no further progression is observed, adhesiolysis is performed. Restoration of esophageal continuity becomes feasible once the esophageal pouches have gained sufficient length and overlap^{36,37}.

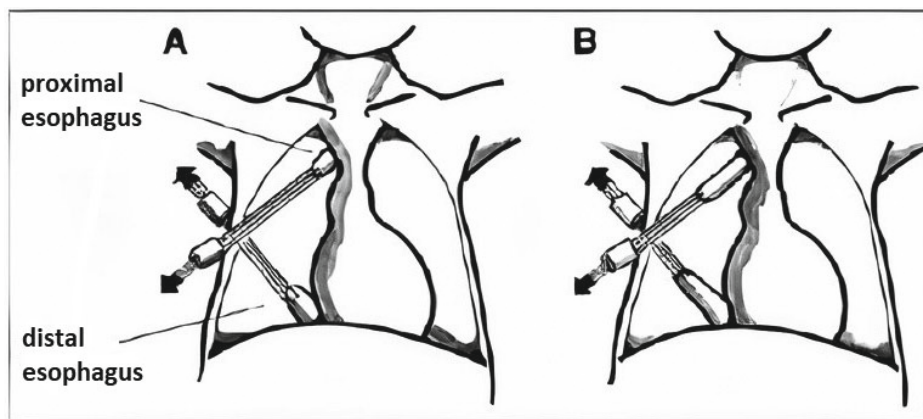


Figure 5. Thoracoscopic traction technique

A) distance between the esophageal pouches at start of traction. B) elongation of pouches over the days of traction. van der Zee, D.C., Gallo, G. & Tytgat, S.H.A. Thoracoscopic traction technique in long gap esophageal atresia: entering a new era. *Surg Endosc* 29, 3324–3330 (2015).

Long-term morbidity

The survival rate for esophageal atresia has significantly improved over the years due to advances in peri-operative medical care and surgical techniques. The survival rate is predominantly based on the presence of associated comorbidities^{38,39}. Studies have demonstrated survival rates exceeding 95% in patients with EA⁴⁰. Consequently, there has been a shift in focus towards long-term morbidities in these patients. Complications and comorbidities may present shortly after birth and may persist throughout life, underlining the significance of recognition and effective treatment. Long-term morbidity in EA patients encompasses gastrointestinal, nutritional and respiratory morbidity⁴¹. Furthermore, there is a growing emphasis on evaluating the quality of life experienced by individuals with EA.

Gastrointestinal morbidity

Gastrointestinal symptoms after EA repair are prevalent. Dysphagia is a common symptom in EA patients. Dysphagia in EA patients arises from various underlying factors, including anatomic abnormalities (i.e. anastomotic stenosis) and impaired neuromuscular coordination, resulting in dysmotility of the esophagus. The severity of dysphagia seems to decrease over time and can be evaluated by the Functional Oral Intake Scale (FOIS)⁴². The FOIS includes seven levels concerning functional oral intake, ranging from nothing by mouth (level 1) to a total oral diet without restrictions (level 7).

Another frequently reported gastrointestinal symptom, especially in LGEA, is gastroesophageal reflux (GER). GER has a prevalence of up to 63%^{7,43,44} and is a major risk factor for the development of (recurrent) anastomotic strictures. Repeated exposure of gastric acid in the esophagus can result in inflammation of the anastomosis, which contributes to the development of anastomotic strictures. An anastomotic stricture of the esophagus occurs in up to 59% of EA patients, mostly within the first year of life⁴⁵. These strictures result in dysphagia and usually require dilatation.

Furthermore, GER can lead to esophagitis and feeding difficulties⁷. A fundoplication may be warranted in severe gastroesophageal reflux disease (GERD)⁴⁶. Chronic GER may eventually cause alterations of the esophageal epithelium and result in Barrett's esophagus or adenocarcinoma of the esophagus⁴⁷.

In the literature, several questionnaires are described to assess reflux symptoms. However, the Reflux Disease Questionnaire (RDQ) is a validated questionnaire to determine gastroesophageal reflux symptoms and has been validated to correctly identify GERD by comparing it to the gold standard of 24-hour pH-monitoring^{48,49}. The questionnaire contains questions on the frequency and severity of regurgitation, heartburn and dyspepsia in the past seven days, which are scored on a 6-point Likert scale from 0 (never/none) to 5 (daily/most severe).

Respiratory morbidity

EA patients frequently suffer from respiratory problems⁵⁰⁻⁵², especially during childhood⁵³. These respiratory problems may be associated with TM, which occurs in up to 90% of EA patients⁵⁴.

TM entails an excessive collapse of the trachea, resulting in a reduction of its diameter⁵⁵⁻⁵⁷. Weakness of the trachea can manifest either anteriorly, due to flattened anterior tracheal rings, or posteriorly, due to a floppy and broadened posterior membrane^{56,58}. TM can result in a wide spectrum of respiratory symptoms, including

stridor, wheezing, respiratory tract infections and brief resolved unexplained events (BRUEs)⁵⁸. In severe TM surgical intervention may be warranted^{56,59}. The preferred surgical treatment depends on the type of TM and includes aortopexy to lift the aortic compression on the anterior flaccid cartilaginous rings^{60,61}, or posterior tracheopexy (PT) of the floppy membrane, in which the posterior membrane is fixed to the spinal ligament, to prevent posterior tracheal intrusion^{62,63}. This PT can be performed either primarily during the initial esophageal repair or secondarily after EA repair^{15,63}. Prior to a surgical intervention for TM, a chest CT must be performed to exclude anatomical abnormalities (i.e. vascular anomalies) that cause tracheal compression⁶⁴. Furthermore, severe GER can lead to aspiration of stomach contents into the airway resulting in coughing, choking and recurrent respiratory tract infections. Consequently, this may lead to inflammation and irritation of the respiratory tract, resulting in respiratory distress.

A laryngeal cleft is diagnosed in 20% of EA patients, which is associated with clinical symptoms as mild stridor, swallowing dysfunction aspiration or recurrent pneumonia^{65,66}.

Studies have also described various lung function abnormalities, including restrictive, obstructive and combined patterns^{52,67-69}. Rib-fusions (or associated congenital, e.g. vertebral abnormalities or secondary kyphoscoliotic complications) after thoracotomy are potential causes of restrictive pulmonary function patterns.

Quality of life

Quality of life is becoming increasingly important, since mortality in EA tends to decrease and focus shifted to long-term morbidities after EA repair. EA may affect various aspects of daily life, including eating, physical activity, social interactions, and emotional well-being. Understanding and addressing these challenges is essential for optimizing Quality of Life (QoL).

Different QoL questionnaires are used in scientific reports focusing on health-related quality of life (e.g. PedSQL, TACQoL), general quality of life (e.g. CHQ-CF87), as well as disease-specific quality of life (e.g. GIQLI, EA-QoL). Even though it is important to report on the QoL, literature on QoL in EA patients is scarce. Some studies found health-related QoL to be diminished in EA patients⁴³ while others showed it to be within normal range^{70,71}. Disease-specific QoL questionnaires may provide a better understanding of the QoL in EA patients. Recently, disease-specific questionnaires have been developed and translation validation is in process⁷²⁻⁷⁵.

Aims and outline of this thesis

The overall aim of this thesis is to explore and highlight the significance of long-term outcome measures in EA and to evaluate the multiple challenges that are faced in EA. Surgical procedures in EA are technically challenging, especially the more recent traction technique for LGEA and the primary posterior tracheopexy. EA is a rare and complex anomaly in newborns and several complications and comorbidities can be encountered throughout life. Evaluating the long-term consequences of the different techniques for EA may contribute to optimized clinical management. Furthermore, this thesis gives better insight into the comorbidities of EA patients, which may result in optimized counseling of patients and their parents. To date, literature on the long-term outcome after the relatively new surgical techniques for EA is scarce. Therefore, this thesis focuses on exploring gastrointestinal and respiratory outcome, nutritional status and quality of life in patients who underwent EA correction.

This thesis consists of three parts. The *first part* aims to describe the technical details of the surgical procedure and focusses on the complications of thoracoscopic EA repair (**chapter 2**). The *second part* focusses on LGEA treatment using esophageal replacement techniques as well as a relatively new thoracoscopic surgical procedure. First, a multicenter study aims to evaluate the clinical and gastrointestinal outcome and macroscopic and microscopic changes after esophageal replacement by gastric pull-up and jejunal interposition (**chapter 3**). Thereafter, quality of life after esophageal replacement is explored (**chapter 4**). As from 2006, patients with LGEA are treated in our center with the thoracoscopic traction technique. Gastrointestinal outcome, nutritional status and quality of life in childhood after introduction of this technique is evaluated (**chapter 5**).

The *third part* evaluates respiratory morbidity in EA patients. First, a new surgical technique is presented, the primary posterior tracheopexy technique, which has been developed to prevent severe symptoms of tracheomalacia (**chapter 6**). **Chapter 7** focusses on respiratory morbidity after implementation of this technique, followed by a study on hospital costs analyses (**chapter 8**). **Chapter 9** presents a laboratory pilot study investigating concurrent primary ciliary dyskinesia in EA patients. Finally, **chapter 10** explores lower airway bacterial colonization in EA patients. This thesis concludes with a general discussion and future perspectives (**chapter 11**).

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PART I

THORACOSCOPIC REPAIR OF ESOPHAGEAL ATRESIA



CHAPTER 2

THORACOSCOPIC REPAIR OF ESOPHAGEAL ATRESIA

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ABSTRACT

Background

Esophageal atresia (EA) is a rare congenital malformation of the esophagus. Surgical treatment is required to restore the continuity of the esophagus. This can be performed through thoracotomy. However, an increasing number of hospitals is performing minimal invasive surgery (MIS). In this article, we describe the technique of thoracoscopic repair of EA in neonates in more detail and show the outcome of a patient cohort operated by young pediatric surgeons in training.

Methods

Between 2014 and 2019 correction was performed in 64 EA type C patients at the UMC Utrecht, Wilhelmina Children's Hospital, mainly by young pediatric surgeons in training.

Results

All patients were corrected through MIS, 3 days after birth. The median operation duration was 181 (127-334) minutes. Nasogastric tube feeding was started on the first postoperative day, and oral feeding 6 days postop. Postoperative complications included leakage (14,1%), stenosis (51,1%) and recurrent tracheoesophageal fistula (7,8%).

Conclusion

Thoracoscopic repair of EA can be performed safely, with good outcome and all the benefits of MIS. However, it remains a challenging procedure and should be performed only in pediatric centers with a vast experience in MIS, especially when training young pediatric surgeons. These centers must have access to a multidisciplinary team of neonatologists, pediatric anesthesiologists, surgeons and ENT-specialists to ensure the best possible care in hemodynamic, respiratory and cerebral monitoring and gastrointestinal- and developmental outcome.

INTRODUCTION

Esophageal atresia (EA) is an anomaly of the esophagus with a prevalence in Europe of ~2.43 in 10,000 live births.¹ The most common type (85%) is Gross type C, with a distal tracheoesophageal fistula (TEF). Long-gap EA (Gross type A and B) is a rare type of EA and occurs in ~10%.² In almost 50% of the patients, EA is accompanied by one or multiple associated anomalies, often as part of the VACTERL association. The VACTERL association includes vertebral, anorectal, cardiac, tracheo-esophageal, renal or limb anomalies.^{3,4}

EA requires surgical correction to restore the continuity of the esophagus. Due to improved surgical interventions and perioperative care, survival rates now exceed 95% and mortality is mainly caused by severe associated anomalies or prematurity.⁵⁻⁸ Previously, EA repair was performed via thoracotomy. Nowadays, EA repair is increasingly performed via minimal invasive surgery (MIS).^{9,10} However, gaining sufficient surgical experience for treatment of this rare anomaly is difficult since numbers are low. Centralization of care and teaching centers of excellence with vast experience in MIS for EA repair are warranted to train young pediatric surgeons in this area of expertise.

This chapter is focused on the thoracoscopic correction of EA type C (EA + TEF) in more detail.

Prenatal diagnosis

Prenatal diagnosis of esophageal atresia remains challenging. Suspicion of EA is based on a polyhydramnios, a small or absent stomach bubble or a blind ending dilated upper esophageal pouch ("pouch sign") on ultrasound. A subsequent MRI can be performed to detect EA.¹¹ When EA is suspected, prenatal counseling is performed and delivery will preferably occur in a center of expertise.

Pre-operative phase

Clinical signs in newborns with EA usually include blowing bubbles, inability to swallow saliva/feeds and respiratory distress. The diagnosis can be confirmed when the introduction of a nasogastric tube hampers. A subsequent abdominal/chest X-ray is performed to show a curled nasogastric tube in the proximal pouch. If abdominal air on the X-ray is absent, this might indicate a long-gap EA, in which there is no distal TEF (Gross type A and B). After confirmation of the diagnosis, the nasogastric tube is replaced by a Replogle® tube, to prevent aspiration of saliva. Preferably, the surgical repair is planned within a few days after birth.

Screening for associated anomalies and pre-operative workup

All EA patients are screened extensively for further potential associated anomalies (VACTERL). Physical examination is performed by the neonatologist. Patients undergo a preoperative cardiac ultrasound to exclude any cardiac or major vascular pathology and to confirm a left-sided descending aorta. An ultrasound of the kidneys, spinal column X-ray and genetic counseling is performed before or after surgery. A multidisciplinary preoperative planning of the operation is always performed by the pediatric anesthesiologist, surgeon, otorhinolaryngologist (ENT) and neonatologist. Proton pump inhibitors are initiated directly after diagnosis.

Preoperative bronchoscopy

Before induction, all patients are monitored by a Near Infra-Red Spectroscopy (NIRS) to safeguard the regional cerebral oxygen saturation.

A preoperative rigid bronchoscopy is performed by the ENT during induction. The bronchoscopy is performed under spontaneous breathing, if the patient's respiratory status permits it. It is carried out to determine the position of the distal TEF, to exclude a proximal TEF and to evaluate the severity of tracheomalacia. Tracheomalacia may be present anteriorly, due to deformation and/or weakness of the tracheal rings or posteriorly, due to a floppy and widened pars membranacea or both. The collapse of the trachea is evaluated on three different levels: the proximal 1/3rd of the trachea, the middle 1/3rd of the trachea and the distal 1/3rd of the trachea.

Positioning

The patient will then be turned into a left $\frac{3}{4}$ prone position on the left side of the operating table. The right arm is placed over the head of the patient. This position of the patient is secured to allow further rotation of the operating table, resulting in a more prone position during the course of the surgery. With this maneuver, a better view of the esophagus is facilitated, as the lung will fall towards a more ventral position.

Technique – Gross type C***Step 1: Introduction***

An open introduction of a 5mm trocar for the camera is performed 1cm below and anterior to the inferior angle of the scapula. Then, insufflation is initiated with CO₂ with 3mmHg and a flow of 1L/min. Under optic vision, two additional 3mm trocars are placed in a triangle on both sides of the camera port, one lateral to the nipple of the right breast, the other ~2 intercostal spaces more caudally and more posteriorly to the camera port (**Figure 1**). Directly 1cm posteriorly to this trocar a 2mm endograsper can

be introduced. The collaboration between the pediatric surgeon and anesthesiologist is crucial to ensure a stable hemodynamic and respiratory state.



Figure 1. The patient is placed in a left 3/4 prone position on the left side of the operating table. A 5 mm trocar for the camera is placed 1 cm below and anterior to the inferior angle of the scapula. Two 3 mm trocars are placed in a triangle on both sides

Step 2: Localization of the distal esophagus and tracheoesophageal fistula

First, the distal esophagus is localized. The azygos vein is a landmark and crosses the distal esophagus. Below the azygos vein, the vagal nerve is identified. Opening the visceral pleura adjacent to the vagal nerve, will show the distal esophagus. After mobilization of the distal esophagus, a vessel loop can be wrapped around the distal esophagus (**Figure 2**). The 2mm endograsper can lift this vessel loop to enable mobilization of the distal esophagus bimanually with two Maryland forceps without crushing the tissue of the esophagus (minimal touch technique). If possible, the azygos vein should be preserved. However, if this is not possible, the vein can be taken down carefully by coagulation. The distal TEF can then be mobilized until the level of the

trachea. Then, an extraluminal transfixing suture Vicryl® 3x0 is placed around the distal TEF at the level of the trachea (**Figure 3**). Thereafter, the TEF can be cut on the esophageal side. To prevent the distal esophagus from retracting, care must be taken to cut the TEF up to only $\frac{3}{4}$ of its diameter. The lumen of the distal esophagus can then be clearly identified (**Figure 4**).

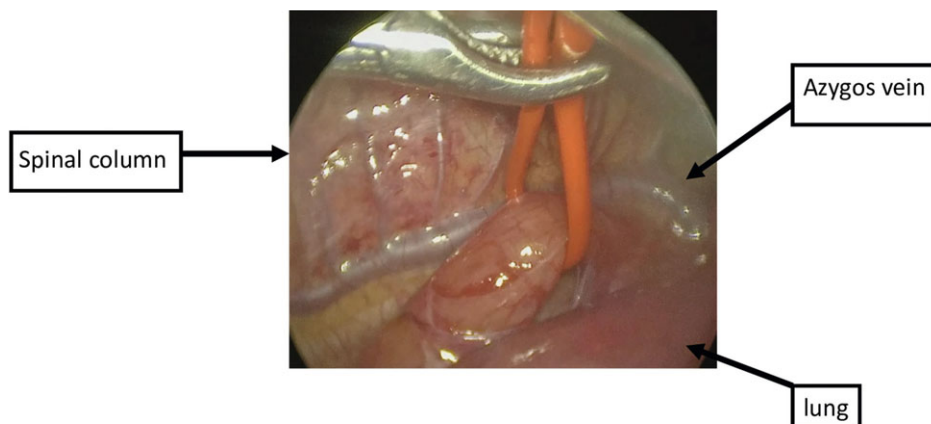


Figure 2. Vessel loop wrapped around the distal esophagus

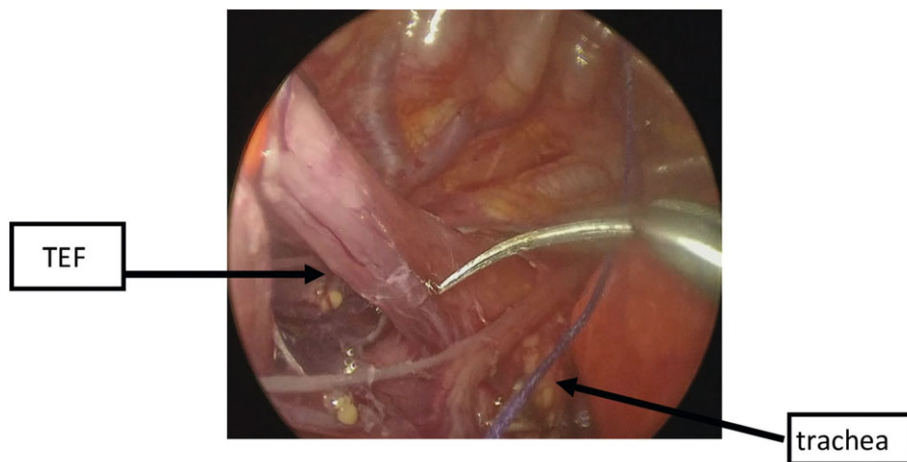


Figure 3. A transfixing suture Vicryl® 3 × 0 is placed around the distal TEF at the level of the trachea. TEF, tracheoesophageal fistula

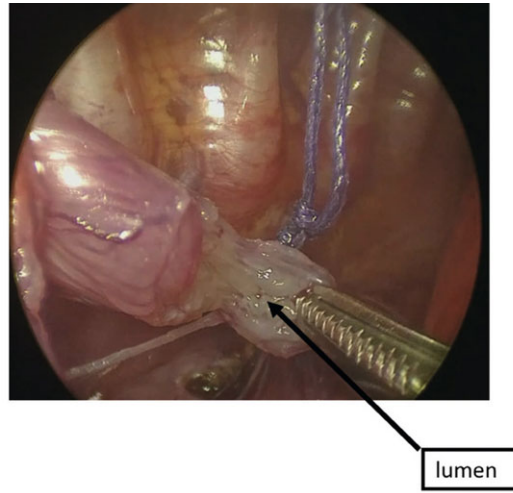


Figure 4. The TEF has been cut up to 3/4 of its diameter. The lumen of the distal esophagus can then be clearly identified. TEF, tracheoesophageal fistula

Step 3: Localization of the proximal esophagus

The anesthesiologist is asked to push the Replogle® tube to facilitate the localization of the proximal esophageal pouch. The pleura is opened with two Maryland forceps and the proximal esophagus can be mobilized. The more difficult part will be to dissect the esophageal wall from the tracheal wall. Again, a minimal touch technique can be applied, to prevent molding the esophageal tissue of the proximal pouch. **Figure 5** shows that holding up the esophagus without grasping it can provide enough countertraction to dissect the two walls from each other.

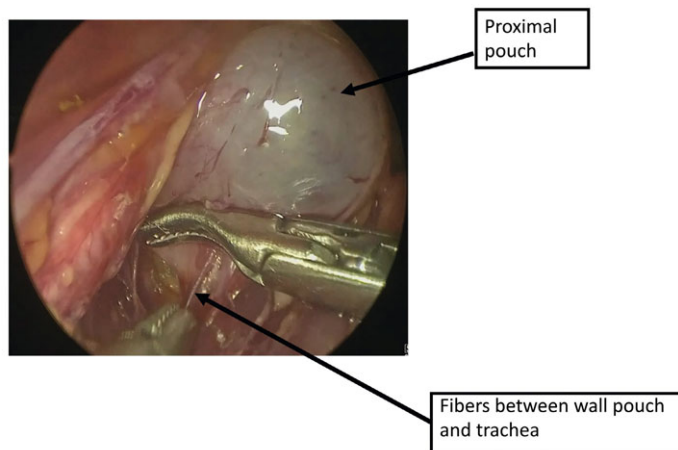


Figure 5. The proximal pouch is held up by a Maryland forceps, without grasping the esophageal tissue, to provide enough countertraction to dissect the esophageal wall from the tracheal wall. Individual tissue fibers can then be bluntly dissected

Step 4: Esophageal anastomosis

Two Vicryl® 5x0 sutures with a length of 10-12cm (depending on the length of the gap) are placed through the proximal pouch (still closed) and through the muscularis and mucosa of the distal pouch with a sliding knot technique. Then, the TEF is completely transected and the tip of the proximal pouch is excised. The esophageal ends can be approximated using the sliding knot technique and two to three sutures can be added on the posterior wall of the esophagus (**Figure 6**). The Replogle® tube can be removed and replaced by a 6 French nasogastric tube (**Figure 7**). Finally, the anterior wall can be anastomosed with either running sutures or standing sutures.

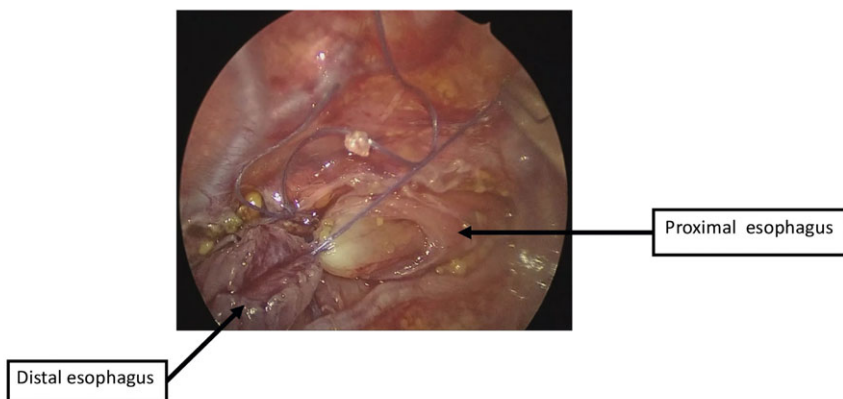


Figure 6. The posterior wall is approximated



Figure 7. After completion of the posterior wall, a nasogastric tube is inserted. Hereafter, the anterior wall sutures can be performed

Step 5: Chest tube (if indicated)

Principally, a chest tube is not necessary, unless there is a high suspicion of leakage of the anastomosis or if iatrogenic damage to the lungs has occurred. The tube may

be introduced through the posterior 3mm trocar opening and placed alongside the esophagus.

Postoperative care

Postoperatively, patients are admitted to the neonatal ICU and can usually be extubated after 1-2 days. Antibiotic treatment is continued for 24 hours. Nasogastric tube feeding can usually be started the day after surgery. Oral feeding can be introduced 1 day after extubation if the postoperative clinical course is uncomplicated and the patient can swallow his/her own saliva. Feeding should be adjusted according to the neonatal protocol. All parents receive a resuscitation course before discharge. Routine follow-up is scheduled, including appointments with the pediatric surgeon, pediatrician, pulmonologist, neonatologist, dietician and speech therapist. Proton pump inhibitors are continued until the patient is 1 year old according to the international ESPGHAN-NASPGHAN guidelines.¹²

RESULTS

Nowadays, most of the EA type C patients are operated on by our young pediatric surgeons (in training), always supervised by our staff of experienced EA minimal invasive pediatric surgeons. Centralization of care in the Netherlands has caused the number of patients referred to our Center of Expertise to increase. International referrals have also increased significantly since then. Between 2014 and 2019 we have operated on 64 EA type C patients.

All patients were corrected through MIS. Surgical repair of the esophagus was performed at a median of 3 days after birth. The median duration of EA repair type C was 181 (127-334) minutes. Patients were extubated 1.5 days after surgery and admitted to the Neonatal Intensive Care Unit (NICU) for a median of 7 days. Nasogastric tube feeding was started the first day postoperatively and introduction of oral feeding was introduced after a median of 6 (2-62) days postoperatively. At our center, the median total length of hospital stay was 24 (10-178) days.

Postoperative complications include leakage, anastomotic stenosis, and recurrent TEF. In our cohort, leakage occurred in 14,1% of patients. In all patients, the leakage was successfully treated with antibiotics, nil by mouth, continuous suction through a Replogle® tube in the proximal esophagus cranially to the anastomosis, and a chest tube.

In half of the EA patients, a stenosis occurred requiring dilatation (51.1%). Treatment consisted of balloon dilatation or dilatation with Savary bougies. Recurrence of a TEF was present in 7.8% of patients.

DISCUSSION

MIS for EA repair^{9,10} is performed in an increasing number of pediatric centers and has several advantages compared to thoracotomy. A meta-analysis that compared thoracoscopy and thoracotomy showed no significant difference in postoperative complications and showed that operating time in thoracoscopy is significantly longer compared to thoracotomy.¹³ However, time to extubation, time to introduction of oral feeding, and duration of hospital stay were all significantly shorter after thoracoscopy for esophageal atresia repair.¹³ The main advantage of thoracoscopy is the excellent visualization of the thoracoscopic cavity. Furthermore, no thoracotomy incision is required in MIS. Up to 60% of patients that had undergone a thoracotomy for EA, had developed thoracic wall deformities later on.¹⁴

The problem with minimal invasive EA repair, however, is gaining sufficient expertise since numbers in EA patients are low. Centralization and teaching programs run by centers of expertise could contribute to the increase in technical skills, but also to gain more knowledge on the multidisciplinary approach, which is crucial in the treatment of rare congenital anomalies. In our Center of Expertise fellows and young pediatric surgeons are offered the opportunity to start early in their career with minimal invasive repair of EA under the supervision of our experienced minimal invasive pediatric surgeons. This has led to zero conversions to thoracotomy and a postoperative outcome comparable to our own historical data and literature.

Anastomotic stenosis is the most frequent postoperative complication, occurring in 30-57% of patients.^{15,16} This is comparable to our study cohort. Risk factors for stenosis are anastomotic tension, leakage and gastroesophageal reflux.^{17,18} Postoperative leakage occurred in 14% of our patients. This is also comparable to the data found in other studies ranging from 10% to 23%.^{16,19} The incidence of recurrent TEF (5-10%) is also similar to the 7.8% found in our cohort.²⁰

The increasing number of referred patients with EA has provided us the opportunity to implement MIS with comparable outcome as open EA repair. Moreover, it has made it possible to teach young pediatric surgeons technical MIS skills early in their career whilst maintaining similar patient outcome. These young pediatric surgeons will have

the opportunity to not only further improve their technical skills and knowledge, but also further improve the outcome of the patients and perhaps develop innovative (MIS) techniques.

In conclusion, we believe that thoracoscopic repair of EA can be performed safely, with good outcome and all the benefits of MIS. However, it remains a challenging procedure and should be performed only in pediatric centers with a vast experience in MIS, especially when training young pediatric surgeons in this area of expertise. Furthermore, these centers must have access to a multidisciplinary team of neonatologists, pediatric anesthesiologists, surgeons and ENT-specialists to ensure the best possible care in hemodynamic, respiratory, and cerebral monitoring and gastrointestinal and developmental outcome.

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PART II

LONG-GAP ESOPHAGEAL ATRESIA



CHAPTER 3

GRAFT DILATATION AND BARRETT'S ESOPHAGUS IN ADULTS AFTER GASTRIC PULL- UP AND JEJUNAL INTERPOSITION FOR LONG- GAP ESOPHAGEAL ATRESIA

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ABSTRACT

Background

Esophageal replacement (ER) with gastric pull-up (GPU) or jejunal interposition (JI) used to be the standard treatment for long-gap esophageal atresia (LGEA). Changes of the ER grafts on a macro- and microscopic level however, are unknown.

Aim

To evaluate long-term clinical symptoms and anatomical and mucosal changes in adolescents and adults after ER for LGEA.

Methods

A cohort study was conducted including all LGEA patients ≥ 16 years who had undergone GPU or JI between 1985-2003 at two tertiary referral centers in the Netherlands. Patients underwent clinical assessment, contrast study and endoscopy with biopsy. Data was collected prospectively. Group differences between JI and GPU patients, and associations between different outcome measures were assessed using the Fisher's exact test for bivariate variables and the Mann-Whitney *U*-test for continuous variables. Differences with a *P*-value < 0.05 were considered statistically significant.

Results

Nine GPU patients and eleven JI patients were included. Median age at follow-up was 21.5 years and 24.4 years, respectively. Reflux was reported in six GPU patients (67%) vs four JI patients (36%) ($P = 0.37$). Dysphagia symptoms were reported in 64% of JI patients, compared to 22% of GPU patients ($P = 0.09$). Contrast studies showed dilatation of the jejunal graft in six patients (55%) and graft lengthening in four of these six patients. Endoscopy revealed columnar-lined esophagus in three GPU patients (33%) and intestinal metaplasia was histologically confirmed in two patients (22%). No association was found between reflux symptoms and macroscopic anomalies or intestinal metaplasia. Three GPU patients (33%) experienced severe feeding problems vs none in the JI group. The median body mass index of JI patients was 20.9 kg/m² vs 19.5 kg/m² in GPU patients ($P = 0.08$).

Conclusion

The majority of GPU patients had reflux and intestinal metaplasia in 22%. The majority of JI patients had dysphagia and a dilated graft. Follow-up after ER for LGEA is essential.

INTRODUCTION

Long-gap esophageal atresia (LGEA) is present in approximately 10% of all EA¹ and remains a surgical challenge^{2,3}. Preservation of the native esophagus in LGEA is the treatment of choice, which can be accomplished by delayed primary anastomosis^{4,5} or elongation techniques⁶⁻¹⁰ in experienced centers. Previously however, almost all LGEA patients underwent esophageal replacement (ER) with gastric¹¹, jejunal¹² or colonic¹³ conduit.

Since survival rates have improved up to 90% in EA¹⁴, focus has shifted to the investigation and treatment of long-term morbidities and quality of life. Gastrointestinal symptoms, including gastroesophageal reflux (GER) and dysphagia, are frequent in EA¹⁵. The incidence of (severe) reflux is expected to be even higher in patients after a gastric pull-up (GPU)¹⁶. This may be explained by mobilization of the stomach into the mediastinum. This results in alteration of the shape of the gastroesophageal junction and consequently the loss of the angle of His, which is one of the anti-reflux barriers. Moreover, the negative intrathoracic pressure and the positive intraluminal pressure in the transposed stomach may increase GER¹⁷. Micro-aspiration due to GER may contribute to chronic cough and asthma-like symptoms^{18,19}. Chronic GER may lead to esophageal mucosal alterations with a four times higher incidence of Barrett's esophagus compared to healthy controls²⁰. Literature on the long-term outcome of ER is scarce^{16,21-23}. Studies on long-term endoscopic findings in LGEA patients are lacking. Therefore, this study aims to evaluate the long-term outcome of jejunal interposition (JI) and GPU on clinical symptoms and anatomical and mucosal changes in adolescents and adults after LGEA.

MATERIALS AND METHODS

Study design and participants

A cohort study was conducted including all LGEA patients ≥ 16 years old who had undergone JI or GPU at the University Medical Center Utrecht (UMCU) and the University Medical Center Groningen between 1985 and 2003. As of 2018, all 17-year-old EA patients are routinely referred to the gastroenterologist for clinical assessment and endoscopic and histologic screening for esophageal mucosal lesions. All adult LGEA patients (> 17 years), that were not yet included in the routine follow-up, were invited for screening. Patients that had ER for LGEA underwent an one-time barium contrast study, to evaluate the anatomy of the graft. Data was collected prospectively. Gastroscopies that were performed after the age of 17 years and within the last four years, were reviewed retrospectively.

Surgical procedures

All ERs had been performed by experienced pediatric surgeons. The GPU was performed as previously described by Spitz *et al.*^{11,24} In short, after mobilization of the stomach and a pyloromyotomy transhiatal posterior mediastinal tunnel is created and the stomach is transposed into the thorax through the esophageal hiatus. Thereafter, the proximal esophagus and the apex of the stomach are anastomosed in the neck. JI was performed as described in these studies^{12,25,26}. The pedicle graft is created: The jejunum is transected close to Treitz ligament and at the level of the third mesenteric artery branch. The uppermost part of the graft is tunneled into the right chest, behind the stomach and through the posterior part of the hiatus. Thereafter, two anastomosis are performed, one between the proximal esophagus and the jejunal graft and another between the distal esophagus and the jejunal graft.

Clinical assessment

Baseline characteristics, including gender, age, type of EA and associated anomalies were obtained from the electronic medical records.

Gastro-intestinal symptoms: Gastrointestinal symptom assessment (*e.g.*, reflux, dysphagia) was derived from the routine outpatient follow-up at the Gastroenterology Department.

Contrast study: Upper gastrointestinal barium contrast studies were analyzed by an experienced radiologist and pediatric surgeon for the following parameters: Anastomotic stenosis, stasis of contrast, reflux, graft-dilatation and graft-lengthening (resulting in a siphon shaped graft) of the JI and the position of the stomach in GPU patients.

Upper endoscopy and histology: Upper endoscopy was performed by a gastroenterologist to assess the esophagus, the anastomotic site(s), the grafts, the gastroesophageal junction and the stomach. Reflux esophagitis and intestinal metaplasia were scored according to the Los Angeles (LA) classification²⁷ and Prague criteria²⁸. Barrett's esophagus was defined as columnar lined esophagus on endoscopy in combination with intestinal metaplasia on histology. In patients with JI, biopsies were taken from both the distal and proximal esophagus. Jejunal grafts were evaluated on proximal or distal stenosis, (distal) dilatation of the graft and on macroscopic lesions. Biopsies of the jejunal graft were taken if mucosal abnormalities were present. The GPU was evaluated on anastomotic stenosis, macroscopic lesions and altered anatomy. In patients with GPU, biopsies were taken just proximal to the anastomosis. In case of macroscopic abnormalities of the GPU, biopsies were taken. Endoscopies were reviewed by an experienced gastroenterologist and a pediatric surgeon. Biopsies were evaluated

for inflammation, eosinophilia and metaplasia by the Pathology Department by an expert gastrointestinal pathologist.

Ethical approval

This study was part of a larger cohort study on the long-term outcome in LGEA patients. The study protocol was submitted to the UMCU Ethics Committee (METC 18-458/C). According to the Medical Research Involving Human Subject Act, no ethical approval was required.

Statistical analysis

Continuous skewed variables were presented as median and range, categorical data were presented as frequencies and percentage. Group differences between JI and GPU patients, and associations between different outcome measures were assessed using the Fisher's exact test for bivariate variables and the Mann-Whitney *U*-test for continuous variables. Differences with a *P*-value < 0.05 were considered statistically significant. The analyses were performed using SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY).

RESULTS

Between 1985 and 2003, a total of 24 patients underwent ER for LGEA (**Figure 1**). One JI patient was deceased at the age of 10 years due to massive aspiration. After following the exclusion criteria, twenty patients were included in this study. Nine patients underwent GPU and eleven underwent JI. Median age at follow-up was 21.5 years (range 20.2-34.1) for GPU patients and 24.4 years (range 16.1-31.2) for JI patients. Five JI patients (46%) and all GPU patients were male ($P = 0.01$). Associated anomalies (e.g., cardiac, renal, musculoskeletal anomalies) were more present in GPU patients than in JI patients (100% vs 55%, $P = 0.04$). In both groups severe mental retardation and Down syndrome were present in one patient. Patient characteristics are shown in **Table 1**. Preoperative gastrostomy was present in all JI patients and in eight (89%) GPU patients. Anastomotic strictures requiring dilatation had developed in eight JI patients (73%) and five GPU patients (55%). Fundoplication was required in one JI patient at the age of 2 years (**Table 2**).

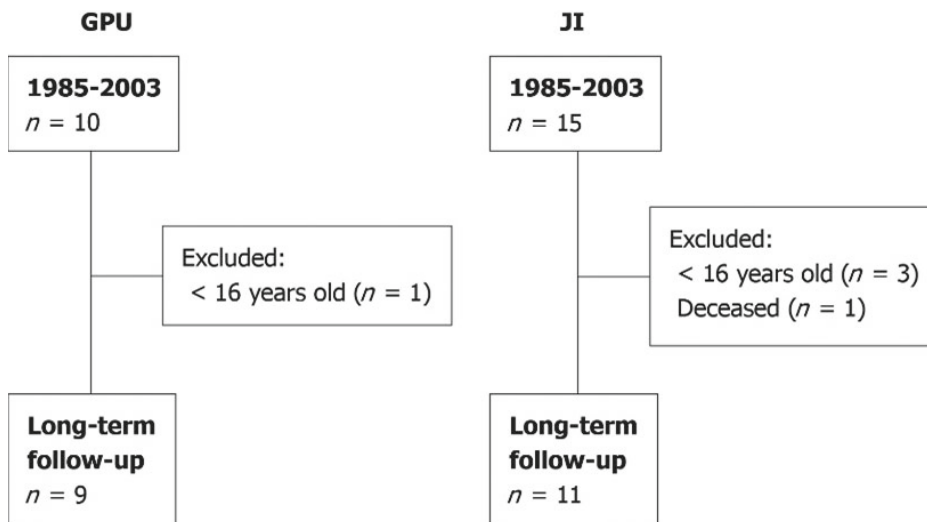


Figure 1. Flowchart of patients included in the study

GPU: Gastric pull-up; JI: Jejunal interposition.

Table 1. Patient characteristics gastric pull-up and jejunal interposition

Value	GPU (n=9)	JI (n=11)	p-value
Male	9 (100%)	5 (46%)	0.01*
Gestational age (weeks)	33.9 (29-39)	34.7 (32.3-41.3)	0.15
Premature	7 (78%)	8 (73%)	1.0
Birthweight (grams)	1680 (1030-3040)	2010 (1115-3755)	0.49
Gross type EA			0.63
A	5 (56%)	4 (36%)	
B	3 (33%)	6 (55%)	
C	1 (11%)	1 (9%)	
Associated anomalies ^a	9 (100%)	6 (55%)	0.04*
Down's syndrome	1 (11%)	1 (9%)	
Anorectal malformations	1 (11%)	1 (9%)	
Duodenal atresia	1 (11%)	1 (9%)	
Musculoskeletal	4 (44%)	3 (27%)	
Cardiac	1 (11%)	2 (18%)	
Renal anomaly	4 (44%)	1 (9%)	
Palatoschisis	2 (22%)	0	

All data are presented as median (range) or n (%)

^aSome patients have multiple anomalies

*Indicating statistical significance

Table 2. GI outcome in gastric pull-up and jejunal interposition

Variable	GPU (n=9)	Jl (n=11)	p-value
Age at surgery (d)	128 (1-323)	67 (41-149)	0.21
Gastrostomy (n,%)	8 (89%)	11 (100%)	0.45
Fundoplication (n,%)	0	1 (9.1%)	1.0
Stenosis ^a (n,%)	5 (56%)	8 (73%)	0.64
Dilatations total (n)	3 (1-4)	3 (1-15)	0.76
Dilatations within 1st year (n)	1 (1-3)	2.5 (0-15)	0.26

^aStenosis requiring intervention

Data are presented as median (range) or n (%)

Clinical assessment

Reflux complaints were reported in six of the nine GPU patients (67%) and in four out of 11 Jl patients (36%) ($P = 0.37$). Dysphagia symptoms were scored in seven Jl patients (64%) vs two GPU patients (22%) ($P = 0.09$). Three GPU patients (33%) experienced severe feeding problems. Due to swallowing disabilities, one patient was still fully dependent on jejunostomy feeding, with minimal attempts of liquid oral feeds. Another patient required additional jejunostomy feeding until the age of 21 years, but has recently reached a full oral diet. One patient required additional drink nutrition to achieve a full oral diet. In the Jl group, no severe feeding problems were observed.

The median body mass index (BMI) of Jl patients was 20.9 kg/m² (range 17.9-27.6) vs 19.5 kg/m² (range 17.5-21.6) in GPU patients ($P = 0.08$). Two Jl patients (18%) were underweight (BMI < 18.5 kg/m²) and one patient was overweight (BMI > 25 kg/m²) (**Table 3**). Three GPU patients (33%) were underweight, none of the patients were overweight.

Table 3. Clinical data

Variable	GPU (n=9)	Jl (n=11)	p-value
Age at follow-up (median, years)	21.5 (20.2-34.1)	24.4 (16.1-31.2)	0.85
GER complaints	6 (67%)	4 (36%)	0.37
Dysphagia	2 (22%)	7 (64%)	0.09
FOIS			
Total oral diet with no restrictions	5	5	
Specific food limitations	1	2	
Multiple consistencies, requiring special preparation	1	0	
Tube-dependent	1	0	
Missing	1	4	
PPI use	4 (44%)	3 (27%)	0.38
BMI (kg/m ²)	19.5 (17.5-21.6)	20.9 (17.9-27.6)	0.08

Data are presented as median (range) or n (%)

Contrast study

GPU: Barium contrast studies were performed in five of the nine GPU patients (56%). In one patient, the stomach was completely transposed into the thorax. This patient showed some lengthening of the distal esophagus and stasis of liquids in the distal esophagus. Another patient, with Down syndrome, also showed stasis of contrast in the esophagus. No reflux was observed in these patients.

Four out of nine GPU patients did not undergo a contrast study; three patients did not consent because they did not experience major gastro-intestinal complaints. One patient with mental retardation was unable to perform a contrast study due to severe swallowing difficulties.

Jl: Barium contrast studies were performed in all 11 Jl patients. Ten patients (91%) showed stasis of contrast in the ER graft. None of the patients had a proximal or distal stenosis. The jejunal graft was dilated in six (55%) patients. In two of these patients, graft dilatation was severe. In four of these six patients, mild to moderate lengthening of the distal part of the jejunal graft was observed (**Figure 2**).

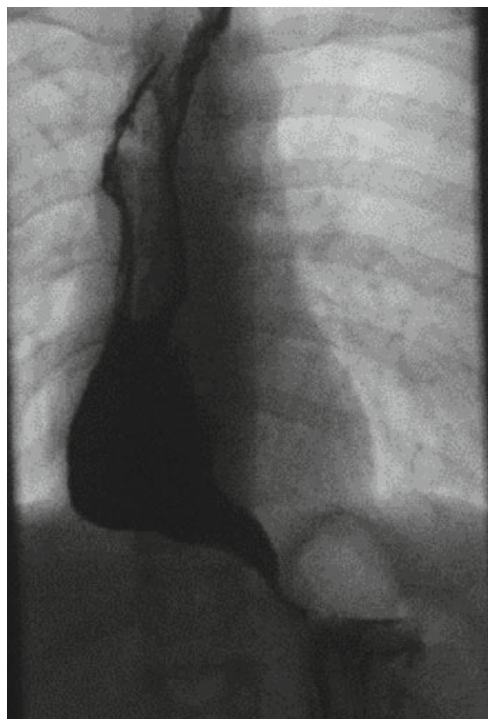


Figure 2. Lengthening and dilatation of the distal jejunal graft

Endoscopic results

GPU: All GPU patients ($n = 9$) had undergone gastroscopy. The median distance from the incisors to the anastomosis was 19 cm (range 17-24). Macroscopic anomalies of the native esophagus were seen in five patients (56%); three patients showed columnar lined esophagus (33%) (C0M2, C0M2, C1M2) (**Figure 3**). One patient had an erosion at the distal part of the esophagus and another patient, who was jejunostomy dependent due to severe swallowing difficulties, had a pinpoint stenosis of the anastomosis (**Table 4**).

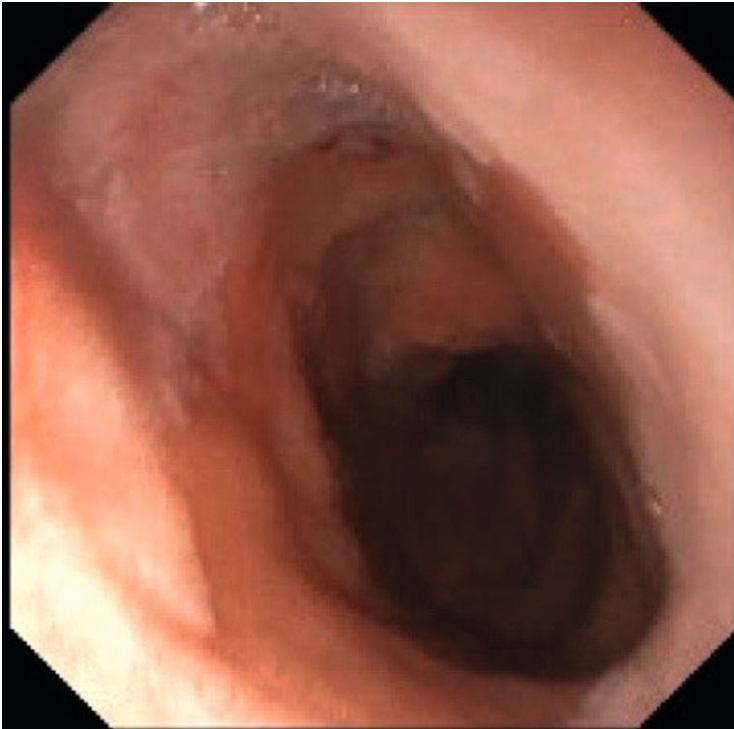


Figure 3. Barrett's esophagus (C0M2) in a gastric pull-up patients

Jl: All Jl patients ($n = 11$) had undergone upper endoscopy. The median distance from the incisors to the proximal anastomosis was 21 cm (range 18-25), the median length of the jejunal graft was 15 cm (range 12-22) and the median length of the distal esophagus was 4.5 cm (range 0-8). In none of the patients a proximal or distal anastomotic stenosis was present. Macroscopic anomalies were seen in five patients (45%): Two patients showed macroscopic esophagitis of the distal esophagus according to the LA classification (grade A, $n = 1$; grade B, $n = 1$), one patient had fields of squamous epithelium in the proximal part of the jejunal graft, one patient showed elevation of normal mucosa in the distal esophagus and a neurological impaired patient had stasis of food and an

ulcer at the distal part of the jejunal graft. None of the JI patients showed columnar-lined esophagus (**Table 4**).

Table 4. Radiologic, endoscopic and histologic data

Variable	GPU (n=9)	JI (n=11)	p-value
Barium contrast results	<i>n=5</i>	<i>n=11</i>	
Stasis	3 (60%)	10 (91%)	0.14
Stricture	0	0	-
Dilated JI graft	N/A	4 (36%)	N/A
Mild		2 (18%)	
Severe			
Lengthening of JI graft	N/A	4 (36%)	N/A
Endoscopy results	<i>n=9</i>	<i>n=11</i>	
Length proximal esophagus (cm)	20 (17-24)	21 (18-25)	-
Length jejunal graft (cm)	N/A	15 (12-22)	-
Length distal esophagus (cm)	N/A	4.5 (0-8)	-
Macroscopic anomalies	5 (56%)	5 (45%)	1.0
Macroscopic esophagitis ^a			
Grade A	0	1 (9%)	-
Grade B	0	1 (9%)	-
Columnar-lined esophagus	3 (33%)	0	0.07
Histology results	<i>n=8</i>	<i>n=7</i>	
Normal mucosa	1(13%)	3 (43%)	0.58
Inflammation	2 (25%)	1 (14%)	1
Intestinal metaplasia	2 (25%)	0	0.47
Other	3 (38%)	3 (43%)	1.0

^a According to the Los Angeles classification
Data are presented as median (range) or n (%)

Histologic results

GPU: In three patients with macroscopic columnar-lined esophagus, biopsies of the native distal esophagus showed intestinal metaplasia in two patients (22%), both with Prague classification COM2 (2 men; median age 21.6 years). In two patients, biopsies of the distal esophagus showed chronic inflammation. Biopsies in another two patients showed hyperplastic squamous epithelium without dysplasia. In one patient, histopathology revealed that biopsies of cardia and corpus were obtained. Histopathology showed no signs of dysplasia in any of the patients. In one patient without macroscopic anomalies, no biopsies specimens were taken (**Table 4**).

J1: In three patients, histology of the native distal esophagus showed normal esophageal mucosa. In one patient, biopsy of the native distal esophagus showed a single glandular tube with signs of intestinal metaplasia. A target biopsy of a small mucosal elevation of the distal esophagus in another patient showed mild reactive changes of the mucosa. In two patients, biopsies of the stomach were obtained. Biopsies in one patient showed no abnormalities. In the other patient without macroscopic anomalies, biopsy of the stomach showed lymphoid infiltration, further investigation excluded lymphoma. None of the biopsies showed signs of esophageal dysplasia. In four patients without suspected macroscopic anomalies (36%), no biopsies specimens were taken (**Table 4**).

Symptom and graft analysis

Columnar-lined esophagus of the native esophagus occurred more often in the GPU group compared to the J1-group (3 vs 0 patients, $P = 0.07$). No associations were found in GPU patients between reflux symptoms and macroscopic mucosal abnormalities during upper endoscopy or with intestinal metaplasia. Both patients that had confirmed intestinal metaplasia, reported reflux symptoms and were treated with proton-pump inhibitors (PPIs). No association was found between intestinal metaplasia and GER symptoms. No association was found between BMI and reflux.

Of the six patients with a dilated J1-graft, five (83%) reported dysphagia complaints. Of the four patients with lengthening of the J1-graft, three (75%) reported dysphagia symptoms. However, there was no statistically significant association between dilatation or lengthening and dysphagia.

DISCUSSION

This is the first study to evaluate very long-term changes in ER grafts for LGEA by contrast study and endoscopy, showing intestinal metaplasia in 22% of GPU patients and graft dilatation in J1 patients. Furthermore, this study evaluates gastrointestinal symptoms during a long-term follow-up.

We found that the majority of GPU patients had reflux symptoms, which is in line with the outcome of the study of Hannon *et al.*²¹ In our study, reflux symptoms were assessed at the outpatient clinic by a gastroenterologist. EA patients might consider reflux symptoms as normal after prolonged periods of reflux. Symptom-related questions asked by a specialist may identify patients with reflux symptoms who would otherwise consider themselves free of symptoms²⁹. This can explain the high incidence of reflux found in this study.

This study showed that reflux symptoms occurred less in JI patients compared to GPU patients. This difference may be explained by the fact that several physiological anti-reflux mechanisms are altered in GPU patients, such as the intrathoracic position of the stomach with a negative intrathoracic pressure and loss of the His angle¹⁷. In the JI patient group, the distal esophagus remained intact with an intra-abdominal position in all but one patient. Although peristalsis of the graft is not as efficient as a native esophagus, the other antireflux barriers are preserved.

Postoperative dysphagia was present in the majority of JI patients. Their nutritional status, however, was good on the long term and all JI patients had a full oral intake. This is in contrast to previous studies^{30,31}, with only 33%-57% of JI patients tolerating a complete oral intake. This difference may be explained by the occurrence of severe postoperative complications in both studies, including graft loss.

In our study, GPU patients reported less dysphagia symptoms compared to JI patients. Our GPU group also reported less dysphagia symptoms than the GPU group of Hannon *et al.*²¹, although this difference is relatively small. Lower BMI has been described in GPU patients compared to primary repair EA patients²¹. This is in line with our findings, in which one third of the GPU patients were underweight and needed nutritional supplements. One might speculate that reflux negatively influences the achievement of an adequate caloric intake and consequent lower BMI^{32,33}. However, in our study, an association between reflux and BMI could not be found.

Our study showed that the majority of patients had a dilated JI graft. Although almost all of these patients reported dysphagia complaints, an association between the dilatation and dysphagia was not statistically significant. The dilatation of the jejunal graft may be explained by the slower motility of the jejunal graft compared to the faster motility of the esophagus. Stasis of food due to dysmotility of the jejunal graft and the distal esophageal remnant may result in dilatation of the graft and may cause dysphagia symptoms in these patients. Lengthening of the JI graft may also contribute to dysmotility and therefore dysphagia due to the siphon shape. Previously, JI graft dilatation has only been described by Saeki *et al.*²² In his study on JI for LGEA (mean age 10 years) dilatation of a graft was observed in one patient. This was due to a stenosis of the distal anastomosis. In our study, lengthening of the jejunal graft was seen in 36% of JI patients, which is in line with previous studies^{22,23}.

Upper endoscopy showed columnar-lined esophagus in one third of the GPU patients and in none of the JI patients in our study. Histology reported intestinal metaplasia in 22% of GPU patients and in none of the JI patient. These findings are in contrast

to the only other published study using endoscopy in adults after LGEA by Vergouwe *et al.*²⁰ The latter showed no signs of Barrett's esophagus in LGEA patients with ER. However, they showed an incidence of 6.6% Barrett's esophagus in their total cohort of 151 adult EA patients. Vergouwe *et al.*²⁰ also showed two patients with esophageal cancer. Esophageal cancer after primary repair of EA at the site of the anastomosis in a patient with severe reflux has also been described³⁴. In our study, no patients were found with esophageal cancer.

Our findings reveal that the macroscopic and microscopic tissue changes seen in the GPU grafts were not significantly associated with reflux symptoms. This may be explained by the fact that many patients were treated with PPIs. Also, metaplasia of the esophageal mucosa can protect against acid reflux and therefore prevent symptoms of discomfort. Furthermore, one can expect that EA patients may get used to reflux symptoms, although this is not evidence based. Reflux symptoms can thus not be used as a reliable detector for the presence of intestinal metaplasia. Since GPU is the most frequently performed ER procedure for LGEA and intestinal metaplasia or Barrett's esophagus may occur more frequently in this subset of patients, further follow-up of GPU in the long-term may clarify this concern. Barrett's esophagus in the normal population increases steeply from young adulthood until the 6th decade of life. Since our cohort consists of young patients, the prevalence of Barrett's esophagus will become more clear after long term follow-up.

Due to the rarity of LGEA, data are scarce. This inevitably limits our study and therefore, interpretations must be made with caution. Furthermore, treatment for LGEA is being corrected by using the thoracoscopic traction technique in our center. In our opinion, this is now the treatment of choice for LGEA, but only in experienced centers. Alternatively, if experience in this challenging procedure is not available, a GPU can be performed.

Other limitations in this study include the retrospective design of the study and the missing histology in five JI patients and one GPU patient. Although the macroscopic aspects during endoscopy seemed normal in these patients, histological evidence would be preferred. Also, contrast studies were missing in four GPU patients. Furthermore, review of contrast studies is not standardized and therefore subjective. However, all contrast studies were analyzed by an experienced radiologist and pediatric surgeon to minimize bias.

CONCLUSION

This study shows that ER grafts show significant macroscopic and microscopic abnormalities after long-term follow-up. Dilatation of the graft and dysphagia symptoms were present in the majority of JI patients. GPU patients may have an increased risk of intestinal metaplasia. Therefore, increased awareness and endoscopic follow-up during adulthood is suggested for LGEA patients after ER. Especially since GPU has been and still is the most frequently used treatment for LGEA.

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CHAPTER 4

QUALITY OF LIFE AFTER ESOPHAGEAL REPLACEMENT IN CHILDREN

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ABSTRACT

Purpose

Assessing quality of life (QoL) after esophageal replacement (ER) for long gap esophageal atresia (LGEA).

Methods

All patients after ER for LGEA with gastric pull-up (GPU n=9) or jejunum interposition (JI n=14) in University Medical Center Groningen and Utrecht (1985- 2007) were included. QoL was assessed with 1) gastrointestinal-related QoL using the Gastrointestinal Quality of Life Index (GIQLI), 2) general QoL (Child Health questionnaire CHF87-BREF (children)/ World Health Organization questionnaire WHOQOL-BREF (adults)), and 3) health-related QoL (HRQoL) (TNO AZL TACQoL/TAAQoL). Association of morbidity (heartburn, dysphagia, dyspnea on exertion, recurrent cough) and (HR)QoL was evaluated.

Results

Six patients after GPU (75%) and eight patients after JI (57%) responded to the questionnaires (mean age 15.7, SD 5.9, 12 male, two female). Mean gastrointestinal, general and health-related QoL total scores of the patients were comparable to healthy controls. However young adults reported a worse physical functioning ($p=0.02$) but better social functioning compared to peers ($p=0.01$). Morbidity was not associated with significant differences in (HR)QoL.

Conclusions

With the current validated QoL most patients after ER with GPU and JI for LGEA have normal generic en disease specific QoL scores. Postoperative morbidity does not seem to influence (HR)QoL.

INTRODUCTION

Esophageal atresia (EA) is a rare congenital disorder characterized by absence of esophageal continuity. In most patients, a primary anastomosis can be performed. However, if the distance between the two esophageal remnants is too wide for primary repair, esophageal replacement (ER) strategies may have to be deployed. Replacement with jejunum¹⁻³, colon⁴, or stomach⁵ have all been advocated.

Gastrointestinal and respiratory morbidity have been investigated after primary anastomosis for EA⁶⁻¹¹. Long term morbidity after primary EA repair has considered to be moderate and QoL in adults patients has demonstrated to be excellent¹²⁻¹³. However long-term morbidity for long gap esophageal atresia (LGEA) appears to be significant. Only a few studies have investigated QoL after ER and mostly without using validated tools. QoL after jejunum interposition has never been analyzed before. We hypothesized that the long term QoL will be diminished in patients who underwent ER in comparison to healthy controls. For optimal care of children after ER and their transition from pediatric to adult healthcare, we should have knowledge of their medical, as well as psycho-social status. Therefore, this study aims to investigate QoL after ER for LGEA in children and young adults and analyze whether morbidity might influence patients' well-being.

PATIENTS AND METHODS

A cross-sectional cohort study was performed. All patients that had undergone a gastric pull-up (GPU) at the University Medical Center Groningen (UMCG) between 1985-2006 and jejunal interposition (JI) at the University Medical Center Utrecht (UMCU) between 1988-2007 for LGEA were included. At the time of the study GPU was the preferred method in the UMCG and a JI was the preferred method in the UMCU. In this cohort, patient were diagnosed with a LGEA if a primary end-to-end anastomosis was not feasible due to the distance between the proximal and distal esophagus measured under fluoroscopy. Primary endpoint of the present study was the assessment of HRQoL and QoL outcome in LGEA patients after JI or GPU. Secondary endpoint was the evaluation of morbidity parameters associated with (HR)QoL.

Ethical Approval

This assessment was conducted in accordance with the local medical ethics review boards of the University Medical Center Groningen (UMCG, Ref. M14.159735) and University Medical Center Utrecht (UMCU, Ref. WAG/om/15/001186).

Measurements

Patient characteristics were collected from the medical records. Sociodemographic aspects were assessed using structured questions on marital status, education and occupation.

Quality of Life measurements

QoL was assessed using validated questionnaires. The QoL measures were self-report measurements. Three areas were investigated: Disease-Specific QoL using the Gastrointestinal Quality of Life Index (GIQLI), general QoL using the CHF87- BREF (children) and WHOQOL-BREF questionnaire (adults), and health-related QoL using the TACQoL (children 6-15 years old) and TAAQoL (patients aged 16 years and older).

Disease-Specific QoL

The GIQLI, introduced by Eypasch et al.¹⁵, is a validated tool to assess HRQoL in patients with gastrointestinal (GI) disease and especially in those who underwent surgery. The questionnaire contains 36 items, each with five response categories concerning gastrointestinal disease-related symptoms, physical status, emotions and psychosocial functions. The questionnaire is developed with 5-point Likert scale, ranging from 0 to 4, with 4 implying the least complaints (a higher score represents a better QoL). The theoretical maximum score is 144 points. A GIQLI score less than 105 indicates that the responder experiences persistent GI symptoms¹⁴. Patients with a total score of less than 105 were therefore considered as symptomatic.

General QoL

The Child Health Questionnaire Child Form (CHQ-CF87)¹⁶ measures psychosocial and physical well-being in patients of 5 to 18 years of age. It provides a qualitative assessment of overall health status across multiple domains. It consists of 87 items divided into 10 multi-item scales, per scale items are summed up and transformed into a 0 (worst possible score) to 100 (best possible score) scale.

The WHOQOL-BREF¹⁷ is a QoL assessment developed by the WHOQOL group for adults. It consists of 26 items in four different domains and a general QoL facet. The domains are physical health, psychological health, social relationships, and family/social environment. The response scales are 5-point Likert scales. A higher score represents a better QoL.

Health-related QoL

HRQoL is a combination of health problems and emotional responses towards these health problems. It reflects the subjective perception of health and is increasingly

recognized as a relevant 'patient-reported outcome' since it measures the emotional impact of self-reported functional problems¹⁸⁻¹⁹.

HRQoL was assessed using TACQOL/TAAQOL²⁰⁻²³ questionnaires developed by The Netherlands Organization (TNO) for Applied Scientific Research and the Academic Hospital in Leiden (LUMC), which explicitly offers respondents the possibility to differentiate between their functioning and the way they feel about it.

The TACQOL (for children 6-15 years old) contains 7 domains: social functioning, autonomous functioning, physical complaints, motoric functioning, cognitive functioning, positive emotions and negative emotions.

The TAAQOL (for patients aged 16 years and older) consists of 12 domains: gross motor functioning, fine motor functioning, cognition, sleep, pain, social contacts, daily activities, sex, vitality, happiness, depressive mood and anger. Items are scored on a 0–4 point Likert scale. Scales are transformed to a 0–100 scale, with higher scores representing a better HRQoL.

Parameters of morbidity and QoL

Relation between (HR)QoL measurements and post-operative symptoms such as heartburn, dysphagia, dyspnea on exertion, recurrent pneumonia and cough and post-operative surgical re-intervention (anastomotic revision and esophageal dilatations) were investigated.

Statistical analysis

Data were entered into a SPSS database and statistical analysis was performed using SPSS (SPSS version 23 9SPSS Inc., Chicago, IL). Data were expressed as mean \pm SD. Continuous variables, group differences were analyzed using one sample t-test, and two sample t-test for CHQ. To examine differences in (HR)QoL between GPU and JI, the means of the two groups were compared using two sample t-tests. Because children completed either the TACQOL or the TAAQOL, depending on age, age-appropriate z-scores of the two were compared. (HR)QoL measurements of patients reporting a specific complain at last follow-up (e.g. heartburn) were compared with those of patients not presenting that symptom using Mann-Whitney U test. Statistical differences were considered as significant for p-value < 0.05.

RESULTS

In total nine GPU and 14 JI patients had undergone an ER for LGEA at the UMCG and UMCU respectively. Six of the GPU and eight JI patients had responded to the questionnaires and could be evaluated for this study. Mean age of the 14 responders was 15.7 \pm 5.9 SD (12male, two female).

No differences were found in patient characteristics between responders and non-responders (**Table 1a**). Characteristics of patients joining the study are shown in **Table 1b**. Sociodemographic factors did not differ in the two groups (**Table 2**). The median follow-up duration after surgery was 12 years (4-24): 12 years (4-17) after GPU and 14 years (7-24) after JI (**Table 3**).

Table 1a. Responders vs non-responders patients characteristics. GPU (gastric pull-up), JI (jejunum interposition)

	Responders (n=14)	Non-responders (n=9)	P-value
Gestational age (<i>weeks</i>)	35.2 (\pm 2.9)	34.4 (\pm 3.2)	0.5
Weight at birth (<i>gr</i>)	2150 (\pm 755)	2154 (\pm 740)	0.8
Type atresia A	5	1	0.3
Type atresia B	8	7	0.4
Type atresia C	1	1	1
Age at surgery (<i>days</i>)	124 (\pm 104)	100 (\pm 89)	0.4
Any VACTERL anomalies	8 (57%)	5 (55%)	1
Cardiac			
Renal	4	2	1
Anorectal	2	3	0.3
Vertebral	2	1	1
	3	3	1
GPU	6 (21%)	3 (33%)	1
JI	8 (57%)	6 (66%)	1

Table 1b. Patient characteristics

	Total (n=14)	GPU (n=6)	Jl (n=8)	P value
Gestational age (<i>weeks</i>)	35.2 (+/-2.9)	34.6 (+/-3.6)	35.6 (+/-2.5)	0.6
Weight at birth (<i>gr</i>)	2150 (+/-755)	2054 (+/-685)	2221 (+/-842)	0.8
Type atresia A	5	4	1	0.09
Type atresia B	8	1	7	0.02
Type atresia C	1	1	0	0.4
Gastrostomy	14	6 (100%)	8 (100%)	1
Age at surgery (<i>days</i>)	124 (+/-104)	140.5 (+/-90)	111.8 (+/-118)	0.3
Any VACTERL anomalies	8 (57%)	5(83%)	3(37%)	0.1
Cardiac	4	2	2	1
Renal	2	2	0	0.1
Anorectal	2	1	1	1
Vertebral	3	3	0	0.05
Anastomotic leak requiring re-intervention	3 (21%)	0	3 (37.5%)	0.2

Table 2. Sociodemographic factors

	Total (n=14)	GPU (n=6)	Jl (n=8)	P value
Mean age	15.7 +/-5.9 (6-28)	17.7 +/- 5.5 (8-28)	14.3 +/- 6.2 (6-25)	0.4
Still student	43% (6)	33% (2)	50% (4)	0.6
Ever flunked	50% (7)	66.7% (4)	37.5% (3)	0.5
Additional job	21.4% (3)	33% (2)	12.5% (1)	0.5
Finished with studies and unemployed	- (0)	- (0)	- (0)	-
Currently full time job	14.3% (2)	16.7% (1)	12.5% (1)	1
Partner	7% (1)	- (0)	12.5% (1)	1
Living alone	28.6% (4)	16.7% (1)	37.5% (3)	0.5
Living with partner	- (0)	- (0)	- (0)	-
Living with parents	71.4% (10)	83.3% (5)	62.5% (3)	0.5
Having children	- (0)	- (0)	- (0)	-

Table 3. Postoperative morbidity

	GPU (n=6)	Jl (n=8)	TOTAL (n=14)
Heartburn	1 (16%)	1 (12%)	2 (14%)
Esophageal dilatation	3 (50%)	1 (12%)	4 (28%)
Episodic dysphagia	3 (50%)	4 (50%)	7 (50%)
Asthma-like symptoms	2 (33%)	0 (-)	2 (14%)
Recurrent pneumonia	1 (15%)	2 (25%)	3 (21%)
Dyspnea on exertion	3 (50%)	2 (25%)	5 (35%)
Recurrent cough	2 (33%)	3 (37%)	5 (14%)
Re-operation	0 (-)	3 (37%)	3 (21%)

Gastrointestinal QoL (GIQLI)

There was no significant differences between the total mean score of both patients groups (n14) (124.2, SD 11.0 vs) 125.8, SD 13.0, $p=0.6$) and healthy controls. One JI patient reported a total score of less than 105 and was considered symptomatic (**Table 4**). No significant differences were found between the different domains of the GIQLI.

Table 4. Disease specific QoL evaluated using GIQLI

	GPU (n=6)		Jl (n=8)		P value
	Mean	SD	Mean	SD	
Physical well being	23	5.1	23.5	3.5	0.9
Gastrointestinal symptoms	65.8	4	63.1	8.7	0.8
Social well being	19.3	1	18.7	17.3	0.3
Emotional well being	18	1.6	17.4	1.9	0.4
Total	126.1	10.9	122.7	13.1	0.6

Generic QoL

There were no significant differences between the total mean score of the children after ER and healthy controls (**Table 5**). Three children after ER (21%), had a very low mean score ($<-2SD$) in the domains pain, general behavior and emotional functioning.

There were no significant differences between the total mean score of the young adults after ER and healthy controls. In the domain physical functioning young adults scored significantly lower compared to healthy controls (16.9 (SD 1.5) vs 18.3 (SD 3), $p=0.02$). In the domain environment, mean scores were higher than in healthy controls (17.2 (SD 1.7) vs 15.9 (SD 2.8), $p=0.05$). None of the young adults scored below $-2SD$ (**Table 6**). No statistically significant differences were found between GPU and JI in QoL measurements, the mean z-score of QoL after GPU was 0.0015 (SD 0.9) and after JI was 0.09 (SD 0.7), $p=0.6$.

Table 5. QoL evaluated using CHQ

	Patients (n=7)		Controls		P value
	Mean	SD	Mean	SD	
Physical functioning	97.3	3.5	96.8	5.4	0.7
Role functioning-emotional	90.4	20.7	92.3	16.8	0.8
Pain	75.7	26.9	78.2	19.5	0.8
General behaviour	82.1	16.5	83.6	10.2	0.8
Self esteem	76.7	5.2	75.4	12.5	0.5
General health	65.2	11.7	74.6	15.9	0.07
Mental health	84.3	8.6	78.2	13	0.1
Family cohesion	86.4	18	75.7	23.1	0.1

Table 6. QoL evaluated using WHOQoL

	Patients (n=9)		Controls		P value
	Mean	SD	Mean	SD	
Physical functioning	16.9	1.5	18.3	3	0.02
Psychological functioning	16.3	1.6	16.1	2.8	0.6
Social Relationship	16.5	2.2	15.8	3.3	0.3
Environment	17.2	1.7	15.9	2.8	0.05

HRQoL

Children after ER scored significantly higher than healthy controls in both the positive (15.6 (SD 0.5) vs 13.0 (SD 2.8), $p=0.00$) and negative (13.6 (SD 1.6) vs controls 11.6 (SD 2.5), $p=0.01$) emotion domains. One child after JI scored $<-2SD$ in the domain autonomy. In the other domains no differences were found (**Table 7**).

In the domain social functioning, young adults scored significantly better than the controls (95.8 (SD 7.5) vs 83.7 (19.2 SD) $p=0.01$). More aggressive emotions (98.1, SD 4.5) were reported by young adults compared with healthy controls (87.6, SD 16.8, $p=0.002$). In the other domains no differences were found. One young adult after JI scored $<-2SD$ in the domain sleep (**Table 8**). No statistically significant differences were found between GPU and JI in HRQoL measurements, the mean z- score of HRQoL after GPU was 0.409 (SD 0.62) and after JI was 0.171 (SD 0.82), $p=0.077$.

Parameters associated with QoL

Re-intervention due to anastomotic leakage and esophageal dilatations were not associated in a change in (HR)QoL. Post-operative symptoms were not associated with significant differences in (HR)QoL measurements (**Table 9a, 9b, 10**).

Table 7. HRQoL evaluated using TACQOL

	Patients (n=9)		Controls		P value
	Mean	SD	Mean	SD	
Physical functioning	26.0	3.2	23.6	5.3	0.07
Motor functioning	29.6	2.6	29.7	3.2	0.9
Cognitive functioning	27.2	3.5	27.5	4.1	0.8
Autonomy	30.7	3.5	31.0	2.9	0.8
Positive moods	15.6	0.5	13.0	2.8	0.00
Negative moods	13.6	1.6	11.6	2.5	0.01

Table 8. HRQoL evaluated using TAAQOL

	Patients (n=7)		Controls		P value
	Mean	SD	Mean	SD	
Cognitive functioning	89.5	10.2	82.7	22.8	0.1
Sleep	67.7	21.8	73.8	26.1	0.5
Pain	82.2	18.7	73.2	24.2	0.2
Social functioning	95.8	7.5	83.7	19.2	0.01
Daily activities	86.4	20.3	83.4	24.8	0.7
Sexuality	87.5	13.6	84.4	25.7	0.6
Vitality	54.1	18	63.8	23.9	0.2
Positive emotions	76.3	14.3	64.5	21.8	0.8
Depressive emotions	81.9	13.3	77.9	20.6	0.4
Aggressive emotions	98.1	4.5	87.6	16.8	0.002

Table 9a. Relation between morbidity and HRQoL measurements in patients up to 15 years old (TACQoL)

	Physical function	Motor function	Cognitive function	Autonomy	Positive moods	Negative moods
Heartburn	1	0.5	0.8	0.5	0.8	0.3
Esophageal dilatation	1	0.6	0.4	0.2	0.6	0.7
Dysphagia	0.5	0.1	0.7	0.3	0.6	0.1
Asthma-like symptoms	0.4	0.5	0.7	0.6	0.3	0.1
Recurrent pneumonia	1	0.5	0.8	0.5	0.8	0.3
Dyspnea on exertion	0.4	0.2	0.7	0.6	0.3	0.4
Recurrent cough	1	0.4	0.1	0.2	0.6	0.2
Re-operation	0.1	0.09	0.4	0.6	0.2	0.7

Data are reported as p value. A p value < 0.05 indicates a symptom associated with significant lower HRQoL measurement.

Table 9b. Relation between HRQoL measurements in patients aged 16 years and older (TAAQoL) and morbidity

	Heart-burn	Esophageal dilatation	Episodic dysphagia	Asthma-like symptoms	Recurrent pneumonia	Dyspnea on exertion	Recurrent cough	Reoperation
Cognitive functioning	0.1	0.3	0.6	0.8	0.2	0.6	0.1	0.2
Sleep	0.1	0.5	1	0.6	0.4	0.2	0.1	0.4
Pain	0.2	1	0.8	0.4	1	0.6	0.2	0.2
Social functioning	0.4	0.7	0.2	0.4	0.4	0.2	0.4	0.2
Daily activities	0.3	0.8	0.6	0.1	0.6	0.1	0.3	0.6
Sexuality	0.3	0.4	1	0.1	1	0.1	0.3	1
Vitality	0.3	0.2	1	0.6	0.2	0.4	0.3	0.2
Positive emotions	1	1	0.4	0.4	0.4	0.4	1	0.2
Depressive emotions	1	0.3	0.3	1	0.4	0.8	1	0.5
Aggressive emotions	0.6	0.3	0.4	0.1	0.1	0.4	0.6	0.4

Data are reported as p value. A p value < 0.05 indicates a symptom associated with significant lower HRQoL measurement.

Table 10. Relation between morbidity and QoL measurements (WHOQoL)

	Physical function	Psychological function	Social relations	Environment
Heartburn	0.8	0.4	0.2	0.8
Esophageal dilatation	0.2	0.4	0.1	0.1
Dysphagia	0.3	1	0.1	0.9
Asthma-like symptoms	0.3	0.1	0.6	0.6
Recurrent pneumonia	0.8	1	1	0.7
Dyspnea on exertion	0.6	1	0.6	0.7
Recurrent cough	0.8	0.4	0.2	0.8
Re-operation	0.8	0.5	0.1	0.5

Data are reported as p value. A p value <0.05 indicates a symptom associated with significant lower QoL measurement.

DISCUSSION

This study investigated (HR)QoL in children and young adults after ER for LGEA. It is the first study on (HR)QoL after JI in children and young adults. We found that generic and disease specific QoL in the majority of patients after ER is comparable to normal QoL scores as measured in healthy population. No significant differences in (HR)QoL were found between GPU and JI patients. Furthermore, postoperative morbidity is not associated with changes into (HR)QoL.

In this study we found gastrointestinal-related QoL (GIQLI) to be generally good: only one patient (JI) scored below the cut-off for symptomatic patients, no significant differences were found between the groups and the controls, nor between the two groups. Recently Hannon et al. analyzed gastrointestinal-related QoL using GIQLI in 32 patients after GPU. Eighteen of them had a GPU for LGEA while in fourteen patients GPU was performed as rescue procedure after failed primary repair or colon interposition²⁶. Results showed that the median gastrointestinal-related QoL according to GIQLI was 113, therefore above the cut-off point of symptomatic impairment (105), comparable to our findings. Dingemann et al. investigated gastrointestinal-related QoL in 27 patients who had an ER for complex/complicated esophageal atresia. GIQLI scores were found significantly worse when compared to the reference group²⁵. A recent systematic review¹⁴ reported significant worse GIQLI measurements for LGEA patients compared to the norm population, however the majority of patients included underwent colon interposition as ER procedure. These results appear to be in contrast with our findings, however differences in the surgical strategies make comparison complicated.

In our study general QoL in children after ER appeared comparable to the healthy population. There was no difference in the general QoL in young adults compared to healthy controls. However, young adults scored significantly worse on the domain physical functioning. Despite the physical limitation, the general QoL seems normal in young adults.

HRQoL was comparable to population average for both children and young adults. Young adults perceive their social functioning better than controls but described more aggressive emotions compared to the population average. This appears to be in contrast with previous studies investigating social functioning of children with chronic illness²⁷⁻²⁸, and it might reflect a shift in the coping mechanisms of patients after ER towards a higher emotional sensitivity. Dingemann et al.²⁵ analyzed also HRQoL (KIDSCREEN27). Conform to our findings HRQoL was perceived as generally good and with regard to the domain physical well-being patients scored even better than controls. However, a correlation between long-term morbidity and HRQoL was not investigated in this series. We did not identify significant differences in (HR)QoL after the two surgical procedures. Patients after GPU reported HRQOL measurements higher than JI patients although not statistically significant ($p = 0.077$).

In this study the relationship between postoperative morbidity and (HR)QoL was analyzed. gastrointestinal and respiratory parameters were not associated with significant differences in (HR)QoL measurements. This outcome might suggest that physical complaints in ER patients do not affect patients' perception of well-being. This may be due to the fact that LGEA patients and their families have accepted this morbidity. Patients and their families might have developed efficient coping strategies in order to face the challenges of life after ER. Interestingly, it has been suggested that patients with congenital diseases might report even better QoL scores than children with acquired conditions, due to stronger coping strategies elaborated from early childhood³⁰⁻³¹. Fifty-seven patients that had a primary correction of EA demonstrated indeed better QoL measurements compared to children with diabetes and asthma³².

Patients after ER might seek stability by evolving their expectations and conceptions of themselves and their social role³³. LGEA patients might have developed different internal standards for daily activities compared to peers. They might have elaborated different life values and might have re-conceptualized their physical limitations, leading to paradoxical satisfactory findings when responding to the present questionnaires. Family influences on patient's daily life have to be considered as well. Parents of chronically ill children tend to overprotect their sick children³⁴. One might assume that this happens for patients after ER as well. Although this is comprehensible parental

behavior it might represent a limitation to develop children's social functioning during adolescence. Moreover, somatic morbidity may affect the development of their personal identity and consequently may lead to social marginalization during a time when self-esteem largely depends on the acceptancy by peers. Therefore, physicians should encourage the family of patients after ER to promote and sustain the social contacts and autonomy of their children. However, even if we noticed a shift towards more emotional sensitivity during transition into adulthood, emotional development seems adequate, with outcomes such as vitality, social and cognitive functioning comparable to controls.

Limitations of this study is the small sample size that may lead to the lack of significant differences between the two groups.

The GIQLI questionnaire represents a valid tool for evaluation of disease-specific QoL in patients with gastrointestinal disorder but it is not tailored for patients with esophageal atresia. Dellenmark-Blom et al.³⁵ recently developed and validated a German and Swedish condition-specific HRQoL tool for patients who had a primary correction of EA. When implementing this for children with LGEA and ER it might represent a more appropriate instrument to investigate disease-specific QoL in our patients. To date, however, this questionnaire has not yet been validated for the Dutch population.

CONCLUSION

With the current validated QoL questionnaires most patients after ER with GPU and JI for LGEA have normal generic and disease specific QoL scores. Postoperative morbidity and surgical reintervention do not seem to influence (HR)QoL. The question remains if non condition specific HRQoL tools are suitable for this specific patients group. Condition specific HROLQ tools may provide more detailed information on HRQoL for all EA patients. We expect that these tools may provide a tailor-made support if necessary.

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CHAPTER 5

CHILDHOOD OUTCOME AFTER CORRECTION OF LONG-GAP ESOPHAGEAL ATRESIA BY THORACOSCOPIC EXTERNAL TRACTION TECHNIQUE

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ABSTRACT

Background

Thoracoscopic external traction technique (TTT) is a relatively new surgical intervention for patients with long-gap esophageal atresia (LGEA) that preserves the native esophagus. The major accomplishment with TTT is that esophageal repair can be achieved within days after birth. This study evaluates the childhood outcome in LGEA patients treated with TTT, including gastrointestinal outcome, nutritional status and Health-Related Quality of Life (HRQoL).

Methods

A cohort study including all LGEA patients that underwent TTT between 2006-2017 was conducted. Patients and/or their parents were invited to fill out questionnaires regarding reflux symptoms and HRQoL.

Results

TTT was successful in 11/13 patients (85%). Esophageal anastomosis was accomplished at a median age of 12 days (range 7-138), first oral feeding was started at a median of 16 days postoperatively (range 5-37). All patients required multiple dilatations and 10 patients required anti-reflux surgery. At median follow-up of seven years, five patients reported mild and one moderate reflux complaints. All patients but one reached age-appropriate oral diet. Most patients (80%) were within normal growth range. Overall HRQoL was comparable to healthy controls.

Conclusion

TTT provides acceptable results in childhood. Oral feeding can be started as soon as two weeks postoperatively. Almost all patients are able to eat an age-appropriate oral diet. Overall HRQoL was comparable to healthy controls.

INTRODUCTION

Long-gap esophageal atresia (LGEA) is a rare and complex type of esophageal atresia (EA) and accounts for approximately 10% of all newborns with EA ¹⁻³. In literature the definition of LGEA is inconsistent. Recently, however, the International Network of Esophageal Atresia (INoEA) has defined LGEA as “any esophageal atresia without abdominal air”, corresponding to Gross type A and B ⁴.

Bridging the wide gap in LGEA remains a challenge for pediatric surgeons ⁵ and several surgical approaches have been described. Esophageal repair can be performed by esophageal replacement (e.g. jejunal or colon interposition or by gastric pull-up ⁶⁻⁸). However, most surgeons agree that the native esophagus is the best esophagus ⁹. Preservation of the native esophagus can be accomplished by delayed primary anastomosis or by open or thoracoscopic traction technique ^{10,11}. Delayed primary anastomosis entails that the esophagus is restored two to three months after birth ¹². Prolonged delay of esophageal continuity may lead to several disadvantages, including swallowing difficulties due to postponed oral feeding and prolonged hospital stay ¹³⁻¹⁵. With the thoracoscopic external traction technique (TTT) however, as also developed by our center, esophageal repair can be accomplished within days after birth ^{5,11}. Although several studies have been conducted on the outcome after esophageal replacement and delayed primary anastomosis in LGEA, this is the first study that evaluates the childhood outcome after the TTT.

The aim of this study is to evaluate the outcome in childhood in LGEA patients treated with TTT, including gastrointestinal outcome, nutritional status and Health-Related Quality of Life (HRQoL).

METHODS

Study design and participants

A retrospective cohort study was conducted including all LGEA patients corrected via the thoracoscopic external traction technique (TTT) at the University Medical Center Utrecht, Wilhelmina Children's Hospital, between 2006 and 2017. Electronic medical records were reviewed. All LGEA patients since 2006 were treated with TTT and patients were considered eligible for the study if TTT for repair of LGEA was completed. Only patients with Gross type A or B (no distal tracheoesophageal fistula) were included. Patients with a failed procedure were excluded from further analysis. Patients with Down syndrome were excluded from analysis of questionnaires.

Surgical procedure

Prior to surgery, a standard rigid bronchoscopy was performed in almost all EA patients to evaluate the presence of a proximal fistula and to evaluate the severity of tracheomalacia. The subsequent TTT has previously been described by Van der Zee et al^{5,11}. In short, thoracoscopic traction sutures were placed at both esophageal ends and were fixed externally with mosquito forceps. Approximation of the esophageal ends was evaluated by postoperative X-rays. When this approximation hampered prematurely, thoracoscopic adhesiolysis was performed. Both ends were anastomosed during a final thoracoscopic procedure. A chest tube was positioned next to the esophageal anastomosis. Initially a gastrostomy was placed for feeding, in later patients a laparoscopic gastropexy was performed to prevent the stomach from migrating into the thorax. Patients were kept on parenteral feeding during the traction period.

Clinical assessment

Baseline characteristics, including gender, gestational age, birthweight, type EA and associated anomalies were collected from the medical records. All patients had regular check-ups at the Wilhelmina Children's Hospital and since 2017 a multidisciplinary routine follow-up schedule (age 0 up to 17 years) had been introduced for all EA patients. Gastrointestinal and respiratory symptoms, development and health-related-quality of life parameters were assessed.

Surgical outcome

Surgical data, including age at surgery, traction time and gastrostomy or gastropexy placement were obtained. Postoperative data, including ventilation time, NICU and hospital length of stay, postoperative complications (i.e. leakage, stenosis) and first enteral and oral feeding were collected.

Gastroesophageal reflux

Validated reflux-questionnaires were used to define gastroesophageal reflux (GER). Two different questionnaires were used for evaluation of GER and dysphagia. The age-adjusted Gastroesophageal Reflux Symptom Questionnaire (GSQ)¹⁶ was used for patients from 2 to 12 years old and the Reflux Disease Questionnaire (RDQ)^{17,18} was used for children of 12 years and older. The GSQ-questionnaire was available as parent-proxy report and contains questions on the frequency (n) and severity of reflux and dysphagia in the past seven days, which was scored for severity on a 7-point Likert scale ranging from 1 (none) to 7 (most severe). The RDQ was available as self-report and contains questions on the frequency and severity of regurgitation, heartburn and dyspepsia in the past seven days, which were scored on a 6-point Likert scale from 0 (never/none) to 5 (daily/most severe). Symptoms for all questionnaires were divided in

four categories: no symptoms, mild (mild symptoms weekly), moderate (mild symptoms daily or severe symptoms weekly) and severe symptoms (severe symptoms daily).

Functional oral intake scale (FOIS)

The functional oral intake scale (FOIS) was used to evaluate oral intake. It consists of a numeric scale concerning oral intake, ranging from 1 (nothing by mouth) to 7 (full oral diet, no restrictions)¹⁹.

Nutritional status

Weight and height measurements were collected and converted into the weight-for-length z-score using the Netherlands Organization for Applied Scientific Research (TNO) growth standards²⁰. A z-score below -2SD was considered pathological^{21,22}.

Health-Related Quality of Life (HRQoL)

Health-Related Quality of Life was evaluated using the age-adjusted Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales questionnaire. Patients and/or their parents were asked to fill out this questionnaire. It encompasses the domains physical functioning, emotional functioning, social functioning and (pre-)school functioning and it was scored for frequency on a 5-point Likert scale from 0 (never) to 4 (almost always). Scores were transformed to a 0-100 scale, with a higher score representing a better HRQoL. Scores were compared to healthy controls with a total scale cut-off point score of -1SD below the population sample mean (69.7 for child self-report and 65.4 for parent-proxy report). Scores of 1 SD below the mean of the healthy population are at risk for an impaired HRQoL²³.

Statistical analysis

Nonparametric variables are presented as median and range and categorical data is presented as frequencies and percentages. Mean differences are presented with 95% confidence intervals. Data from children and their parents was treated as paired. The analyses were performed with SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY) and R 4.0.0 (R Core Team, Auckland, New Zealand).

Ethical approval

This cohort study was submitted to the UMCU Ethics Committee. No ethical approval was required according to the Medical Research Involving Human Subject Act. The study was carried out in accordance with the Declaration of Helsinki. Informed consent from all patients, and/or their parent if applicable, was obtained before sending the questionnaires.

RESULTS

Between 2006 and 2017, a total of 14 patients with long-gap esophageal atresia were operated in the Wilhelmina Children's Hospital. Three patients were excluded from further analysis: a primary thoracoscopic repair was feasible in one patient and the elongation procedure failed in two patients. Of the two failed patients, the traction sutures tore down in the first patient (type A) and a subsequent jejunal position was performed. The length of hospital stay was 44 days. There was no sign of leakage and the patient required no fundoplication. In the second patient (type B), the proximal pouch was perforated by the Replogle tube and a gastric pull-up was performed. This patient was premature (33 weeks) and had a concomitant anorectal malformation. The length of hospital stay was 133 days. Since TTT failed in these patients, they were not evaluated in the analysis of the follow-up. All subsequent TTT procedures since 2013 were successful.

TTT could be completed in eleven patients, of which five (46%) were male. The median gestational age was 34^{+4} weeks (range 30^{+2} – 39^{+6}) with a median birthweight of 1915 grams (range 1360–3643). Five patients (46%) had a proximal fistula (type B) and six patients (54%) had EA type A. Eight patients (73%) had associated anomalies (e.g. musculoskeletal, cardiac). Patient characteristics are presented in **Table 1**.

Table 1. Patient characteristics

Variable	n= 11
Male (n, %)	5 (46%)
Gestational age (weeks) (median, range)	34^{+4} (range 30^{+2} – 39^{+6})
Birthweight (g) (median, range)	1915 (range 1360–3643)
Apgar score (median, range)	
1 min	7 (range 2–9)
5 min	8.5 (range 5–9)
Gross type EA (n,%)	
Type A	6 (55%)
Type B	5 (46%)
Associated anomalies (n,%)	8 (73%)
Down's syndrome	1 (9%)
VACTERL	1 (9%)
ARM	1 (9%)
Renal	1 (9%)
Musculoskeletal	3 (27%)
Cardiac	2 (18%)
Other	3 (27%)
Tracheomalacia (n,%)	6 (55%)

EA=esophageal atresia; ARM=anorectal malformations; VACTERL=Vertebral defects, Anal atresia, Cardiac defects, Trachea-Esophageal malformation, Renal anomalies and Limb abnormalities.

Other: microcephaly, hemangiomas, microtia, retrognathia, hearing loss

Surgical outcome

Traction sutures were placed at a median age of 9 days (range 2-134) and esophageal anastomosis was accomplished at a median age of 12 days (range 7-138). A definitive reconstruction was performed with two thoracoscopic procedures in four patients and with three procedures in seven patients. Four patients were transferred from either another Dutch hospital or from abroad (the child that was operated at the age of 134 days). In these four patients that were transferred from another hospital a gastrostomy had been placed before referral. At the Wilhelmina Children's Hospital only the first patient had a laparoscopic gastrostomy. In the other six patients, a TTT was performed without a gastrostomy. In four out of these six patients a laparoscopic gastropexy was performed when the traction sutures were placed, to prevent the stomach from sliding up into the chest. In the other two patients neither a gastropexy nor a gastrostomy was performed. The first patient developed a partial migration of the stomach into the thorax and a subsequent laparoscopic fundoplication was performed after 9 weeks. In the second patient, there was no tension on the distal esophageal pouch and therefore a gastropexy was not indicated.

Postoperative outcome

After final surgery, in which the esophagus was successfully anastomosed, patients remained at the NICU for a median time of 18 days (range 3-37) with a median ventilation time of four days (range 2-14). The median initial hospital length of stay was 47 days (range 27-170). The patient who had been admitted for 170 days, suffered from respiratory incidents due to severe tracheomalacia and needed an aortopexy and redo aortopexy. During his hospital stay, the patient also required multiple anastomotic dilatations, a fundoplication and a redo fundoplication. Postoperative leakage occurred in 5 patients (46%). All leakages were treated conservatively with chest tubes and antibiotics. Surgical outcome data is presented in **Table 2**.

Table 2. Surgical data

Variable (days)	n=11 (median, range)
Age at first surgery for EA	9 (2-134)
Age at final anastomosis	12 (7-138)
Traction days	4 (2-10)
Postoperative ventilation time	4 (2-14)
Postoperative ICU stay	18 (3-37)
LOS	47 (27-170)

EA=esophageal atresia; ICU=intensive care unit; LOS=length of hospital stay (for esophageal repair)

Tracheomalacia

Preoperative bronchoscopy was not performed in the first TTT patient, because it was not yet introduced as routine care for EA patients in our clinic. Six from the subsequent 10 patients were diagnosed with tracheomalacia during their evaluation of the airway with preoperative bronchoscopy. Two patients had severe postoperative tracheomalacia related symptoms, requiring aortopexy. One patient required thoracoscopic aortopexy at the age of 11 weeks and needed a redo thoracoscopic aortopexy at the age of 16 weeks. In the other patient a thoracoscopic aortopexy was performed at the age of 19 months.

Early gastrointestinal outcome

First oral feeding was started at a median of 16 days after performing the esophageal anastomosis (range 5-37). In one patient with Down syndrome with postoperative anastomotic leakage and respiratory instability, oral feeding was introduced after 37 days. All patients required multiple dilatations for anastomotic stenosis. The majority of dilatations (80%) was performed within the first year of life. A fundoplication was performed in 10 patients (91%) at a median age of 3.9 months (range 1.8-6.6 months). Six of these 10 patients required a redo fundoplication after a median of 6.3 months (range 2.9-58.7 months) (**Table 3**). The patient with Down syndrome later developed an esophagobronchial fistula, which was closed at the age of one year.

Table 3. Gastrointestinal outcome

Variable	n=11
First enteral feeding (postoperative)	3 (0-21) days
No-gastrostomy	3 (1-7) days
Gastrostomy	3 (0-21) days
Full enteral feeding (postoperative)	10 (0-27) days
No-gastrostomy	10 (5-14) days
Gastrostomy	11 (0-27) days
First oral feeding (postoperative)	16 (5-37) days
Anastomotic leakage (n,%)	5 (46%)
Esophago-bronchial fistula	1 (9%)
No. of dilatations (n, range)	6 (2-20)
Fundoplication (n,%)	10 (91%)
Age at fundoplication (median, range)	3.9 months (1.8–6.6)
Redo fundoplication (n,%)	6 (55%)
Weight-for-height z-score (SD)	-0.80 (-2.20-2.40)

Follow-up

Reflux symptoms

The median age at follow-up was 7.0 years (range 3.3-13.4). Nine patients (82%) were using GER medication at time of this study. Nine out of ten subjects filled out the reflux-questionnaires (90%). Three patients (33%) reported no GER complaints, five patients (56%) reported mild complaints and one patient (11%) had moderate GER complaints. Of the patients that reported no reflux symptoms, all had a fundoplication and two a redo-fundoplication. Of the five patients that reported mild symptoms, four patients had a fundoplication of three of which also had a redo-fundoplication. The patient with moderate reflux symptoms had both a fundoplication and a redo-fundoplication.

Oral intake

Seven patients (70%) had no food limitations (FOIS 7), one patient had specific food limitations (difficulties with carrots and meat, FOIS 6) and one patient required special preparation of food (thickening of liquids, FOIS 5), but had no other food limitations. One patient with Down syndrome had achieved full oral intake, but had later regressed to tube-feeding with minimal attempts of oral food intake (FOIS 2).

Growth

Most patients had a decrease in weight-for-height z-score within the first year of life and a catch-up in the weight-for-height z-score over time; the median weight-for-height z-score at the age of 1 year was -1.77 (range -2.89 to -0.71), compared to a median weight-for-height z-score at last follow-up of -0.80 (range -2.20 to 2.40) (n=10). **Figure 1** shows the weight-for-height z-scores over time for all included patients.

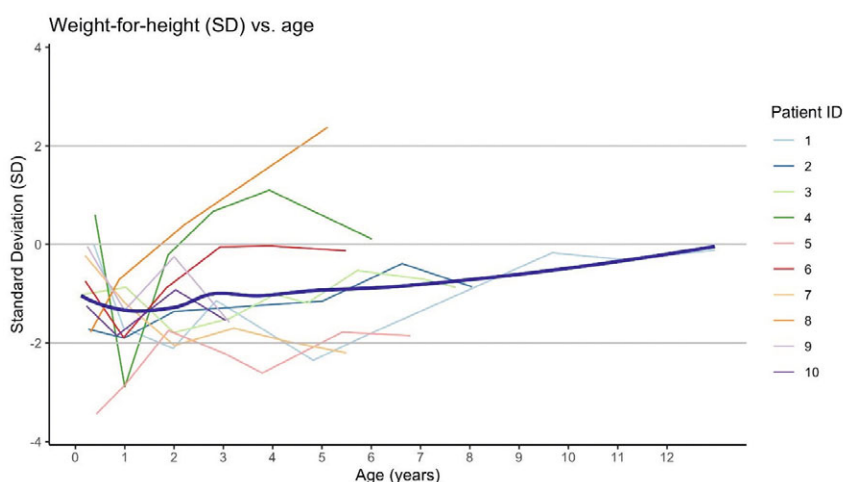


Figure 1. Weight-for-height z-score of individual patients (n=10). The dark blue line represents the mean weight-for-height z-score of the whole group

At end of follow-up, one patient had a weight-for-height z-score below -2SD due to unknown causes. Another patient had a weight-for-height z-score above 2SD, due to a small height and a normal weight-for-age. All other patients (80%) were within normal growth range.

Health-related quality of life

Nine out of ten PedsQL™ 4.0 questionnaires (90%) were returned. HRQoL parent-proxy report scores for patients younger than 5 years-old were higher than the cut-off points (1SD below the mean) on all domains (**Figure 2a**).

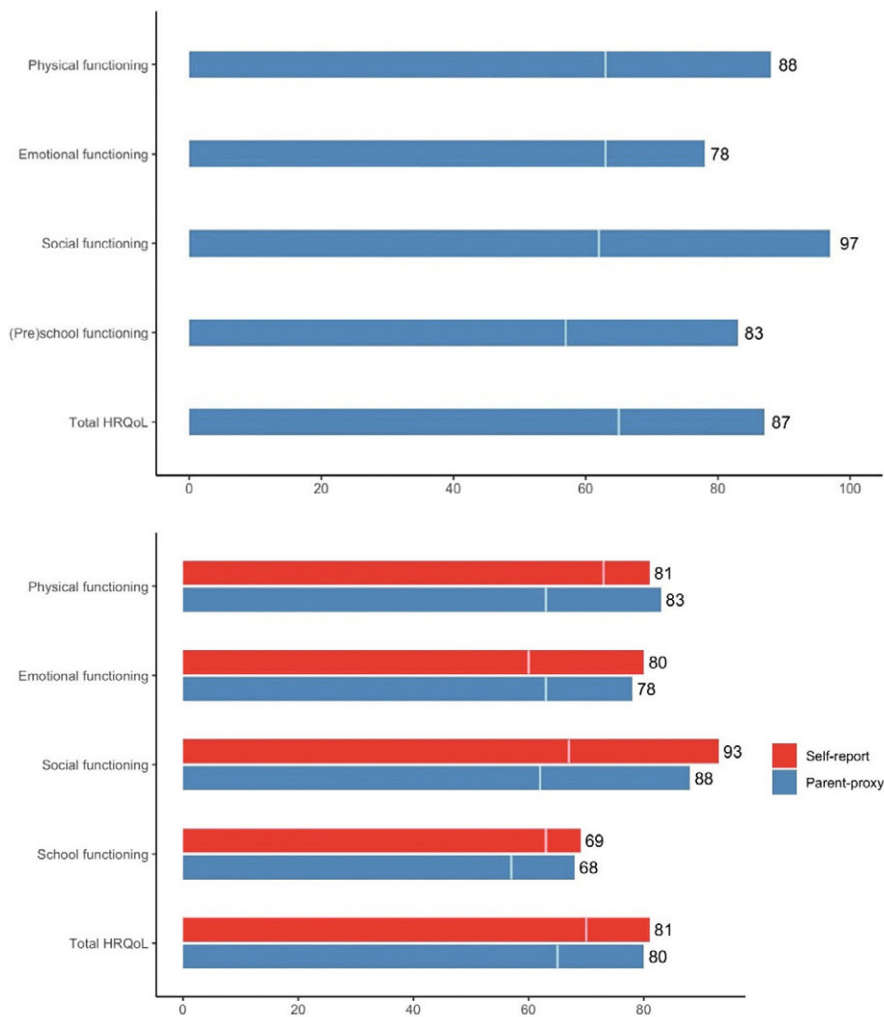


Figure 2a. HRQoL in patients <5 years old (parent-proxy report). **b.** HRQoL in patients ≥5 years-old (self-report and parent-proxy report). The vertical light lines represent scores of the cut-off point of 1 SD below the mean in the healthy population

The mean total score in patients older than 5 years was 80.1 for parent-proxy and 80.8 for child self-report (mean difference 0.7, 95%CI -5.2-3.7). These total scores were similar to the means of healthy controls (81.3 and 82.9, respectively). Both child self-report and parent-proxy report scored lowest on the school functioning domain (median of 69 and 68 respectively, compared to 77 and 80 in healthy controls), but above the threshold of 1 SD below the mean (67 and 62, respectively). Patients scored best on the social functioning domain (93 and 88, respectively) (**Figure 2b**).

One patient scored below the PedsQL™ 4.0 total score cut-off point with a score of 63.0 on child-self report, which is 6.7 points below the score cut-off point of 69.7. His total lowered score was mainly due to a low score on the emotional and school functioning domain.

DISCUSSION

This is the first study to evaluate the childhood outcome of LGEA patients treated with the thoracoscopic traction technique. TTT was successful in 11/13 patients (85%). This study shows that after TTT patients are able to initiate oral feeding as soon as 16 days after esophageal correction and almost all patients achieved an age-appropriate oral diet and growth patterns within normal range. The overall HRQoL is comparable to healthy children. This study further shows that reflux is common in LGEA patients after TTT. All patients required multiple dilatations for anastomotic stenosis and almost all patients (91%) required a fundoplication.

Postoperative stenosis is the most frequent postoperative complication after EA repair¹². In this study, all LGEA patients needed multiple dilatations for recurrent anastomotic stenosis. A high stenosis rate in LGEA patients after TTT may be explained by the risk factors for anastomotic stenosis, including anastomotic tension, leakage and GER²⁴⁻²⁷. All patients needed multiple dilatations. Most dilatations (80%) were performed within the first year of life. EA patients have a greater risk of developing GER and this is especially common in LGEA patients. It has been reported in 66-88% of LGEA patients after delayed primary anastomosis (DPA)^{28,29}. This is in line with our findings, in which GER symptoms were reported in 67%.

In this study, esophageal anastomosis was performed at a median age of 12 days. Oral feeding could be started 16 days postoperatively. In delayed primary anastomosis, the anastomosis is usually performed at the age of two to three months¹². Therefore, oral feeding can only be introduced thereafter, and patients will be fed by a gastrostomy

in the period before esophageal anastomosis¹². Feeding difficulties are common in EA patients and include eating slowly, food refusal and choking³⁰⁻³². Since infants develop their feeding and swallowing skills within the first two years of life, later introduction of oral feeding may lead to delayed positive oral experiences^{33,34}. Consequently, later introduction of an oral diet may impair the development of adequate feeding and swallowing skills^{34,35}. Cavallaro et al.¹⁵ reported severe feeding problems after DPA in five patients compared to no feeding problems in 20 EA-TEF patients. Bevilacqua et al.³³ showed that LGEA was associated with not reaching self-feeding at the age of 3 years. This is in contrast to our study, showing that almost all patients achieved an age-appropriate oral diet. Therefore, early introduction of oral feeding seems to be an advantage of TTT compared to DPA. We believe early oral feeding may contribute to patients' oral feeding performance and reduces the long-term feeding difficulties that are common in LGEA patients. Moreover, due to an early esophageal anastomosis (median day 12), patients do not require a preoperative gastrostomy, which may be associated with a high complication rate³⁶. The total hospital length of stay is subsequently shorter in TTT compared to DPA (47 days vs. 120-150 days)^{28,29}.

Previous studies have reported that EA patients are at risk for growth problems, especially within the first years of life^{22,37,38}. This is in line with our findings, which showed a decrease in weight-for-height z-scores within the first year of life. However, a catch-up in weight-for-height z-scores was seen over time. Almost all children were within normal growth range (-2SD and 2SD) at end of follow-up, although nutritional status in most children was still below the population mean.

In line with our findings, Peetsold et al.³⁹ reported a similar HRQoL in EA patients compared to healthy controls. Dingemann et al.⁴⁰ studied HRQoL in complex and complicated EA, including DPA, and showed a HRQoL comparable to healthy controls. Legrand et al.⁴¹ reported that the QoL in EA patients is lower compared to healthy controls, but higher compared to patients with other chronic diseases. Our study shows that the overall HRQoL is comparable to healthy controls.

The main limitation of this study is the small sample size, which makes statistical comparison to healthy controls impossible. However, LGEA is a rare anomaly and only patients older than two years of age that had pure LGEA (Gross type A and B) were included. Ideally, a prospective multicenter study should be conducted to increase the sample size and to evaluate and compare the long-term outcome of the different techniques used for esophageal repair in LGEA. However, since the rarity of this disease, it might prove to be very difficult to conduct such a prospective study. A second limitation of this study entails the wide study period, in which we changed from paper

records into digital records, therefore some data could not be included (duration of parental nutrition, durations central venous catheter dependency).

In conclusion, TTT was successful in 13 of 15 patients (85%). Major advantages of the TTT are preservation of the native esophagus, early introduction of oral feeding and a shorter total hospital length of stay. Almost all patients are able to eat an age-appropriate oral diet and have a growth pattern within normal ranges. Feeding problems later in life may be prevented by TTT. Overall HRQoL in LGEA patients treated with TTT is comparable to healthy controls.

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PART III

RESPIRATORY EFFECTS



CHAPTER 6

THORACOSCOPIC POSTERIOR TRACHEOPEXY DURING PRIMARY ESOPHAGEAL ATRESIA REPAIR: A NEW APPROACH TO PREVENT TRACHEOMALACIA COMPLICATIONS

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ABSTRACT

Background

Esophageal atresia (EA) is usually accompanied by some form of tracheomalacia (TM). During the early phases in life, excessive dynamic collapse of the trachea can cause a wide spectrum of symptoms ranging from mild complaints to apparent life-threatening events (ALTE's) or brief resolved unexplained events (BRUE's). Therapeutic strategies for severe TM include aortopexy to lift the anterior weakened cartilaginous rings or posterior tracheopexy of the floppy membranous tracheal intrusion. In this study, we describe the development of a new approach in which the posterior tracheopexy is performed directly during the primary thoracoscopic correction of EA.

Methods

In 2017, all nine consecutive EA patients with trachea-esophageal fistula underwent a rigid tracheobronchoscopy (RTB) evaluation during induction of anesthesia prior to the thoracoscopic EA repair. A floppy posterior membrane was diagnosed in four patients. During the subsequent thoracoscopic procedure, the posterior membranous trachea was fixed to the anterior longitudinal spinal ligament with non-absorbable sutures. Then, the anastomosis was made between the two esophageal pouches.

Results

On preoperative RTB, two patients had a severe (70–90%) mid-tracheal collapse of the pars membranacea and two patients had a moderate (33–40%) mid-tracheal collapse. Thoracoscopic posterior tracheopexy with two or three sutures was possible in all four patients, prior to the formation of the esophageal anastomosis. Median time per suture was 6 min (range 4–12 min). All operative procedures were uneventful. A median follow-up of 6 months (range 4–9 months) revealed that all patients showed further recovery without any TM symptoms or ALTE/BRUE.

Conclusions

This is the first report that introduces a new approach to thoracoscopic posterior tracheopexy during primary EA repair. We believe that this technique can prevent the potentially deleterious sequelae of mild to severe TM that may complicate the lives of EA patients. Also, a second, sometimes complex surgical procedure can be prevented as the posterior tracheopexy is performed during the primary thoracoscopic EA correction.

INTRODUCTION

Esophageal atresia (EA) is usually accompanied by some form of tracheomalacia (TM)¹. TM is a process characterized by flaccidity of the supporting tracheal cartilage, widening of the posterior membranous wall, and reduced anterior–posterior airway caliber. These factors cause tracheal collapse, especially during times of increased expiration, such as coughing, crying, or during feeding. In neonates, this diagnosis can be difficult to recognize, as the respiratory symptoms are not very specific. At an older age, collapse of the airway might cause apparent life-threatening events (ALTE) or brief resolved unexplained events (BRUE), apneas and asthma-like symptoms².

Symptomatic TM affects up to 16–33% of patients after EA and trachea-esophageal fistula (TEF) repair^{3–5}. EA patients with severe TM often require tracheostomy ventilation and secondary surgery at a later age^{6,7}. Surgical strategies to treat severe TM include aortopexy via thoracotomy or thoracoscopy to lift the aorta and anterior trachea to relieve the tracheal collapse^{8,9}. However, if a floppy pars membranacea is causing the TM, posterior tracheopexy to the anterior longitudinal spinal ligament is indicated. This procedure is performed through thoracotomy or sternotomy in case of concurrent cardiac surgery^{10,11} or by thoracoscopy¹².

In this paper, we introduce a new approach to thoracoscopic posterior tracheopexy. This technique was initially developed in patients that had undergone previous EA repair and needed renewed mobilization of the esophagus in order to approach the posterior tracheal membrane. This has led us to perform the posterior tracheopexy immediately during primary thoracoscopic repair of EA with TEF, in case flaccidity of the posterior membrane was diagnosed on rigid tracheabronchoscopy (RTB). The aim of this approach is to prevent the possible deleterious consequences of TM that may complicate the lives of patients with EA with TEF.

MATERIALS AND METHODS

Patients

In 2017, all nine consecutive EA with TEF patients underwent an RTB evaluation during induction of anesthesia prior to the thoracoscopic EA repair. The severity of the TM was estimated, and the collapse of the bronchi and trachea at three levels (lower, middle and upper level) were scored in a standardized way¹³. Patients were considered eligible for posterior tracheopexy as a preventive measure when moderate (33–66%) or severe

(67–100%) tracheal collapse by posterior membranous intrusion was noted⁴. TM was diagnosed in four of the nine patients.

Evolution of technique

We developed the technique of thoracoscopic posterior tracheopexy in three patients after previous EA repair. Two of the patients came from another institute after previous EA correction through a right-sided extrapleural thoracotomy approach. One of these two patients had a tracheal diverticulum (old TEF remnant), and one had a recurrent TEF. The third patient had a thoracoscopic EA correction 5 weeks before and had developed TM symptoms in the postoperative course. Although the thoracoscopic re-interventions were feasible, the thoracoscopic mobilization of the esophagus is technically demanding and can cause postoperative morbidity. The first patient had an uneventful recovery, but the second patient needed a re-intervention to further alleviate tracheal collapse by thoracoscopic aortopexy. This patient subsequently developed a chylothorax. In the third patient, the esophageal anastomosis showed signs of leakage after the early re-intervention, only 5 weeks after the initial thoracoscopic EA correction. This patient required chest tube drainage and prolonged antibiotic treatment (**Table 1a**). Based on the course of these three patients, we then decided to perform preventive posterior tracheopexy in patients with a flaccid posterior tracheal membrane on RTB during the primary thoracoscopic EA and TEF repair.

Surgical technique

Thoracoscopic posterior tracheopexy is performed with the patient in a 3/4 left-lateral position at the left side of the table. The esophagus and trachea are dissected with 3-mm instruments. Usually, three or four intercostal trocars are placed to access the right hemithorax. A CO₂ pneumothorax is installed with a maximum pressure of 3–5 mmHg and a flow of 1 L/min. Details of primary posterior tracheopexy are illustrated in **Figure 1**. First, the TEF is closed with a transfixing suture and transected. Then, the proximal pouch is mobilized from the membranous posterior tracheal wall. In redo surgery, sometimes a tracheal diverticulum has to be resected or a recurrent TEF has to be closed. The posterior tracheopexy is performed by placing two or three non-absorbable sutures (4 × 0 Ethibond®, Cincinnati, OH) that pull the membranous posterior tracheal wall to the anterior longitudinal spinal ligament (**Figure 2**). The proximal esophagus is mobilized from its position between the trachea and the spinal column. The two ends of the esophagus are approximated and joined by an end-to-end anastomosis. The pneumothorax is evacuated; the wounds are closed with absorbable sutures without leaving a thorax drain. With an endotracheal fiberoptic scope, the initial result of the tracheopexy on the posterior tracheal wall can be evaluated at the end of the procedure.

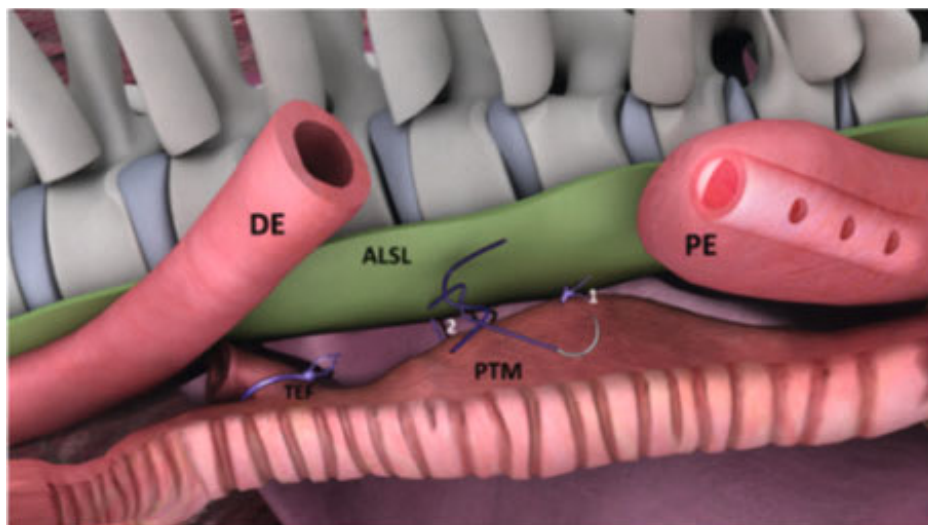


Figure 1. Illustration of the thoracoscopic posterior tracheopexy during primary esophageal atresia correction. After closure and transection of the tracheo-esophageal fistula (TEF), the proximal esophageal (PE) pouch is mobilized from the posterior tracheal membrane (PTM). A nasal tube lifts the PE away from its position between the trachea and the spinal column. The posterior tracheopexy is performed by placing non-absorbable sutures (1,2) that pull and fixate the PTM to the anterior longitudinal spinal ligament (ALSL). Then, the PE and distal esophagus (DE) are approximated and joined by an end-to-end anastomosis

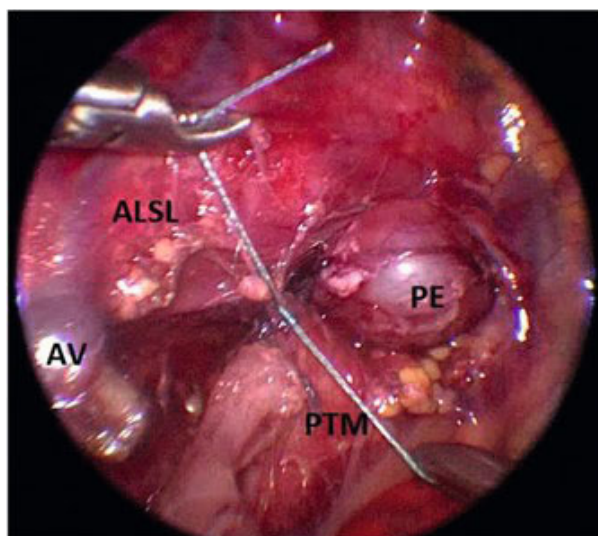


Figure 2. Thoracoscopic posterior tracheopexy during primary esophageal atresia repair. Sutures are placed from the posterior tracheal wall to the anterior spinal ligament after the upper esophageal pouch has been mobilized and prior to esophageal anastomosis. PTM: posterior tracheal membrane; ALSL: anterior longitudinal spinal ligament; PE: proximal esophageal pouch; AV: azygos vein (transected)

RESULTS

All nine consecutive EA patients were evaluated by RTB during induction of anesthesia prior to the thoracoscopic EA repair. Two patients had a severe (70–90%) mid-tracheal collapse of the pars membranacea, and two patients had a moderate (33–40%) mid-tracheal collapse. Thoracoscopic posterior tracheopexy with two or three sutures was possible in all four patients, prior to the formation of the esophageal anastomosis. All operative procedures were uneventful. Median time per suture placement required 6 min (range 4–12 min). A median follow-up of 6 months (range 4–9 months) revealed that all patients showed further recovery without any TM symptoms or ALTE/BRUE. Patients’ characteristics and RTB findings are summarized in **Table 1b**.

One patient with primary posterior tracheopexy required an additional anesthesia for esophageal stenosis treatment 4 weeks after the esophageal anastomosis. RTB at induction of anesthesia showed a marked improvement of the posterior collapse from 90% to 10% (**Figure 3a, b**). The other three patients had no RTB during their followup as no additional procedure under anesthesia was necessary.

Table 1a. Characteristics of patients that were operated by secondary thoracoscopic posterior tracheopexy after EA correction

Patients number, gender	Gestational age (weeks) Birth weight (grams)	Age at surgery	Pre-operative tracheomalacia symptoms	% Tracheal obstruction on RTB Additional surgical procedure	Complications
Patient 1, male	28+3 2400	3 months	ALTE/BRUE 10 times Tracheal diverticulum	95% Resection tracheal diverticulum	-
Patient 2, female	30+5 1370	16 months	Tracheostoma canula Recurrent TEF	90% TEF closure	Additional thoracoscopic Aortopexy Chylothorax
Patient 3, male	41+4 2885	5 weeks	Cyanosis Expiratory stridor Oxygen dependence	99%	Esophageal anastomosis leakage

Table 1b. Characteristics of patients that were operated by primary thoracoscopic posterior tracheopexy during EA correction

Patients number, gender Associated morbidity	Gestational age (weeks) Birth weight (grams)	Age at surgery	Post-operative tracheomalacia symptoms	% Tracheal obstruction on RTB Additional surgical procedure	Complications
Patient 1, male	38+1 2945	5 days	-	90%	Esophageal stenosis requiring dilatation
Patient 2, male Ventricular septal defect	38+2 2550	3 days	-	70%	-
Patient 3, male Infantile hemangiomas	28+2 1200	2 days	-	33%	-
Patient 4, female Cleft lip and palate	41+3 3060	2 days	-	40%	-

EA = esophageal atresia; RTB = rigid tracheo-bronchoscopy; ALTE = apparent life-threatening event; BRUE = brief resolved unexplained event; TEF = tracheo-esophageal fistula.

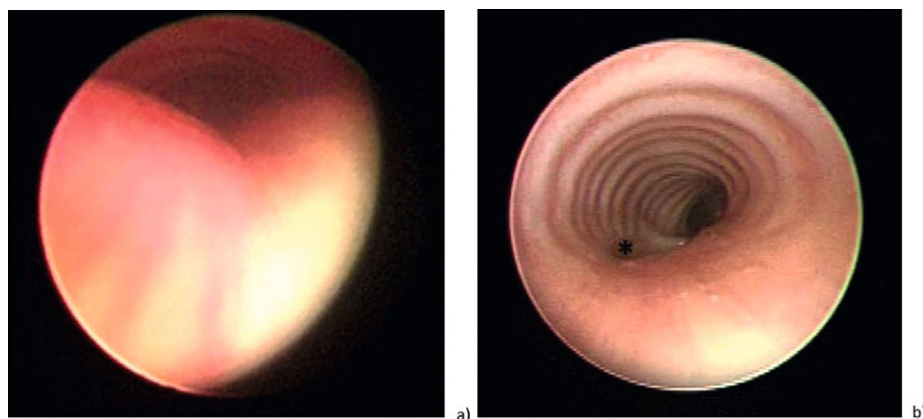


Figure 3. a) Rigid trachea-bronchoscopy (RTB) prior to thoracoscopic EA repair. The flaccid posterior tracheal membrane blocks 90% of the lumen (still from video of dynamic collapsing posterior tracheal membrane). **b)** RTB of the same patient 4 weeks after posterior tracheopexy. Collapse of the lumen is limited to 10%

*: closed distal tracheoesophageal fistula.

DISCUSSION

This is the first study to publish an innovative minimally invasive surgical approach to the prevention of TM symptoms in EA patients with TEF. TM is a deformity of the trachea that causes the airway to collapse by increased intrathoracic pressure or by compression from outside structures. Primary TM is caused by the disturbed maturation of the cartilage of the tracheal rings and/or by the posterior intrusion of the broadened floppy tracheal membrane¹⁴. Secondary TM is caused by vascular compression, mediastinal masses or by tracheostomy cannula-induced degeneration (2). The overall incidence of primary TM in children is 0.05%¹⁵. The incidence of tracheal collapse after surgical repair in patients with EA and TEF is more than 91%^{3,6}.

In the first phase of life, TM symptoms are usually mild and nonspecific. They may include barking cough, wheezing, dyspnea, gasping, blue spells and feeding difficulties. Older children may show signs of apnea or asthma- or croup-like symptoms, have prolonged recurrent respiratory infections or may have ALTE/BRUE. During ALTE/BRUE, the child asphyxiates because of the complete obstruction of the collapsed airway².

Early diagnosis of TM is important because these children usually have signs of insufficient breathing, impaired mucus clearance and multiple respiratory infections. The infections may eventually lead to permanent lung damage in 27% of the patients^{1,11,16,17}. Children with severe TM often develop growth retardation, and they may have an impaired quality of life^{8,18}. Usually, patients with severe TM are referred to a pediatric airway treatment center after prolonged antibiotic and corticosteroid treatment. Indications for TM surgery are severe recurrent respiratory infections and ALTE/BRUE. Some patients even require a tracheostomy and home ventilation^{19,20}.

To date, aortopexy has been the most effective strategy for the treatment of severe TM. In this procedure, the aorta is pulled against the posterior side of the sternum and fixed with non-absorbable transsternal sutures. By pulling the aorta ventrally, the tracheal compression is alleviated. Although no randomized trials have proven its effect, the procedure has an efficacy of treating severe TM symptoms of more than 80%. The overall complication rate, however, is more than 16%, and mortality rate is 6%, which is mainly because of comorbidity^{8,20}. In our center more than 10% of patients needed a thoracoscopic aortopexy after earlier EA repair^{9,21}. Usually, aortopexy is performed via a left anterior thoracotomy, although a left-sided thoracoscopic approach is also feasible⁹. The efficacy of aortopexy is limited by the fact that it has no effect on the malformed tracheal rings and that it does not address posterior membranous intrusion. Also, a tracheal diverticulum, which is a remnant of the previous TEF, or a recurrent TEF cannot be corrected.

Recently, a new posterior tracheal approach has been introduced to overcome these limitations¹⁰. In this procedure, the posterior floppy pars membranacea of the trachea is fixed to the anterior longitudinal spinal ligament. In a larger recently published series, treatment by posterior tracheopexy has demonstrated significant clinical improvement in patients with severe prolonged TM symptoms¹¹. Patients in these series had a median age of 15 months, and all of them had severe TM- related morbidity.

In our center, we developed a new thoracoscopic approach to treat posterior membranous tracheal intrusion¹². We first developed the technique in patients that had severe symptomatic TM, after they had previous TEF closure and EA correction. Mobilization of the esophagus after recent tracheo-esophageal surgery (via extrapleural thoracotomy or thoracoscopy) was somewhat cumbersome, and two of three patients had postoperative complications.

With this study, we introduce a new approach to thoracoscopic posterior tracheopexy during the primary repair of EA, when warranted by the degree of TM on RTB. We chose to include patients with moderate and severe posterior membranous tracheal intrusion because it is our experience that, by transecting the TE fistula, the floppy pars membranacea is no longer restrained and it may close up the tracheal space postoperatively. The tracheopexy to the anterior longitudinal spinal ligament is technically feasible and does not require much additional operative time. Short-term follow-up showed no TM-related symptoms in these patients, which had shown moderate or severe mid-tracheal collapse during RTB.

We realize that there is a limitation to the conclusions that can be drawn from the very small number of patients in this study that were treated by primary thoracoscopic posterior tracheopexy. Also, only short-term follow-up is available. On the other hand, the procedure is technically feasible, it does not add much operative time, and it may potentially prevent the future sequelae of TM. Longer follow-up studies are required to determine whether the added surgical intervention is warranted, especially in the moderate cases. It still has to be proven that the fixation of the floppy posterior membrane is beneficial in preventing respiratory symptoms in these patients.

In conclusion, with this study, a new approach for EA patients with TM and TEF is introduced. The aim is to prevent severe post EA-repair TM symptoms and avoid an intrusive secondary surgical intervention. Longer term follow-up is needed to truly be able to evaluate the efficacy of this approach, as currently the long-term sequelae of posterior tracheopexy are still largely unknown.

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CHAPTER 7

PRIMARY POSTERIOR TRACHEOPEXY IN ESOPHAGEAL ATRESIA DECREASES RESPIRATORY TRACT INFECTIONS

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ABSTRACT

Background

Esophageal atresia (EA) is often accompanied by tracheomalacia (TM). TM can lead to severe respiratory complaints requiring invasive treatment. This study aims to evaluate if thoracoscopic primary posterior tracheopexy (PPT) can prevent the potential sequelae of TM in patients with EA.

Methods

A cohort study including all consecutive EA patients treated between 2014 and July 2019 at the Wilhelmina Children's Hospital was conducted. Two groups were distinguished: (group 1) all EA patients born between January 2014 and December 2016 and (group 2) all EA patients born between January 2017 and July 2019, after introduction of PPT. In the latter group, PPT was performed in EA patients with moderate (33-66%) or severe (67-100%) tracheomalacia, seen during preoperative bronchoscopy. Group differences were assessed using the Fisher's exact test for bivariate variables and the Mann Whitney U-test for continuous variables.

Results

A total of 64 patients were included in this study (28 patients in group 1; 36 patients in group 2). In group 2, PPT was performed in 14 patients. Respiratory tract infections (RTIs) requiring antibiotics within the first year of life occurred significantly less in group 2 (61% vs. 25%, $p=0.004$). Brief resolved unexplained events (BRUEs) seemed to diminish in group 2 compared to group 1 (39% vs. 19%, $p=0.09$).

Conclusion

Thoracoscopic primary posterior tracheopexy decreases the number of respiratory tract infections in EA patients. The clinical impact of reducing RTIs combined with the minimal additional operating time and safety of PPT outweighs the risk of overtreatment.

INTRODUCTION

In up to 87% of patients, esophageal atresia (EA) can be associated with some form of tracheomalacia (TM)¹. TM can be caused by flaccidity of the cartilaginous anterior rings, a floppy posterior membrane, or both and may lead to a dynamic collapse of the tracheal lumen^{2,3}. This collapse of the trachea can result in a wide spectrum of symptoms and sequelae ranging from mild complaints, such as stridor or wheezing, to brief resolved unexplained events (BRUEs)³. Furthermore, collapse of the trachea may lead to an ineffective cough and impaired clearance of secretions, increasing the risk of respiratory tract infections^{4,5}. In severe TM, invasive treatment might be warranted^{6,7}. Surgical treatment of preference depends on the type of TM and includes aortopexy to lift the aortic compression on the anterior flaccid cartilaginous rings^{3,8}, or posterior tracheopexy of the floppy membrane to prevent posterior tracheal intrusion⁹. In a previous study, we have introduced a new approach in which a posterior tracheopexy is performed during the thoracoscopic correction of EA. Results showed this approach to be feasible¹⁰.

The aim of this study is to evaluate if thoracoscopic primary posterior tracheopexy (PPT) can prevent the potential respiratory sequelae of tracheomalacia in patients with EA and concurrent TM.

METHODS

Study design and participants

A cohort study including all consecutive EA patients between January 2014 and July 2019 was conducted at the University Medical Center Utrecht, Wilhelmina Children's Hospital. The variables of interest were collected prospectively at standardized time points for all children according to standard clinical practice. The comparative design was applied after data collection. Patients were excluded for follow-up if they had died before the age of one year. In January 2017 thoracoscopic PPT for moderate or severe TM was introduced in our hospital. Two patient subgroups were distinguished: (group 1) all EA patients born between January 2014 and December 2016 and (group 2) all EA patients born between January 2017 and July 2019, after the introduction of PPT. Data of patients that underwent thoracoscopic PPT were prospectively collected.

Surgical procedure

Since 2014 almost all infants with EA underwent a rigid bronchoscopy prior to surgery to evaluate the presence of TM and to exclude a proximal fistula. Since 2017,

a standardized scoring system for TM has been introduced¹¹. Patients with moderate to severe tracheomalacia were eligible for PPT. Tracheal obstruction, evaluated by bronchoscopy, was defined as collapse of the tracheal wall at three different levels, the upper third, middle third and lower third of the trachea¹¹. TM was considered moderate when the tracheal lumen collapsed 33-66% and severe when 67-100%. The surgical procedure of thoracoscopic PPT during esophageal repair has been described previously¹⁰. In short, during the procedure for thoracoscopic esophageal repair, the posterior tracheal membrane is fixed to the anterior spinal ligament with one to three non-absorbable sutures (**Figure 1**), prior to the anastomosis of the esophageal ends (**Figure 2**).

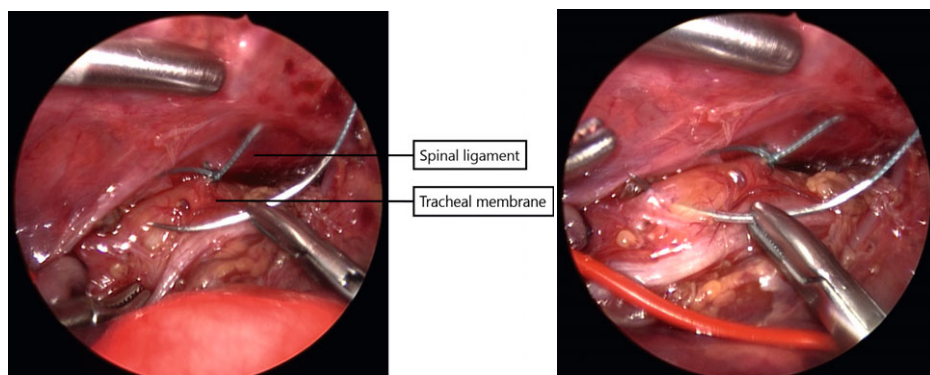


Figure 1. The posterior tracheal membrane is fixed to the anterior spinal ligament with one to three non-absorbable sutures

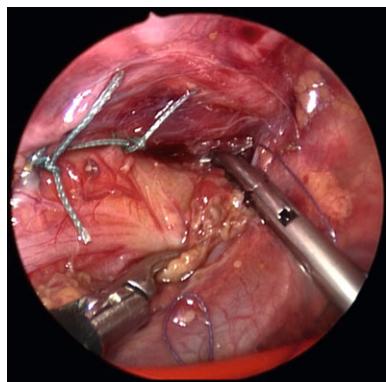


Figure 2. After performing the tracheopexy, the proximal and distal esophagus are anastomosed

Clinical assessment

All baseline characteristics, including gender, type of EA and associated anomalies, and all surgical data including age at time of surgery, postoperative complications and length

of hospital and NICU stay, were collected. Prospective data of patients that underwent PPT was obtained during standard EA follow-up in outpatient care at 4 weeks and 3, 6, 12 months of age.

Respiratory outcome

Patients underwent standardized clinical assessment regarding respiratory symptoms. The primary outcome measures were respiratory symptoms, including respiratory tract infections (RTIs) requiring antibiotics within the first year of life and occurrence of BRUEs. BRUE is defined as an event in which an infant younger than one year old presents with cyanosis, pallor, altered breathing, hypotonia or hypertonia and/or altered responsiveness¹².

Statistical Analysis

Continuous variables were presented as median and range and categorical data were presented as frequencies and percentage. To assess group differences for bivariate variables the Fisher's exact test was used. Group differences for continuous variables were assessed using the Mann-Whitney U-test. A p-value <0.05 was considered significant. The analyses were performed with SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY).

Ethical approval

This cohort study was submitted to the UMCU Ethics Committee. No ethical approval was required according to the Medical Research Involving Human Subject Act. The study was carried out in accordance with the Declaration of Helsinki.

RESULTS

In total, 67 consecutive EA patients were admitted at the Wilhelmina Children's Hospital between January 2014 and July 2019. Three patients that died within the first weeks after birth were excluded from further analysis. One patient died before esophageal repair due to severe prematurity with pulmonary bleeding. Two patients died after esophageal repair due to causes unrelated to surgery (cardiac anomalies and cerebral abscesses). The 64 remaining patients were all evaluated in our outpatient clinic at 4 weeks and 3, 6, 12 months. The patients were divided into two groups: the first group, before the introduction of PPT, consisted of 28 consecutive patients admitted between 2014-2016 (group 1). The second group, after the introduction of PPT, consisted of 36 patients admitted between 2017-2019 (group 2). Patient characteristics were comparable between the two groups, as shown in **Table 1**.

In group 2, a PPT was performed in 14 patients (39%). Of these 14 patients, 12 patients (86%) had EA Gross type C and 2 patients (14%) type D. Patient characteristics are presented in **Table 2**. There were no relevant significant differences between the no-PPT patients and the PPT patients within group 2.

Table 1. Patient characteristics of group 1 and group 2

Variable	Group 1 (2014-2016) n=28	Group 2 (2017-2019) n=36	p-value
Male	16 (57%)	24 (67%)	0.45
Gestational age (weeks)	39.2 (31.6-41.6)	37.3 (28.3-42.3)	0.08
Premature	7 (25%)	16 (44%)	0.12
Twin	3 (11%)	2 (6%)	0.65
Birthweight (g)	2755 (1585-4170)	2692 (1050-3950)	0.37
Apgar score			
1 min	8 (2-9)	9 (3-10)	0.17
5 min	9 (3-10)	9 (5-10)	0.48
Type EA			0.38
A	3 (11%)	1 (3%)	
B	1 (3.6%)	0	
C	23 (82%)	32 (89%)	
D	0	2 (5.6%)	
E	1 (3.6%)	1 (2.8%)	
Associated anomalies [#]			
Trisomy 21	2 (7%)	1 (3%)	0.57
VACTERL	6 (21%)	8 (22%)	1.0
Musculoskeletal	10 (36%)	15 (42%)	0.80
Urogenital	8 (29%)	5 (14%)	0.33
Cardiovascular	12 (43%)	15 (42%)	1.0
Gastrointestinal	4 (14%)	2 (6%)	0.40

EA=esophageal atresia

All data are presented as median (range) or n (%).

[#]Some patients had multiple anomalies.

Table 2. Patient characteristics of group 2 (2017-2019)

Variable	No-PPT, n=22	PPT, n=14	p-value
Male	14 (64%)	10 (71%)	0.73
Gestational age (weeks)	36.7 (29.1-42.3)	38.4 (28.3-41.4)	0.35
Premature	12 (55%)	4 (29%)	0.18
Twin	2 (9%)	0 (0%)	0.51
Birthweight (g)	2249 (1220-3950)	3008 (1050-3550)	0.22
Apgar score			
1 min	9 (4-10)	8.5 (3-9)	0.84
5 min	9 (7-10)	9 (5-10)	0.74
Type EA			0.20
A	1 (4.5%)	0	
C	20 (91%)	12 (86%)	
D	0	2 (14%)	
E	1 (4.5%)	0	
Associated anomalies [#]			
Trisomy 21	1 (4.5%)	0	1.0
VACTERL	3 (14%)	5 (36%)	0.22
Musculoskeletal	10 (45.5%)	5 (36%)	0.73
Urogenital	0	5 (36%)	0.005*
Cardiovascular	9 (41%)	6 (43%)	1.0
Gastrointestinal	1 (4.5%)	1 (7%)	1.0

PPT=primary posterior tracheopexy; EA=esophageal atresia

All data are presented as median (range) or n (%)

[#]Some patients had multiple anomalies.

*Indicating statistical significance

Surgical outcome

Overall analyses of group 1 and group 2 showed no significant differences in age at EA surgery, postoperative NICU time, length of hospital stay or anastomotic leakage between the two groups (**Table 3a**). In group 2, moderate to severe tracheal collapse was diagnosed in 13 patients (**Table 4**). In two patients with mild TM (20% tracheal collapse) on bronchoscopy, increased flaccidity of the posterior tracheal membrane was seen during thoracoscopy after ligation and transection of the distal tracheoesophageal fistula. Therefore, a PPT was also performed in these two patients. The middle and distal third of the trachea were most often affected with a median tracheal collapse of 50% (range 20-90%). Thoracoscopic PPT was uncomplicated and successful in all patients with a median of 2 sutures (range 1-3). Median time per suture was 6 minutes (range 4-12 min). Anastomotic leakage occurred in 21% and could be treated conservatively in all patients. There were no significant differences in surgical outcome between patients with or without PPT in group 2 (**Table 3b**).

Patients that underwent PPT were operated at a median age of 3.5 days (range 1-35 days). Surgery was postponed due to respiratory instability in one patient of group 2, a premature neonate of 1050 grams (28.7 weeks). One patient of group 2 was operated in an emergency setting because of a gastric perforation and pneumothorax that occurred during CPR shortly after birth.

Table 3a. Surgical data of group 1 and group 2

Variable (median, range)	Group 1 (2014-2016) n=28	Group 2 (2017-2019) N=36	p-value
Age at EA surgery (d)	3 (0-58)	3.5 (1-54)	0.17
NICU time (d)	9 (3-126)	8 (3-81)	0.91
LOS (d)	20 (10-159)	25.5 (12-178)	0.14
Leakage	3 (11%)	6 (17%)	0.72

EA=esophageal atresia; LOS=length of hospital stay

Table 3b. Surgical data of group 2 (2017-2019)

Variable (median, range)	No-PPT, n=22	PPT, n=14	p-value
Age at EA surgery (d)	3.5 (1-54)	3.5 (1-35)	0.28
NICU time (d)	8 (3-81)	11 (3-59)	0.83
LOS (d)	24 (13-178)	28 (12-93)	0.81
Leakage	3 (14%)	3 (21%)	0.66

PPT=primary posterior tracheopexy; EA=esophageal atresia; LOS=length of hospital stay

Table 4. Tracheomalacia evaluated during bronchoscopy before EA repair in group 2

Variable	Group 2 (2017-2019) n=36
No TM	5 (14%)
TM mild	15 (42%)
TM moderate/severe	13 (36%)
No TM evaluation possible	3 (8%)

EA=esophageal atresia; TM=tracheomalacia

Overall respiratory outcome

In group 1, eleven patients (39%) experienced at least one BRUE, compared to seven patients (19%) in group 2 ($p=0.09$). RTIs requiring antibiotics within the first year of life occurred significantly less often after introduction of PPT (group 1 vs. group 2; 61% vs. 25%, $p=0.004$) (**Table 5**).

In group 1, three patients underwent an aortopexy at the median age of 12 days (range 12-29). In two of these three patients, severe TM was evaluated preoperatively with bronchoscopy. In one patient after aortopexy, TM persisted and consequently a posterior tracheopexy was performed.

In group 2, redo tracheopexy was not warranted in any of the PPT-patients. Bronchoscopy was incomplete in three patients of group 2 and TM could not be evaluated, because spontaneous breathing during bronchoscopy was impaired due to ventilation problems. Of these three patients, one had to undergo a secondary posterior tracheopexy and another patient was treated by aortopexy.

Four patients, two in each group, all with multiple comorbidities, needed a tracheostomy. One patient with a tracheostomy and Down's syndrome in group 1, died during follow-up due to accidental decannulation.

Table 5. Respiratory outcome in group 1 and group 2

Variable	Group 1 (2014-2016) n=28	Group 2 (2017-2019) n=36	p-value
BRUE	11 (39%)	7 (19%)	0.09
RTI <1 year	17 (61%)	9 (25%)	0.004*

BRUE=brief resolved unexplained event; RTI=respiratory tract infection requiring antibiotics

*Indicating statistical significance

Respiratory outcome after PPT introduction

Subgroup analysis of group 2 showed occurrence of BRUEs in one patient (7%) in the PPT-patients group versus 6 patients (27%) in the no-PPT patients group (**Table 6**). This difference, however, was non-significant. The one patient with BRUEs after PPT had two tracheoesophageal fistulas (the distal fistula was located in the carina, and the proximal fistula in the middle part of the trachea) and a severe TM in the middle part of the trachea on preoperative bronchoscopy. Therefore, this patient underwent selective PPT only at the level of this middle part of the trachea. Postoperative bronchoscopy in this patient with multiple comorbidities, including a subglottic stenosis and retrognathia, revealed a severe TM in the distal part of the trachea.

RTIs requiring antibiotics within the first year were seen in 21% in the PPT-patients versus 27% in the no-PPT patients group. One patient in the PPT-patient group experienced postoperative respiratory distress caused by a suture granuloma. After removal of the granuloma by bronchoscopy, no further respiratory problems occurred.

Table 6. Respiratory outcome in group 2 (2017-2019)

Variable	No-PPT, n=22	PPT, n=14	p-value
BRUE	6 (27%)	1 (7%)	0.21
RTI <1 year	6 (27%)	3 (21%)	1.0

PPT=primary posterior tracheopexy; BRUE=brief resolved unexplained event; RTI=respiratory tract infection requiring antibiotics

DISCUSSION

This is the first prospective study to evaluate respiratory outcome after thoracoscopic primary posterior tracheopexy in EA patients with tracheomalacia.

This novel PPT technique decreases the number of respiratory tract infections (RTIs) in EA patients with moderate or severe TM. The number of BRUEs also seemed to decrease after introduction of PPT, although this was not statistically significant. Furthermore, the PPT-procedure takes only short additional operative time and there were no differences in hospital length of stay, NICU stay and postoperative leakage between the PPT-group and the no-PPT group.

Respiratory morbidity in EA is very common during early childhood¹³. EA patients often suffer from RTIs during the first year of life¹⁴⁻¹⁷. This is in line with our findings, showing 61% of patients with RTIs within the first year of life before introduction of PPT. After the introduction of PPT, RTIs requiring antibiotics were significantly decreased in both EA patients that underwent a PPT, as well as the entire EA cohort (EA patients with and without PPT between 2017-2019). Therefore, selecting EA patients with moderate to severe TM for PPT improves the respiratory outcome of EA patients as a whole. In a previous study on PPT¹⁸, a decrease in RTIs was not seen. However, results are difficult to compare, since this study compared preoperative data to postoperative data within a group of 18 patients and follow-up duration was shorter (5 months).

Another possibly life-threatening aspect of respiratory morbidity is posed by BRUEs. Although the decrease in number of BRUEs after the introduction of PPT from 39% to 19% seemed evident, it was not statistically significant. However, this may be explained by the small number of patients. In the study by Shieh et al.¹⁸, a decrease in BRUEs was shown (p=0.049). However, in this study, almost 30% of patients were re-operated for persistent collapse of the trachea.

In a previous study¹⁰, we showed thoracoscopic PPT to be feasible and safe, with favorable short-term outcome. During the longer follow-up in this study, one patient experienced respiratory problems, caused by a suture granuloma. After bronchoscopic removal of the granuloma, no more respiratory problems had occurred. Flexible bronchoscopic visualization during posterior tracheopexy may prevent this type of complication from occurring. Therefore, this has now been implemented as routine procedure during PPT in our center. Moreover, this may also optimize positioning of the sutures in the tracheal wall.

In three patients, TM could not be evaluated due to ventilation difficulties during bronchoscopy. In these patients, PPT was not performed since the extent of TM was unknown. In this study, in two out of three patients, a secondary surgical intervention for severe TM was warranted. In these patients posterior tracheopexy was challenging because of multiple adhesions and risk of damaging the esophageal anastomosis. Therefore, median duration of secondary tracheopexy takes significantly longer than PPT (hours versus minutes) and can be associated with complications^{3,10}.

Attention for respiratory morbidity in EA patients, and especially for TM, has raised over the past few years^{1,19,20}. Therefore, routine preoperative rigid bronchoscopy is performed in all EA patients in the University Medical Center Utrecht, Wilhelmina Children's Hospital since 2015. The introduction of a standardized scoring system for TM in 2017¹¹ by the dedicated congenital esophageal and airway team has led to increased awareness and improved recordings at our center.

A limitation of this study was that the rigid bronchoscopy was not repeated after PPT. In order to evaluate the effect of PPT, collapse of the trachea should be compared by rigid bronchoscopy before and after PPT. This would, however, require a second anesthesia for rigid bronchoscopy since spontaneous breathing is not possible directly after thoracoscopic EA repair and PPT. Therefore, our congenital esophageal and airway team has chosen not to evaluate the trachea by means of a second invasive procedure.

Although the data of the no-PPT patients was assessed retrospectively, the variables of interest were collected prospectively at standardized moments for all patients. Standardized questionnaires were not used, however, structured interviews regarding gastrointestinal and respiratory symptoms were conducted in every patient at our Congenital Esophageal and Airway outpatient clinic.

Another limitation is that no standardized scoring system was used during preoperative bronchoscopy in group 1. However, the baseline characteristics were similar within the

two groups and therefore we expect that there are no significant differences on severity of tracheomalacia between the two groups.

Preferably, a prospective trial in EA patients with moderate or severe TM randomizing for PPT or no-PPT is needed to provide the best level of evidence. This comparative study shows the potential benefits of primary posterior tracheopexy in EA patients with concurrent moderate to severe tracheomalacia with a low complication rate.

CONCLUSIONS

In conclusion, this study shows that thoracoscopic primary posterior tracheopexy during esophageal atresia repair can significantly decrease respiratory tract infections that require antibiotics during the first year of life. The clinical impact of reducing respiratory tract infections combined with the relatively minimal additional operating time and safety of PPT may outweigh the risk of overtreatment. This, however, should be evaluated in an international, multicenter randomized controlled trial comparing PPT to no-PPT in neonates with EA.

Naturally, this advanced technique should only be performed in centers with a team of experienced pediatric upper GI- and airway surgeons, otolaryngologists, pulmonologists and anesthesiologists.

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CHAPTER 8

PRIMARY POSTERIOR TRACHEOPEXY IN ESOPHAGEAL ATRESIA PATIENTS WITH CONCURRENT TRACHEOMALACIA; A COST ANALYSIS STUDY

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ABSTRACT

Background

The introduction primary posterior tracheopexy (PPT) in patients with esophageal atresia (EA) and concurrent tracheomalacia (TM) resulted in a decrease in respiratory tract infections (RTIs) within the first year of life. It is unknown whether this also led to a reduction in healthcare costs. This study aims to compare all hospital costs and subsequently all costs for respiratory admissions within the first year of life before and after the introduction of the PPT.

Methods

A retrospective cost-analysis was conducted including all hospital costs of consecutive EA patients between 2014-2019 that underwent esophageal repair at the Wilhelmina Children's Hospital. In 2017, PPT was introduced in EA patients with concurrent moderate to severe TM. Two groups were distinguished: group 1 including all EA patients between 2014-2016 and group 2 including all EA patients between 2017-2019. All hospitals admissions were manually registered and labeled. Outliers were assessed.

Results

Group 1 consisted of 28 patients, compared to 36 patients in group 2. Patients in group 1 were admitted for a mean of 72 vs 68 days in group 2 within the first year of life. For respiratory reasons, patients were admitted for 16 days in group 1 and seven days in group 2. The average total healthcare costs were comparable in both groups. Average costs for respiratory admissions were €27,389 before compared to €19,036 after PPT introduction, corresponding to a 30% decrease in costs. After exclusion of outliers (>201 admission days), the decrease in costs for respiratory admissions was 90%.

Conclusion

This cost analyses shows total inpatient treatment costs were comparable between both groups. A decrease in costs for respiratory admissions of 30% was observed. After exclusion of outliers in both groups, this decrease in costs is 90%. However, further research is warranted to confirm this observation.

INTRODUCTION

Esophageal atresia (EA) is a congenital anomaly of the esophagus, requiring surgical repair within the first days of life. In approximately half of the patients, EA is accompanied by one or more associated anomalies (e.g. cardiac, renal and vertebral anomalies)¹. Furthermore, almost 90% of EA patients have concurrent tracheomalacia (TM)². Tracheomalacia may cause (severe) respiratory morbidity, including chronic cough, (recurrent) respiratory tract infections and even blue spells³. In patients with severe TM, a secondary surgical intervention, including aortopexy or posterior tracheopexy⁴⁻⁶, may be inevitable. A secondary intervention may result in a complex and prolonged procedure with risk of complications.

In 2017, a novel surgical approach has been introduced at our center for EA patients with concurrent TM⁶. In EA patients with moderate to severe collapse of the trachea, due to flaccidity of the posterior tracheal membrane, a posterior tracheopexy is performed directly during EA repair. This procedure, the primary posterior tracheopexy (PPT), has proven to be safe and feasible and may prevent the secondary, complex surgical intervention. Furthermore, PPT resulted in a decrease in respiratory tract infections requiring antibiotic treatment within the first year of life⁷. This effect raises the question whether PPT is not only beneficial for the patients' health, but also if it contributes to a reduction in health care costs. Therefore, this study aims to compare all hospital costs and subsequently all respiratory hospital costs within the first year of life of EA patients before and after introduction of primary posterior tracheopexy in 2017.

METHODS

Study design and participants

A retrospective cost analysis study was conducted at the Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU) including all consecutive EA patients between January 2014 and July 2019. In 2017, PPT has been introduced at our center for all EA patients with moderate to severe collapse of the trachea during preoperative bronchoscopy. The EA patients were divided into two groups. Group 1 consisted of all EA patients between 2014 and December 2016, before the introduction of PPT. Group 2 consisted of all EA patients between 2017 and July 2019, after the implementation of PPT. Patients that had died within the first year of life were excluded from this study.

Primary posterior tracheopexy

Since January 2017, a primary posterior tracheopexy has been performed in all EA patients with concurrent moderate (33-66% collapse) or severe (67-100% collapse) tracheomalacia evaluated on preoperative bronchoscopy. PPT is performed as described in more detail in a previous study⁶. In short, the posterior tracheal membrane is fixed to the anterior spinal ligament with a median of two sutures, that prevents the tracheal wall from collapsing. Thereafter, the esophageal ends will be anastomosed.

Admission details

All registered hospital admissions, including admission dates and admission reasons, were collected by a researcher blinded for the group of the patient. Respiratory admissions included e.g. admission for aortopexy or secondary posterior tracheopexy, respiratory tract infections and dyspnea. If the reason of admission changed, the admission was divided accordingly. All inpatient episodes within the first year of life were compared between group 1 and group 2.

Hospital costs*Unit costs*

Unit costs were derived from the Healthcare authorities [Nza; rz19a 2019 tarievenlijst] for 2019 or data available in Dutch guidelines in 2014 (corrected for inflation upon 2019) [handleiding kostenonderzoek, CPI CBS]. When costs were not available in previous datasets, unit costs were estimated based on the average time and instrument spending in the operation room and estimated costs of medical specialists. Surgical reconstructions for anorectal malformations were performed at the Wilhelmina Children's Hospital until 2017 however, due to centralization of surgical procedures, they are no longer performed at our center. Therefore, the costs of these procedures were set to be zero.

Analysis

To measure real world hospital costs, financial data were extracted from the healthcare information system of the UMCU. All hospital costs were collected, starting from the first healthcare activity at the Wilhelmina Children's Hospital until one year thereafter. Only costs during an inpatient period were assessed using the previously described manually registered episodes. Healthcare activities having an execution date between the start date and end date of a labeled episode were included in this analysis. All healthcare activities were labeled in subgroups. Finally, all healthcare activities were labeled with admission details, unit costs and subgroup details.

Statistical analysis

Group 1 was compared to group 2. Skewed continuous variables were presented as mean, median and range and categorical data were presented as frequencies and percentage. Group differences for baseline characteristics were assessed using Fisher's exact test for dichotomous variables and Mann-Whitney U-test for continuous variables. A p-value <0.05 was considered statistically significant. Groups were compared using visual inspection on the total cost per patient distribution, the mean cost and the median cost. Statistical analyses were performed with SPSS v25 (IBM Corp, Armonk, NY), Microsoft Excel and R 4.0.0 (R Core Team, Auckland, New Zealand).

Sensitivity analysis - Exclusion of outliers

Outliers were assessed by using the distribution of total admission days in both groups. Subjects marked as outliers according to the boxplot method: $75\% \text{ quartile} + 1.5 * IQR$, were considered outliers.

RESULTS

Patient characteristics

A total of 64 EA patients that underwent surgical repair of the esophagus at the Wilhelmina Children's Hospital between 2014 and July 2019 were included in this study. Group 1, prior to introduction of the PPT, consisted of 28 patients (2014-2016) and group 2, after introduction of the PPT, consisted of 36 patients (2017-July 2019). There were no relevant significant differences in baseline characteristics and surgical data between the two groups. Patient characteristics are presented in **Table 1**.

Admission days

Patients from group 1 and 2 were admitted for a total of 4,454 days within the first year of life. Patients in group 1 were admitted for a mean of 72 days per patient (median 45, range 11-254), compared to a mean of 68 days in group 2 (median 42, range 16-273). In group 1, patients were admitted for a mean of 16 days (range 0-178) for respiratory reasons. In group 2, patients were admitted for a mean of 7 days for respiratory reasons (range 0-153). Thirty-six percent of the patients in group 1 (10 patients; mean 44 admission days) was admitted for respiratory reasons, compared to 25% (9 patients; mean 29 admission days) of group 2.

Table 1. patient characteristics of group 1 and group 2

Variable	Group 1 (2014-2016) n=28	Group 2 (2017-2019) n=36	p-value
Male	16 (57%)	24 (67%)	0.45
Gestational age (weeks)	39.2 (31.6-41.6)	37.3 (28.3-42.3)	0.08
Premature	7 (25%)	16 (44%)	0.12
Twin	3 (11%)	2 (6%)	0.65
Birthweight (g)	2755 (1585-4170)	2692 (1050-3950)	0.37
Apgar score			
1 min	8 (2-9)	9 (3-10)	0.17
5 min	9 (3-10)	9 (5-10)	0.48
Type EA			0.38
A	3 (11%)	1 (3%)	
B	1 (3.6%)	0	
C	23 (82%)	32 (89%)	
D	0	2 (5.6%)	
E	1 (3.6%)	1 (2.8%)	
Associated anomalies [#]			
Trisomy 21	2 (7%)	1 (3%)	0.57
VACTERL	6 (21%)	8 (22%)	1.0
Musculoskeletal	10 (36%)	15 (42%)	0.80
Urogenital	8 (29%)	5 (14%)	0.33
Cardiovascular	12 (43%)	15 (42%)	1.0
Gastrointestinal	4 (14%)	2 (6%)	0.40
Surgical data			
Age at surgery	3 (0-58)	3.5 (1-54)	0.17
NICU time (d)	9 (3-16)	8 (3-81)	0.91
LOS (d)	20 (10-159)	25.5 (12-216)	0.14
Leakage	3 (11%)	6 (17%)	0.72

EA=esophageal atresia; LOS=length of hospital stay

All data are presented as median (range) or n (%).

[#]Some patients had multiple anomalies.

Total costs

The average healthcare costs before introduction of the PPT were €123,466 (median €66,835, range €27,904-€496,635) compared to an average of €121,956 (median €71,188, range €32,783-€491,162) after introduction of PPT (**Table 2**). Distribution of total costs per patient showed similarity between the two groups (**Figure 1**). Admission days comprised the major part of all hospital costs, with average costs of €76,093 (median €40,054, range €27,052-€284,130) in group 1 and €81,831 in group 2 (median €51,933, range €30,682-€311,808).

Table 2. Total hospital costs and days per admission type

Admission reason	Mean cost	Median Cost	Range	Adm. Days*	Pt no.	Mean cost	Median Cost	Range	Adm. Days*	Pt no.
PRE										
Esophageal atresia	€ 76,093	€ 40,054	€ 27,052 - € 284,130	1,026	28	€ 81,831	€ 51,933	€ 30,682 - € 311,808	1,416	36
Respiratory	€ 27,389	NA	€ 0 - € 348,325	492	10	€ 19,036	NA	€ 0 - € 314,977	412	9
Stenosis-related	€ 7,187	€ 384	€ 0 - € 47,394	203	14	€ 8,732	NA -	€ 0 - € 139,916	370	12
Fundopli-cation	€ 2,077	NA	€ 0 - € 22,562	52	5	€ 895	NA	€ 0 - € 15,040	22	3
Associated anomalies	€ 3,295	NA	€ 0 - € 51,146	79	3	€ 2,879	NA	€ 0 - € 85,615	43	3
Other	€ 7,426	€ 384	€ 0 - € 116,908	172	14	€ 4,627	NA	€ 0 - € 80,027	167	14
Total	€ 123,466	€ 66,835	€ 27,904 - € 496,635	2,024	28	€ 121,956	€ 71,188	€ 32,783 - € 491,162	2,430	36
POST										

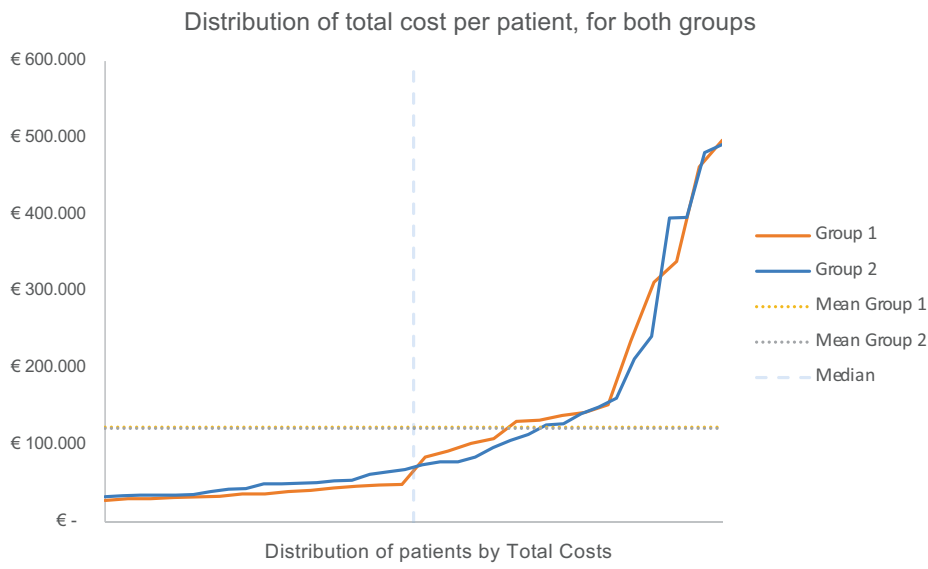


Figure 1. Distribution of hospital costs per subject for both groups. This distribution figure shows that the average healthcare costs in both groups are overall comparable. The average healthcare costs of the patients before the median seem to be lower in group 1 compared to group 2. This is in contrast with the average healthcare costs of patients after the median, which seems to be lower in group 2 compared to group 1. Data is right-skewed, which indicates that patients with high healthcare costs influence the mean results

Total costs for respiratory admissions

The average healthcare costs for respiratory admissions before introduction of the PPT were €27,389 (range €0-€348,325) compared to €19,036 (range €0-€314,977) after introduction of PPT, which corresponds with a decrease of €8,353 (30%) per patient (**Figure 2**). Respiratory related admissions accounted for 22% of all healthcare costs in group 1 and 15% in group 2. The costs for other than EA or respiratory admission reasons were relatively low compared to the mean.

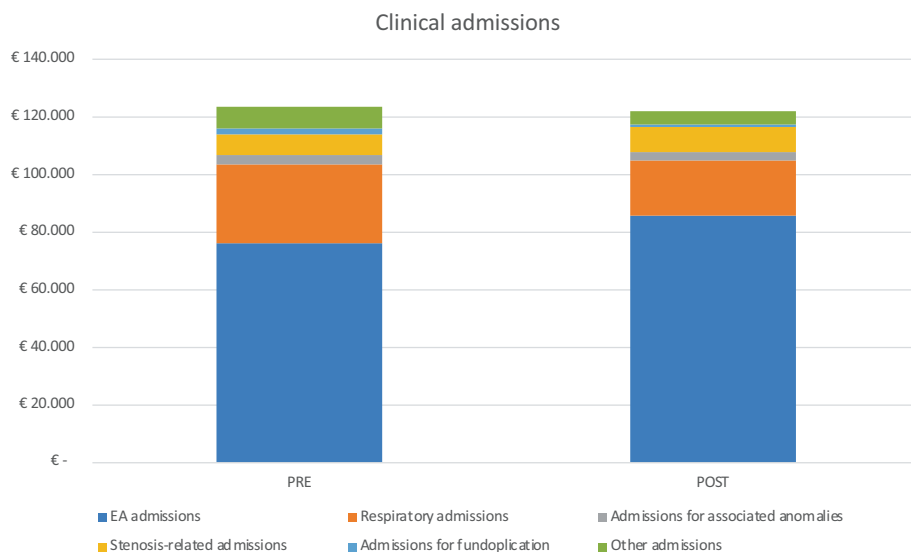


Figure 2. Distribution of healthcare cost before (PRE) and after introduction of PPT (POST)

Scenario analysis

Patients with more than 201 admission days were excluded based on the formula described in the methods section. A total of five outliers were excluded from further analysis, of which one patient from group 1 and four patients from group 2. All excluded patients had (severe) multiple associated anomalies (**Table 3**). After exclusion of outliers, the average healthcare costs for respiratory admissions were €19,246 (range €0-€348,325) before introduction and €1,810 (range €0-€40,694) after introduction of PPT, which is a decrease in average respiratory costs of €17,436 (91%) (**Figure 3**).

Table 3. Patient characteristics outliers (within 1st year of life)

Patient	Premature	Group	Type EA	Ass. Anomalies	Gastrostomy	Leakage	NICU-time postop	LOS 1st admission	Stenosis, Fundoplication	Respiratory surgical intervention	Rec fistula
1, female	No	1	C	Dextrocardia	Yes	-	126	145	1x -	Tracheostomy	-
2, male	Yes	2	C	VSD	Yes	Yes	50	170	1x Yes	-	-
3, male	Yes	2	C	<u>VACTERL</u> , e.g. laryngeal cleft gr II-III	Yes	-	46	178	4x Yes	Aortopexy	-
4, female	No	2	C	<u>VACTERL</u>	-	Yes	9	26	15x Yes	PPT	-
5, male	Yes	2	D	<u>VACTERL</u> , e.g. retrognathia, large ASD, HLHC, subglottic stenosis	-	-	13	216	5x -	PPT, tracheostomy	-

EA=esophageal atresia; HLHC=hypoplastic left heart complex; PPT=primary posterior tracheopexy; ASD=atrial septal defect; VSD=ventricular septal defect

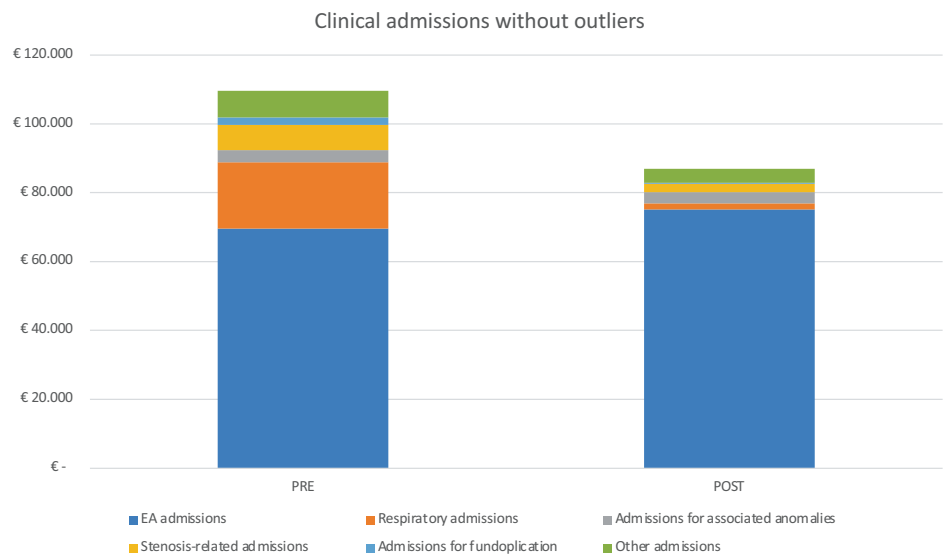


Figure 3. Distribution of healthcare costs after exclusion of outliers before (PRE) and after introduction of PPT (POST)

DISCUSSION

This is the first study on cost analysis that evaluated hospital costs in EA patients before and after the introduction of PPT for TM.

This study shows that the introduction of PPT resulted in a reduction of the number of patients that were admitted with respiratory symptoms resulting in a reduction of hospital costs for respiratory problems. Furthermore, the introduction of PPT resulted in a mean decrease in costs of 30% for respiratory admissions. The sensitivity analysis however, in which outliers (>201 admission days within the 1st year) were excluded, showed a decrease of 90% in mean costs for respiratory admissions.

The overall mean hospital costs were similar within the two groups. The distribution of total costs in both groups shows a comparable pattern, indicating that the two groups are comparable in total cost expenses. The observed decrease in costs for respiratory admissions in group 2 seems to be outweighed by higher mean costs for EA admissions. This may be explained by the fact that group 2 entailed more premature patients (44% vs 25%), although this difference was not statistically significant. Furthermore, EA is often accompanied by one or multiple comorbidities that may require prolonged hospital admission.

Sensitivity analysis showed that after exclusion of the outliers (admission >201 days), the decrease in respiratory costs was up to 90% after the implementation of the PPT, compared to a 30% decrease before exclusion of outliers. Due to the small sample size as well as the heterogeneous patient population, the outliers in group 2 (all patients with severe comorbidities) were accountable for a major part of the respiratory costs.

The use of real-world data in cost analysis studies is difficult, because not all factors can be accounted for in the analysis. Preferably, one would also examine costs of societal perspective, including lost workdays of parents and travel expenses. This is difficult information to obtain in an observational setting and may explain the lack of cost analysis studies for esophageal atresia treatment. In this study only medical interventions from the UMC Utrecht were included. Due to privacy regulations and study design, it was not feasible to take costs from other hospitals into account. However, since these patients undergo extensive routine follow-up at our center, it is unlikely that patients were admitted at other centers, especially during their first year of life. Furthermore, the observational comparative design of the study before and after a certain cut-off point, causes our results to be sensitive for time-dependent changes. Changes in disease management or treatment plans over time could affect our results and change outcome

measures. However, despite the introduction of the PPT, no other changes in treatment were introduced during the study period.

In conclusion, this study shows that fewer patients are admitted for respiratory problems after PPT. Also, there seems to be a tendency of decreased respiratory costs after introduction of the PPT. Overall hospital costs are comparable before and after introduction of the PPT. After exclusion of outliers, a significant decrease in respiratory costs is observed. A future randomized controlled trial should be conducted to clarify this concern and further explore the burden of healthcare and societal costs.

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CHAPTER 9

AIRWAY EPITHELIAL CULTURES OF CHILDREN WITH ESOPHAGEAL ATRESIA AS A MODEL TO STUDY RESPIRATORY TRACT DISORDERS

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ABSTRACT

Esophageal atresia (EA) is a rare birth defect in which respiratory tract disorders are a major cause of morbidity. It remains unclear whether respiratory tract disorders are in part caused by alterations in airway epithelial cell functions such as the activity of motile cilia. This can be studied using airway epithelial cell culture models of patients with EA. Therefore, the aim of this study was to evaluate the feasibility to culture and functionally characterize motile cilia function in the differentiated air-liquid interface cultured airway epithelial cells and 3D organoids derived from nasal brushings and bronchoalveolar lavage (BAL) fluid from children with EA. We demonstrate the feasibility of culturing differentiated airway epithelia and organoids of nasal brushings and BAL fluid of children with EA, which display normal motile cilia function. EA patient-derived airway epithelial cultures can be further used to examine whether alterations in epithelial functions contribute to respiratory disorders in EA.

INTRODUCTION

Esophageal atresia (EA) is a rare birth defect in which the esophagus is fused to the trachea or interrupted. Respiratory tract disorders, including chronic cough, recurrent respiratory tract infections, pneumonia or even life-threatening brief resolved unexplained events (BRUEs), are a major cause of long-term problems in these patients^{1,2}. These symptoms are most common during infancy and childhood^{1,3}. The majority of children with EA have restrictive and/or obstructive pulmonary function and a smaller lung capacity compared to healthy children⁴⁻⁷. However, the cause of respiratory morbidity in EA is not yet clearly understood.

Previous studies suggested functional abnormality of the tracheal airway epithelium in EA patients^{5,8,9}. It is expected that cilia are lacking at the original location of the tracheo-esophageal fistula which may affect mucus clearance and cause colonization of microbes that are continuously inhaled, explaining recurrent respiratory tract infections. Similar to chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), environmental risk factors such as microbial infections may cause imprinted defects in airway epithelial cell functions, which persist in cell culture¹⁰⁻¹². Airway epithelial cells of individuals with EA may also display impaired epithelial functions due to patient-specific genetic risk factors that are associated with congenital birth defects in EA¹³. For instance, genetic defects in the transcription factor SOX2 may lead to impaired separation of the foregut into the esophagus and trachea¹⁴, while SOX2 has also been described as a key regulator of airway basal stem and progenitor cells. A potential mechanism affected in the airway epithelium of patients with EA is dysmotility of the cilia, which can impair the clearance of mucus from the respiratory tract. However, no previous studies have been conducted to assess ciliary function in the epithelial cells of individuals with EA.

We and others previously described methods for culturing airway epithelial cells from nasal brushings and BAL fluid from individuals with respiratory diseases such as cystic fibrosis (CF), asthma, or COPD¹⁵⁻¹⁹. These technical reports show that non-invasive methods such as nasal brushings or leftover materials from diagnostic tests can be used to isolate airway epithelium cells and to model patient-derived tissues in vitro. The cultured cells can then be used to study airway diseases or infections in a controlled and defined environment²⁰⁻²⁴.

Here, we report for the first time that also airway epithelial cells of EA patients can be isolated and cultured by these protocols. We show that EA patient-derived airway epithelial cell cultures can be used to study alterations in epithelial cell function

and morphology. We, therefore, evaluated the feasibility to culture airway epithelial cells derived from nasal brushings and BAL fluid of patients with EA in mucociliary differentiated air-liquid interface (ALI) cultures and 3D airway organoids. As a proof-of-concept of studying airway epithelial functions, we furthermore examined motile cilia activity in differentiated airway epithelial cell cultures of patients with EA, which was compared to healthy individuals and a patient with primary ciliary dyskinesia (PCD).

MATERIALS AND METHODS

Human Materials and Informed Consent

An observational study was conducted including seven EA patients (**Table 1**) that underwent general anesthesia and had an indication for bronchoalveolar lavage (BAL) between July and December 2019. Patients were considered eligible for this study if they had any type of esophageal atresia and they had to undergo general anesthesia. Furthermore, nasal brushings from a healthy individual (age 32, no symptoms) and a patient (age 23, mild respiratory symptoms) with PCD were included as reference samples. Informed consent from the parents was obtained and entailed. This study was approved by the Ethical Board for the use of Biobanked materials TcBIO (Toetsingscommissie Biobanks Utrecht, The Netherlands), an institutional Medical Research Ethics Committee of the University Medical Center Utrecht (protocol number: 19/763; approved on 29 May 2020). All experimental procedures were conducted between June 2020 and August 2022.

Table 1. Characteristics of the included EA patients

Gender, Age	Type EA	Associated Anomalies	Tracheomalacia	Respiratory History
1, female, 6.4 months	C	VACTERL	Yes, severe	No infections, mild respiratory symptoms
2, male, 4 days	A	Macrocefalie	None	No symptoms
3, male, 1.6 years	C	None	Yes, mild	Mild respiratory symptoms, cough
4, male, 4.8 years	C	None	Yes, mild	Multiple RTIs, cough
5, male, 1.2 months	C	VACTERL	Yes, mild	Mild respiratory symptoms, cough
6, female, 1 year	C	VACTERL	Yes, moderate	PPT, Cough
7, female, 7 days	A	Hypoplastic rib	None	Mild

VACTERL = vertebra, anal, cardiac, tracheo-esophageal, renal, limb; PPT = primary posterior tracheopexy; RTI = respiratory tract infections.

Isolation and Differentiation of Airway Cells

Nasal brushings were collected with a cytology brush (C0004, CooperSurgical, Trumbull, CT, USA) under general anesthesia as previously described by Rodenburg et al.¹⁵ Different sizes of brushes were available, depending on the age of the patient. The brush was rinsed with phosphate-buffered saline (PBS), prior to insertion of the nostril and the brush was inserted until a resistance was felt with rotating and linear movements. The brush was removed from the nostril and placed in a tube containing 5 mL of cell culture medium with antibiotics (Advanced DMEM/F12 (12634-028, Thermo Fisher Scientific, Waltham, MA, USA) with GlutaMax (35050-061, Thermo Fisher Scientific), Hepes (15630080, Thermo Fisher Scientific), Penicillin-Streptomycin (15070-063, Thermo Fisher Scientific), and primocin (ant-pm-2, InvivoGen, San Diego, CA, USA))¹⁵. A nasal brushing was performed from both the left and right nostrils. The bronchoalveolar lavage (BAL) was carried out by the anesthesiologist after the nasal brushings were performed. Normal sterile saline (0.9% NaCl solution), ranging from 5–20 mL, was flushed through the endotracheal tube and was retrieved by mechanical aspiration. Half of the collected BAL sample was used for diagnostic purposes. The leftover material was used for airway epithelial stem cell isolation within four hours after sampling. Nasal and bronchial airway epithelial cells were isolated, expanded, and differentiated as previously described¹⁵. In short, airway basal stem cells were isolated by making a single cell suspension of the pellet yielded from nasal brush or BAL sample. After expansion, the stem cells were differentiated in ALI cultures using Transwell® inserts (3470, Corning, Corning, NY, USA) for at least 18 days. Airway organoids were generated from epithelial fragments of a differentiated ALI culture as previously described¹⁵.

Fixation and Immunofluorescent Microscopy

Differentiated nasal and bronchial ALI cultures (n = 3) were fixed and stained as previously described²⁵. Primary antibodies (β -tubulin IV (MU178-UC, Emergo Biogenex, Fremont, CA, USA), MUC5AC (ab198294, Abcam, Cambridge, UK), were incubated for 1 h at RT. Afterward, secondary antibodies (A-21240 and A11034, Invitrogen, Waltham, MA, USA), together with phalloidin (A34055, Mol. Probes, Eugene, OR, USA) and DAPI (D9542, Sigma, St. Louis, MO, USA), were added for 30 min. Both primary and secondary antibodies were diluted 1:500 in blocking buffer (1% BSA + 0.3 Triton X-100 (T8787, Sigma-Aldrich, St. Louis, MO, USA) in PBS). Images were acquired with a Zeiss LSM800 confocal microscope (40 \times objective). Image quantification was performed using Fiji (Max Planck Institute, Dresden, Germany) and CellProfiler (Broad Institute, Cambridge, MA, USA). Cultures did not show contamination with other cell types such as fibroblasts.

Analysis of Ciliary Beat Frequency (CBF)

Ciliary beat frequency (CBF) was determined in differentiated ALI cultures and organoids by high-speed video microscopy (HSVM) on a Thunder Imager 3D live Cell using a DFC9000

GTC camera (Leica). ALI cultures were imaged in phase contrast (40× dry objective) and 3D organoids were captured in brightfield (40× dry objective) at 37 °C and 5% CO₂. Videos were recorded at 203 frames per second (fps) for 512 frames in total or 404 fps for 1024 frames. For ALI filters, five different locations with moving cilia were selected for each video and beating was determined twice for two seconds. For determination of the wave pattern in organoids, cilia on different cells per condition were observed to validate the presence of an effective and recovery stroke. The same cilia were followed twice for 1–2 s to determine CBF. CBF was performed randomized on coded videos.

RESULTS

Characteristics of Patients with Esophageal Atresia

Patient characteristics are presented in **Table 1**. Three donors were female and four were male. The median age was 6.4 months. Five patients had esophageal atresia Type C (with a distal tracheo-esophageal fistula) and two patients had type A (esophageal atresia without fistula). Associated anomalies were present in five out of seven patients. All but one had respiratory symptoms; patient 2 (male, 4 days) is the only patient without any respiratory symptoms.

In Vitro Differentiation of EA Patient Derived Airway Cultures

We first determine the feasibility to isolate, expand, and differentiate nasal and bronchial airway epithelial cells from individuals with EA derived from nasal brushings and BAL fluid, respectively (**Figure 1**). Culturing of all nasal brushings and four out of seven BAL samples was successful. Analysis of differentiated ALI-HNEC (human nasal epithelial cells) and –BAL of EA patients by immunofluorescence imaging showed the presence of β -tubulin IV+ ciliated and MUC5AC+ goblet cells in both nasal as well as bronchial cultures after 18 days of differentiation (**Figure 2A**). Image quantification of differentiated cells observed at the cell surface showed on average 31.1% goblet cells and 39.8% ciliated cells in nasal cultures and 29.6% goblet cells and 42.8% ciliated cells in bronchial cultures (**Figure 2B**).

Ciliary Activity

To assess the cilia activity of the differentiated ALI cultures of EA patients, HSVM was performed after 18 days of differentiation (**Figure 2C**). Differentiated ALI cultures of nasal cells from a healthy individual and a PCD patient were used as positive and negative control, respectively. CBF of the healthy control was between 14–22 Hz (**Figure 2D**). Beat frequency of all EA donors was between 9–23 Hz with an average of 17.6 Hz

in nasal cultures and 16.1 Hz in bronchial cultures (**Figure 2E**). No ciliary beating could be detected in the PCD donor.

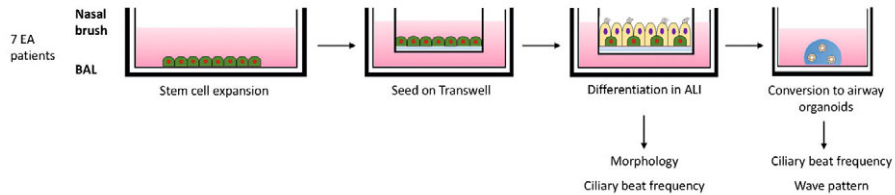


Figure 1. Schematic overview of culturing and analysis of differentiated airway epithelial cells of EA patients. Nasal brushings and BAL fluid from 7 EA patients were collected and airway epithelial cells were expanded in 2D cell cultures. After reaching confluence, the cells were seeded on Transwell inserts. After reaching confluency the apical medium was removed and cells were differentiated in an air-exposed condition. After 18 days of differentiation, cells were either imaged to determine the ciliary beat frequency (CBF) and fixed or converted into airway organoids. After a few days organoids were imaged to determine CBF and wave pattern

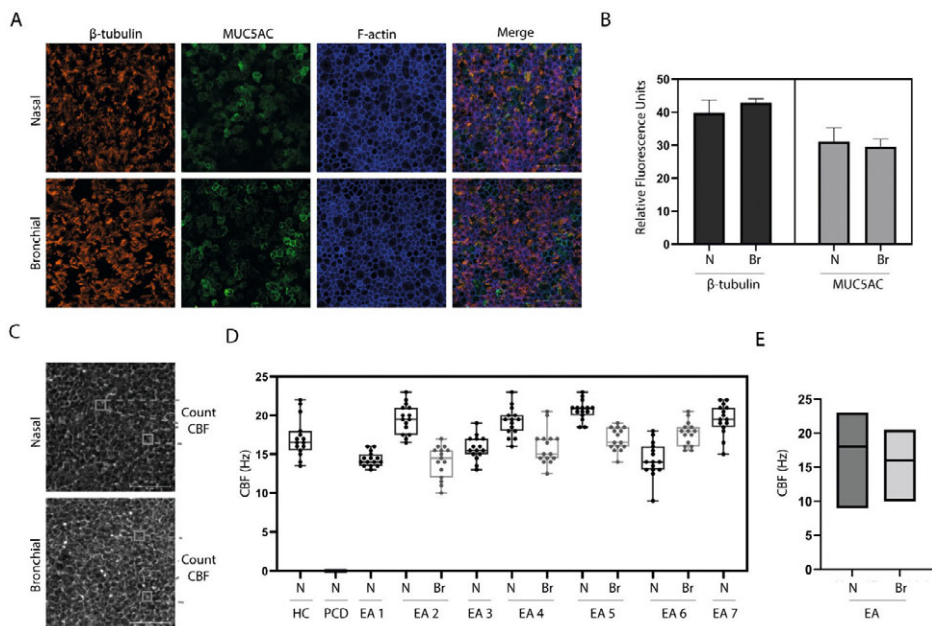


Figure 2. Characterization of ALI cultures from individuals with EA. (A) Immunofluorescence (IF) staining of differentiated ALI cultures of EA patients, generated from nasal (N) brushing and bronchial (Br) sample of randomly selected representative donor (Donor 2). β -tubulin IV is shown in orange, MUC5AC is shown in green and f-actin is shown in blue. (B) Quantification of IF staining of EA patients ($n = 3$) showing the relative fluorescence units. (C) Phase-contrast image of a nasal and BAL-derived ALI culture of randomly selected representative donor (Donor 2). (D) Ciliary beat frequency (CBF) determined in ALI cultures of a healthy control (HC) donor, an individual with primary ciliary dyskinesia (PCD) patient and 7 donors with esophageal atresia (EA). N = nasal; Br = bronchial. (E) Comparison of CBF in nasal versus bronchial ALI cultures from all EA patients

To enable observation of ciliary movement from the lateral side, differentiated ALI cultures were converted into 3D airway organoids. Similar to ALI cultures, airway organoids displayed goblet and ciliated cells, as confirmed by immunofluorescence imaging (**Figure 3A**). The cilia wave pattern was assessed by eye and the presence of an effective and recovery stroke was confirmed in selected ciliated cells (**Figure 3B**). CBF in airway organoids of individuals with EA (6–19 Hz) was in a similar range as the CBF counted in the healthy donor (11.5–20 Hz) (Figure 3C). The nasal organoids of donors with EA had an average frequency of 11 Hz and bronchial organoids 12.7 Hz (**Figure 3D**). In contrast, nasal organoids from an individual with PCD did not show any ciliary movement.

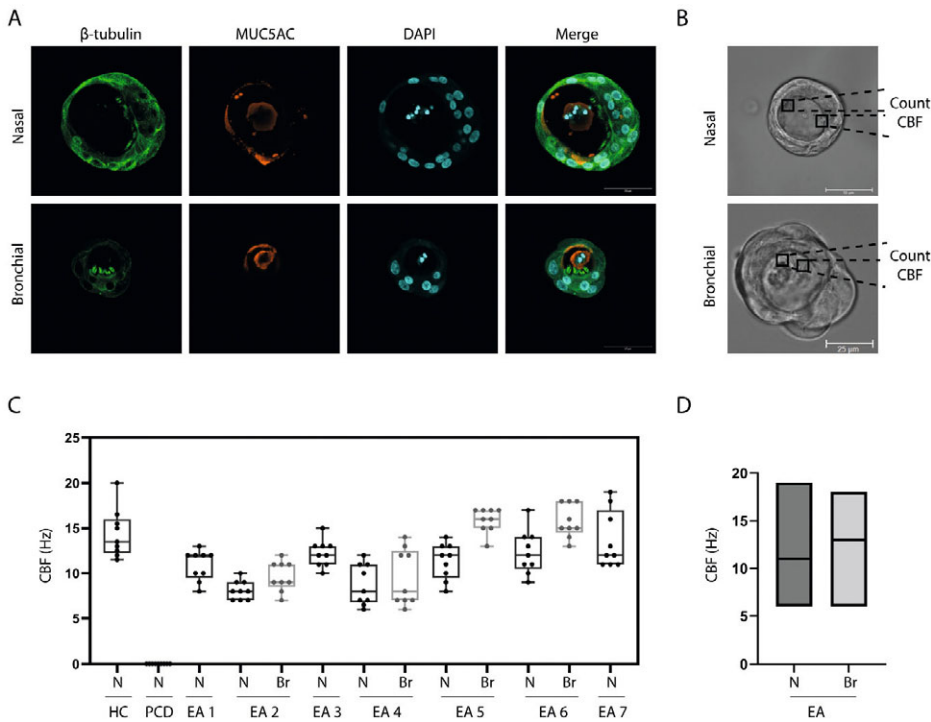


Figure 3. Ciliary beating in 3D airway organoids of patients with EA. (A) IF staining of organoids generated from a nasal brushing (Donor 1) and BAL sample (Donor 4). Images were randomly selected from representative donors. (B) Bright field image (40 \times) of a nasal organoid (Donor 1) and a BAL derived organoid (donor 4). Images were randomly selected from representative donors. (C) Ciliary beat frequency (CBF) determined in organoids from a healthy control (HC) donor, primary ciliary dyskinesia (PCD) patient, and all 7 donors with esophageal atresia (EA). N = nasal; Br = bronchial. (D) Comparison of CBF in nasal versus bronchial organoids from all EA patients

DISCUSSION

In this study, we showed that it is feasible to isolate and differentiate airway epithelial cells from nasal as well as bronchial airway samples from individuals with EA. We found a lower success rate of airway epithelial cells isolated from BAL samples compared to nasal brushings. We were able to isolate epithelial cells from 4 out of 7 BAL samples, due to recurrent infections and insufficient growth of isolated epithelial cells in three cases. Upon successful isolation, we were able to differentiate both nasal and bronchial airway epithelial cells in ALI cultures, which displayed both ciliated and goblet cells. Moreover, we were able to culture 3D airway organoids derived from differentiated ALI –culture-derived epithelial fragments.

Nasal and bronchial culture models could be used to evaluate motile cilia activity. In both nasal and BAL-derived airway epithelial cell cultures from individuals with EA, we observed a similar beat frequency and wave pattern compared to a healthy control subject, which was in contrast to the ciliary wave pattern of an individual with PCD. This suggests that there was no primary ciliary defect present in the EA patients, as proposed by Engeseath et al.²⁶

The use of leftover materials from diagnostic tests and the isolation of epithelial cells from nasal brushings in combination with efficient protocols for in vitro cell differentiation are a non-invasive alternative for when lung tissue cannot be obtained and should be considered for future studies. For example, the mechanism of secondary ciliary dyskinesia can be further studied by in vitro stimulation experiments such as effects of respiratory infection in cell cultures from individuals with EA. Recent studies showed that respiratory cell cultures derived from various isolation techniques can be used to study airway diseases or infections in a controlled and defined environment (**Table 2**). In addition, it may be assessed in future studies whether other airway epithelial cell functions are affected in EA, such as epithelial barrier integrity, wound healing, mucus secretion, and the expression and release of pro-inflammatory mediators.

Our study was limited to a small number of donor materials. Future studies in a larger subgroup of individuals with EA may be required to gain further insight in potential ciliary defects. The lower success rate of culturing cells from BAL samples is probably caused by the nature of this sampling technique^{16,22,27}. Blind washings in general result in a lower cellular load when compared to brushings of the epithelial surface, as conducted for nasal sampling. We have, however, included these samples because they were leftover materials for diagnostic tests, and no additional procedure needed to be conducted. How sampling of airway cells with different methods affects the impact of cell isolation

should be investigated in more depth in future studies. None of the chosen sampling techniques target the epithelial tissue located at the prior tracheoesophageal fistula specifically. It is unknown whether the transition tissue consists of tracheal epithelium, esophageal epithelium or both. It might be that ciliary cells are lacking at the location of the prior TEF. Moreover, often a small dent is seen at the place of the TEF. This may result in a loss of the mucociliary transport function of the trachea. Future studies should examine the tissue located at the prior tracheoesophageal fistula in more detail by studying bronchial brushings of this specific area or by analyzing the tissue removed from the trachea during surgery.

Table 2. Respiratory cell culture models

Isolation Technique	Risk for Donor	Respiratory Model	Literature
Leftover tissue from operation	Not invasive	Cigarette smoke, lung cancer, Rhinovirus, RSV, SARS- CoV-2	[16,17,20,23,28],
Tracheal aspirates	Not invasive	Cigarette smoke, homeostasis	[18,23]
Nasal brush/wash	Minimal invasive	Asthma, CF, COPD, PCD, RSV, SARS- CoV-2	[15,21,24,29–32]
Bronchial biopsy/ brushing	Medium invasive	Asthma, COPD, PCD, Rhinovirus, SARS-CoV-2	[27,33–36]
BAL	Medium invasive	Asthma, lung cancer, RSV	[16,22,29]

CF = cystic fibrosis; COPD = and chronic obstructive pulmonary disease; PCD = primary ciliary dyskinesia; RSV = respiratory syncytial virus.

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CHAPTER 10

BACTERIAL COLONIZATION OF THE LOWER AIRWAYS IN CHILDREN WITH ESOPHAGEAL ATRESIA

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ABSTRACT

Background

Esophageal atresia (EA) is most often accompanied by some degree of tracheomalacia (TM), which negatively influences the airway by ineffective clearance of secretions. This can lead to lower airway bacterial colonization (LABC), which may cause recurrent respiratory tract infections (RTIs). This study aims to evaluate the prevalence and specific pathogens of LABC in EA patients.

Methods

A 5-year retrospective single-site cohort study was conducted including all EA patients that had undergone an intraoperative bronchoalveolar lavage (BAL) during various routine surgical interventions. Concentrations of >10 cfu were considered evidence of LABC.

Results

We recruited 68 EA patients, of which 12 were excluded based on the exclusion criteria. In the remaining 56 patients, a total of 90 BAL samples were obtained. In 57% of the patients, at least one BAL-sample was positive for LABC. Respiratory symptoms were reported in 21 patients at time of the BAL, of which 10 (48%) had LABC. *Haemophilus influenzae* (14%) and *Staphylococcus aureus* (16%) were most frequently found in the BAL-samples. The number of respiratory tract infections and the existence of a recurrent fistula were significantly associated with LABC ($p=0.008$ and $p=0.04$, respectively).

Conclusions

This is the first study showing that patients with esophageal atresia have a high prevalence of bacterial colonization of the lower airways which may be a leading mechanism of severe and recurrent respiratory complications.

INTRODUCTION

Esophageal atresia is a rare congenital anomaly of the esophagus, occurring in 2.43 per 10,000 live births. According to the Gross classification, five types of esophageal atresia can be distinguished. Approximately 85% of EA patients have type C, in which the atresia is accompanied by a distal tracheoesophageal fistula. In up to half of the patients, esophageal atresia is accompanied by one or multiple associated anomalies. Surgical thoracoscopic repair is warranted and will be performed within the first days of life. Respiratory problems are a major cause of long-term morbidity in esophageal atresia (EA) patients. Clinical presentation of respiratory morbidity includes chronic cough, recurrent respiratory tract infections (RTIs), dyspnea and blue spells¹. Respiratory problems in EA patients are not yet fully understood and there are several potential causes. Tracheomalacia (TM) is reported in up to 90% of EA patients² and increases the risk of respiratory illness³. An inadequate cough due to the flaccidity of the posterior tracheal wall in TM may lead to impaired clearance of respiratory secretions⁴⁻⁸, resulting in bacterial colonization of the lower airways⁹. Furthermore, gastroesophageal reflux (GER) may predispose to aspiration of gastric contents, leading to pulmonary problems¹⁰. Recurrence of a tracheoesophageal fistula has been described in 5-15% of EA patients and may also cause respiratory morbidity^{2,11,12}.

Former studies have shown bacterial colonization of the lower airway in patients with diseases that affect the airways, such as cystic fibrosis (CF)¹³ and patients with isolated TM¹⁴. Despite the frequent respiratory problems in EA patients, bacterial colonization of the lower airways in EA patients has never been evaluated. Therefore, this study aims to determine the prevalence of LABC in EA patients that underwent a surgical procedure under anesthesia at the Wilhelmina Children's Hospital, Utrecht.

METHODS

A retrospective cohort study was conducted including all EA patients that had undergone bronchoalveolar lavage (BAL) at the Wilhelmina Children's Hospital between 2015 and 2020. Patients were excluded if there was missing data (e.g. referral from other hospital) and/or preoperative endotracheal intubation for more than 20 hours.

Bronchoalveolar lavage (BAL) procedure

Since 2015, a BAL has been performed in EA patients during various routine surgical interventions to evaluate the prevalence of lower airway bacterial colonization. This allowed for targeting antibiotic treatment in case of RTI. BAL is carried out under general

anesthesia, prior to the start of the surgical intervention. Normal sterile saline (0.9% NaCl solution) on body temperature, ranging from 5-20 mL, is used for BAL. A catheter is inserted through the endotracheal tube, with the tip near the carina. Thereafter, the sterile saline is flushed through the catheter and the fluid is retrieved via mechanical aspiration. BAL-samples are examined by the medical microbiologist at the Medical Microbiology Department of the Wilhelmina Children's Hospital Utrecht. Colony-forming units (cfu) of >10 are considered positive for LABC.

Clinical assessment

Baseline characteristics, surgical data and postoperative data were collected from the medical charts.

Respiratory outcome

Respiratory tract infection (RTI) was defined as any infection of the airways requiring antibiotic treatment. Patients were considered having doctor-diagnosed asthma, if asthma was diagnosed by the pediatric pulmonologist or if asthma medication was continued after evaluation by the pediatric pulmonologist. Diagnosis of TM was based either on rigid bronchoscopy (while breathing spontaneously) or on clinical symptoms assessed by the pediatric pulmonologist. If patients were using antibiotic prophylaxis within three months prior to the BAL, this was recorded in the database. All respiratory symptoms at time of the BAL were recorded.

Ethical approval

This retrospective cohort study was submitted to the UMCU Ethics Committee. No ethical approval was required according to the Medical Research Involving Human Subject Act. The study was carried out in accordance with the Declaration of Helsinki.

Statistical analysis

Skewed continuous variables were presented as median and range, categorical variables were presented as frequencies and percentage. Associations between parameters (tracheomalacia, reflux, asthma, prophylactic antibiotics, recurrent fistula and RTIs) and a positive LABC were assessed using the Fisher's exact test for bivariate variables and the Mann Whitney U-test for continuous data. Patients with multiple BAL-samples were considered to have had an LABC when at least one of their BAL-samples was positive. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS version 25.0 (IBM, USA).

RESULTS

A total of 68 pediatric EA patients underwent a surgical procedure including BAL between 2015 and 2020 at the Wilhelmina Children's Hospital. Twelve patients were excluded based on the exclusion criteria (missing data of patients referred from other hospitals (n=7), intubation >20 hours (n=3), refusal for participation in medical research (n=2)). Of the remaining 56 patients the median age at time of the BAL was 1.1 years (range 0-16.9 years). Thirty-four patients were male (61%) and 27 were born prematurely (48%). Forty-seven patients (84%) had EA type C. Associated anomalies were present in 38 patients (68%), including cardiac anomalies in 25 patients (45%) and musculoskeletal anomalies in 20 patients (35%). Nine patients (16%) had recurrent fistula. In five patients the recurrent fistula had been corrected prior to the BAL. In four patients the recurrent fistula was still present. Baseline characteristics are presented in **Table 1**.

Table 1. Baseline characteristics

Variable	Positive BAL (N=33)	Negative BAL (N=23)	p-value
Male	22 (67%)	12 (52%)	0.41
Premature (<37 weeks)	17 (52%)	10 (44%)	0.59
Gestational age (days)	253 (201-293)	261 (209-290)	0.71
Birthweight (g)	2563 (1050-4490)	2420 (1025-3550)	0.44
Type EA			0.70
Type A	4 (12%)	3 (13%)	
Type B	1 (3%)	-	
Type C	27 (82%)	20 (87%)	
Type E	1 (3%)	-	
Associated anomalies			
Down	1 (3%)	-	1.0
VACTERL	4 (12%)	5 (22%)	0.46
Cardiac	12 (36%)	13 (57%)	0.37
ARM	4 (12%)	2 (9%)	1.0
Musculoskeletal	9 (27%)	11 (48%)	0.48
Recurrent fistula	7 (21%)	2 (9%)	0.28

EA=esophageal atresia; VACTERL=vertebral, anorectal, cardiac, tracheo-esophageal, renal, limb anomalies; ARM=anorectal malformations

All data is presented as median (range) or n (%)

Respiratory symptoms

TM was present in 45 patients (80%) and doctor-diagnosed asthma in eight patients (11%). Nineteen patients (34%) experienced BRUEs and at least one RTI occurred in 43 patients (71%), with a median of two infections (range 1-13). A primary thoracoscopic posterior tracheopexy (at time of EA repair) had been performed in seven patients

(13%), a secondary tracheopexy in three patients (5%) and an aortopexy in five patients (9%) prior to the BAL (**Table 2**).

Table 2. Respiratory status

Variable	Positive BAL (N=33)	Negative BAL (N=23)	p-value
Tracheomalacia	27 (82%)	18 (78%)	0.75
Asthma	3 (9%)	5 (22%)	0.25
RTIs (n, range)	2 (0-13)	0 (0-13)	0.02*
BRUEs	12 (36%)	7 (30%)	0.78
Posterior tracheopexy			
Primary	3 (9%)	4 (17%)	0.4
Secondary	3 (9%)	0	0.26
Aortopexy	3 (9%)	2 (9%)	1.0

RTI=respiratory tract infections; BRUE=brief resolved unexplained event

*Indicating statistical significance

Lower airway bacterial colonization (LABC)

A total of 90 BALs were obtained from 56 patients. A positive BAL sample (>10 cfu) was obtained at least once in 32 of 56 patients (57%) and in 41 of the 90 BAL samples (46%). *Staphylococcus aureus* and *Haemophilus influenzae* were most frequently found in the BAL-samples, in 14 (16%) and 13 (14%) samples, respectively. *Moraxella catarrhalis* was found in eight BAL-samples (9%). Twelve samples (13%) were positive for a second bacterium. Of the 49 negative BAL-samples, 17 samples yielded low concentrations (0-10 cfu) of pathogens and these were considered negative (**Figure 1**).

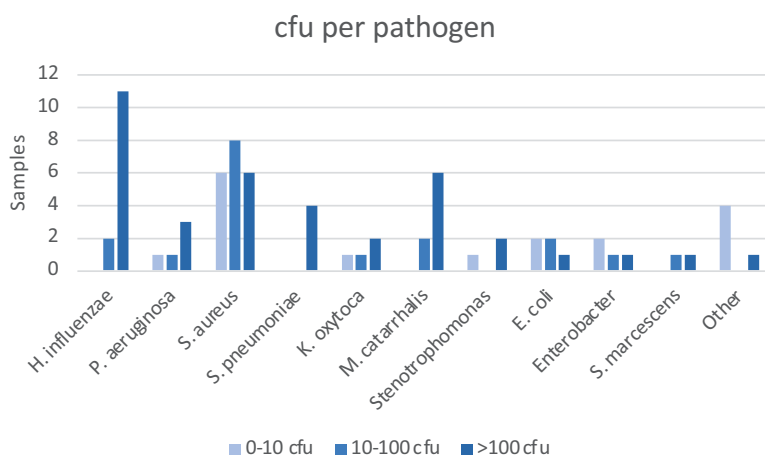


Figure 1. Colony forming units per pathogen

Parameters associated with LABC

In 35 of the 90 BAL-samples, patients had been using prophylactic antibiotics within 3 months prior to the BAL. In 16 of these 35 BAL-samples (46%) positive BAL-cultures were found.

In 55 of the 90 BAL-samples, patients had not received antibiotic treatment prior to the BAL. Of these 55 samples, 25 BAL-samples (45%) were positive. Patients reported respiratory symptoms at the time of the BAL in 21 of the 90 procedures (23%). Ten out of these 21 BAL-samples (48%) were positive. Four patients had a recurrent fistula at the time of the BAL, in these four patients seven samples in total were retrieved. Of these seven samples, six BAL-samples (86%) were positive for LABC. Recurrence of a tracheoesophageal fistula was significantly associated with a positive BAL-culture ($p=0.04$). Patients with at least one positive BAL-sample had a median of two RTIs requiring antibiotics (range 0-13) compared to a median of zero RTIs (range 0-13) in patients with a negative BAL-sample. The number of respiratory tract infections requiring antibiotic treatment was significantly associated with LABC ($p=0.008$). No association was found between tracheomalacia, asthma, reflux or use of prophylactic antibiotics and LABC.

DISCUSSION

This is the first study that evaluates the microbial status of the lower airways in patients with esophageal atresia. A positive BAL-culture was obtained in up to 60% of the EA patients. *Staphylococcus aureus* and *Haemophilus influenzae* were most frequently cultured. Recurrence of the tracheoesophageal fistula and the number of RTIs appear to be associated with a positive BAL-sample.

Routine cultures of the lower airways are usually negative, although Actinobacteria, Proteobacteria, Bacteroidetes, and Firmicutes ribosomal DNA have been found in healthy people's lungs¹⁵. In our study, a positive BAL-culture was obtained in almost 60% of the 56 EA patients. In a study on pediatric patients with isolated airway malacia, a positive BAL-culture was obtained in up to 80% of the patients¹⁴. The difference between the percentage of positive BAL-cultures between the two studies can be explained by two factors. First, there is a difference in percentage of airway malacia in the included patients (100% vs 80%). Secondly, there is a difference in severity of malacia between the two studies: malacia is defined as a collapse of >50% in the study of Boogaard et al.¹⁴. In our study, the severity of the malacia varied widely (mild to severe). The flaccidity

of the posterior wall in TM leads to inefficient clearance of respiratory secretions, which may result in bacterial colonization of the lower airways^{5,6}.

In the study on isolated TM and respiratory problems, *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae* were cultured most frequently¹⁴. In our study, *Staphylococcus aureus* and *Haemophilus influenzae* were found most frequently. *Streptococcus pneumoniae* was only found in four patients. In another study⁷ that included children <5 years old suffering from respiratory problems who had a positive BAL-culture, TM was found in 74%. BAL-cultures in these patients showed predominantly *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. In a study on CF patients, the most common pathogens that were obtained from the BAL-fluids showed *Staphylococcus aureus* and *Haemophilus influenzae*^{16,17}. This is in line with our findings. However, the microbial flora in CF patients changes over time into colonization with several opportunistic pathogens. *Pseudomonas aeruginosa* was the most important pathogen in CF patients. In our study, *Pseudomonas aeruginosa* was found in three BAL-cultures.

Parameters associated with a positive BAL-culture were the number of RTIs requiring antibiotics and the recurrence of a tracheoesophageal fistula at time of the BAL. Respiratory tract infections are common in esophageal atresia patients^{1,18–20}. This may be explained by colonization of the lower airways. The outcome of this study justifies early antibiotic treatment in EA patients with recurrent respiratory tract infections. Early antibiotic treatment may result in adequate treatment of respiratory tract infections and may prevent sequelae, such as pneumonia and severe respiratory symptoms.

Recurrence of a tracheoesophageal fistula results in a direct connection between the trachea and the esophagus, which may result in aspiration of gastric contents. Aspiration can cause respiratory symptoms, and eventually may lead to bronchiectasis²¹. Therefore, early detection and treatment of a recurrent fistula is important to prevent sequelae due to chronic aspiration.

The main limitation of this study is that only EA patients that underwent a surgical procedure were included. However, many EA patients undergo one or multiple surgical interventions after esophageal repair, such as anastomotic dilatation. Therefore, we think that this study is a good representation of the average EA population. Favorably, all EA patients would undergo a BAL. However, since this would require a deep bronchial culture under general anesthesia, it would not be ethical to perform a BAL in all EA patients. A prospective study should be conducted to examine whether there is a

correlation between age, severity of TM, asthma, reflux symptoms and the existence of certain pathogens.

Our results show that esophageal atresia patients have a high prevalence of bacterial colonization of the lower airways, which appears to be associated with the number of respiratory tract infections. These findings support the need for surveillance of pathogens in EA patients during surgical interventions. In case of respiratory illness, early detection may allow to start antibiotic treatment in an earlier stage. Hopefully, this may prevent respiratory sequelae. Future prospective studies should further explore factors associated with bacterial colonization and its prognostic value to prevent more chronic respiratory effects.

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CHAPTER 11

SUMMARY AND GENERAL DISCUSSION

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Esophageal atresia (EA) is a rare congenital anomaly of the esophagus that occurs in 2.43 per 10,000 live births¹. Surgical repair of the esophagus is indicated within the first days of life. Currently, surgical repair is performed by minimal invasive thoracoscopic techniques^{2,3}. Improved surgical interventions and peri-operative care have resulted in a shift of focus from mortality to long-term morbidity and quality-of-life⁴. Common long-term complications in EA patients include gastrointestinal and respiratory problems⁵. Esophageal atresia is often associated with tracheomalacia (TM) and may cause severe respiratory symptoms due to the collapse of the trachea⁶.

The studies in this thesis evaluate numerous challenges that are encountered in EA. The thoracoscopic repair of EA is described, which requires a certain level of expertise. Another challenge is the surgical procedure for long-gap esophageal atresia (LGEA), due to the wide gap between the proximal and distal esophageal pouch⁷. Follow-up in these patients was observed, with emphasis on gastrointestinal morbidity. Finally, this thesis focuses on respiratory challenges in EA patients, such as tracheomalacia (TM). A new treatment method for TM was evaluated and several potential causes for respiratory morbidity were explored.

In **chapter one** a general introduction was presented on the incidence of EA, the different EA types and several surgical procedures to restore the continuity in EA. The long-term morbidities after EA repair were discussed, focusing on gastrointestinal and respiratory symptoms and the diagnostic tools to evaluate those issues. The aims of the different studies were described, and an outline of this thesis was summarized.

PART I. THORACOSCOPIC REPAIR OF ESOPHAGEAL ATRESIA

Previously, EA repair was performed via thoracotomy. Nowadays, treatment with minimal invasive surgery for EA is becoming more widely implemented in various centers^{2,3,8,9}.

Chapter 2 focused on the pre-operative phase and the surgical technique of the thoracoscopic correction of EA type C (with distal fistula). Newborns with confirmed esophageal atresia are screened for associated anomalies and a multidisciplinary preoperative planning of the operation is performed. During induction, the otorhinolaryngologist performs a rigid bronchoscopy under spontaneous breathing, to evaluate the position of the trachea-esophageal fistula (TEF) and the severity of TM.

This article encompasses a detailed description of the surgical technique in EA type C in several steps. Furthermore, a cohort of newborns with EA type C that underwent surgical repair at the Wilhelmina Children's Hospital Utrecht, is described. Surgical outcome and complications are described in detail. This study shows that thoracoscopic repair of EA can be performed safely with a good outcome including the benefits of minimal invasive surgery. However, the thoracoscopic repair of EA remains challenging and should only be performed by experienced pediatric surgeons in centralized centers.

PART II. LONG-GAP ESOPHAGEAL ATRESIA

A rare type of esophageal atresia includes long-gap esophageal atresia (LGEA), in which there is usually a wider gap between the proximal and distal esophageal pouch. The International Network of Esophageal Atresia (INoEA) recently defined LGEA as 'any esophageal atresia without abdominal air', corresponding with Gross type A and B¹⁰. Several techniques have been advocated to overcome this wide gap, including esophageal replacement techniques (e.g. colon¹¹, jejunum¹² and stomach¹³) and several lengthening techniques^{14,15}. The native esophagus is considered as the best esophagus¹⁶.

Esophageal replacement (ER)

Before the introduction of lengthening techniques for LGEA, most patients underwent ER surgery. A survey among pediatric surgeons showed that gastric pull-up (GPU) was most preferred¹⁷. Literature on long-term outcome after ER is scarce^{18,19} and endoscopic follow-up after LGEA is lacking. In **chapter 3**, the findings of a cohort study including all patients with long-gap esophageal atresia ≥ 16 years old who had undergone GPU or jejunal interposition (JI) between 1985 and 2003 at the Wilhelmina Children's Hospital Utrecht or University Medical Center Groningen were described. Long-term clinical symptoms, anatomical and mucosal changes were evaluated.

Nine GPU patients and 11 JI patients were included, with a median age at follow-up of 21.5 years and 24.4 years, respectively. Reflux was reported in 67% of GPU patients vs 36% of JI patients. Dysphagia symptoms were reported in 64% of JI patients compared to 22% of GPU patients. Contrast studies showed dilatation of the jejunal graft in six patients (55%) and graft lengthening in four of these six patients. Endoscopy revealed columnar-lined epithelium esophagus in three GPU patients (33%) and intestinal metaplasia was histologically confirmed in 22%. No association was found between reflux symptoms and macroscopic abnormalities or intestinal metaplasia. GPU patients experienced severe feeding problems in 33% versus none in the JI group. The median BMI of JI patients was 20.9 kg/m² versus 19.5 kg/m² in GPU patients ($p=0.08$).

In conclusion, GPU patients may have an increased risk of intestinal metaplasia and therefore increased awareness and follow-up is suggested for LGEA patients after GPU.

The long-term morbidity in LGEA patients may influence the quality of life (QoL). **Chapter 4** evaluates the QoL after esophageal replacement with GPU of JI for LGEA. All patients between 1985-2007 that were treated with GPU or JI at the Wilhelmina Children's Hospital Utrecht or University Medical Center Groningen were included. (Health-related) QoL was assessed with validated questionnaires. Response rate was 75% for GPU patients and 57% in JI patients (mean age 15.7 years). Mean health-related QoL was comparable to healthy controls. However, young adults reported worse physical functioning ($p=0.02$) and a better social functioning ($p=0.01$) compared to peers. Morbidity was not significantly associated with differences in (Health-related) QoL.

Thoracoscopic traction technique

A relatively new procedure, developed at the Wilhelmina Children's Hospital, is the thoracoscopic traction technique (TTT)^{7,15}. In **chapter 5** we described the follow-up in LGEA patients treated with TTT, including gastrointestinal outcome, nutritional status and Health-Related Quality of Life (HRQoL). Between 2006 and 2017, eleven patients were successfully treated using TTT. Esophageal anastomosis was accomplished at a median age of 12 days with two or three thoracoscopic procedures. To prevent the stomach from migrating into the chest, a gastropexy was performed. Postoperatively, patients were admitted for a median of 18 days at the NICU with a median ventilation time of four days. Postoperative leakage occurred in 46%. Childhood outcome at a median age of 7 years showed gastroesophageal reflux complaints in 67% of the patients. Most patients had a decrease in weight-for-height score within the first year of life however, a catch-up growth was observed over time. At the end of follow-up (median age 7.0 years (range 3.3-13.4)) 80% of patients were within normal growth range, although below the population mean. HRQoL was comparable to healthy controls.

PART III. RESPIRATORY EFFECTS

Long-term respiratory problems are common in EA patients²⁰ and up to 90% of EA patients have concurrent TM⁶. The collapse of the trachea in TM may result in a wide spectrum of symptoms, ranging from a (chronic) barking cough to brief resolved unexplained events (BRUEs)²¹. In severe TM, surgical treatment may be warranted. Previously, an aortopexy was the treatment of choice, in which the aorta is lifted and fixed to the sternum and the pressure of the aorta on the trachea is reduced^{21,22}. A newer surgical procedure for TM is the posterior tracheopexy, in which the posterior

tracheal wall is fixed to the anterior spinal ligament, to prevent the tracheal wall from collapsing²³.

Chapter 6 describes a new approach for the treatment of concurrent TM in EA patients via posterior tracheopexy performed during the primary esophageal atresia repair: the primary posterior tracheopexy (PPT). In 2017, a total of nine consecutive patients with EA underwent rigid bronchoscopy under spontaneous breathing during induction of anesthesia. The severity of TM was estimated at three levels of the trachea (lower, middle and upper trachea) and scored by the otorhinolaryngologist. Patients were considered eligible for PPT when moderate or severe collapse of the posterior tracheal wall was observed. Of the nine consecutive EA patients, four showed moderate or severe collapse of the posterior tracheal wall. These patients were selected to undergo thoracoscopic posterior tracheopexy.

During the procedure for esophageal atresia repair, the tracheoesophageal fistula is first located and transected. Then, the proximal pouch is mobilized from the posterior tracheal wall. The posterior tracheopexy is performed by placing two or three non-absorbable sutures that pull the membranous posterior wall of the trachea to the anterior spinal ligament. Thereafter, the proximal and distal esophageal ends are anastomosed. Thoracoscopic posterior tracheopexy was successfully performed in all four patients, with a median time per suture of 6 minutes. A median time of follow-up of 6 months revealed that all patients showed further recovery without TM symptoms or BRUEs.

Chapter 7 evaluates the 1-year clinical respiratory outcome in EA patients after introduction of the PPT. A comparative cohort study was conducted, including all consecutive EA patients between 2014 and 2019 at the Wilhelmina Children's Hospital Utrecht. Two subgroups were distinguished: group 1 before the introduction of the PPT and group 2 after the introduction of PPT. A total of 64 patients were included in this study (28 patients in group 1; 36 patients in group 2). In group 2, PPT was performed in 14 patients (39%). Respiratory tract infections requiring antibiotics within the first year of life occurred significantly less in group 2 (61 vs. 25%, $p = 0.004$). BRUEs were seen less frequently in group 2 compared to group 1 (39 vs. 19%, $p = 0.09$). In conclusion, thoracoscopic PPT decreases the number of respiratory tract infections requiring antibiotics in EA patients. The clinical impact of reducing these severe respiratory tract infections combined with the minimal additional operating time and safety of PPT outweighs the risk of overtreatment.

To assess whether this decrease in number of respiratory tract infections requiring antibiotics after the introduction of PPT also led to a decrease in hospital costs, we

conducted a cost-analysis study in **chapter 8**. Patients in group 1 (no-PPT) were admitted for a mean of 72 days vs 68 days in group 2 (PPT) within the first year of life. For respiratory reasons, patients were admitted for 16 days in group 1 and seven days in group 2. The average total healthcare costs were comparable in both groups. However, costs for respiratory admissions decreased 30% after introduction of PPT. After exclusion of outliers, the decrease in respiratory morbidity associated costs was 90%. However, further research is warranted to confirm this observation.

The cause for respiratory morbidity in EA is not yet clearly understood and is considered to be multifactorial^{20,24}. Engesaeth et al.²⁵ suggested that EA may be related to primary ciliary dyskinesia (PCD). To study this feature, in **chapter 9** we evaluated the feasibility to culture respiratory epithelial cells of individuals with EA and to examine their ciliary function. Nasal brushings and bronchoalveolar lavage (BAL) fluid were collected from infants with EA (n=7 donors) that underwent a surgical procedure. Nasal brushings from a healthy control and a patient with PCD were included as reference samples. Nasal and bronchial airway epithelial stem cells were isolated respectively from nasal brushings and BAL. Thereafter, stem cells were differentiated in an air-liquid interface and converted to a 3D organoid model. Mucociliary differentiation of paired nasal and bronchial airway epithelial cultures were evaluated by immunofluorescence confocal imaging. High-speed video microscopy was used to compare cilia activity, i.e., ciliary beat frequency and wave pattern of the EA cultures to healthy and primary ciliary dyskinesia donor derived airway cultures.

Median age of donors was 6.4 months, five patients had EA type C and two type A. Almost all patients experienced respiratory symptoms. Airway epithelial stem cells were successfully differentiated from all nasal samples and in four bronchial samples. All samples displayed ciliated cells with a normal beat frequency. Furthermore, a normal wave pattern was observed in 3D organoids from all donors. This study demonstrated that culturing airway epithelial cells from upper and lower airway samples from individuals with EA is feasible and a normal ciliary activity was observed in both nasal and bronchial epithelial cells. In other words, there is no indication of primary ciliary dyskinesia in EA patients.

EA is most often accompanied by some degree of TM⁶, which negatively influences the airway clearance of secretions²⁶⁻³⁰. Subsequently, this may lead to lower airway bacterial colonization (LABC)³¹. In **chapter 10**, a 5-year cohort study was conducted including all EA patients that had undergone an intraoperative bronchoalveolar lavage (BAL) during various routine surgical interventions. In 56 patients, a total of 90 BAL samples were obtained. In 57% of the patients, at least one BAL-sample was positive for LABC.

Respiratory symptoms were reported in 21 patients at time of the BAL, of which 10 (48%) had LABC. *Haemophilus influenzae* (14%) and *Staphylococcus aureus* (16%) were most frequently found in the BAL-samples. The number of respiratory tract infections and the presence of a recurrent fistula were significantly associated with LABC ($p=0.008$ and $p=0.04$, respectively). This is the first study showing that patients with esophageal atresia have a high prevalence of bacterial colonization of the lower airways which may explain severe and recurrent respiratory complications in these patients.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Throughout the years, many obstacles in the treatment of EA have been overcome, leading to a very good survival rate of newborns born with this anomaly. Still, several challenges exist which can have an important impact on outcome of the patient. This thesis explores challenges associated with the complex treatment of LGEA. It introduces a new surgical technique for tracheomalacia and focuses on diagnosis, treatment, and future research on respiratory morbidity in EA patients.

Previously, thoracotomy was the gold standard for esophageal repair. Since the introduction of minimal invasive surgery (MIS)³², the thoracoscopic repair of esophageal atresia is being increasingly performed. A recent meta-analysis³³ compared thoracoscopic EA repair with thoracotomy and showed no significant difference in postoperative complications. Although surgical time showed to be significantly longer in thoracoscopic repair, time to extubation, time to introduction of oral feeding and duration of hospital stay were all significantly shorter. Furthermore, a main advantage is the excellent visualization of the thoracoscopic cavity³³. The most frequent complications after esophageal atresia repair include postoperative stenosis and leakage. In our study, a postoperative stenosis requiring dilatation occurred in 51% of the patients and postoperative leakage in 14%, which is in line with previous studies^{34–36}. Therefore, thoracoscopic repair of esophageal atresia can be performed safely with good outcome³⁷.

Previously, the treatment for long-gap esophageal atresia consisted of esophageal replacement surgery in a large number of patients. In **chapter 3** and **4** the long-term clinical and endoscopic outcome after gastric pull-up and jejunal interposition were reported. We found that the majority of GPU patients had reflux symptoms, which is in line with the study of Hannon et al¹⁸. The high prevalence of reflux symptoms in GPU patients may be explained by the altered anatomy³⁸. Furthermore, intestinal metaplasia was present in 22% of GPU patients. This is somewhat higher compared to previous

studies, where only 7% of patients with ER had Barrett's esophagus³⁹. However, in this study, almost all ER patients had undergone colon interposition³⁹. Endoscopic surveillance for Barrett's esophagus starting at the age of 20 years was recommended for all EA patients. We suggest a more extensive follow-up for patients with GPU. An endoscopic surveillance program is advised by the INoEA⁴⁰, every 5 years between the age of 18 and 28 years and every 3 years between 28 and 40 years. However, a recent study showed it to be safe to start with endoscopic screening at the age of 20 years with a surveillance interval of 10 years until the age of 40 years³⁹. The surveillance program is not only indicated for LGEA, but also for EA type C.

On the matter of dysphagia, this was present in the majority of JI patients but not in GPU patients. The majority of JI patients had a dilated JI graft and most of them reported dysphagia complaints, however no significant association was found. This finding is not in line with the outcomes presented in the study of Ring et al.¹⁹ In their study, mild dysphagia was reported in only 13% after JI for EA at a mean age of 25 years. If dysphagia symptoms persist over an extended period, patients may perceive these symptoms as normal and consequently may not report them as complaints when not specifically asked for. In our study gastroenterologist explicitly evaluated gastrointestinal symptoms including dysphagia, which might explain the higher dysphagia rate.

Postoperative dysphagia was present in the majority of JI patients. However, all patients reached a full oral intake with a normal nutritional status. This is in contrast to other studies, with only 33-57% of JI patients tolerating a full oral intake^{41,42}. This difference may be explained by the high complication rates in both studies.

A systematic review evaluating the (Health-Related) Quality of Life in LGEA patients showed no significant difference HRQoL outcome between LGEA and EA patients⁴³. This is similar to our study, in which the (HR)QoL is comparable to healthy people^{41,42}. Recently, a disease-specific questionnaire was developed and validated by Dellenmark-Blom et al.^{44,45} and may provide a better insight in disease-specific QoL in EA patients. Therefore, future studies should incorporate disease specific questionnaires when evaluating QoL in EA patients.

Feeding difficulties are common in esophageal atresia. Development of feeding and swallowing skills occurs within the first 2 years of life. Late introduction of oral feeding may impair the development of these skills^{46,47}. Previous studies showed severe feeding problems in LGEA^{48,49}. This may be caused by the delayed introduction of oral feeding due to a late anastomosis for LGEA via ER or delayed primary anastomosis (DPA)⁵⁰. Conversely, the thoracoscopic traction technique (TTT) for patients with LGEA shows

favorable results in childhood⁵¹. The early anastomosis (median 12 days) after TTT results in an early introduction of oral food (median 16 days postoperatively). Almost all patients reached an age-appropriate oral diet.

After TTT, patients showed a decrease in weight-for-height within the first year of life. This is in line with previous reports⁵¹⁻⁵³. However, almost all children reached a normal weight-for-height score at end of follow-up (median 7 years). The question is whether this weight-for-height remains within normal range during adolescence and adulthood. Unfortunately, to date there are no long-term studies available. Future follow-up studies should focus on the long-term outcome measures in adolescence and adulthood.

After EA repair, complications can occur. Postoperative stenosis is the most frequent complication, especially after LGEA. In this study, all LGEA patients needed multiple dilatations for recurrent anastomotic stenosis. The high stenosis rate in LGEA patients after TTT may be explained by the following risk factors: anastomotic tension, leakage and GER^{35,54-56}. EA patients have a greater risk of developing GER and this is especially common in LGEA patients. It has been reported in 66-88% of LGEA patients after delayed primary anastomosis (DPA)^{57,58}. This is in line with our findings, in which GER symptoms were reported in 67%.

This thesis aimed to evaluate different causes for the respiratory morbidity in esophageal atresia patients. Up to 90% of the EA patients have some form of TM⁶. In **chapter 6, 7 and 8** we evaluate the respiratory morbidity after introduction of primary posterior tracheopexy (PPT). PPT was safe and feasible and minimal additional operation time was required. Short-term outcome in EA patients with moderate to severe TM on preoperative rigid bronchoscopy showed no TM related symptoms after PPT. Our 1-year comparative follow-up study described a decrease in the number of respiratory tract infections after the introduction of PPT for moderate or severe TM. This is in line with the study of Shieh et al.⁵⁹ They also found a decrease in respiratory tract infections, but in their study this was not statistically significant. However, results are difficult to compare, since their study compared preoperative data to postoperative data within a group of 18 patients and follow-up duration was much shorter (5 months).

We hypothesized that the decrease in RTI we found in our patients would lead to a decrease in hospital admissions and costs. Chapter 8 described that the introduction of PPT resulted in a reduction of the number of patients that were admitted for respiratory symptoms resulting in a 30% reduction of hospital costs for respiratory problems. Zhou et al.⁶⁰ also reported a decreased risk of hospital admission for RTI after PPT within the first year, but this was not statistically significant. This could be due to a smaller number

of patients. Regarding cost analysis, there are no other studies available in literature. The introduction of PPT may lead to lower overall healthcare expenses in EA patients. Considering the substantial healthcare expenses for EA treatment it is important to further evaluate PPT as a potential factor for lowering these expenses.

Several studies have mentioned a functional abnormality of the tracheal epithelium in EA patients^{61–63}, however the ciliary activity has never been evaluated. In **chapter 9** upper and lower airway epithelial cells from EA patients were successfully differentiated and a normal ciliary activity was observed. This excludes the presence of primary ciliary dyskinesia in EA patients. However, animal studies have observed diminished mucociliary transport after intubation or tracheostomy. This may be due to a disturbance of mucociliary transport pathway after closing of the tracheoesophageal fistula. In addition, an inadequate cough due to the flaccidity of the posterior tracheal wall in TM might contribute to impaired clearance of respiratory secretions^{26–30}, leading to bacterial colonization of the lower airways⁶⁴. Despite the frequent respiratory problems in EA patients, bacterial colonization of the lower airways in EA patients had never been evaluated. In **chapter 10**, we describe positive BAL-cultures in almost 60% of the 56 EA patients. In a study on pediatric patients with isolated airway malacia, a positive BAL-culture was obtained in up to 80% of the patients⁶⁵. The difference between the percentage of positive BAL-cultures between the two studies can be explained by two factors. First, there is a difference in percentage of airway malacia in the included patients (100% vs 80%). Secondly, there is a difference in severity of malacia between patients included in the two studies: in the study of Boogaard et al.⁶⁵ only patients with a tracheal collapse of >50% were defined as having tracheomalacia.⁶² In our study, the severity of tracheomalacia varied widely (mild to severe).

CONCLUSION

Esophageal atresia poses challenges in its treatment and follow-up. Long-term follow-up after GPU and JI for LGEA reveals long-term clinical symptoms such as dysphagia and reflux, accompanied by macroscopic and microscopic abnormalities. Preserving the native esophagus, by means of the TTT however, has demonstrated good results during childhood follow-up, potentially preventing feeding problems later in life. This minimally invasive approach proves to be a promising alternative for managing LGEA, significantly improving long-term outcomes. However, GER and anastomotic stenosis remain frequent complications.

Another frequent problem is posed by respiratory morbidity. This may have various causes, such as tracheomalacia. TM occurs in the majority of EA patients. When severe, a primary posterior tracheopexy is a safe and feasible treatment. PPT significantly decreases respiratory tract infections and other respiratory symptoms within the first year of life. Subsequently, this may have a positive effect on a decrease in hospital admissions and healthcare costs. Respiratory tract infections are significantly associated with lower airway bacterial colonization in EA patients. Early treatment with antibiotics for respiratory tract infections in EA patients may be justified.

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APPENDICES

**NEDERLANDSE SAMENVATTING
LIST OF PUBLICATIONS
CURRICULUM VITAE
DANKWOORD**

NEDERLANDSE SAMENVATTING

Oesofagusatresie is een zeldzame aangeboren onderbreking van de slokdarm die voorkomt bij 2,43 op de 10.000 levendgeborenen. Chirurgisch herstel van de slokdarm is noodzakelijk binnen enkele dagen na de geboorte. In gespecialiseerde centra wordt de oesofagusatresie operatie meestal uitgevoerd middels minimaal invasieve thoroscopische technieken (kijkoperatie). Door verbeteringen in chirurgische ingrepen en perioperatieve zorg is de focus verschoven van mortaliteit naar morbiditeit op de lange termijn en de kwaliteit van leven. Veelvoorkomende lange termijn complicaties bij oesofagusatresie patiënten zijn gastro-intestinale en respiratoire problemen. Oesofagusatresie gaat vaak samen met een slapte van de luchtpijp (tracheomalacie), wat (ernstige) ademhalings symptomen kan veroorzaken door het samenvallen van de luchtpijp.

De studies in dit proefschrift onderzoeken verschillende uitdagingen die zich voordoen bij de behandeling van oesofagusatresie. De thoroscopische operatietechniek voor oesofagusatresie wordt beschreven, waarbij aanzienlijke expertise in het behandelteam vereist is. Een andere uitdaging is de chirurgische procedure voor het subtype oesofagusatresie over een lang traject (type A en B, long-gap oesofagusatresie), vanwege het grote defect tussen de proximale en distale slokdarm. De follow-up van deze patiënten wordt beschreven, met de nadruk op gastro-intestinale morbiditeit en kwaliteit van leven. Tot slot richt dit proefschrift zich op respiratoire problemen bij oesofagusatresie patiënten, zoals tracheomalacie. Een nieuwe behandelmethode voor tracheomalacie wordt geëvalueerd en verschillende mogelijke oorzaken van respiratoire morbiditeit worden onderzocht.

Hoofdstuk 1 geeft een algemene introductie van oesofagusatresie en beschrijft de incidentie, de verschillende typen oesofagusatresie en de diverse chirurgische ingrepen om het defect bij oesofagusatresie te herstellen. De lange termijn morbiditeit na oesofagusatresie herstel wordt besproken, met de nadruk op gastro-intestinale en respiratoire symptomen.

DEEL I. THORACOSCOPISCHE REPARATIE VAN OESOFAGUS-ATRESIE

Eerder werd een oesofagusatresie operatie uitgevoerd middels een thoracotomie. Tegenwoordig wordt de behandeling van een oesofagusatresie in steeds meer centra uitgevoerd middels minimaal invasieve chirurgie.

Hoofdstuk 2 gaat in op de preoperatieve fase en de chirurgische techniek van de thoroscopische correctie van oesofagusatresie type C (met distale fistel). Pasgeborenen met bewezen oesofagusatresie worden geselecteerd op geassocieerde aangeboren afwijkingen. Preoperatief wordt een multidisciplinair overleg gehouden. Tijdens de inleiding van de operatie voert de KNO-arts een starre bronchoscope uit tijdens spontane ademhaling, om de locatie van de tracheo-oesofageale fistel en de ernst van tracheomalacie te beoordelen. Deze studie beschrijft stapsgewijs de chirurgische techniek bij oesofagusatresie type C. Daarnaast wordt een cohort van pasgeborenen met oesofagusatresie type C in het Wilhelmina Kinderziekenhuis Utrecht beschreven, met aandacht voor de chirurgische uitkomst en complicaties. Deze studie toont aan dat de thoroscopische correctie van oesofagusatresie veilig uitgevoerd kan worden met goede resultaten, inclusief de voordelen van minimaal invasieve chirurgie. Desondanks blijft de thoroscopische correctie van oesofagusatresie uitdagend en zou deze uitsluitend moeten worden uitgevoerd door ervaren kinderchirurgen in gespecialiseerde centra.

DEEL II. LONG-GAP OESOFAGUSATRESIE

Een zeldzaam type oesofagusatresie is long-gap oesofagusatresie, waarbij er een groter defect is tussen het proximale en distale deel van de slokdarm. Het International Network of Esophageal Atresia (INoEA) heeft onlangs long-gap oesofagusatresie gedefinieerd als 'elke oesofagusatresie zonder abdominaal lucht', overeenkomend met type A en B volgens de Gross classificatie. Verschillende technieken zijn voorgesteld om dit grotere defect te overbruggen, waaronder slokdarm vervangende technieken (o.a. middels colon, jejunum of maag) en verschillende slokdarm verlengende technieken. Behoud van de eigen slokdarm wordt beschouwd als de beste optie in vergelijking met slokdarm vervangende operaties.

Slokdarmvervanging

Voor de introductie van slokdarm verlengende technieken voor long-gap oesofagusatresie ondergingen de meeste patiënten een slokdarm vervanging. Een enquête onder kinderchirurgen toonde aan dat de gastric pull-up (GPU, vervanging van de slokdarm door maag) de meest gebruikte methode was. Literatuur over langetermijnresultaten na slokdarm vervanging is schaars en endoscopische follow-up na herstel van long-gap oesofagusatresie ontbreekt.

In **hoofdstuk 3** worden de bevindingen van een cohortstudie beschreven van alle patiënten met long-gap oesofagusatresie van 15 jaar en ouder die tussen 1985 en

2003 een gastric pull-up of jejunuminterpositie (JI, vervanging van de slokdarm door dunne darm) hebben ondergaan in het Wilhelmina Kinderziekenhuis Utrecht of Universitair Medisch Centrum Groningen. Langetermijn uitkomsten werden bekeken, waaronder anatomische en slijmvlies veranderingen. Negen GPU-patiënten en elf JI-patiënten werden geïnccludeerd in de studie, met een mediane leeftijd bij follow-up van respectievelijk 21,5 jaar en 24,4 jaar. Reflux werd gerapporteerd bij 67% van de GPU-patiënten vergeleken met 36% van de JI-patiënten. Dysfagie symptomen kwamen bij 64% van de JI-patiënten voor vergeleken met 22% van de GPU-patiënten. Contraststudies toonden dilatatie van het jejunumtransplantaat bij zes patiënten (55%) en lengtetoeename van het transplantaat in vier van deze zes patiënten. Endoscopie liet een slokdarm met epitheel beklede cellen zien bij drie GPU-patiënten (33%) en intestinale metaplasie werd histologisch bevestigd bij twee patiënten (22%). Er werd geen verband gevonden tussen refluxsymptomen en macroscopische afwijkingen of intestinale metaplasie. Ernstige voedingsproblemen kwamen voor bij 33% van de GPU-patiënten, vergeleken met geen voedingsproblemen in de JI-groep. De mediane BMI van JI-patiënten was 20,9 kg/m² vergeleken met 19,5 kg/m² bij GPU-patiënten ($p = 0,08$). Concluderend hebben GPU-patiënten mogelijk een verhoogd risico op intestinale metaplasie van de slokdarm, wat aandacht verdient in de follow-up voor long-gap oesofagusatresie patiënten na een gastric pull-up.

De lange termijn morbiditeit bij long-gap oesofagusatresie patiënten kan de kwaliteit van leven beïnvloeden. **Hoofdstuk 4** evalueert de kwaliteit van leven na slokdarmvervanging met gastric pull-up of jejunuminterpositie voor long-gap oesofagusatresie. Alle patiënten tussen 1985-2007 die behandeld waren met GPU of JI in het Wilhelmina Kinderziekenhuis Utrecht of Universitair Medisch Centrum Groningen werden geïnccludeerd in de studie. Kwaliteit van leven werd beoordeeld met verschillende gevalideerde vragenlijsten. De respons was 75% bij GPU-patiënten en 57% bij JI-patiënten (gemiddelde leeftijd 15,7 jaar). De gemiddelde gezondheid gerelateerde kwaliteit van leven was vergelijkbaar met de gezonde populatie. Echter, jongvolwassenen met long-gap oesofagusatresie scoorden slechter op het domein lichamelijke functies ($p = 0,02$) en beter op het domein sociale functies ($p = 0,01$) in vergelijking met gezonde leeftijdsgenoten. Morbiditeit was niet significant geassocieerd met verschillen in (gezondheid gerelateerde) kwaliteit van leven.

Thoracoscopische tractietechniek

De thoracoscopische tractietechniek (TTT) is een relatief nieuwe procedure voor long-gap oesofagusatresie, ontwikkeld in het Wilhelmina Kinderziekenhuis. **Hoofdstuk 5** beschrijft de follow-up van long-gap oesofagusatresie patiënten die behandeld werden met TTT, inclusief gastro-intestinale uitkomst, voedingstoestand en kwaliteit van leven. Tussen 2006 en 2017 werden elf patiënten succesvol behandeld met TTT. Na twee of drie

thoroscopische procedures voor het oprekken van de proximale en distale oesofagus, werd op een mediane leeftijd van 12 dagen de anastomose aangelegd. Om te voorkomen dat de maag naar de borstholte migreert, werd een gastropexie (vasthechten van de maag aan de buikwand) uitgevoerd. Postoperatief verbleven patiënten gemiddeld 18 dagen op de NICU met een mediane beademingstijd van vier dagen. Postoperatieve lekkage trad op bij 46%. De uitkomst op een mediane leeftijd van 7 jaar toonde gastro-oesofageale refluxklachten bij 67% van de patiënten. In het eerste levensjaar vertoonden de meeste patiënten een afname van hun gewicht-voor-lengte-score, maar tijdens de vervolperiode werd een inhaalgroei waargenomen. Aan het einde van de follow-up (mediaan 7,0 jaar, bereik 3,3-13,4 jaar) bevond 80% van de patiënten zich binnen het normale groeibereik, zij het onder het populatiegemiddelde. De gezondheid gerelateerde kwaliteit van leven was vergelijkbaar met gezonde controles.

DEEL III. RESPIRATOIRE EFFECTEN

Respiratoire problemen op de lange termijn komen vaak voor bij oesofagusatresie patiënten en tot 90% van de oesofagusatresie patiënten heeft ook tracheomalacie. Het samenvallen van de luchtpijp bij tracheomalacie kan leiden tot een breed scala aan symptomen, variërend van een (chronische) blaffende hoest tot kortdurende onverklaarbare gebeurtenissen (brief resolved unexplained events; BRUE), waarbij een kind een afwijkende ademhaling heeft of blauw aanloopt. Bij ernstige tracheomalacie kan een chirurgische behandeling nodig zijn. Vroeger was aortopexie de behandeling van keuze, waarbij de aorta wordt opgetild en aan het borstbeen wordt bevestigd, wat de druk van de aorta op de luchtpijp vermindert. Een nieuwere chirurgische procedure voor tracheomalacie is de posterieure tracheopexie, waarbij de achterste luchtpijpwand wordt bevestigd aan het voorste wervelligament om te voorkomen dat de luchtpijp samenvalt.

Hoofdstuk 6 beschrijft een nieuwe benadering voor de behandeling van tracheomalacie bij oesofagusatresie patiënten, waarbij een tracheopexie wordt verricht tijdens de primaire slokdarmatresie operatie: de primaire posterieure tracheopexie (PPT). In 2017 kregen in totaal negen patiënten met oesofagusatresie een rigide bronchoscopie met spontane ademhaling tijdens de inleiding van de anesthesie. De ernst van tracheomalacie werd bekeken op drie niveaus van de luchtpijp (onderste, middelste en bovenste luchtpijp) en beoordeeld door de KNO-arts. Patiënten kwamen in aanmerking voor PPT bij matig of ernstig dichtklappen van de achterwand van de trachea. Van de negen oesofagusatresie patiënten vertoonden vier patiënten een matig of ernstig samenvallen van de trachea. Deze patiënten werden geselecteerd om een thoroscopische posterieure tracheopexie te ondergaan. Tijdens de procedure voor oesofagusatresie werd eerst de tracheo-

oesofageale fistel gelokaliseerd, afgebonden en doorgenomen. Vervolgens werd het proximale deel van de oesofagus losgemaakt van de achterste tracheawand. De tracheopexie werd uitgevoerd door twee of drie niet-oplosbare hechtingen te plaatsen waarbij de achterwand van de trachea aan het voorste wervelligament wordt bevestigd. Daarna werden de proximale en distale slokdarmuiteinden aan elkaar gemaakt. De thoracoscopische posterieure tracheopexie werd succesvol uitgevoerd bij alle vier de patiënten, met een mediane tijdsduur van 6 minuten per hechting. Een mediane follow-up van zes maanden toonde aan dat alle patiënten verdere verbetering vertoonden zonder tracheomalacie symptomen of BRUE's.

Hoofdstuk 7 beschrijft de respiratoire uitkomst na 1 jaar bij oesofagusatresie patiënten na introductie van de PPT. Een vergelijkende cohortstudie wordt beschreven met alle oesofagusatresie patiënten tussen 2014 en 2019 in het Wilhelmina Kinderziekenhuis Utrecht. Twee subgroepen werden onderscheiden: groep 1 vóór de introductie van de PPT en groep 2 na de introductie van PPT. In totaal werden 64 patiënten geïnccludeerd in deze studie (28 patiënten in groep 1; 36 patiënten in groep 2). In groep 2 werd PPT uitgevoerd bij 14 patiënten (39%). Luchtweginfecties die antibiotica vereisten binnen het eerste levensjaar kwamen significant minder voor in groep 2 (61% tegenover 25%, $p = 0,004$). Ook BRUE's werden minder vaak gezien in groep 2 in vergelijking met groep 1 (39% tegenover 19%, $p = 0,09$). Concluderend vermindert de thoracoscopische PPT het aantal luchtweginfecties die antibiotica vereisen bij oesofagusatresie patiënten. Het klinische effect van het verminderen van deze ernstige luchtweginfecties, in combinatie met de minimale extra operatietijd en de veiligheid van de PPT, wegen op tegen het risico van eventuele overbehandeling.

Om te beoordelen of deze afname van het aantal luchtweginfecties na de introductie van PPT ook leidde tot een afname van de ziekenhuiskosten, werd er een kosteneffectiviteitsstudie uitgevoerd in **hoofdstuk 8**. In het eerste levensjaar werden patiënten in groep 1 (geen PPT) gemiddeld 72 dagen opgenomen, vergeleken met gemiddeld 68 dagen in groep 2 (PPT). Patiënten in groep 1 werden gemiddeld 16 dagen opgenomen vanwege luchtwegklachten, vergeleken met zeven dagen in groep 2. De gemiddelde totale kosten voor gezondheidszorg in het eerste jaar waren vergelijkbaar in beide groepen. De kosten voor opnames vanwege luchtweg problemen daalden echter met 30% na de introductie van PPT. Na de exclusie van uitschieters was de afname in kosten voor opname in verband met luchtweg morbiditeit 90%. Verder onderzoek is echter nodig om deze waarneming te bevestigen.

De oorzaak van respiratoire morbiditeit bij oesofagusatresie is nog niet volledig begrepen en wordt waarschijnlijk door meerdere factoren beïnvloed. Eerder is gesuggereerd dat

oesofagusatresie gerelateerd is aan primaire ciliaire dyskinesie (PCD, afwijkende trilhaar functie van het luchtwegepitheel). In **hoofdstuk 9** wordt het kweken van luchtweg-epitheelcellen van patiënten met oesofagusatresie onderzocht en wordt de ciliaire functie bekeken. Monsters van neusslijmvlies en bronchoalveolaire lavage (BAL) vloeistof werden verzameld bij zuigelingen met oesofagusatresie (n = 7) die een chirurgische ingreep ondergingen. Monsters van neusslijmvlies van een gezonde controle patiënt en van een patiënt met PCD werden gebruikt als referentiesamples. Epitheelstamcellen van de neus en bronchiën werden respectievelijk geïsoleerd uit het materiaal van de neusborstels en de BAL. Vervolgens werden stamcellen gedifferentieerd in een lucht-vloeistofinterface en omgezet in een 3D-organoïde model. Mucociliaire differentiatie van gepaarde neus- en bronchiale luchtwegkweken werd geëvalueerd door immunofluorescentie confocale beeldvorming. Hoge-snelheids videomicroscopie werd gebruikt om de ciliaire activiteit te vergelijken; de slagfrequentie en slagbeweging van de cilia in de kweken van de oesofagusatresie patiënten werden vergeleken met de kweken van de gezonde controle patiënt en de patiënt met PCD. De mediane leeftijd van de patiënten was 6,4 maanden, vijf patiënten hadden oesofagusatresie type C en twee type A. Bijna alle patiënten hadden respiratoire symptomen. Luchtwegslijmvliesepitheelcellen werden met succes gedifferentieerd uit alle neusmonsters en in vier BAL monsters. Alle monsters lieten cellen zien met cilia met een normale slagfrequentie. Daarnaast werd een normale slagbeweging gezien in 3D-organoïden van alle patiënten. Deze studie toonde aan dat het kweken van luchtwegepitheelcellen uit bovenste en onderste luchtwegmonsters van patiënten met oesofagusatresie haalbaar is en een normale ciliaire activiteit werd waargenomen in zowel neus- als bronchiaal epitheel.

Oesofagusatresie komt vaak samen voor met tracheomalacie, wat kan bijdragen aan een verminderde klaring van het slijm in de luchtwegen. Dit kan vervolgens leiden tot bacteriële kolonisatie van de onderste luchtwegen (LABC). In **hoofdstuk 10** wordt een vijfjarige cohortstudie beschreven waarin alle oesofagusatresie patiënten zijn geïncludeerd die tijdens routinematige chirurgische ingrepen een peroperatieve bronchoalveolaire lavage (BAL) hebben ondergaan. Bij 56 patiënten werden in totaal 90 BAL-monsters verkregen. Bij 57% van de patiënten was minstens één BAL-monster positief voor LABC. Respiratoire symptomen werden beschreven bij 21 patiënten ten tijde van de BAL, waarvan 10 (48%) LABC hadden. *Haemophilus influenzae* (14%) en *Staphylococcus aureus* (16%) werden het vaakst aangetroffen in de BAL-monsters. Het aantal luchtweginfecties en de aanwezigheid van een recidiverende tracheo-oesofageale fistel waren significant geassocieerd met LABC ($p=0,008$ en $p=0,04$, respectievelijk). Dit is de eerste studie die aantoont dat oesofagusatresie patiënten een hoge prevalentie van bacteriële kolonisatie in de lagere luchtwegen hebben, wat ernstige en terugkerende respiratoire klachten bij deze patiënten kan verklaren.

LIST OF PUBLICATIONS

van Tuyl van Serooskerken ES, Gallo G, Weusten BL, Westerhof J, Brosens LA, Zwaveling S, Ruiterkamp J, Hulscher JB, Arets HG, Bittermann AJ, van der Zee DC, Tytgat SH, Lindeboom MY. Graft dilatation and Barrett's esophagus in adults after gastric pull-up and jejunal interposition for long-gap esophageal atresia. *World Journal of Gastrointestinal Endoscopy*. 2023 Sep 16;15(9):553-563

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CURRICULUM VITAE

Sofie van Tuyll van Serooskerken werd geboren op 26 januari 1992 te Amsterdam. Sofie is de oudste dochter van Chris en Renée. Ze is opgegroeid in Buren (Gelderland) en ging naar het gymnasium op de middelbare school in Culemborg, het Koningin Wilhelmina Collega (KWC). Na haar middelbare school ging ze in Utrecht studeren en begon zij aan een studie Rechtsgeleerdheid aan de Universiteit van Utrecht. Na een tweede uitloting voor de studie Geneeskunde, ging Sofie naar Instituut Blankestijn, waar zij cum laude slaagde voor haar Atheneum diploma. In 2012 begon ze aan haar studie Geneeskunde.



Tijdens haar studie was Sofie lid van de studentenvereniging U.V.S.V./N.V.V.S.U. Daarnaast was Sofie tijdens haar studententijd actief als vrijwilliger bij Kids Camp Kenya. Zij organiseerde tweemaal (2013 en 2015) een spelletjes kamp voor kinderen uit de grootste sloppenwijk van Kenia. In 2013 richtte zij een stichting op, stichting Teach to Reach, die ambitieuze vrouwen uit de sloppenwijk Kibera (Nairobi, Kenia) financieel ondersteunt in het volgen van een studie.

Tijdens haar coschappen had Sofie ook grote affiniteit met het buitenland. Het coschap Oogheelkunde deed zij in een oogziekenhuis in Pokhara, Nepal. Een keuzecoschap Tropengeneeskunde heeft zij gedaan in Nkhoma, Malawi.

Tijdens het 5e jaar van haar studie deed zij een onderzoeksstage bij de kinderchirurgie, waarna zij dit onderzoek tijdens haar wetenschappelijke stage in haar 6e jaar vervolgde. Na haar studie mondde dit onderzoek uit in een promotietraject onder leiding van Maud Lindeboom en Stefaan Tytgat.

In 2020 begon zij als arts-assistent chirurgie in het Spaarne Gasthuis Haarlem/Hoofddorp. In 2021 werd zij aangenomen voor een opleidingsplaats bij de Huisartsgeneeskunde aan de Vu Medisch Centrum. Haar eerste huisartsjaar ronde zij met veel plezier af in Huisartsencentrum Bloemendaal. Momenteel zit zij in haar laatste jaar van de huisartsenopleiding in Huisartsenpraktijk Westzijderveld in Koog aan de Zaan.

Sofie woont samen met Reinier in Amsterdam.

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