Long-term Surgical and Functional Outcome of Acquired Pediatric Laryngotracheal Stenosis

Bas Pullens

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This research was financially supported by Trustfonds Rotterdam.
Publication of this thesis was financially supported by: Olympus Nederland B.V., Stöpler B.V., Advanced Bionics Benelux B.V., MC Europe medical products, Dos Medical B.V., Entercare B.V., Mediq Tefa, Atos Medical, Carl Zeiss B.V., Smith Medical Nederland B.V., Meda Pharma B.V., ALK-Abello B.V., Cochlear Benelux N.V. and Medicidesk Rabobank Rotterdam.

ISBN: 978-94-6295-612-4

Printing and lay-out: ProefschriftMaken // www.proefschriftmaken.nl

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Lange-termijn chirurgische en functionele uitkomst van verworven pediatrische laryngotracheale stenose

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 22 maart 2017 om 15:30 uur

door

Bas Pullens
geboren te Elburg

Promotiecommissie

Promotor:	Prof.dr. R.J. Baatenburg de Jong
Overige leden:	Prof.dr. I.M.J. Mathijssen Prof.dr. J.C. de Jongste Prof.dr. H.A.M. Marres
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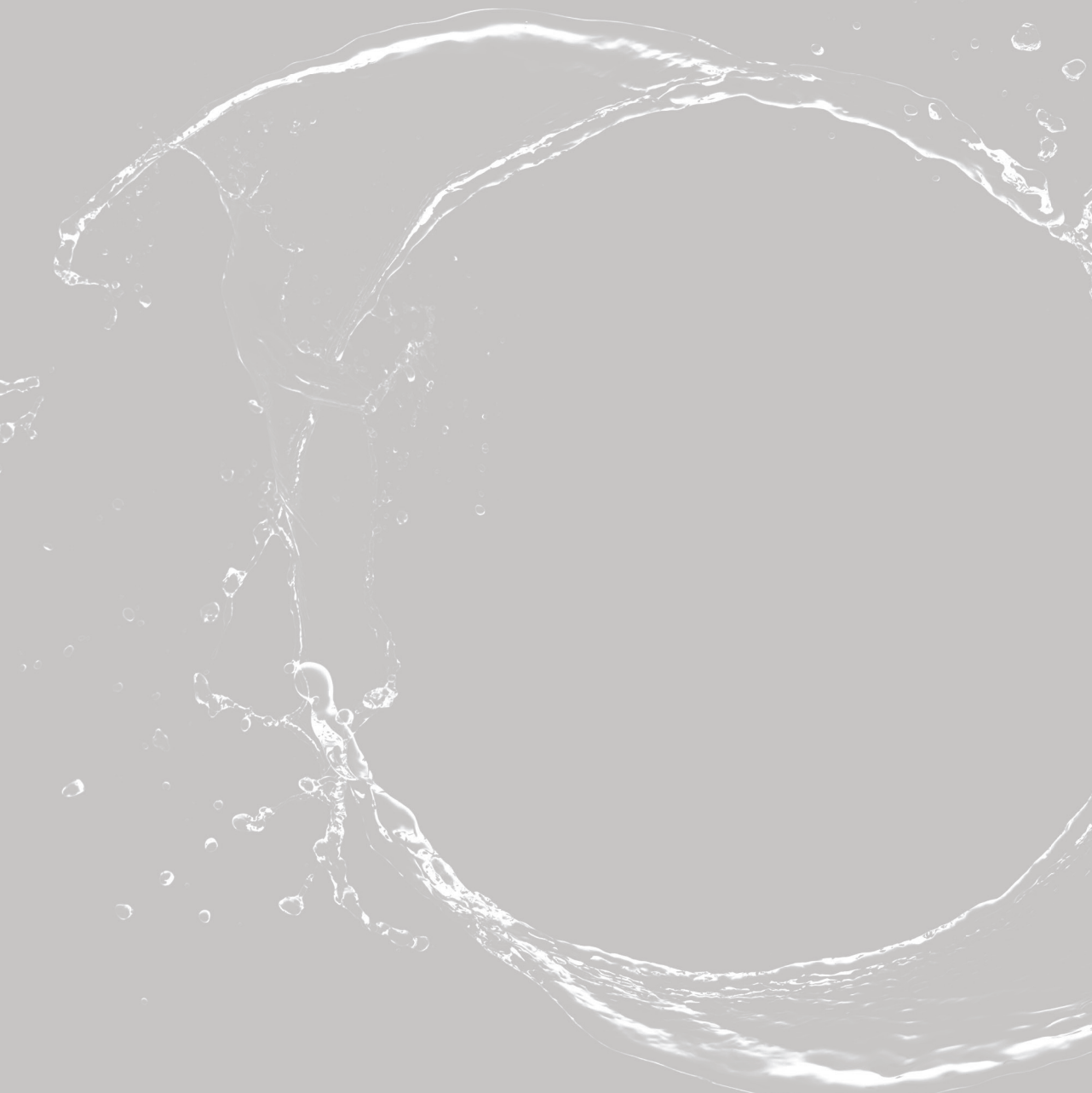

chapter 1

General Introduction

Introduction

Acquired pediatric laryngotracheal stenosis (LTS) is a rare but life-threatening disease which usually occurs after a prolonged period of intubation. The presence of the endotracheal tube in the laryngotracheal area can cause a chain of events that can culminate into an LTS. Despite the innovations and advances that have been made over the years, the management of pediatric LTS still proves to be very challenging for pediatric otorhinolaryngologists.

Risk factors for acquired pediatric laryngotracheal stenosis

Although every episode of intubation has the potential to cause laryngotracheal damage and stenosis, certain patients are more at risk than others. A number of significant risk factors have been identified for developing acquired LTS: duration of intubation, multiple intubations and infection. Next to these, it is generally believed that age, low gestational age, low birth weight, gender, pre-existing narrow larynx, traumatic intubation, shock and gastro-esophageal reflux also contribute to the formation of LTS although robust evidence in literature is lacking.[1-6]

Given these risk factors it is not surprising that LTS is most common in the preterm neonatal population where long-term intubation in very low birthweight infants is most common. With the introduction of prolonged intubation and ventilation in children in the 60s came the rise in acquired LTS which had an estimated incidence of up to 8% in those early years. Advances in medical management of neonatal pulmonary disease and non-invasive forms of ventilation have caused a significant drop in the incidence of LTS which is now estimated to be under 2%.[7]

Pathophysiology

In many cases, long-term ventilation necessitates prolonged endotracheal intubation. The endotracheal tube has a point of maximum pressure in the posterior glottis at the medial aspect of the arytenoid cartilages, at the superior part of the cricoid lamina and in the cricoid itself where the complete cartilaginous ring causes the mucosa to be more susceptible to damage by the pressure of the ventilation tube.[8]

When the pressure of the endotracheal tube exceeds the capillary mucosal perfusion pressure, it can cause erosion of the mucosa which leads to an inflammatory reaction and can cause ischemic necrosis. This causes erosions and ulceration with denuded cartilage which is in turn susceptible to infection, causing perichondritis. At this stage, the natural healing process after the tube has been removed includes the formation of granulation tissue and the formation of cicatricial scar tissue in the areas involved. Studies that assessed the larynx at time of extubation report incidences of laryngeal injury of up to 40%.[3, 6]

The reactive edema and granulation tissue can cause extubation failure with typical signs of acute or subacute upper airway obstruction: inspiratory stridor, chest retractions and dyspnea. Medical management at this stage consists of administration of corticosteroids and/or adrenaline as an inhalation agent to treat the edema, combined with antibiotics for infection and proton-pump inhibitors (PPI's) for acid gastro-esophageal reflux.[9] Granulations can be removed by endoscopic microlaryngeal surgery and balloon dilatation can be done to widen the subglottic space, or treat the edema, if present. The anterior cricoid ring can be split endoscopically or through an open approach in order to enlarge the subglottis area. Often, a renewed period of intubation is necessary before a new extubation attempt is done. [10-12]

Organization of the granulations and scarring of the denuded cartilage with perichondritis can give rise to formation of extensive scar tissue. The scarring typically occurs at the subglottic site and/or in the posterior glottic area where the cicatricial tissue can cause an impairment in vocal cord abduction on inspiration. The amount of respiratory distress caused by the LTS depends on the residual airway diameter, the ability for the vocal cords to abduct on inspiration as well as associated factors such as laryngomalacia, tracheomalacia or pulmonary disease.

A number of grading systems have been developed for LTS but the most internationally used grading system is the one proposed by Myer-Cotton where the percentage of stenotic subglottic airway is divided in 4 grades (figure 1). Bogdasarian has proposed a classification for the extent of posterior glottic stenosis (figure 2).[13-16]

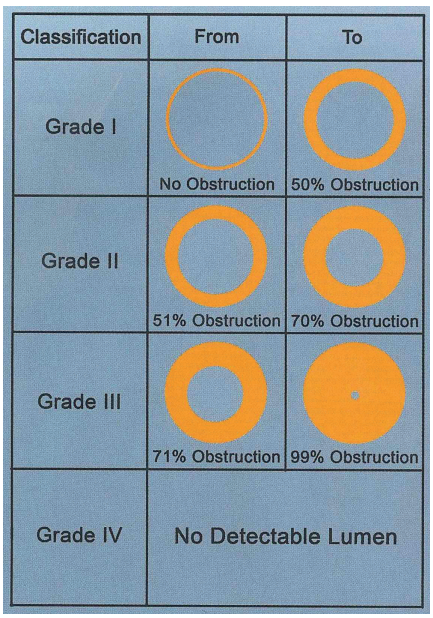

Figure 1: Myer-Cotton grading system for subglottic stenosis.

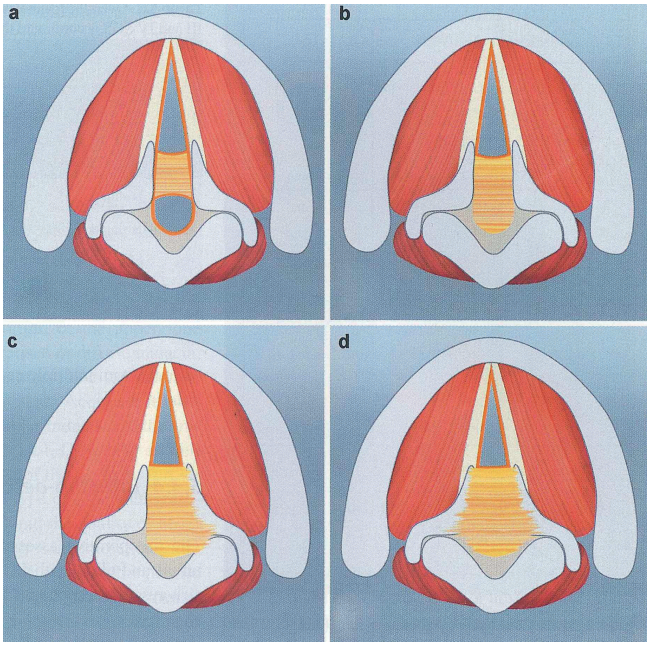

Figure 2: Bogdasarian classification of posterior glottic stenosis. a: Interarytenoid adhesion, b: Interarytenoid and posterior commissure scarring, c: Scarring of posterior commissure with unilateral cricoarytenoid joint fixation, d: Scarring of posterior commissure with bilateral cricoarytenoid joint fixation.

When the airway stenosis is severe, a tracheostomy is necessary for the child's survival and ventilation.

Pediatric tracheostomy

Caring for a child with a tracheostomy has a tremendous impact on family life and is a large burden for the child's caregivers. Pediatric tracheostomy is known to be associated with a high incidence of complications such as accidental decannulations, granuloma formation and tube occlusions, both in the postoperative phase and at long-term follow-up with frequent re-admissions to the hospital. In fact, most complications occur at home, where the caregivers are supposed to provide the medical care that is required at that moment. Improvement in standardized care and training of caregivers at home has caused mortality to decrease significantly, but tracheostomy-related deaths still exists and can occur at home with a plugged cannula or failed tube change.[17-19] A small number of studies describe quality of life and caregiver burden in pediatric tracheostomy; a significantly higher burden of the caregivers was found with negative effect on mental health, sleeping pattern, relationships and family life.[20, 21] Next to the precautions and medical procedures caregivers are supposed to give at home, changing of the tracheostomy tube in particular causes concern and distress among parents, the cannula being the one device that keeps their child alive.

Treatment

Treatment for LTS aims to resolve the airway stenosis and, if present, relieve the child of his or her tracheostomy whilst maintaining adequate vocal and swallow functions. Open airway surgery in adults was first described in the 1950s by Rethi et al. who augmented the airway without removing the scar tissue by splitting the anterior and posterior cricoid ring followed by a period of stenting.[22] This operation formed the basis for the major airway reconstructions in the pediatric population. After the rise in incidence of pediatric LTS in the 60s, a number of modifications of Rethi's original laryngotracheoplasty (LTP) was introduced over the years and reasonable results were reported in the pediatric population with decannulation rates of up to 90% after long-term stenting, usually lasting several months.[23, 24]

The real game changer was introduced in the 1970s, with the introduction of the laryngotracheal reconstruction (LTR). In this open surgical technique, the stenotic airway is incised and widened by using autologous cartilage as a graft without actually removing the scar tissue. The autologous cartilage grafts are mostly harvested from costal cartilage and placed between the split halves of the cricoid. Augmentation of the subglottic area was first described with an anterior graft.[25, 26] The addition of a posterior cartilage graft opened up possibilities to treat more severe cases of LTS.[27-29] Until then, all these patients were operated with a prolonged period of post-operative stenting, later named the double stage laryngotracheal reconstruction (ds-LTR). The introduction of the single stage laryngotracheal reconstruction (ss-LTR) with a relatively short period of intubation, ranging from days to two weeks, instead of long-term stenting provided surgeons a technique to reconstruct the airway and decannulate the patient in one operative session.[30, 31]

Despite these advances, the LTR approach still had disappointing results for severe cases of higher grade (severe Myer-Cotton grade III and IV) LTS. As a novel treatment for severe pediatric LTS, the cricotracheal resection (CTR), already an established procedure for severe LTS in adults at that time, was described for the pediatric population by Ranne et al.[32] In the CTR, the lateral and anterior parts of the cricoid ring including the stenotic airway segment are removed and an end-to-end anastomosis is made between the thyroid and normal trachea. Remarkably, the authors did not spark a lot of enthusiasm until the first reasonably large case series of CTR for pediatric LTS was published by Monnier et al.[33] Over the years, a number of refinements have been made for this procedure, including an operation where the CTR is combined with a posterior costal cartilage graft (CCG) with or without stenting to address the posterior glottic stenosis.

In the last two decades, less invasive endoscopic surgical techniques have gained in popularity with the increased use of laser surgery and dilatation balloons. These techniques can be used as single or repeat surgical procedures to treat LTS, or as a post-operative procedure after open airway surgery. [12, 34, 35]

Reported outcome of surgical treatment

Airway outcome

Most studies on outcome of open surgery for LTS focus on the airway aspect of the disease. The most commonly used objective outcome measure is the decannulation rate; the number of patients who can successfully be decannulated after surgery, given in percentage. Most studies report operation specific decannulation rate (OSDR) and overall decannulation rate (ODR). The first means the number of children decannulated after a single operation, the latter the number of patients decannulated overall, including revision operations. When reviewing published series on surgical outcome of at least 40 patients, overall decannulation rates of 64-98% are reported (table 1). The follow-up time, when reported, usually is more than two years mean, but has a large range in most studies.

Strangely, there seems to be no consensus on how the decannulation rate is calculated, since two different methods of calculation are used in the various studies published on the subject.

Objective measurements of airway patency

Next to the decannulation rate, no other objective outcome as far as airway patency after surgery is reported in the literature. A number of studies report subjective outcome parameters such as improvement of airway complaints, or airway diameter as judged by endoscopic evaluation.[35,40] Robust objective data on the patency of the reconstructed airway at long-term follow-up after decannulation is lacking.

Voice outcome

Surgery on the larynx is always a balance between the different functions of the larynx: respiration, voice production and airway protection when swallowing. A number of studies report the (long-term) voice outcome after airway reconstruction. The published studies (table 2) show a large heterogeneity in methodology and study population, but are unanimous in reporting significant voice disturbance in patients after surgery for LTS.[45-49] Robust data on the prevalence of dysphonia after surgery for LTS is lacking. The published studies also make clear that there is no consensus on the best way to objectively evaluate the quality of the voice in the pediatric population.

Quality of life

Although quality of life reporting is quite common in other severe pediatric diseases, there are no studies which address quality of life as an outcome measure after surgery for laryngotracheal stenosis.[57-60]

Table 1: Overview of current reports on decannulation rate after surgery for pediatric LTS

Author	Clinic	Year	Follow-up	n	Type of surgery	Decannulation rate		Calc.
						OSDR	ODR	
Yamamoto et al.[36]	Lausanne	2014	17.6 mo. (2-126)	45	4 ss-LTR, 41 ds-LTR	66,7	86,7	Method B
Rodriguez et al.[37]	Buenos Aires	2013	2 yrs. (range not given)	71	5 ss-LTR, 50 ds-LTR, 10 CTR, 6 ant split	84,5	98,6	Method B
Yamamoto et al.[38]	Lausanne	2015	52,4 mo. (1-228)	129	ss-CTR, ds-CTR	80,6	89,9	Method B
Saunders et al.[39]	GOSH	1999	Not given	69	ss-LTR, ds-LTR	Not given	64.4[2]	Method A
Bajaj et al.[40]	GOSH	2012	Not given	185[1]	ss-LTR, ds-LTR, ss-CTR, ds-CTR	Not given	85.8%	Method A
White et al.[41]	Cincinnati	2005	5.2 yrs. (4mo-11.2 yrs.)	93	CTR	70,9%	93,5%	Method B
Hartnick et al.[42]	Cincinnati	2001	Not given	199	ss/ds-LTR, ss/ds-CTR	66,8%	84%	Method B
Ochi et al.[43]	GOSH	1992	Minimum 2yr	108	ds-LTP, ds-LTR	Not given	83,3%	Method A
Gustafson et al.[44]	Cincinnati	2000	5.5 yrs. (1-11.9)	190	ss-LTR	85.9%[2]	93,8%[2]	Method B

Ss-LTR = single stage laryngotracheal reconstruction. Ds-LTR = double stage laryngotracheal reconstruction. CTR = cricotracheal resection. Ds-LTP = double stage laryngotracheoplasty. GOSH = Great Ormond Street Hospital, London. OSDR = operation specific decannulation rate. ODR = overall decannulation rate. Calc. = calculation method. [1] stomal reconstruction as mentioned in the study not included in this table. [2]ODR not given in the article; calculated from the text.

Method A = (Number of children succesfully decannulated after surgery)/(Total number of children with a pre-op cannula)
Method B = (Number of children succesfully decannulated after surgery)/(Total number of surgically treated children)

Table 2: Overview of reported voice outcome after surgery for LTS.

Author	Clinic	Year	Setting	N	Voice assessment subjective (S)/ objective (O)
Krival et al.[50]	Cincinnati	2007	Retrospective records voice clinic	16	S: Endoscopy, perceptual analysis (CAPE-V) O: fundamental frequency
Zacharias et al.[49]	Cincinnati	2015	Retrospective records voice clinic	32	S: stroboscopy, perceptual analysis (CAPE-V) O: pVHI, acoustic measurements
Weinrich et al.[51]	Cincinnati	2007	Prospective, non-randomised voice clinic	12	S: endoscopy, CAPE-V O: aerodynamic assessment
Zur et al.[52]	Cincinnati	2007	Prospective voice clinic	33	O: pVHI
Clary et al.[46]	GOSH	1996	Prospective follow-up cohort	50	S: endoscopy, perceptual analysis (Vocal profile Analysis) O: non-validated questionnaire
Dohar et al.[53]	Pittsburgh	2013	Retrospective records dysphonic patients	23	S: stroboscopy, perceptual analysis (CAPE-V) O: pVHI, aerodynamic measures
Geneid et al.[54]	Helsinki	2011	Prospective follow-up cohort without voice complaints	10	O: Pediatric Voice Outcomes Survey (PVOS), S: VAS score on voice samples
De Alarcon et al.[55]	Cincinnati	2009	Retrospective records voice clinic	42	O: pVHI S: CAPE-V
Kelchner et al.[56]	Cincinnati	2010	Retrospective chart review children with dysphonia after airway surgery	21	O: acoustic and aerodynamic measurements S: stroboscopy

CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice. pVHI = pediatric voice handicap inventory. GOSH = Great Ormond Street Hospital, London.

Objective of this research project

A number of questions remain unanswered in the field of pediatric LTS. There is a lack of long-term outcome reporting and uncertainty on the best way to objectively evaluate the reconstructed airway. Furthermore, it is unknown what surgical and patient factors are associated with long-term outcome.

This research project was started to evaluate our own surgical outcome for acquired pediatric LTS at long-term follow-up. By evaluating our outcome in a large surgical cohort, we hope to draw important conclusions on past treatment, make changes if necessary and improve our future outcome. Next to this, we hope that our research contributes to the existing evidence on the surgical treatment of pediatric LTS and answers some of the questions that still remain in pediatric LTS.

Outline of this thesis

This thesis focuses on long-term functional outcome after open airway surgery for acquired pediatric LTS in our tertiary referral clinic.

Chapter two of this thesis analyzes the surgical outcome of open airway surgery for LTS in terms of decannulation. Our results will be compared with those previously published by other centers. Next to this, the various pre-operative factors will be analyzed and factors associated with poorer or better outcome will be identified as far as decannulation or complicated post-operative course are concerned.

Chapter three focuses on respiratory outcome after long-term follow-up in a large cohort of children who have been treated for LTS and are currently without a tracheal cannula; pulmonary function testing and the Bruce treadmill test will be introduced as a means to objectively assess the reconstructed airway and exercise capacity. Significant factors associated with poorer respiratory outcome will be identified, which will have a great impact on our daily practice.

In chapter four, long-term health-related quality of life (HRQoL) in our cohort of surgically treated children will be reported. The overall HRQoL will be compared to the norm population and parent proxy and patient self-assessment will be compared. Once again pre- and perioperative factors associated with outcome will be identified.

In chapter five, the pediatric voice handicap inventory (pVHI) for the Dutch population will be translated and validated and norm values will be established.

In chapter six, voice and voice-related quality of life outcome at long-term follow-up will be presented. The challenges involved in objective voice assessment in the pediatric population

will be addressed and our experience with the use of the dysphonia severity index (DSI) for this purpose will be reported.

In chapter seven, a summary of the most important findings of our research project will be given.

In chapter eight, the most important conclusions of our research will be discussed. We will present what was learned from this project and offer recommendations for future practice.

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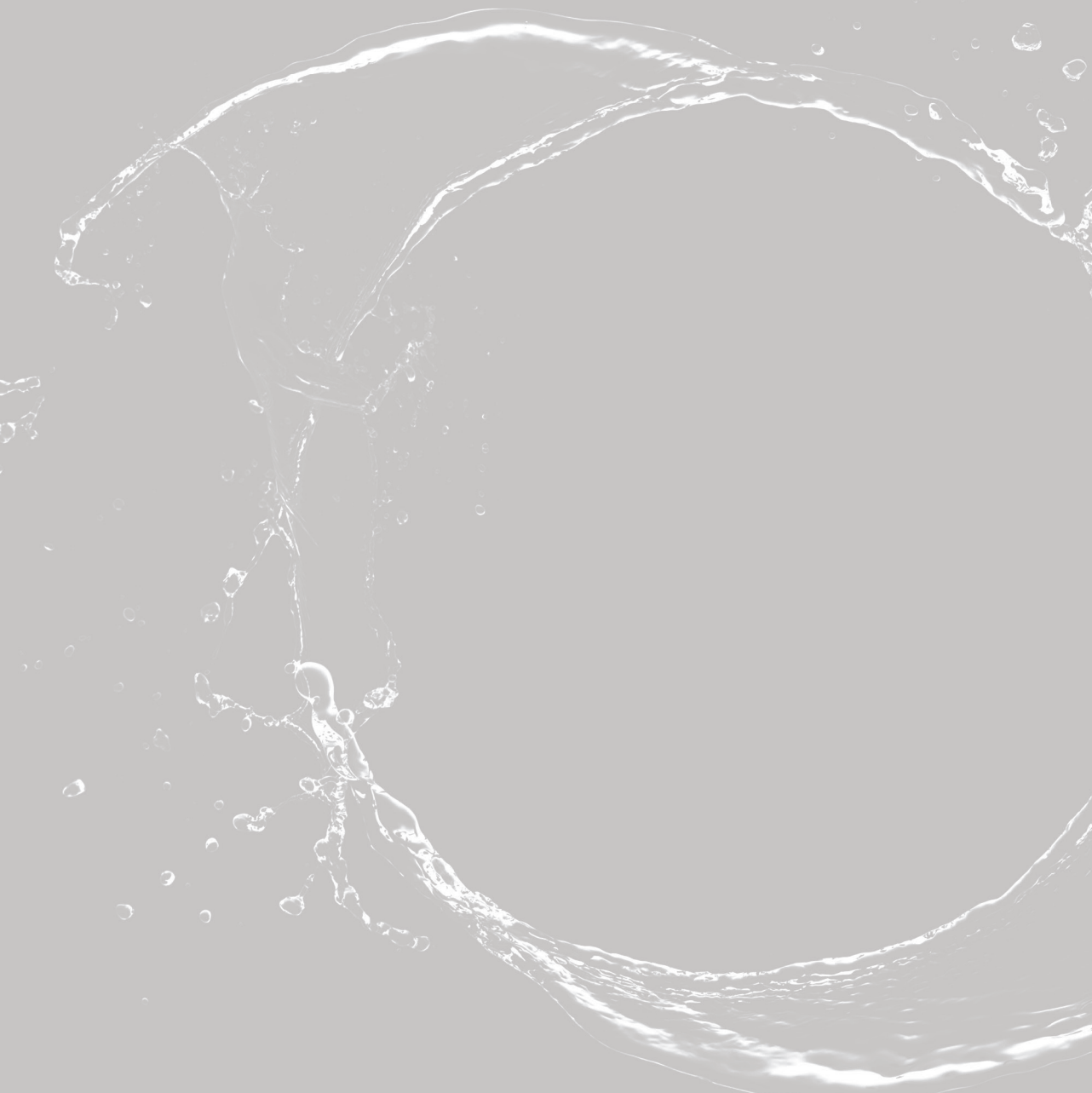


chapter 2

Decannulation Rate of 98 Infants and Children Surgically Treated for Acquired Laryngotracheal Stenosis

Pullens B., Hoeve L.J., Timmerman M.K., Van der Schroeff M.P., Joosten K.F.M.

Characteristics and surgical outcome of 98 infants and children surgically treated for a laryngotracheal stenosis after endotracheal intubation: excellent outcome for higher grades of stenosis after SS-LTR

Int J Pediatr Otorhinolaryngol. 2014 Sep 78(9):1444-8

Abstract

Objectives. *To describe the characteristics and surgical outcome of 98 infants and children treated for an acquired laryngeal stenosis after intubation for respiratory support.*

Material and methods. *We retrospectively reviewed our data from the last 18 years (1994-2013) concerning infants and children with an acquired laryngotracheal stenosis who were treated in our hospital with a laryngotracheal reconstruction or a cricotracheal resection. Outcome was defined by decannulation rate.*

Results. *Of the 98 infants and children who were studied, 54% were preterm, 18% neonates, 13% infants and 14% children. Ninety-one SS-LTR's, two DS-LTR's and five CTR's were performed as primary surgery; three revision operations were performed (DS-LTR). Seventy-seven children had a tracheostomy prior to surgery; Decannulation rate was 93% after primary surgery and 95% after inclusion of revision surgery. For SS-LTR, the decannulation rate was 93%, including grade III stenosis with comorbidities. Male sex and glottic involvement of the stenosis are correlated to failure of decannulation. Intubation in the term neonatal period is correlated to complicated postoperative course after SS-LTR.*

Conclusions. *Excellent results of surgery for acquired laryngotracheal stenosis can be obtained with a high decannulation rate. Even for higher grades of stenosis with comorbidities and glottic involvement, an SS-LTR is an effective surgical treatment for acquired laryngeal stenosis.*

Introduction

Acquired laryngotracheal stenosis (LTS) in children is a serious long-term complication of (prolonged) endotracheal intubation.[1] The incidence in children who are intubated for more than 24 hours, varied thirty years ago between 1 and 10%, but has nowadays decreased to less than 1%.[2-8] Only a small number of these children develop a laryngotracheal stenosis. Supposed risk factors for the development of laryngotracheal stenosis after intubation in children are low birth weight, premature birth, younger age, pre-existing narrow larynx, duration of intubation, oversized tube, traumatic intubation, multiple re-intubations, shock, infection and gastro esophageal reflux.[2,3,9-12]

Since the 1980s, laryngotracheal reconstruction (LTR) and cricotracheal resection (CTR) have gained widespread adoption in the treatment of severe laryngotracheal stenosis. Overall, a high rate of decannulation is reported. Uncertainty remains on the factors associated with unfavorable outcome and on the optimal surgical strategy in challenging situations. [13,14]

In this retrospective analysis, we present the patient characteristics and surgical outcomes of 98 patients who underwent a laryngotracheal reconstruction or a cricotracheal resection for acquired post-intubation laryngotracheal stenosis. We try to clarify the factors associated with unfavorable outcome and compare our approach and results to other published series.

Material and Methods

A retrospective study was performed on all pediatric patients with an acquired laryngotracheal stenosis, treated with a laryngotracheal reconstruction or a cricotracheal resection between September 1994 and January 2013 in the Sophia Children's Hospital in Rotterdam, The Netherlands. Patients with a congenital laryngotracheal stenosis were excluded. Surgery was performed or supervised by LJH.

Before the surgical procedure, the diagnosis of laryngeal stenosis was confirmed by endoscopy, as part of the standard airway assessment procedure including flexible and rigid laryngotracheobronchoscopy.

The clinical records of each patient were reviewed for gender, gestational age, birth weight, comorbidities, age at and indication for initial intubation and the presence of a tracheostomy before surgery. Patients were divided in four groups according to their age at intubation: preterm neonates (<36 weeks gestational age); term neonates (>36 weeks gestational age, < 1 month); infants (>1 month, < 1 year) and children (>1 year, < 16 years).

The presence of comorbidities was noted. Possible comorbidities are: obstructive sleep apnoea, tracheomalacia, cardiac disease, neurologic or mental impairment, GERD, congenital syndrome or pulmonary disease (including bronchopulmonary dysplasia).

Information on the stenosis and laryngotracheal anatomy was taken from the operating theatre report of the endoscopies undertaken before surgery. The location of stenosis (posterior glottis, subglottic, supraglottic or a combination), the presence of vocal cord dysfunction as well as the severity of stenosis using the grading system according to Myer-Cotton[15] was noted. In our institution, diagnosis of LTS is made by flexible and rigid laryngotracheobronchoscopy in general anesthesia. Surgery is planned when the stenosis shows no sign of active inflammation (e.g. presence of granulation or edema). The patients in whom we encountered laryngeal edema were treated routinely with PPI's. All patients with a tracheostomy are routinely treated with PPI's and antibiotic prophylaxis. When persistent edema was encountered despite adequate PPI treatment, pH-metry was performed and a fundoplication was advised.

In general, all grade IV stenosis are treated with a cricotracheal resection (CTR), all other grades of stenosis are treated with either a Single Stage LTR (SS-LTR), a Double Stage LTR (DS-LTR) or CTR. Stenting is done on indication with a silicone Berkovits stent attached to a metal cannula.[16] The stent is renewed every 3 weeks until the airway looks well healed without granulation or active inflammation. Our post-operative protocol used for SS-LTR is given in box 1. Extubation after a planned period of intubation after SS-LTR is done in the operating theatre. The patient is extubated in general anesthesia without muscle relaxants after which an endoscopy of the airway is undertaken. When no sign of respiratory distress is seen, the patient was kept extubated and moved to the IC ward for further observation.

Box 1: post–operative protocol after SS–LTR

Nasal intubation for 3-4 days; stay in IC ward
Spontaneous breathing, under sedation, when possible.
Standard antibiotics & PPI's for 6 weeks
Dexamethasone is routinely administered 6 hrs. and 1 hr. prior to extubation
Extubation and endoscopy under general anesthesia, spontaneous breathing in OR
Post-operative administration of topical adrenaline or pulmicort if applicable

IC = intensive care, PPI = proton-pump inhibitor

Outcome of surgical treatment was expressed in the decannulation rate. A subgroup analysis was done on the children who underwent an SS-LTR. We stratified for two post-operative outcomes; an uncomplicated and complicated post-operative course. An uncomplicated course was defined as an uneventful planned extubation after surgery. A complicated course was noted when the child needed re-intubation or re-tracheostomy after initial extubation. This includes the children who failed decannulation after surgery, or needed revision open surgery for the stenosis. The children with a complicated post-operative course were analysed in an attempt to isolate predictive values for a complicated post-operative course in future cases.

Statistical analysis

IBM SPSS Statistics version 20 was used for statistical analysis. Depending on distribution, values were expressed as median (range) or as a percentage. To compare continuous variables, the T-test was used for normal distribution and the Mann-Whitney U test for a not-normal distribution. For categorical variables the chi-square was used. Multivariate analysis on a non-complicated postoperative course after SS-LTR and on decannulation after all treatment modalities was done using binary logistic regression. Any difference was considered to be statistically significant if a P value ≤ 0.05 was found.

Results

A total of 98 patients with an acquired laryngotracheal stenosis were treated with an LTR or CTR from 1994 until 2013.

Patients (table 1)

53% of the patients were female; all patients had a history of intubation. On intubation, 53 patients were preterm neonate, 18 were term neonate, 13 were infants and 14 were children. Fifty-nine patients were intubated immediately after birth; the median age at intubation of the remaining patients was 92 days. The 53 preterm babies had a mean age of 28 weeks at birth and a mean birth weight of 1128 grams. Forty-three of the preterm infants (86%) had a birth weight under 1500 gr and 28 (56%) had a birth weight under 1000 gr.

Reasons for intubation were respiratory failure in 76% (including the preterm infants), elective intubation for planned surgery in 11%, intubation on the scene for trauma in 9 % and other reasons in 4%.

Neonates and preterm patients were mostly intubated for respiratory failure, infants for planned surgery and children for trauma, or infectious diseases such as subglottic laryngitis or RS virus.

Comorbidities were present in 63 children; of these, 23 children presented with multiple comorbidities. The most common comorbidities were pulmonary disease (38 patients), including bronchopulmonary dysplasia (31 patients), tracheomalacia (14 patients, including tracheomalacia concurring with esophageal atresia), neurologic or mental impairment (10 patients), or congenital heart disease (8 patients).

Of the patients with comorbidities, 15 had a congenital syndrome. Eight had Down's syndrome, 2 patients had VACTERL, others had Fragile X, CHARGE, Larsen syndrome, Opitz syndrome or chromosome 5 deficit. When considering the age at intubation, congenital syndromes were most common in the infant age groups (46%) and less common in preterm neonatal, term neonatal and child age groups (6%, 22% and 14% respectively) (p= 0.003).

Table 1: Patient characteristics; n = 98

Gender	
Female	52
Age group at intubation	
Preterm	53
Neonate	18
Infant	13
Child	14
Reasons for intubation	
Respiratory failure	76%
Planned surgery	11%
Trauma	9%
Other	4%
Comorbidities	
Pulmonary disease	38
Tracheomalacia	14
Neurologic or mental impairment	10
Congenital heart disease	8
Congenital syndrome	15

Preoperative factors (table 2)

Prior to surgery, 77 patients were tracheostomy dependent. On first endoscopic evaluation, 1 patient had a grade I stenosis, 25 a grade II, 69 grade III and 3 patients had a grade IV stenosis.

The stenosis was solely subglottic in 55 patients, solely posterior glottic in 23 patient, posterior glottic and subglottic in 19 patients and posterior glottic and supraglottic in one patient.

Information on vocal cord function as assessed during flexible endoscopy in the spontaneously breathing child under general anesthesia was present in 87 children: Forty-eight had normal functioning vocal cords (55%). Thirty-nine children (45%) had vocal cord dysfunction; 31 bilateral dysfunction (79%), 5 left vocal cord dysfunction (13%) and 3 children had a right vocal cord dysfunction (8%). Vocal cord dysfunction was significantly more common when the site of stenosis involved the posterior glottis when compared to solely subglottic stenosis (69% vs 31%, p= 0,000).

There was no correlation between age group at time of intubation and grade of stenosis or between sex and grade of stenosis.

Table 2: Pre–operative factors

Tracheostomy dependence	77
Grade of stenosis (Myer-Cotton)	
Grade I	1
Grade II	25
Grade III	69
Grade IV	3
Location of stenosis	
Subglottis	55
Posterior glottis	23
Subglottic & posterior glottis	19
Posterior glottis & supraglottis	1
Vocal cord function	
Normal	48
Bilateral dysfunction	31
Left vocal cord dysfunction	5
Right vocal cord dysfunction	3

Operative factors (table 3)

In our study period, a total of 101 open airway procedures were performed on 98 patients. Median age at surgery was 2 years, 8 months; the youngest patient was 6 months, the oldest was 15 years, 8 months at surgery. Thirty-seven patients were under two years of age at time of surgery.

A total of 93 patients were treated with a laryngotracheal reconstruction (LTR); 91 as a single stage procedure (SS-LTR) and 2 as a double stage procedure (DS-LTR) with a period of stenting. Costal cartilage was used as grafting material in all cases of LTR. Table 4 summarizes the grafts used in our LTR patients. The choice of graft used has no significant influence on outcome when decannulation or complicated postoperative course after SS-LTR are concerned.

Five children were treated with a cricotracheal resection (CTR) with stenting. All grade IV stenosis were treated with a CTR and all grade II stenosis with an SS-LTR. Of the 69 grade III stenosis, 65 were treated with a SS-LTR, 2 were treated with a DS-LTR and two with a CTR.

Seven patients needed revision surgery; three needed revision surgery of an earlier laryngofissure operation before 1994. One patient needed revision surgery of a CTR performed in another hospital. Three patients needed revision surgery after primary surgery failed in our own hospital within the timeframe of this study. Of the latter three, only the primary surgical procedure was included in the statistical analysis.

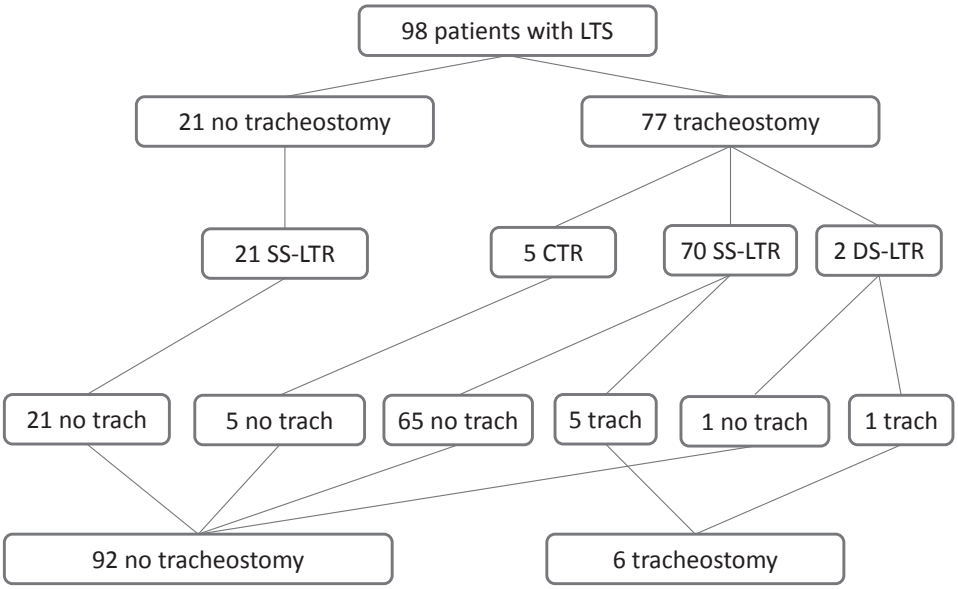
Table 3: operative factors

Age at surgery	
Median in months	32
Type of surgery	
SS-LTR	91
DS-LTR	2
CTR	5

Table 4: grafts used in LTR procedures

Only anterior graft	2
Only posterior graft	8
Anterior graft and posterior split	2
Anterior and posterior graft	81
Total	93

Figure 1: Decannulation outcome after primary surgery



Different treatment modalities for primary surgery (LTS = laryngotracheal stenosis, SS-LTR = Single Stage Laryngotracheal reconstruction, CTR = Cricotracheal resection, DS-LTR = double stage laryngotracheal reconstruction, trach = tracheostomy).

Figure 1 gives a schematic overview of the different treatment modalities and the number of decannulated patients. After primary surgery, 71 out of 77 patients with a tracheostomy pre-op could be decannulated after surgery, giving a decannulation rate of 92%. All six patients who could not be decannulated were treated with an LTR; five had a single stage and one a double stage procedure with stenting. All six patients who failed decannulation had a grade III stenosis (p=0.516). Five out of six patients who failed decannulation had comorbidities prior to surgery (p= 0.269). All children treated with a CTR could be decannulated.

The mean planned intubation period after SS-LTR was 18 days when surgery was performed before April 1998; after this, a protocol change was made and the mean intubation period was 4 days. There was no significant correlation of this protocol change on outcome when decannulation or complicated post-operative course after SS-LTR are concerned.

A subgroup analysis was done on the 91 children who underwent an SS-LTR (table 5); seventy-three children (80%) had an uncomplicated post-operative course; direct extubation could be achieved after a planned post-operative period of intubation. Eighteen patients (20%) had a complicated post-operative course: five patients could not be decannulated at all,

four patients required temporary re-tracheostomy with eventually successful decannulation without revision surgery and nine patients required temporary re-intubation with eventually successful extubation. When considering age at intubation, a complicated post-operative course was most common in the term neonatal age group (50%) when compared to the preterm, infant and child age group (14%, 23% and 0% respectively). This observation was significant p=0.004.

Table 5: subgroup analysis SS–LTR (n=91)

Decannulation rate (65 out of 70)	93%
Uncomplicated post-operative course	73
Complicated post-operative course	18
Failed decannulation	5
Re-intubation	9
Re-tracheostomy with successful decannulation eventually	4

Seventy patients (77%) had a tracheostomy prior to SS-LTR. Sixty-five of these patients could successfully be decannulated; fifty-three immediately following surgery and after a brief period of planned intubation. The remaining twelve patients had a complicated postoperative course with re-intubation or temporary re-tracheostomy with eventual successful decannulation. This results in a decannulation rate of 93% for single SS-LTR procedures on tracheostomised patients in our institution.

Three patients needed revision surgery after initial failure of decannulation: two patients were treated with a DS-LTR; one patient with a revision SS-LTR and later on a DS-LTR. Two of these patients could successfully be decannulated, making the overall decannulation rate when including revision surgery 95%

Statistical analysis

A multivariate analysis with binary logistics regression was performed in order to identify factors associated with failure of decannulation after surgery or a complicated post-operative course after SS-LTR. The factors included in the equation were: stenosis localisation, vocal cord pathology, presence of comorbidities, age group at time of intubation, age at surgery (< or > 2 yrs.), Myer-Cotton grade of stenosis and sex.

When failure of decannulation is concerned, male sex *(p=0.05)* and glottic involvement of the stenosis *(p=0.062)* are associated with a smaller chance for decannulation. When multivariate analysis on complicated course after SS-LTR is concerned, age group at time of intubation is the only significant factor; intubation during the term neonatal period was associated with a higher chance on a complicated course after SS-LTR.

Because of limited numbers we did not perform a multivariate analysis on complicated follow-up after DS-LTR and CTR.

Discussion

Laryngotracheal reconstruction and cricotracheal resection have long proven their value and reliability in the treatment of laryngotracheal stenosis.[13] We present the patient characteristics and surgical outcome of the last 98 pediatric patients operated on for acquired post-intubation LTS. As in other large published series, we have a large number of children of preterm birth, children with multiple comorbidities and children with congenital syndromes, signifying the increased risk of developing a laryngotracheal stenosis after intubation in these groups of patients.[2,3,17]

We can report excellent results when decannulation rate is concerned. The decannulation rate was 92% (71 out of 77) for all primary open surgical procedures. When the revision operations are included, the total decannulation rate is 95%. When only the SS-LTR's are concerned, the decannulation rate is 93%.[18,19]

What stands out when comparing our data with other published reports on surgical strategy and outcome for LTS, is the high number of Single Stage Laryngotracheal Reconstructions (SS-LTR) even for higher grades of stenosis with glottic involvement and comorbidities. We performed SS-LTR procedures for Myer-Cotton grade III stenosis in 65 cases, with comorbidities (23 cases) and glottic involvement (24 cases). Sixty of these sixty-five patients had a tracheostomy prior to treatment. Fifty-five of these patients could successfully be decannulated after a single SS-LTR procedure.

The successful use of the single stage procedure for these complex cases is an extraordinary finding, since it is generally assumed that stenting or cricotracheal resection is necessary for complex cases with higher grades of stenosis.[14,20] Indeed, other series published on LTR outcome report greater numbers of DS-LTR with stenting and CTR for higher grades of stenosis. [14,18,19,21]

Choosing the optimal surgical strategy for treatment of LTS remains challenging, especially in complex cases.[13] Monnier et al. has proposed incorporating glottic involvement and the presence of comorbidities into the well-known grades of stenosis by Myer-Cotton and has recommended an algorithm for treating complex cases.[14] We found that our approach differed from Monnier's proposed algorithm in no less than 83 cases, in which we performed a Single-Stage procedure while a double stage was recommended by Monnier et al.

The Single Stage procedure has the apparent advantage of not needing a laryngotracheal stent, completely blocking the airway proximal to the tracheostomy. However, the postoperative care of patients after SS-LTR is challenging; in 20% of our children a complicated

postoperative course was seen, necessitating immediate interventions like re-intubation and/ or re-tracheostomy. A well-equipped and experienced pediatric ICU is mandatory when performing these procedures.

The multivariate analyses showed male sex and glottic involvement to be associated with failure of decannulation. The relevance of male sex being of predictive value for poor outcome of decannulation remains unclear. No other study reported this observation and this is probably not clinically relevant.[18,19,22] When the patient was intubated in the term neonatal period, there was a significantly bigger chance on a complicated postoperative course after SS-LTR.

A retrospective analysis such as ours has a number of disadvantages. First there is the obvious problem of selection bias: the surgical strategy for these patients was chosen for a reason and this makes comparison between the different types of surgery unfair. Furthermore, there is the problem of missing information when extracting patient information in a retrospective manner. This is especially true for the assessment of GERD. This is not routinely measured through pH-metry in our patients, partly due to the ongoing controversy surrounding this investigation and because we feel that all tracheotomised patients and patients with LTS benefit from PPI treatment.[23-25] Patients are only scheduled for reconstructive surgery when the stenotic area shows no sign of active inflammation or oedema. In the case of ongoing GERD associated oedema and inflammation despite proper PPI use, a fundoplication is advised. This was carried out in 3 patients.

While we can present a reasonably large series of patients, the numbers are still small for proper statistical analysis, like multivariate analysis. One must consider these disadvantages when reading our report and conclusions.

When evaluating outcome, the decannulation rate is widely used as a measure for success of airway surgery. Using mainly SS-LTR even for higher grades of stenosis with comorbidities and glottic involvement, we can report excellent outcomes of surgery with high decannulation rate. While decannulation of a tracheotomised child is an essential part of the treatment of laryngotracheal stenosis, we also feel it is a very rough measure for success in these children. More objective measurements on the functional airway, quality of voice (in our series 45% of the patients had a vocal cord dysfunction) and quality of life is necessary to evaluate functional long-term outcome. The outcome of this evaluation will be presented in a separate article.

Conclusion

Open surgery for acquired post-intubation LTS results in a high decannulation rate in our institution. Our results show a high decannulation rate with the use of the Single Stage laryngotracheal reconstruction even for higher grades of stenosis with comorbidities.

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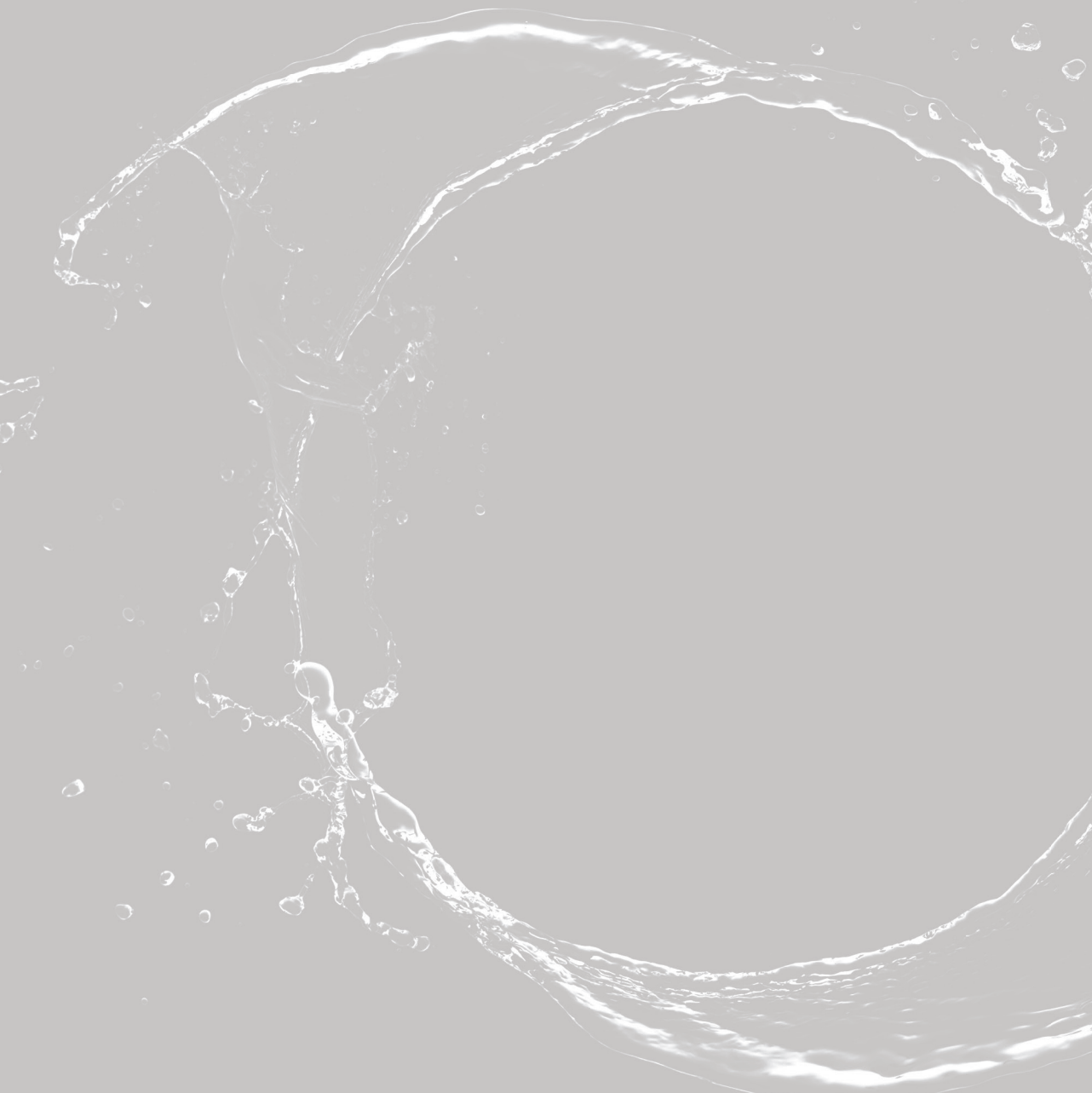

chapter 3

Long-Term Functional Airway Assessment after Open Airway Surgery for Laryngotracheal Stenosis

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Long-term functional airway assessment after open airway surgery for laryngotracheal stenosis
Laryngoscope. 2016 Feb;126(2):472-7

Abstract

Objectives. *The purpose of this study was to evaluate our patient reported and objective long-term outcomes of patients treated for laryngotracheal stenosis.*

Material and Methods. *Sixty-five patients were evaluated after a median follow-up of 7 years after surgery. Follow-up measurements consisted of pulmonary function testing, Bruce treadmill test and Child Health Questionnaires (CHQ).*

Results. *In 43 patients pulmonary function tests were available and 30/43 had abnormal FEV1/FIV1, 25/43 had abnormal FIV1/VCmax and 24/43 had PEF < 80% predicted. One third of patients had reduced exercise tolerance. CHQ revealed significant positive correlations with pulmonary function test results and exercise tolerance. Multivariate analysis showed that glottic involvement of the stenosis and the presence of comorbidities at time of surgery are the only factors for poor long-term functional outcome.*

Conclusions. *The majority of patients show deficits in pulmonary function and exercise tolerance related to lower scores of quality of life. Glottic involvement of the stenosis and the presence of comorbidities are the only significant factors for poor functional outcome. Long-term multidisciplinary follow-up is mandatory after surgery for LTS.*

Introduction

Since its introduction in the 1980s, Laryngotracheal reconstruction (LTR) and cricotracheal resection (CTR) have gained widespread adoption in the treatment of severe laryngotracheal stenosis (LTS) in children. Excellent results have been reported as far as decannulation rate is concerned. [1-4]

Choosing the optimal surgical strategy in complex cases of LTS is challenging and a number of experts in the field have provided algorithms for different clinical situations.[5-8] Recently, endoscopic procedures have been added to the therapeutic arsenal with reasonably good results.[9-12] Our own recently published series on open airway surgery for acquired post-intubation laryngotracheal stenosis shows a high decannulation rate (95%) using mostly single stage laryngotracheal reconstructions, even in complex cases with high grades of stenosis, glottic involvement of stenosis and/or comorbidities.[13]

The decannulation rate is widely used as the main outcome parameter for success of surgery. Although important, the decannulation rate is only a rough reflection of the patency of the reconstructed airway and the functionality of this airway during long-term follow-up. Furthermore, there are no objective outcome measures in children without a pre-operative tracheostomy. Long-term data on airway patency, pulmonary function, exercise tolerance and consequent quality of life in children who underwent surgery are lacking.

Therefore, the aims of our study were to assess long-term patient reported outcomes and objective outcome measures on airway patency after successful open airway surgery for acquired LTS. Secondly, we tried to identify factors associated with outcome in order to evaluate our own surgical strategies and to contribute to new treatment algorithms.

Materials and methods

All children who underwent an LTR or CTR for acquired post intubation laryngotracheal stenosis from September 1994 to September 2009 in the Erasmus Medical Centre- Sophia Children's Hospital, Rotterdam were approached for this study and invited for a follow-up visit. The study protocol was approved by the local ethics committee. Patient characteristics as well as pre-operative data such as Myer-Cotton grade of stenosis and glottic involvement of the stenosis were derived from the clinical records and operation theatre reports. Patients who were four years or older, without a cannula and able to comply with pulmonary function and exercise tests were eligible for inclusion. A thorough history on previous and current complaints was taken during the follow-up visit with special attention to exercise capacity. Presence or absence of stridor at rest or during activity was noted.

Height and weight were measured and body mass index (BMI), weight for age (WFA), height for age (HFA) and weight for height (WFH) were calculated. Height for age was considered

the most important of these parameters since it represents chronic malnutrition (stunting). Further objective measurements consisted of spirometry and the Bruce treadmill test. All patients and/or parents filled in the health-related quality of life Questionnaire.

Spirometry

During the follow-up visit children performed pulmonary function testing (PFT), which included forced expiratory and inspiratory flow-volume loops. Forced vital capacity (FVC), maximal vital capacity (VC max), forced expiratory volume in 1 second (FEV1), maximal expiratory flow at 25% of vital capacity (MEF25%) and Peak Expiratory Flow (PEF) were recorded and expressed as percentage predicted. A separate inspiratory maneuver was performed and Forced Inspiratory Volume in 1 second (FIV1) and FIV1/ VC max were recorded. From the PFT data, the ratio FEV1/FIV1 was calculated. A ratio between 0,8 and 1,0 was considered normal. A ratio <0.8 was considered suggestive of an expiratory obstruction, a ratio >1.0 was considered suggestive of an inspiratory obstruction. Pulmonary function parameters with a standard deviation score < -2.0 were considered abnormal. An FIV1/VC max < 80% of predicted value was considered abnormal.[14] Flow-volume curves were obtained using a dry rolling seal spirometer (MasterScreen electronic spirometer, Jaeger, Würzburg, Germany).

All spirometry measurements were evaluated by a pediatric pulmonologist (MP).

Bruce treadmill test

A motor-driven treadmill test was performed according to the Bruce protocol to voluntary exhaustion while heart rate and O_2 saturation were measured in children four years or older and who were able to comply with the protocol.[15] A heart rate of ≥ 185 beats per min or loss of coordination was considered to indicate maximal performance. The maximal endurance time of exercise was measured. Values with standard deviation below -2.0 according to the reference values for Dutch children were considered abnormal.[16]

Quality of Life

Health-related quality of life (HRQoL) was assessed by the validated Child Health Questionnaire (CHQ).[17] Parents were asked to complete the CHQ-PF50 (for patients 4-18 years); patients 10 years and older completed the CHQ themselves (version CHQ-CF87). Item scores per scale were summed up and transformed into a 0-100 score in which higher scores indicate more favorable subjective health status. Due to small sample size, patients 18 or older were also asked to complete the CHQ-CF87 form.

Statistical analysis

IBM SPSS Statistics version 20 was used for statistical analysis. Depending on distribution, values were expressed as median (range) or as percentage. Multivariate analysis was

performed on the outcomes of PFT, the Bruce treadmill test and outcomes of height for age analysis using binary logistic regression. In order to avoid the risk of overfitting, no more than one predictor was used per ten patients. The factors included in the equation were: glottic involvement of stenosis, presence of comorbidities, age at surgery (< or > 2 years), and Myer-Cotton grade of stenosis. Any difference was considered to be statistically significant if a value ≤ 0.05 was found. When no significant factors were identified, a backward conditional analysis was done in order to identify the factor that best predicts poor outcome. Pearson *r* correlations analysis was used in order to examine correlations between HRQoL scores and the functional tests. This was done for all HRQoL scales.

Results

We retrospectively identified 80 children who were operated in the aforementioned time period. Four patients were excluded: one still had a cannula, one was operated for recurrent laryngotracheal stenosis, and two patients were too young to be included. Seventy-six patients were invited to participate in the study. Five patients were lost to follow-up and six refused participation. This left 65 patients who were included in this study. Out of the 65 included patients, 10 patients refused to visit the outpatient clinic, mainly because of distance issues. None of these 10 patients refused the outpatient clinic visit because of airway compromise. Fifty-five patients eventually visited the outpatient clinic. A number of patients was not able to comply with the spirometry or treadmill test protocol. This was due to mental retardation, young age or insufficient technique on spirometry; no patients failed the functional tests due to airway compromise. This eventually resulted in 43 spirometry and 44 treadmill tests of sufficient quality .

One patient was excluded from the CHQ due to poor understanding of the Dutch language. From the remaining 64 patients, 54 were eligible for and completed the parent form CHQ-PF50 (patients 4-18 years) and 41 were eligible for the child form CHQ-CF87 (10-23 years). Of these 41, 30 completed the CHQ-CF87 form; 8 refused and 3 were not able to comply due to mental retardation.

Table 1 shows the patient characteristics of the 65 patients who were included in the study. Median follow-up time was 7 years (range 2-17 yrs), most patients had a Grade III laryngotracheal stenosis (66%), 27 patients (42%) had glottic involvement of the stenosis at time of surgery. Comorbidities at time of surgery were present in 36 patients (55%) of which 14 had bronchopulmonary dysplasia (BPD) (table 2).

Table 1: Patient characteristics n = 65

Female	35
Median age; range (years)	11 (4-24)
Median follow-up; range (years)	7 (2-17)
Tracheostomy present pre-operatively	49
Grade of stenosis (Myer-Cotton)	
Grade I	1
Grade II	20
Grade III	43
Grade IV	1
Site of stenosis	
Only subglottic	38
Glottic involvement	27
Comorbidities present	36
Bronchopulmonary Dysplasia (BPD)	14
Type of surgery	
SS-LTR	62
DS-LTR	1
CTR	2
Age at time of surgery < 2 years	26
Age at first intubation in age groups	
Preterm	30
Term neonate	14
Infant	10
Child	11

SS-LTR = single stage laryngotracheal reconstruction; DS-LTR = double stage laryngotracheal reconstruction; CTR = cricotracheal resection

Table 2: Comorbidities

	Total (n=65)	**PFT (n=43)**	**Bruce (n=44)**
BPD	14	10	11
Tracheomalacia	9	4	4
Congenital heart disease	5	2	1
Neurologic or mental impairment	2	2	1
Congenital syndrome	11	3	1
Other	5	1	1

Overview of existing comorbidities in the total study group, the PFT group and the Bruce treadmill group. Some patients had multiple comorbidities. PFT = pulmonary function testing; Bruce = Bruce treadmill test; BPD = bronchopulmonary dysplasia

In 32 out of 54 patients, stridor was audible on ENT examination, either at rest or during activity. Stridor was more often audible in patients when there was glottic involvement of the stenosis (19 out of 32, *p*=0.008).

Twenty-two patients or their parents judged their maximum endurance of exercise as poor when compared to their peers. More patients scored poor exercise tolerance when glottic involvement of the stenosis was present (14 out of 22, *p*= 0.015).

BMI and WFH (weight for height) was below -2.0SD in 3 out of 54 patients (5,6%). Weight for age was below -2.0SD in 6 out of 51 patients (11,8%). Height for age was below -2.0SD in 15 out of 54 patients (27.8%).

Spirometry

Forty-three patients performed spirometry of sufficient quality (table 3). FEV1/FIV1, FIV1/VCmax and PEF were the most severely affected pulmonary function parameters in our study with 30 patients (70%), 25 patients (58%) and 24 patients (56%) scoring below normal respectively. Of the 30 patients with abnormal FEV1/FIV1 all but one had a ratio >1.0 suggesting a predominately inspiratory obstruction.

Bruce treadmill test

Forty-four patients completed the Bruce treadmill test (table 3). Fifteen of these patients (34%) had impaired exercise tolerance with scores below -2.0SD.

An audible inspiratory stridor in the outpatient clinic predicted poor inspiratory spirometry result with a positive predictive value of 70% and 80% for respectively FIV1/VCmax < 80% and FEV1/FIV1 ratio >1.0. Subjectively poor exercise tolerance as judged by patients or parents was a poor predictor for impaired exercise tolerance (≤-2.0SD) on the Bruce Treadmill test with a positive predictive value of 40%.

Table 3: Outcomes for spirometry & Bruce test in median (range)

Spirometry (n=43) in % of predicted value		**% < -2.0SD**
FVC	85% (38-107)	32.6%
FEV1	89% (37-114)	32,6%
MEF25%	65% (11-118)	25.6%
VCmax	81% (44-96)	37,2%
FIV1/VCmax	75% (37-98)[1]	58,1%[2]
FEV1/FIV1	1.08 (0.78-1.97)	70%[3]
PEF	93% (17-110)	55,8%
Bruce treadmill test (n=44) in minutes		**% < -2.0SD**
Maximal endurance time	9.44 (4.25-14.0)	34.1%

SD = standard deviation; FVC = forced vital capacity; FEV1 = Forced expiratory volume in 1 second; MEF25% = maximal expiratory flow at 25% of vital capacity; VCmax = maximum vital capacity, FIV1 = forced Inspiratory volume in 1 second; PEF = Peak Expiratory Flow. Data of spirometry presented as percentage of predicted value unless otherwise indicated. [1] actual value, not percentage of predicted value. [2] Percentage of patients below 80% actual value. [3]Percentage of value < 0,8 or > 1,0

Table 4: Health-related quality of life in patients: results of parent-reports (n=54)

CHQ-PF50 (4-18 years)	**VCmax**	**FEV1**	**FIV1/ VCmax**	**PEF**	**Endurance treadmill**
Physical functioning (PF)	***P*<.05**	***P*<.05**	NS	***P*<.05**	***P*<.05**
Role functioning: Emotional Behavior	NS	NS	NS	NS	***P*<.05**
Role functioning: Physical (RP)	NS	NS	***P*<.05**	***P*<.05**	***P*<.05**
Bodily pain (BP)	NS	NS	NS	***P*<.05**	NS
General behavior (GB)	NS	NS	NS	NS	NS
Mental health (MH)	NS	NS	NS	NS	NS
Self-esteem (SE)	NS	NS	NS	NS	***P*<.05**
General health perceptions (GH)	***P*<.05**	***P*<.05**	NS	***P*<.05**	NS
Parental impact: Emotional (PE)	NS	NS	NS	NS	NS
Parental impact: Time (PT)	NS	NS	NS	NS	NS
Family activities (FA)	NS	NS	NS	NS	NS
Family cohesion (FC)	NS	NS	NS	NS	NS
Change in health (CH)	***P*<.05**	NS	NS	NS	NS
Physical summary (PHS)	***P*<.05**	***P*<.05**	NS	***P*<.05**	***P*<.05**
Psychosocial summary (PSS)	NS	NS	NS	NS	NS

Correlations between CHQ-PF50 (Child health questionnaire – parent form) and pulmonary function testing and treadmill test. VCmax = maximum vital capacity; FEV1 = forced expiratory volume in 1 second; FIV1 = forced Inspiratory volume in 1 second; PEF = peak expiratory flow. Significant correlations are given with p<0,05. NS = not significant. All significant correlations are positive with an r> 0.

Quality of Life

Correlations (Pearson's r) between subscales on the CHQ questionnaires and PFT and Bruce treadmill test are shown in table 4 and 5. In children 4-18 years scores on physical domains (physical summary) correlated with PFT but scores on the psychosocial summary did not. In older children general health perceptions and physical functioning correlated best with PFT.

Table 5: Health–related quality of life in patients: results of patient–reports (n=30)

CHQ-CF87 (10-23 years)	VCmax	FEV1	FIV1/VCmax	PEF	Endurance treadmill
Physical functioning (PF)	NS	***P*<0.05**	NS	***P*<0.05**	***P*<0.05**
Role functioning: Emotional (REB)	NS	NS	NS	NS	***P*<0.05**
Role functioning: Behavioral	NS	NS	NS	NS	NS
Role functioning: Physical (RP)	NS	NS	NS	NS	***P*<0.05**
Bodily pain (BP)	***P*<0.05**	***P*<0.05**	NS	NS	NS
General behavior (GB)	NS	NS	NS	NS	NS
Mental health (MH)	NS	NS	NS	NS	NS
Self-esteem (SE)	NS	NS	NS	NS	NS
General health perceptions (GH)	NS	***P*<0.05**	NS	***P*<0.05**	***P*<0.05**
Family activities (FA)	NS	NS	NS	NS	NS
Family cohesion (FC)	NS	NS	NS	NS	NS
Change in health (CH)	NS	NS	***P*<0.05***	NS	NS

Correlations between CHQ-CF87 (child health questionnaire – child form) and pulmonary function testing and treadmill test. VCmax = maximum vital capacity; FEV1 = forced expiratory volume in 1 second; FIV1 = forced inspiratory volume in 1 second; PEF = peak expiratory flow. Significant correlations are given with p<0,05. NS = not significant. All significant correlations are positive with an r>0 except for *

Multivariate analysis

Multivariate analysis demonstrated that glottic involvement of the stenosis and the presence of comorbidities at time of surgery were the only significant factors associated with poor PFT. Glottic involvement of the stenosis was highly associated with poor FIV1/VCmax (p=0.004) and there was an almost significant relation with poor PEF (p= 0.052). The presence of comorbidities was significantly correlated to poor FEV1 (p=0.025). Backward conditional analysis demonstrated that glottic involvement and presence of comorbidities were the best predictive value for poor FEV1/VCmax (p=0.088) and poor VCmax (p=0.110), respectively.

Presence of comorbidities was significantly associated with poor endurance on the Bruce treadmill test (p=0.047) and with poor height for age (p= 0.003), indicating stunting.

Discussion

Our study is the first to report on long-term functional outcomes of decannulated children after open airway surgery for laryngotracheal stenosis (LTS). We found abnormal inspiratory pulmonary function parameters and decreased exercise tolerance in a great number of children after a mean follow-up time of seven years. Health-related quality of life questionnaires revealed positive correlations on a number of (predominately physical) subscales with our objective outcome measurements, implying substantial impact of poor pulmonary function and exercise tolerance on everyday life.

In terms of decannulation, open airway surgery yields excellent results as reported by various renowned centers.[2-4] The decannulation rate is an important outcome parameter and was 95% in our earlier study, but does not reflect the patency and functionality of the reconstructed airway on the long-term. Objective data on long-term functional outcome of airway surgery is lacking up until now in patients treated for LTS with or without a pre-operative tracheostomy. [13]

The most important finding of our study is the disturbed lung function, in particular inspiratory flows, and the reduced exercise tolerance in a great number of patients. The positive correlation of pulmonary function and exercise tolerance with health-related quality of life underlines that in these severely diseased patients airway caliber and comorbidity have an important impact on daily life. Multivariate analysis has identified glottic involvement of the stenosis and the presence of comorbidities at time of surgery as the most important factors for poor pulmonary function test results. Furthermore, the presence of comorbidities was significantly associated with poor endurance on the Bruce treadmill test. To our surprise, the Myer-Cotton grade of stenosis was poorly associated with functional outcome. This may be due to the fact that SS-LTR's were predominately performed on grade II and III stenosis and that the group of patients included in this analysis have been successfully decannulated after surgery with minimal complications.

Without the use of objective measures, a clinician is left with history taking in the outpatient clinic to evaluate the patency of the reconstructed airway. While the presence of inspiratory stridor is a reasonably good predictor for poor inspiratory spirometry results, asking a patient about their everyday exercise tolerance correlates very poorly with the actual objectively measured exercise tolerance on the Bruce treadmill test. This may be explained by patients adapting to their respiratory limitations by avoiding vigorous exercise and by accepting a certain level of exercise intolerance as normal. A positive predictive value of 0.4 renders this question in the outpatient clinic useless. This indicates that objective measurements for the patency of the reconstructed airway are necessary.

In our previously published series, we reported our experience with LTS using mainly single stage laryngotracheal reconstructions for higher grades of stenosis with comorbidities and

glottic involvement.[13] In reports from other renowned centres, a double staged approach with a period of stenting is much more common.[1,2,4,13,18] When comparing treatment algorithms recently proposed by Monnier et al. with our retrospective data, we chose a different surgical strategy in 86% of the patients in our study group. In all of these cases, we chose a single stage LTR approach while the treatment algorithm of Monnier et al would have advised the use of a double staged approach with a period of stenting.[5] Although our overall decannulation rate is excellent (95%), it is striking that in our series with mainly SS-LTR's glottic involvement is such an important factor for unfavourable functional long-term outcome after successful decannulation. This supports a different or more extensive surgical approach in children with glottic involvement for better long-term functional outcome, e.g. by adding endoscopic surgical procedures to address the glottic problem separately or by using a double staged approach with a prolonged period of stenting. However, as long-term objective outcome data are lacking in other studies we cannot be sure which strategy has the best long-term outcomes. Also, added endoscopic surgical procedures for a scarred glottis carries its own risk and endotracheal stents have important disadvantages and complications like infection, granulation tissue formation, stent migration and even mortality[19-21]

Our study results clearly show the importance of the presence of comorbidities and its influence on functional outcome. This emphasizes the need for a multidisciplinary approach in these children in an attempt to optimize the overall health status thus optimizing long-term outcome.

We encourage other centers to evaluate their long-term outcome in order to compare different surgical strategies for LTS. In this way, we can come to a mutual agreement on treatment algorithms and the use of stents when glottic involvement of the stenosis is apparent.

Strengths & limitations

This study is the first to report long-term objective functional outcome after pediatric open airway surgery for LTS. We have looked beyond decannulation and have objectively assessed the long-term patency of the reconstructed airway by using pulmonary function testing and the Bruce treadmill test after decannulation. By doing so, we can conclude that the presence of glottic involvement and comorbidities at time of surgery are the only factors for poor long-term functional outcome. This finding has caused us to reconsider our approach for children with LTS and glottic involvement and has strengthened our belief that a multidisciplinary approach is mandatory in these children.

What are the limitations of our study? First, only children who were able to comply with the study protocol performed the functional tests. As a result, only 43 out of 65 patients could perform pulmonary function tests of adequate quality and the majority of children with a congenital syndrome or comorbidities could not comply with the study protocol. Also, there

is a large range in follow-up (2-17 years) which could influence our results. The retrospective set up of this study causes limitations as well, such as selection bias and missing data.

One might argue that the low pulmonary function results might be caused by the pulmonary problems in the fourteen patients with BPD. However, as inspiratory markers were more often impaired than expiratory markers which one would expect to be impaired in children with BPD, this is probably not the case.[22] When the patients with BPD were excluded from the analysis, we found similar outcomes for pulmonary function parameters (data not shown).

Conclusion

We found deficits in pulmonary function and exercise tolerance with decreased quality of life in the majority of patients treated for LTS after long-term follow-up. In our series with mainly SS-LTRs, glottic involvement of the stenosis and the presence of comorbidities are the only factors for less favorable functional outcome. We found a poor correlation between the subjective evaluation of exercise tolerance and objective measurements, implying that history taking is not very useful in this respect. Long-term multidisciplinary follow-up and objective measurements are mandatory when dealing with children with laryngotracheal stenosis.

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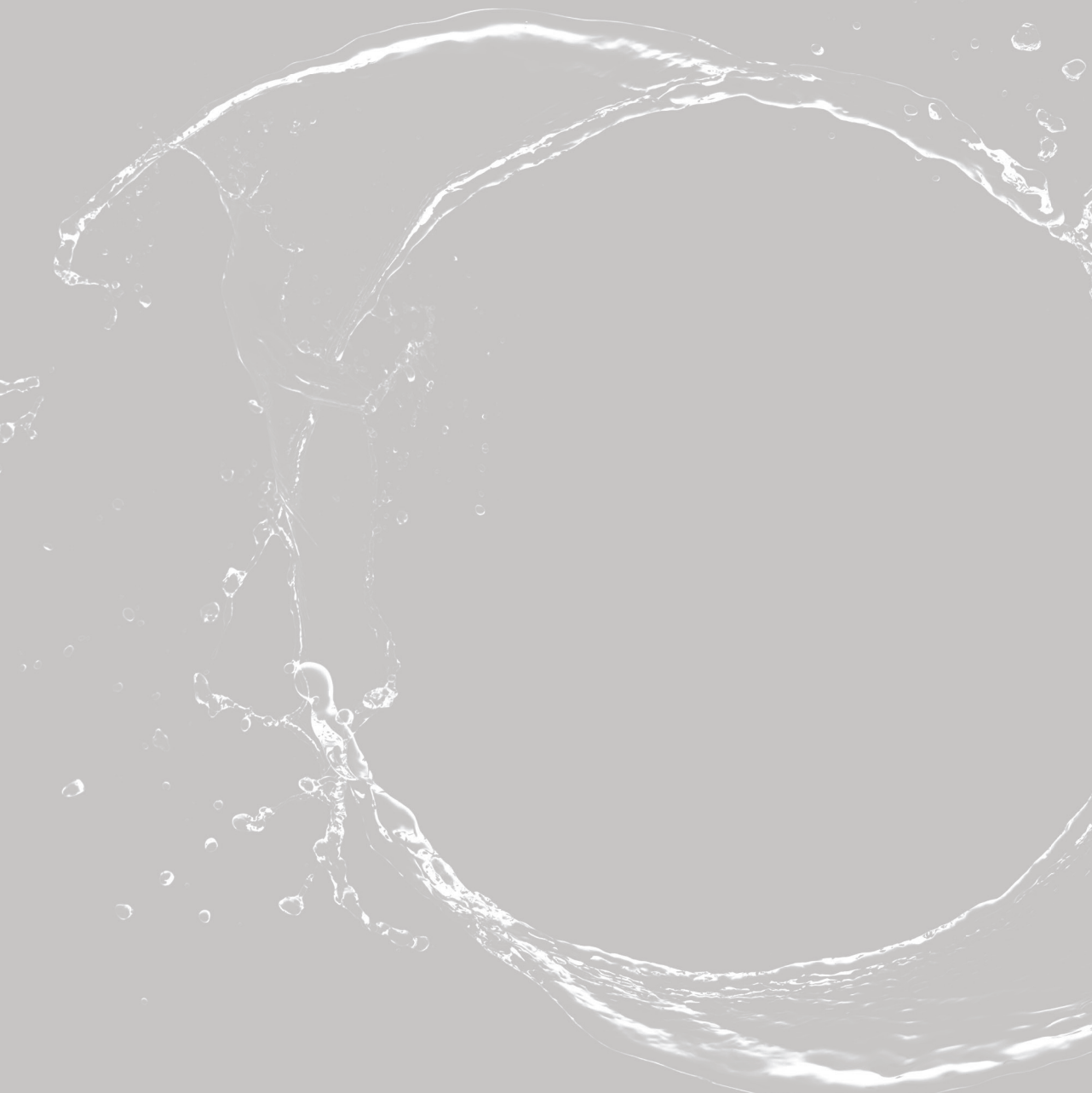

chapter 4

Long-Term Quality of Life in Children after Open Airway Surgery for Laryngotracheal Stenosis

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Int J Pediatr Otorhinolaryngol. 2016 May;84:88-93

Abstract

Objectives. *The purpose of this study is to evaluate the long-term health-related quality of life (HRQoL) in a cohort of children surgically treated for laryngotracheal stenosis (LTS).*

Material and Methods. *Parents of children between 4 and 18 years at follow-up completed the Child Health Questionnaire Parent Form (CHQ-PF50). Children between 11 and 18 years at follow-up completed the Child Health Questionnaire Child Form (CHQ-CF87). Biographical and pre-operative data were extracted from the hospital records. Post-operative measurements consisted of the Bruce Treadmill test and pulmonary function testing (PFT).*

Results. *Fifty-four parents completed the CHQ-PF50; twenty-one children completed the CHQ-CF87. The CHQ-PF50 was significantly worse than the norm population on the subscales physical functioning, role functioning: emotional/behavior, general health perceptions, family activities, parental impact: emotional, and time. CHQ-CF87 was significantly worse than the norm population on physical functioning and better on mental health. After multivariate analysis, presence of comorbidities and glottic stenosis are the most important pre-operative factors for worse scores on general health. As post-operative measurements, the Bruce treadmill test and peak expiratory flow (PEF) correlate well with HRQoL physical subscales.*

Conclusions. *At long-term follow-up after treatment for LTS, deficits in HRQoL may still exist. Presence of comorbidities and glottic stenosis are important negative factors for long-term HRQoL. The Bruce treadmill test and peak expiratory flow on pulmonary function testing correlate well with physical subscales on HRQoL. A long-term multidisciplinary follow-up with assessment of HRQoL is advised in patient treated for LTS.*

Introduction

Acquired laryngotracheal stenosis (LTS) is a life-threatening complication of prolonged intubation for which a tracheostomy is often necessary. Children with laryngotracheal stenosis often have comorbidities; congenital syndromes, bronchopulmonary dysplasia and tracheomalacia are common.[1] Open airway surgery in the form of laryngotracheal reconstruction (LTR) or cricotracheal resection (CTR) has proven its value in the treatment of LTS over the past decades. A number of studies have been published on different treatment modalities, treatment algorithms and surgical outcome. [1-5] Surgical outcome usually focuses on decannulation: the number of patients who have been successfully relieved of their tracheal cannula after surgery. In a recent study, we were the first to report on long-term functional outcome in which we objectively assess the patency of the reconstructed airway.[6] We found that glottic involvement of the stenosis and the presence of comorbidities gave less favorable long-term functional outcome.

To our knowledge, there are no reports on health-related quality of life (HRQoL) in children treated for LTS. This is remarkable, since generic and disease specific quality of life data are in abundance in parents and children with other diseases with large impact and long-term deficits. [7-10] Also, the impact on everyday life of caregivers with children with a tracheostomy has been reported in various previous studies, but long-term HRQoL after successful decannulation has never been reported.[11, 12]

Health-related quality of life measurements give a comprehensive assessment of the patient's health status or health-related quality of life on physical, psychological and social domains and further completes clinical assessment of a patient's well-being. Generic measurements assess the patients HRQoL in a non-disease specific way and are applicable in a wide variety of population samples.[13]

The aim of this study is to describe long-term HRQoL in a cohort of children successfully treated for LTS and identify additional predictors for HRQoL.

Material and methods

This study was part of a large follow-up study of which the methods have been previously described.[6] All children who underwent open airway surgery (LTR or CTR) in the time period of September 1994 until September 2009 for acquired, post-intubation LTS in the Erasmus Medical Center- Sophia Children's Hospital, Rotterdam were approached for this study. Only children who were without a tracheostomy and above the age of four at time of the study were included. The ethics committee approved the study (MEC-2010-298) and informed consent was obtained from all subjects.

Predictor variables: functional health status

Biographical characteristics and pre-operative characteristics

Biographical data comprised of age at time of follow-up and gender. Medical records were checked for age at time of surgery in years, presence of pre-operative tracheostomy, presence of comorbidity Myer-Cotton grade of stenosis, glottic involvement of the stenosis and presence of congenital syndromes.

Medical status at follow–up

Spirometry

During the follow-up visit children performed pulmonary function testing (PFT), which included forced expiratory and inspiratory flow-volume loops. The methods for these measurements are extensively described in our previous publication.[6] Results are given in continuous standard deviations or as percentages in the case of FIV1/VCmax.

Bruce treadmill test

A motor-driven treadmill test was performed according to the Bruce protocol to voluntary exhaustion while heart rate and O_2 saturation were measured in children who were able to comply with the protocol.[14] The methods for this test are extensively described in our previous publication.[6] Results are given in standard deviation (SD) scores. These SD scores are distributed as continuous data.

Outcome measure: Health–Related Quality of Life

HRQoL in children was assessed with the Child Health Questionnaire (CHQ). The Child Health Questionnaire Parent Form (CHQ-PF50, age 4-18 years) was filled out by parents about their child, and Child Health Questionnaire Child Form (CHQ-CF87, age 11-18 years) was filled out by children about themselves.

The Child Health Questionnaire Parent Form (CHQ-PF50) is a generic quality of life instrument measuring subjective health status on both physical and psychosocial domains.[13] Parents were asked to complete 50 items regarding physical and psychosocial concepts, which can be divided into 11 multi-items scales and 2 single-items questions (Family Cohesion and Change in health), see Table 2. Subscale scores range from 0 – 100, where higher scores indicate a better HRQoL.

Raat et al. described satisfactory psychometric properties (subscale Cronbach's α ranged from .39 - .96; mean .72) for the CHQ-PF50. For the CHQ-PF50 normative data were derived from a representative sample of 353 Dutch schoolchildren.[13]

The Child Health Questionnaire Child Form (CHQ-CF87) is a questionnaire with 87 items regarding physical and psychosocial concepts. The CHQ-CF87 consists of 10 multi-items scales and 2 single-items questions (Family Cohesion and Change in health), see Table 2. The

CHQ-PF50 and the CHQ-CF87 have comparable scales with the exception that the CHQ-PF50 contains the subscales Parental Impact: Emotional and Parental Impact: Time. The CHQ-PF50 subscale Role Functioning: Emotional/Behavior is a combination of the CHQ-CF87 Role Functioning: Emotional and Role Functioning: Behavior. The CHQ- CF87 has satisfactory psychometric properties (subscale Cronbach's α ranged from .56 - .90; mean .80. The CHQ-CF87 normative data contained a representative sample of 444 Dutch schoolchildren.[15]

Statistical analysis

Children with complete data for medical history, present medical status, and parent-reported HRQoL were included in the statistical analyses. Comparisons between complete cases (n=65) and non-complete cases (n=11) for age at time of follow-up and age at surgery were done using Mann-Whitney U tests. Pearson's χ2-tests were used to test differences in distributions of gender, presence of pre-operative tracheostomy, presence of comorbidities or congenital syndrome, Myer-Cotton grade of stenosis and glottic involvement of the stenosis.

Due to small sample sizes, comparisons between CHQ-PF50 and CHQ-CF87 were done using non-parametric Wilcoxon signed-rank tests. Comparisons between CHQ-PF50 and CHQ-CF87 means (SD's) and normative data were done with Students' t tests and Cohen's d were calculated.

A two-stage strategy was followed to test the predictive power of functional health status on each subscale of parent-reported HRQoL in multiple linear regression analyses. In phase 1, each pre-operative and post-operative functional health variable was associated with each CHQ-PF50 subscale (univariate analyses). When the association was significant (p<.05), the variables were forced simultaneously into in a cluster analysis (i.e. pre-operative cluster and post-operative cluster). Functional health variables that were not significant (p<.05) in the final model were removed (backward elimination procedure), then the total explained variance (R^2) was calculated. Regression analysis was not performed on the CHQ-CF87 results due to small numbers.

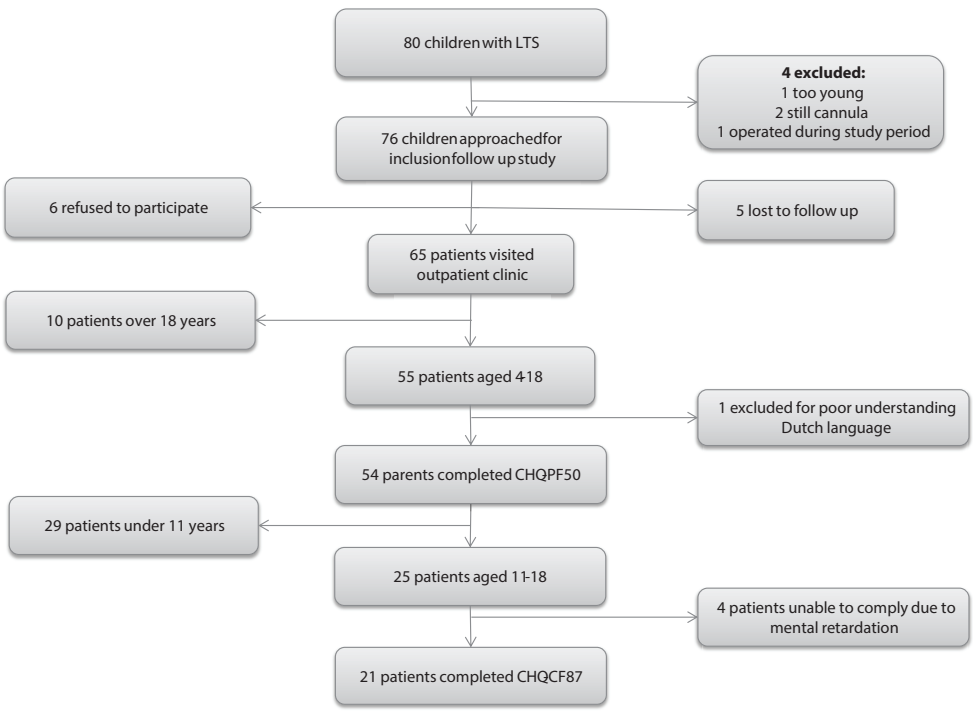
To check multicollinearity, the variance inflation factor (VIF) was calculated. For each model, the average of the VIF's of the entered functional health variables was around 1, which is expedient. Continuous functional health variables (x-axis) were regressed on CHQ-PF50 scales (y-axis) in scatter plots to check the linearity assumption. The scatter plots presented no other than linear relationships for continuous variables. Statistics were conducted using SPSS version 21.0.

Results

Baseline characteristics & pre–operative characteristics

Between September 1994 and September 2009 a total of 80 children were treated with open airway surgery (LTR or CTR) for acquired LTS, of which 76 were eligible and approached for inclusion for this follow-up study, see Figure 1. Six patients refused to participate; five patients were lost to follow-up. The 65 patients who attended the outpatient clinic were considered for the HRQoL questionnaires; fifty-five patients were in the age range 4-18 years and were candidates for the CHQ-PF50. One of these was excluded because of poor understanding of the Dutch language, so fifty-four parents completed the CHQ-PF50. Twenty-one out of twenty-five eligible patients completed the CHQ-CF87; 4 patients were not able to complete the CHQ-CF87 due to mental retardation. Table 1 shows baseline characteristics and medical history of the 54 children included in the CHQ-PF50.

Figure 1: flowchart of in– and exclusion.



LTS = laryngotracheal stenosis, CHQ-PF50 = Child Health Questionnaire Patient Form, CHQ-CF87 = Child Health Questionnaire Child Form

Table 1: Patient characteristics HRQoL CHQ–PF50 (n=54)

Female	29
Median age; range (in years)	11 (4-18)
Median follow-up after surgery; range (in years)	7 (2-16)
Tracheostomy present pre-operatively	43
Grade of stenosis (Myer-Cotton)	
Grade I	1
Grade II	16
Grade III	36
Grade IV	1
Site of stenosis	
Only subglottic	32
Glottic involvement	22
Number of patients with comorbidities[1]	31
Bronchopulmonary Dysplasia (BPD)	10
Tracheomalacia	8
Congenital syndrome	8
Congenital heart disease	4
Other[2]	7
Type of surgery	
Single stage laryngotracheal reconstruction (SS-LTR)	52
Double stage laryngotracheal reconstruction (DS-LTR)	1
Cricotracheal Resection (CTR)	1
Median age at surgery; range (in years)	2 (0-12)

HRQoL = Health-related Quality of Life, CHQ-PF50 = Child Health Questionnaire – Patient Form, SS-LTR = single stage laryngotracheal reconstruction, DS-LTR = double stage laryngotracheal reconstruction, CTR = cricotracheal resection.[1]Seven patients had more than one comorbidity. [2]Comorbidities: other include: Reflux disease, mental retardation and OSAS.

Comparisons between complete cases (n=65) and non-complete cases (n=11) revealed no statistical differences except for the pre-operative Myer-Cotton (MC) grade of stenosis when this was grouped into two categories (category I; MC grade I & II; category II; MC grade III & IV). There was a significantly larger amount of grade III & IV stenosis (category II) in the non-complete group. p= 0.027, namely ten patients with MC grade III, one patient with MC grade IV.

Health–related quality of life (table 2)

Compared with normative data, parents reported significantly lower HRQoL scores on several subscales; physical functioning, role functioning: emotional/behavior, general health perceptions, family activities, parental impact: emotional, and parental impact: time. Cohen's d was largest for the subscales physical functioning (d=1.15), general health perceptions (d=1.45) and parental impact: time (d=0.77).

Children themselves reported comparable scores as normative data, with the exception of the subscales physical functioning and mental health. Children reported significantly worse physical functioning and better mental health compared with healthy peers.

Table 2: Mean scores of Child Health Questionnaire – Parent Form and Child Health Questionnaire – Child Form

CHQ subscale, mean (SD)	CHQ-P50 (4-18 years) n = 54				CHQ-CF87 (10-18 years) n = 21			
	Patients	**Norm**	***p*-value**	**Cohen's d**	**Patients**	**Norm**	***p*-value**	**Cohen's d**
Physical functioning (PF)	83.1 (19.2)	99.1 (4.3)	<.01	1.15	88.7 (16.2)	96.8 (5.4)	.03	0.60
Role functioning: emotional/ behavior (REB)[a]	86.2 (26.3)	97.9 (7.2)	<.01	0.61	90.2 (19.7)	91.9 (15.3)	.70	0.10
Role functioning: Physical (RP)	89.9 (22.5)	95.8 (15.6)	.07	0.30	91.5 (21.3)	96.5 (11.6)	.30	0.29
Bodily pain (BP)	83.7 (21.7)	85.7 (17.2)	.51	0.10	85.2 (21.4)	78.2 (19.2)	.15	0.34
General behavior (GB)	74.7 (15.1)	78.5 (13.1)	.08	0.27	85.7 (10.6)	83.6 (10.2)	.38	0.20
Mental health (MH)	77.1 (14.4)	81.4 (12.1)	.04	0.32	83.8 (9.6)	78.2 (13.0)	.02	0.49
Self-esteem (SE)	75.6 (13.7)	79.2 (11.0)	.07	0.29	78.5 (13.1)	75.4 (12.5)	.29	0.24
General health perceptions (GH)	55.7 (22.9)	82.9 (13.4)	<.01	1.45	70.4 (21.5)	74.6 (15.9)	.38	0.22
Family activities (FA)	82.5 (21.1)	91.5 (11.9)	<.01	0.53	90.7 (13.4)			
Family cohesion (FC)	73.7 (19.6)	72.2 (19.4)	.60	0.08	80.5 (17.5)	75.7 (23.1)	.21	0.23
Change in health (CH)	59.3 (19.0)	56.1 (18.4)	.25	0.17	52.4 (10.9)			
Parental impact: Emotional (PE)	78.4 (18.7)	86.3 (15.2)	<.01	0.50				
Parental impact: Time (PT)	82.5 (24.3)	94.0 (13.0)	<.01	0.77				

SD = standard deviation. Cohen's d: 0.2 ≤ d < 0.5 indicated a small effect, 0.5 ≤ d <0.8 a moderate effect, d ≥ 0.8 a large effect. A negative size meant a higher score with regard to the norm group. [a] Role functioning: emotional/behavior (REB) for CHQ-CF87 is the mean of Role functioning: emotional (mean 92.6 SD 18.4) and Role functioning: behavioral (mean: 87.8 SD 27.9).

Comparison between parent–report and self–report (table 3)

On six of eleven corresponding subscales, parents reported significantly lower HRQoL scores compared with their children.

Table 3: Comparison median scores of Child Health Questionnaire – Parent Form and Child Form in same children (n=21)

CHQ subscale, median (IQR)	Child Health Questionnaire		
	Parent form	Child form	*p*
Physical functioning	88.9 (69.4 – 100.0)	96.3 (85.2 – 100.0)	.01
General health perceptions	60.0 (45.4 – 92.5)	71.7 (54.8 – 89.3)	.02
Role functioning: Physical	100.0 (75.0 – 100.0)	100.0 (80.0 – 100.0)	.22
Bodily pain	100.0 (75.0 – 100.0)	100.0 (80.0 – 100.0)	.62
Role functioning: Emotional/behavior	100.0 (66.7 – 100.0)	100.0 (91.7 – 100.0)	.12
Mental health	75.0 (70.0 – 92.5)	82.8 (75.0 – 91.4)	.02
Self-esteem	75.0 (66.7 – 85.4)	76.8 (70.5 – 91.0)	.34
General behavior	72.5 (68.3 – 88.3)	87.4 (75.4 – 94.9)	.01
Family activities	83.3 (75.0 – 100.0)	95.8 (85.4 – 100.0)	.01
Family cohesion	60.0 (60.0 – 85.0)	85.0 (60.0 – 100.0)	.02
Change in health	50.0 (50.0 – 50.0)	50.0 (50.0 – 50.0)	.66

CHQ = Child Health Questionnaire, IQR = interquartile range

Associations between functional health status and HRQoL (table 4)

To determine the association between functional health status and HRQoL, a two-stage strategy was followed for each CHQ-PF50 scale. Results of the first phase: univariate associations between functional health status and CHQ-PF50 scales are presented in Table 4. The results of phase 2 are reported below.

Table 4: Associations (β) between functional health status (pre–operative and post–operative health status) and Child Health Questionnaire – Parent Form

	Physical health status				Psychosocial health status				Parent		Family		
	PF	**GH**	**RP**	**BP**	**REB**	**MH**	**SE**	**GB**	**PE**	**PT**	**FA**	**FC**	**CH**
Pre-operative health status n = 54													
Biographical demographics													
Age, years	.08	.23	.03	.22	-.08	.03	.02	.07	.10	.03	.01	-.16	-.25
Gender [a]	.06	.16	.14	.15	.25	.07	.14	.08	-.01	.09	-.03	.33*	.28*
Follow-up time, years	.20	.24	.25	.22	.09	.04	.04	.08	.06	.05	.04	-.06	-.10
Medical history													
Age at surgery, years	-.19	-.02	-.33*	-.03	-.25	-.03	-.09	-.01	.03	-.05	-.12	-.12	-.20
Tracheostomy present? [b]	.14	.10	.05	.01	-.13	.16	.02	.01	-.05	.02	-.03	.07	.19
Comorbidity present? [b]	-.19	-.38*	-.05	-.20	-.07	.10	.02	.03	-.21	-.13	-.20	.04	.28*
Glottic involvement [b]	-.25	-.35*	-.31*	-.13	-.16	-.24	-.07	-.07	-.03	-.04	.03	-.11	-.16
Myer-Cotton [c]	.10	.01	.02	-.05	-.12	.14	.07	-.03	-.04	-.01	.06	.11	.12
Congenital syndrome? [b]	.03	-.09	.19	.04	.11	.07	.01	.04	-.04	.03	-.12	.12	.24
Height for Age, SD	.20	.40*	.07	.01	.03	-.11	.05	-.15	-.08	-.02	.10	.01	-.37*
Post-operative health status n = 36													
Spirometry, FIV1/VCmax in %	.31	.38*	.38*	.25	.20	.23	.14	-.02	.09	.19	.07	.08	-.06
Spirometry, VCmax SD	.22	.31	.02	.14	.12	-.24	-.16	-.14	.12	-.06	.20	-.20	-.22
Spirometry, PEF SD	.51*	.50*	.41*	.38*	.31	.09	.12	-.12	.24	.17	.15	-.29	-.13
Spirometry, FEV1 SD	.38*	.45*	.25	.20	.25	.05	.08	-.01	.17	.03	.19	-.13	.10
Bruce treadmill test, SD	.60*	.32	.55*	.16	.53*	.24	.28	.02	.28	.24	.26	-.06	.32

Standardized coefficients β. * indicates a significant association $p< 0.05$. PF = physical functioning, REB= role functioning: emotional/behaviour, RP= role functioning: physical, BP = bodily pain, GB= general behaviour, MH= mental health, SE= self-esteem, GH= general health, PE= parental impact: Emotional, PT= parental impact: Time, FA= Family activities, FC= Family Cohesion, CH= Change in health FIV1 = forced inspiratory volume in 1 second, VCmax = maximum vital capacity, PEF = peak expiratory flow, FEV1 = forced expiratory volume in 1 second SD = standard deviation a) female = 0, male = 1 b) no = 0 , yes = 1, c) Myer-Cotton, 0 = grade I & II, 1 = grade III & IV

Predicting factors for HRQoL (table 5)

The presence of comorbidities was associated with worse general health and more parent-reported positive change in health compared with the previous year.

Glottic involvement of the stenosis was associated with worse general health.

Higher age at surgery was associated with more parent-reported limitations in physical functioning.

Male gender was associated with more parent-reported positive change in health compared with the previous year and higher scores as to family cohesion, the family's ability to get along.

Health status at follow–up and HRQoL (table 5)

In multivariate analyses, inspiratory pulmonary function tests in children did not remain associated with HRQoL.

Higher endurance scores (SD) and higher expiratory peak flow SD scores in children was significantly associated with better physical functioning.

Higher PEF SD scores were associated with better parent-reported general health and with less bodily pain.

Higher endurance SD scores were associated with less limitations in role functioning due to physical health, with less limitations in school and in activities due to emotional or behaviour problems, and with better physical functioning.

Table 5: Final model results of health status associated with Child Health Questionnaire – Parent Form 50

Pre-operative health status n=54	**Constant**	**Unstandardised β**	**SE**	**Standardised β**	***p*-value**	**Multiple R^2**
General Health (GH)						
Comorbidity[1]	71.75	-17.00	5.54	-0.37	<.01	0.26
Presence of glottic involvement [1]		-15.49	5.58	-0.34	<.01	
Role Physical (RP)						
Age at surgery	97.75	-2.67	1.09	-0.33	.02	0.11
Change in health (CH)						
Comorbidity[1]	48.01	10.74	4.89	0.28	.03	0.16
Male gender		10.97	4.85	0.29	.03	
Family Cohesion (FC)						
Male gender	67.76	12.84	5.10	0.33	.02	0.11
Present health status n=36	**Constant**	**Unstandardised β**	**SE**	**Standardised β**	***p*-value**	**Multiple R^2**
Physical functioning (PF)						
Bruce treadmill test, SD score	109.21	7.65	2.44	0.46	<.01	0.43
Spirometry, PEF SD score		7.73	3.50	0.33	.04	
General Health (GH)						
Spirometry, PEF SD score	83.95	13.63	4.10	0.50	<.01	0.25
Role emotional and behavioural (REB)						
Bruce Treadmill Test, SD score	103.30	11.44	3.14	0.53	<.01	0.28
Role Physical (RP)						
Bruce Treadmill Test, SD score	103.79	11.23	2.97	0.54	<.01	0.29
Bodily Pain (BP)						
Spirometry, PEF SD Score	102.36	10.15	4.21	0.38	.02	0.15

SD = standard deviation PEF = Peak Expiratory Flow; 1: 0 = no, 1 = yes

Discussion

This is the first study to investigate the long-term HRQoL in a large cohort of children surgically treated for laryngotracheal stenosis. We found several lower parent-reported HRQoL scores when compared to the normal population. Parents scored their children's HRQoL lower than the children themselves. After multivariate analysis we found significant associations between a number of pre- and post-operative health status variables and several parent-reported HRQoL subscales.

Compared with the norm population, parents reported significantly lower scores for their children, predominately on physical subscales and less so on psychosocial subscales. The mean parent-reported scores strikingly resemble the parent-reported scores of children suffering from asthma.[13] This is an indication that both in children with lower and upper airway obstruction physical limitations may play an important role in the quality of life.

In our study it is remarkable that the self-reported scores from the children hardly differed from the norm population with the exception of worse physical functioning and better mental health. The latter may indicate that children in our cohort feel happier than the norm population, despite their extensive medical history.

The difference in health perceptions between parents and children is further emphasized when comparing the parent form and the child form. Parents reported significantly lower scores than their children on the majority of comparable subscales. This difference in scores between parents and their children has also been reported previously in other studies.[7, 9, 10, 16] As other authors have also stated, this is not a case of one or the other being "right" or "wrong" but rather that both the self-reported and parent-reported questionnaires have their own value in determining the patients HRQoL; both may give a comprehensive insight in the children's well-being. The clinician, however, needs to be aware that the judgment of parents can be clouded by their own mental well-being, past experiences and expectations for the future or the inevitable comparison with healthy peers. On the other hand, children might be inclined to downplay their shortcomings and accept them as normal.

Regarding the pre-operative health status, the presence of comorbidities and presence of glottic stenosis were important factors for lower scores on general health. In our studied group in almost all children a single stage (SS-LTR) approach was done, even in cases with higher grades of stenosis and glottic involvement in which other authors would have proposed a double staged approach with stenting. Because glottic involvement of the stenosis is such an important negative factor for long-term HRQoL it might be advocated that a more extensive approach is necessary for LTS to overcome this; post-operative stenting or addressing the glottis with a separate surgical procedure can be proposed. [1, 3, 6]

Regarding post-operative health status, there was a strong correlation between the Bruce treadmill test and the parent-reported quality of life outcome after long-term follow-up on several physical and socio-emotional subscales. The physical functioning subscale of the parent-reported HRQoL correlates very well with the outcome on the Bruce treadmill test. This could be helpful in the outpatient clinic, for example by using the six questions (What kind of limitations did your child experience in the last four weeks while doing minimal or strenuous exercise, a stroll in the neighborhood, walking the stairs, bending over or during body care and hygiene) of this subscale for a quick assessment of the child's physical functioning. Also, the Bruce treadmill test proved to be an excellent tool for the assessment of long-term functional and HRQoL status.

Concerning pulmonary function tests (PFT), the expiratory peak flow (PEF) corresponded well with the physical subscales of the HRQoL questionnaires. This indicates that the presence of comorbidities of the lower airways (bronchopulmonary disease (BPD), tracheomalacia) play an important part in the quality of life after long-term follow-up. It is remarkable that the inspiratory flow didn't correlate to any HRQoL subscale, since residual LTS in our population should give a limitation in inspiratory flow. A possible explanation for this is that no validated reference values exist for the peak inspiratory flow (PIF) on pulmonary function tests in children. This makes an adequate statistical analysis on peak inspiratory flow impossible.

Given the large number of functional deficits, low HRQoL scores and complex comorbidities, it is paramount that a multidisciplinary long-term follow-up is mandatory after surgery for laryngotracheal stenosis. [1,6] This study shows that adding a generic HRQoL instrument such as the CHQ further strengthens the clinicians understanding of the patient's well-being after long-term follow-up. Both the parent-reported as well as the child-reported questionnaire have value in determining the HRQoL in these patients.

Strengths and limitations

This is the first study to describe the HRQoL in a large cohort of children treated for LTS. We have found several significant biographical, pre-operative and post-operative factors associated with lower scores on quality of life. This can provide caregivers necessary tools when consulting children and their parents on surgery and expectations on the long run. In addition, we have found that both the Bruce Treadmill test and the expiratory peak flow measurement have excellent correlations with the physical subscales of the parent reported Child Health Questionnaires, clearly linking functional deficits with lower Health-related Quality of Life.

As to the limitations: first, this is still a relatively small cohort of children with a large heterogeneity and a large range in follow-up (2-16 yrs.). Most of the biographical demographics and pre-operative factors were acquired retrospectively from the hospital records, which carries the risk of incomplete data. Also, there have been minor alterations

(shorter intubation time, no more use of muscle relaxants, use of antibiotics and PPI's) in the surgical approach and post-operative care of these patients during the last 15 years. The fact that patients were called back for a large follow-up study carries the risk for recall bias; when comparing the inclusions to the non-complete cases, there is a significant difference in severity of the stenosis (Myer-Cotton grade). This could mean that the results in this study do not fully represent the entire cohort, possibly giving an incorrectly positive image.

The fact that the parent-reported questionnaire significantly differed from the self-report questionnaire could be due to the fact that the children downplay their shortcomings and accept their current health status as normal. Another reason could be that the mental health status of the parents influence their judgement. This was not investigated in our study, so this remains uncertain. In future research as well as in our clinical practice, we probably should combine HRQoL questionnaires of the children with a generic psychosocial questionnaire addressing the mental health status of the parents.

Conclusions

At long-term follow-up after successful surgery for LTS, children may suffer from important limitations in HRQoL. Presence of comorbidities and glottic involvement of the stenosis were the most important pre-operative predicting factors for poorer HRQoL. As post-operative measurements, the Bruce treadmill test and peak flow measurement highly correlated with the physical subscales of the HRQoL. Quality of life assessment should be included in daily practice when treating these children and a long-term multidisciplinary follow-up is mandatory.

Acknowledgements

The authors thank Marit van Brandwijk for her work on the quality of life database.

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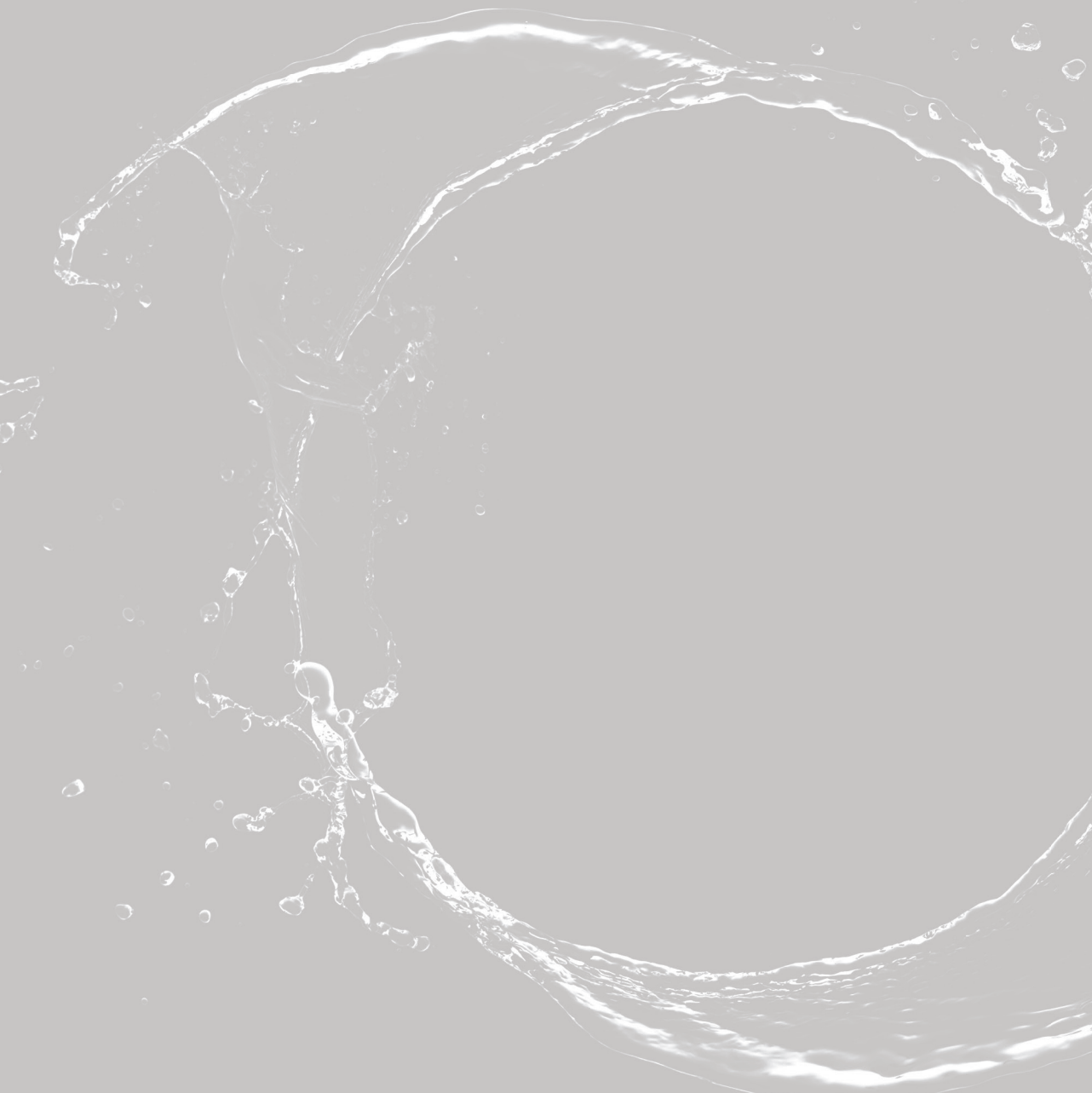

chapter 5

Reliability and Validity of the Dutch Pediatric Voice Handicap Index

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Submitted for publication

Abstract

Objectives. *The pediatric voice handicap index (pVHI) has been developed to provide a better insight into the parents' perception of their child's voice-related quality of life. The purpose of the present study was to validate the Dutch pVHI by evaluating its internal consistency and reliability. Furthermore, we determined the optimal cut-off point for a normal pVHI score.*

Material and Methods. *All items of the English pVHI were translated into Dutch. Parents of children in our dysphonic and control group were asked to fill out the questionnaire. For the test re-test analysis we used a different study group who filled out the pVHI twice as part of a large follow-up study. Internal consistency was analyzed through Cronbach's a coefficient. The test-retest reliability was assessed by determining Pearson's correlation coefficient. Mann-Whitney test was used to compare the scores of the questionnaire of the control group with the dysphonic group. By calculating receiver operating characteristic (ROC) curves, sensitivity and specificity we were able to set a cut-off point.*

Results. *We obtained data from 122 asymptomatic children and from 79 dysphonic children. The scores of the questionnaire significantly differed between both groups. The internal consistency showed an overall Cronbach a coefficient of 0.96 and an excellent test-retest reliability of the total pVHI questionnaire with a Pearson's correlation coefficient of 0.90. A cut-off point for the total pVHI questionnaire was set at 7 points with a specificity of 85% and sensitivity of 100%. A cut-off point for the VAS score was set at 13 with a specificity of 93% and sensitivity of 97%.*

Conclusions. *The Dutch pVHI is a valid and reliable tool for the assessment of children with voice problems. By setting a cut-off point for the score of the total pVHI questionnaire and the VAS score, the pVHI might be used as a screening tool to assess dysphonic complaints and the pVHI might be a useful and complementary tool to identify children with dysphonia.*

Introduction

Reports on childhood dysphonia describe prevalence varying from 6 – 22%.[1,2] The most frequent causes in school-age children are vocal fold nodules, but also edema or irregularity of the vocal fold, laryngeal papillomatosis, cysts and polyps, laryngotracheal stenosis, vocal fold paralysis or a laryngotracheo-esophageal cleft can result in dysphonia. Dysphonia may negatively affect the quality of life in children.[3,4]

A number of tools are available for assessment of dysphonia; traditional endoscopy, perceptual assessment and objective (computer assisted) voice analysis can all be used to assess voice disorders. Given the impact of an impaired voice on the quality of life of a child with effects on the social, emotional and functional well-being, it is important to evaluate the voice-related quality of life.[3,5-8] Zur et al[9] developed the pediatric voice handicap index (pVHI), based on the original voice handicap index (VHI) for adults[10] to assess voice-related quality of life in children. This pVHI is a parent proxy questionnaire which enables practitioners to quantify the impact of voice disturbance on the child's well-being and to evaluate surgical, medical and behavioral interventions. The aim of this study was to validate the Dutch version of the pVHI and to evaluate its usefulness as a diagnostic tool by determining a 'cut-off point' for a normal score of the total pVHI questionnaire and VAS score.

Material and Methods

Development of the Dutch pVHI

The pVHI consists of three parts: a talkativeness scale, a questionnaire and a visual analogue scale (VAS) score. Parents judge their child's talkativeness on a seven-point scale ranging from 1 (quiet listener) to 7 (extremely talkative). The questionnaire consists of 23 questions divided into three domains: functional (7 questions), physical (9 questions) and emotional (7 questions), using a five-point scale ranging from 0 (never) to 4 (always). Scores on the three domains are added up to form the total pVHI questionnaire varying from 0 to 92. Higher scores indicate worse voice-related quality of life. Lastly, parents judge the overall quality of their child's voice on a visual analogue scale (VAS, varying from 0 to 100), where higher scores indicate worse voice quality.

All items of the original, English version of the pVHI (see Appendix A) were translated into Dutch, translated back into English and finally compared with the original items by a bilingual physician and a bilingual, native English speech therapist. The final version was compared with the original version by Zur et al.[9] After some small adaptations based on Zur's comments, the final version of the Dutch pVHI was established (see Appendix B).

Participants

The internal consistency of the Dutch pVHI was analyzed using data obtained from a group of dysphonic children and a group of asymptomatic schoolchildren. Our dysphonic group included patients who visited our pediatric outpatient clinic for dysphonia between July 2010 and November 2014. This group was investigated by a speech therapist and an ear nose throat (ENT) surgeon. If indicated and possible an endoscopic examination was done. During this visit all parents were asked to fill out the pVHI. Data were retrospectively obtained from the records. The control group consisted of asymptomatic children recruited from schools in the neighborhood of the hospital. Children with a history of voice complaints or voice treatment were excluded from participation in this study. The control group was matched to the dysphonic group for age and gender. For the test re-test analysis, we used the pVHI's of a cohort of children with a history of laryngotracheal stenosis who filled out the questionnaire twice as part of a large follow-up study.[11] They completed the pVHI twice with no intervention in between and no access to their previous responses. The study was previously approved by the Clinical Research Ethics Committee at our hospital.

Statistical analysis

Continuous variables were analysed using the non-parametric Mann Whitney U test and categorical variables using the chi-squared test. The internal consistency was assessed using Cronbach's coefficient α. An α greater than 0.9 was considered 'excellent'. The test- retest reliability was assessed by determining the level of agreement between the results of the first and the second pVHI with Pearson's correlation coefficient. A value between 0.41 – 0.60 was considered 'moderate', a value between 0.61 – 0.80 was considered 'substantial ´ and a value ≥ 0.81 was considered 'almost perfect'. Receiver Operating Characteristics (ROC) curves, sensitivity and specificity where calculated to set a cut-off point for total pVHI questionnaire and VAS score. A *p*-value of < 0.05 was considered significant. All statistics and analysis were performed using SPSS version 20 (IBM, Chicago, USA).

Results

Parents of 79 children with voice disorders and 122 parents of children in the control group filled out the questionnaire. Baseline characteristics are given in table 1.

Table 1: Comparison between dysphonic and control group regarding age and gender.

	dysphonic group n = 79	**control group n = 122**	***p* - value**
Age (years)	8.9 (4 - 18)	9.6 (4 - 17)	0.10
Boys	44 (55.7%)	65 (53.3%)	0.74

Age at visit (range in years). Gender is reported in number and percentage (%).

A variety of voice disorders was diagnosed in the dysphonic group, these are given in table 2. Sixteen patients refused endoscopic examination.

Table 2: Voice disorders diagnosed in de dysphonic group.

	Dysphonic group n = 79
Vocal fold nodules	30
Unilateral vocal fold paralysis	8
Vocal cord cyst/ polyp	7
Incomplete posterior glottic closure	7
Laryngeal web	3
Bilateral vocal fold paralysis	1
Papillomatosis	1
Laryngopharyngeal reflux	1
No apparent disorders	5
Endoscopic examination refused by patient	16

The outcome of the talkativeness scale, the questionnaire and the VAS of both groups are given in table 3. Except for talkativeness, all scores differed significantly between the dysphonic group and the control group.

Table 3: The talkativeness, pVHI questionnaire scores including subscores for each domain, and VAS score of the pVHI obtained from the parents of the dysphonic group and the control group.

	dysphonic group n = 79	**control group n = 122**	***p* - value**
Talkativeness	5 (4 - 6)*	4 (4 - 5)***	0.29
Functional	7 (3 - 13)	2 (2 - 4)	< 0.001
Physical	14 (10 - 19)	0 (0 - 1)	< 0.001
Emotional	5 (1 - 10)	0 (0 - 0)	< 0.001
Total pVHI	25 (16 - 41)	2 (2 - 5)	< 0.001
VAS	61 (28 - 76)**	2 (2 - 6)***	< 0.001

Data are presented in median (25% - 75%)
* available in 77 cases. ** available in 76 cases. *** available in 120 cases.

Table 4 shows the results for the internal consistency for each of the three domains and for the total pVHI questionnaire score using data from 201 children, both the control group and the dysphonic group.

Table 4: Cronbach's α coefficient for each of the three domains and for the total pVHI questionnaire score.

	Number of items	**Cronbach's α coefficient (n= 201)**
Functional	7	0.91
Physical	9	0.93
Emotional	7	0.92
Total pVHI questionnaire	23	0.96

For the test re-test analysis parents of 32 children with a history of surgery for laryngotracheal stenosis completed the pVHI twice with an interval of at least 2 days and at most 3 months. This group consisted of 14 boys (44%) and 18 girls (56%), with a median age of 11 years, ranging from 4 to 18 years. The Pearson correlation coefficient *r* of the talkativeness, the questionnaire and the VAS score are shown in table 5.

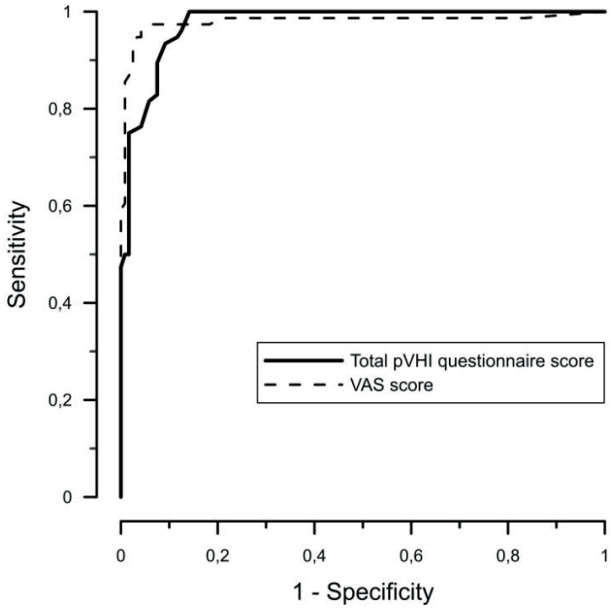
Table 5. Reliability analysis; test re–test

	Pearson's coefficient *r* (n = 32)
Talkativeness	0.53*
Functional	0.90*
Physical	0.89*
Emotional	0.73*
Total pVHI	0.90*
VAS	0.88*

* $p < 0.01$

In order to determine the best cut off point ROC curves, sensitivity and specificity were calculated. The area under the curve (AUC) of the total pVHI questionnaire score was 0.98 (95% confidence interval (CI) 0.96-0.99, $p < 0.0001$). The AUC of the VAS score was 0.98 (95% CI 0.96-1.00, $p < 0.0001$). The optimal cut off point of the total pVHI questionnaire was 7 points with a specificity of 85% and sensitivity of 100% and the optimal cut off point for the VAS score was 13 with a specificity of 93% and sensitivity of 97%. (see figure 1)

Figure 1: ROC curve analysis of total pVHI questionnaire score and VAS score to discriminate dysphonic children from control children.



Discussion

In this study, we have validated the Dutch version of the pVHI. We found an excellent internal consistency and a high test re-test reliability with moderate to almost perfect correlation. When used on a group of dysphonic patients, we found significantly higher scores for the total pVHI questionnaire, its three subdomains and the VAS score when compared to a normal control group.

There is no single instrument that accurately interprets voice problems. Endoscopic examination, perceptual assessment and voice analysis can be used to evaluate laryngeal pathology. However, they do not provide information regarding a child's voice-related quality of life. The pVHI is an easy to use and standardized instrument to evaluate the emotional, physical and functional aspects of a child with voice problems and it has been validated in several languages.[9,12-16] Our study, the largest study group so far, show comparably good results.

In contrast to the pVHI questionnaire scores and the VAS score, we found no differences in talkativeness between the dysphonic group and the control group. This might imply that children do not hold back talking despite their voice problems. In accordance with these results, our research group [11] reported previously a median talkativeness score of 5 in a group

of children treated for laryngotracheal stenosis with a high prevalence of voice complaints. If the talkativeness does not discern dysphonic children from children without voice problems, one could question its value in the pVHI. In previous studies on the validity of the pVHI the results of the talkativeness were not mentioned.

The ROC curves for the total pVHI questionnaire and the VAS score show high accuracy in identifying children with and without voice disorders. With an optimal sensitivity and specificity, we found a cut-off point of 7 points for the total pVHI questionnaire and a cut-off point of 13 for the VAS score. This means that a total pVHI score of 7 or higher, or a VAS score of 13 or higher indicates dysphonia and this finding could be of use as a screening tool to identify children with dysphonia.

We acknowledge the limitations of this study. The characteristics and pVHI scores of the dysphonic group were extracted from the hospital records retrospectively, carrying the risk of incomplete data. We included our dysphonic children on the criterion that they visited our dysphonia outpatient clinic, thereby assuming only children who are dysphonic visit this clinic for voice disorders. However, all total pVHI questionnaire scores were above 7 in the dysphonia group. For the test-retest analysis we used a different study group.

Despite these limitations we feel that our study, with a large sample size and a good quality control group shows results in agreement with previous studies, making the Dutch pVHI a valid and reliable tool to provide insight into the parents' perception of their child's voice-related quality of life.

Conclusion

This large study shows that the Dutch pVHI is a valid and reliable tool for the assessment of children with voice problems. It is an easy to use tool to assess the voice-related quality of life in children and by setting a cut-off point for the score of the total pVHI questionnaire and the VAS score, the pVHI can possibly be used as a screening tool to evaluate prevalence of dysphonia.

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Appendix A

Original version of pVHI

I would rate my/ my child's talkativeness as the following (circle response)

1	2	3	4	5	6	7
Quiet Listener			Average Talker			Extremely Talkative

To be filled out by Staff

F= _____
P= _____
E= _____
Total= _____

Talkativeness: _____

Instructions: These are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience.

0= Never 1 = Almost never 2= Sometimes 3= Almost always 4 = Always

Part I - F					
1) My child's voice makes it difficult for people to hear him/ her	0	1	2	3	4
2) People have difficulty understanding my child in a noisy room	0	1	2	3	4
3) At home, we have difficulty hearing my child we he/ she calls through the house	0	1	2	3	4
4) My child tends to avoid communicating because of his/ her voice	0	1	2	3	4
5) My child speaks with friends, neighbors, or relatives less often because of his/ her voice	0	1	2	3	4
6) People ask my child to repeat him/ herself when speaking face-to-face	0	1	2	3	4
7) My child's voice difficulties restrict personal, educational and social activities	0	1	2	3	4
Part II - P					
1) My child runs out of air when talking	0	1	2	3	4
2) The sound of my child's voice changes throughout the day	0	1	2	3	4
3) People ask, "What's wrong with your child's voice?"	0	1	2	3	4
4) My child's voice sounds dry, raspy, and/ or hoarse	0	1	2	3	4
5) The quality of my child's voice is unpredictable	0	1	2	3	4
6) My child uses a great deal of effort to speak (e.g., straining)	0	1	2	3	4
7) My child's voice is worse in the evening	0	1	2	3	4
8) My child's voice "gives out" when speaking	0	1	2	3	4
9) My child has to yell in order for others to hear him/ her	0	1	2	3	4
Part III - E					
1) My child appears tense when talking to others because of his or her voice	0	1	2	3	4
2) People seem irritated with my child's voice	0	1	2	3	4
3) I find other people don't understand my child's voice problem	0	1	2	3	4
4) My child is frustrated with his/ her voice problem	0	1	2	3	4
5) My child is less outgoing because of his/ her voice problem	0	1	2	3	4
6) My child is annoyed when people ask him/ her to repeat	0	1	2	3	4
7) My child is embarrassed when people ask him/ her to repeat	0	1	2	3	4

Overall Severity Rating of Voice
(Please place "X" mark anywhere along this line to indicate the severity of your child's voice; the verbal descriptions serve as a guide)

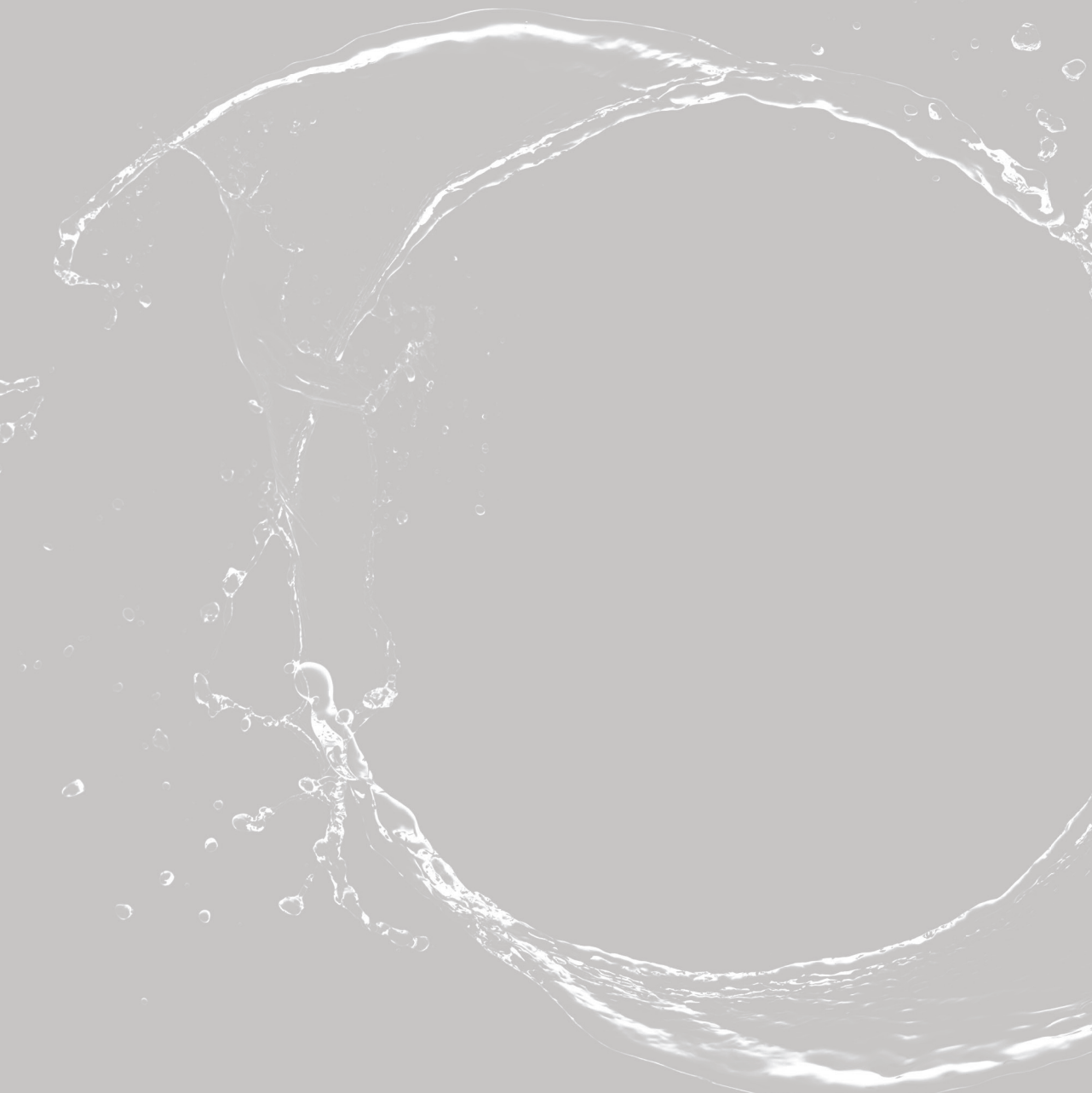
Normal Severe

Appendix B

The Dutch version of the pVHI

A	Ik zou mijn kind beschrijven als: (omcirkel een getal)	**1** Rustige luisteraar	**2**	**3**	**4** Gemiddelde prater	**5**	**6**	**7** Zeer drukke prater
B	Dit zijn uitspraken die mensen gebruiken om hun stem en de effecten van hun stem op hun leven te beschrijven. Kruis het vakje aan bij het antwoord dat aangeeft hoe vaak u dezelfde ervaring heeft.							
			Nooit	**-bijna nooit**	**-soms**	**-bijna altijd**	**-altijd**	
	F							
	1	Door zijn/haar stem vinden mensen het moeilijk mijn kind te horen	❑	❑	❑	❑	❑	
	2	Mensen verstaan mijn kind moeilijk in een rumoerige omgeving	❑	❑	❑	❑	❑	
	3	Als mijn kind ergens in huis roept, kunnen wij hem/haar niet goed horen	❑	❑	❑	❑	❑	
	4	Mijn kind heeft de neiging praten te vermijden vanwege zijn/haar stem	❑	❑	❑	❑	❑	
	5	Mijn kind praat minder met vriendjes, buren en familieleden vanwege zijn/haar stem	❑	❑	❑	❑	❑	
	6	In een één op één gesprek vragen mensen mijn kind soms iets te herhalen	❑	❑	❑	❑	❑	
	7	De stemproblemen van mijn kind beperken hem/haar in persoonlijke, schoolse en sociale activiteiten	❑	❑	❑	❑	❑	
	P							
	1	Mijn kind raakt buiten adem tijdens het praten	❑	❑	❑	❑	❑	
	2	De klank van de stem van mijn kind verandert in de loop van de dag	❑	❑	❑	❑	❑	
	3	Mensen vragen mij: “Wat is er aan de hand met de stem van uw kind?”	❑	❑	❑	❑	❑	
	4	De stem van mijn kind klinkt droog, krakerig en/of hees	❑	❑	❑	❑	❑	
	5	De stemkwaliteit van mijn kind is onvoorspelbaar	❑	❑	❑	❑	❑	
	6	Praten is voor mijn kind een grote inspanning (bijvoorbeeld “forceren”)	❑	❑	❑	❑	❑	
	7	De stem van mijn kind is ‘s avonds slechter	❑	❑	❑	❑	❑	
	8	De stem van mijn kind wordt zwakker tijdens het praten	❑	❑	❑	❑	❑	
	9	Mijn kind moet schreeuwen om te zorgen dat anderen hem/haar horen	❑	❑	❑	❑	❑	
	E							
	1	Mijn kind maakt tijdens praten met anderen een gespannen indruk vanwege zijn/haar stem	❑	❑	❑	❑	❑	
	2	Mensen lijken zich te ergeren aan de stem van mijn kind	❑	❑	❑	❑	❑	
	3	Ik merk dat andere mensen het stemprobleem van mijn kind niet begrijpen	❑	❑	❑	❑	❑	
	4	Mijn kind is gefrustreerd door zijn/haar stemprobleem	❑	❑	❑	❑	❑	
	5	Mijn kind is minder spontaan door zijn/haar stemprobleem	❑	❑	❑	❑	❑	
	6	Het ergert mijn kind als mensen hem/haar vragen iets te herhalen	❑	❑	❑	❑	❑	
	7	Mijn kind schaamt zich als mensen hem/haar vragen iets te herhalen	❑	❑	❑	❑	❑	
C	Algemeen oordeel over de stemkwaliteit van uw kind: Plaats een **X** op de lijn om aan te geven wat u van de stemkwaliteit van uw kind vindt (de beschrijving onder de lijn is hierbij een hulpmiddel). Normale stem ——— Ernstig afwijkende stem							

Score: F+ P + E = (in te vullen door onderzoeker)



chapter 6

Voice Outcome and Voice-related Quality of Life after Surgery for Pediatric Laryngotracheal Stenosis

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Voice outcome and voice-related quality of life after surgery for pediatric laryngotracheal stenosis
Laryngoscope. 2016 Nov 9

Abstract

Objectives. *To evaluate the long-term outcome of voice quality and voice-related quality of life after open airway surgery for pediatric laryngotracheal stenosis.*

Material and Methods. *Children under the age of 18 at time of follow-up and with a history of open airway surgery for acquired laryngotracheal stenosis were included in this analysis. To assess voice-related quality of life, the pediatric voice handicap (pVHI) index was completed by the patients' parents. The dysphonia severity index (DSI) was used as an objective measurement for voice quality.*

Results. *Fifty-five parents completed the pVHI and thirty-eight children completed the DSI. This showed high pVHI values and low total DSI scores, indicating significant voice disturbance. After multivariate analysis, presence of comorbidities and glottic involvement of the stenosis are associated with poor long-term voice-related quality of life.*

Conclusions. *Significant voice disturbance is common after surgery for pediatric laryngotracheal stenosis. Glottic involvement of the stenosis and comorbidities are associated with poor voice-related quality of life. Evaluation of pre- and postoperative voice quality and voice-related quality of life is advised for children treated for laryngotracheal stenosis.*

Introduction

Pediatric laryngotracheal stenosis (LTS) is a life-threatening condition for which a tracheostomy is often necessary. Surgery focuses on creating an adequate airway for spontaneous breathing and aims to relieve the patient of his or her tracheostomy. Using open airway surgery such as laryngotracheal reconstruction (LTR) and cricotracheal resection (CTR), excellent outcomes were achieved as far as decannulation is concerned. However, long-term functional deficits and deficits in health-related quality of life (HRQoL) may still exist.[1-3]

Acquired LTS often involves the glottis, impairing glottic movement with extensive scarring of the posterior aspect of the glottis and ankylosis of the arytenoids. Surgery aims to enlarge the airway by opening the scarred glottis. In theory, this could contribute to post-operative dysphonia.

Over the past decades, a number of centers have published on voice outcome after pediatric airway surgery. Although there is a large heterogeneity, the studies are unanimous in reporting a high incidence of voice disturbance ranging from mild dysphonia to severe voice disorders. Endoscopy usually reveals an abnormal larynx and abnormal phonation. Until now, no study has identified significant factors associated with voice outcome.[4-8]

The aim of this study is to describe the long-term voice outcome and voice-related quality of life after open airway surgery for pediatric laryngotracheal stenosis in our tertiary referral center. We try to identify factors associated with voice outcome.

Material and Methods

This study is part of a large follow-up project. All children who were treated for acquired LTS between 1994 and 2009 by means of an LTR or a CTR were approached for this study and invited for an outpatient, follow-up visit. Children younger than the age of four and those still with a tracheostomy were excluded from this study. Children under 18 years at time of follow-up visit were included in this voice analysis.

Baseline characteristics (gender, age at time of follow-up), operative factors (Myer-Cotton grade of stenosis, pre-operative tracheostomy, presence of comorbidities, congenital syndromes, localization of stenosis, age at time of surgery, and grafts used) were retrospectively extracted from the hospital records.

Health status at time of follow–up

To assess health status at the time of the follow-up outpatient visit, patients performed pulmonary function testing and a Bruce treadmill endurance test while the presence of stridor was noted. The protocols for these measurements have been described in our previous publications.[2]

Pediatric Voice Handicap Inventory

To assess voice-related quality of life, parents were asked to fill out the pediatric Voice Handicap Inventory (pVHI). The pVHI consist of three parts: a talkative scale, a questionnaire and a VAS score. First, parents were asked to judge their children's talkativeness on a seven point scale ranging from one (quiet listener) to seven (very talkative). The pVHI questionnaire consists of 23 questions in three domains: emotional, physical and functional. Each question has a five point scale ranging from zero to four points so the maximum score for 23 questions is 92 points. The higher the score, the lower the parent reported voice-related quality of life is. Last, the parents were asked to rate the quality of their child's voice on a Visual Analog Scale (VAS) ranging from zero (normal voice) to ten (worst possible voice imaginable). The original validated pVHI in English was translated into Dutch by our speech pathologist. Subsequently, a back-translation was done by a native English speaker and this version was compared with the original version.[9]

Dysphonia Severity Index

To objectively assess the quality of the voice the Dysphonia Severity Index (DSI) was used. Measurements for the following four parameters of the DSI were obtained: highest fundamental frequency (Hz), lowest intensity (dB), maximum phonation time (MPT) (s) and jitter (%). These parameters were used to calculate the total DSI score by using the formula published by Wuyts et al.[10] DSI scores range from a negative to a positive value where higher scores indicate better voice quality. A score of -5,0 or lower correlates with a voice of maximum hoarseness, a score of + 5,0 or higher with a voice of no hoarseness. All DSI scores were obtained and calculated by co-author MH, a speech pathologist experienced in the use of the DSI. [11,12] Unfortunately, there are no internationally established norm values for the DSI in the pediatric population. In the few studies on the use of the DSI in children, the normal DSI values differ strongly.[13-16] For this study, we presumed that a total DSI score under 2,0 is associated with significant voice disturbance in the pediatric population.

Statistical analysis

Children under 18 years with complete data for medical history, present medical status, and pVHI were included in the statistical analyses. Comparisons between complete cases (children who attended the outpatient follow-up visit) and non-complete cases (unable to be contacted or refused to participate) for age and age at surgery were done using Mann-Whitney U tests. Pearson's χ^2-tests were used to detect differences in distributions of gender, presence of pre-operative tracheostomy, presence of comorbidities or congenital syndrome, Myer-Cotton grade of stenosis and glottic involvement of the stenosis between the complete and non-complete cases.

A two-stage strategy was followed to determine associations between baseline characteristics, operative factors, follow-up health status and voice outcome total pVHI questionnaire, VAS and DSI.

First, univariate associations (β) between the voice measurements total pVHI questionnaire, VAS and DSI and the baseline characteristics, operative factors and follow-up health status were determined. When multiple factors were significantly associated with voice outcome, a multiple linear regression analysis was done in which significant factors for voice outcome were identified through backward elimination analysis.

All p values < 0,05 were considered statistically significant.

Results

A total of 76 patients were eligible for inclusion and were invited for the follow-up study. Sixty-five out of seventy-six patients (the compete cases) attended the outpatient follow-up visit; six refused to participate and five children could not be contacted, the non-complete cases.

Comparisons between complete cases (n=65) and non-complete cases (n=11) revealed a statistically significant difference for the pre-operative Myer-Cotton (MC) grade of stenosis (category I= MC grade I & II; category II= MC grade III & IV). There was a significantly larger number of grade III & IV stenoses (category II) in the non-complete group, p= 0.027, namely ten patients with MC grade III, one patient with MC grade IV. Nine out of the eleven non-complete cases were treated with a single stage LTR; two were treated with a CTR.

Of the 65 patients who attended the outpatient follow-up visit, 55 children were under the age of 18 years and their parents completed the pVHI.

Baseline characteristics of these 55 patients are given in table 1. Flow chart of in- and exclusions is given in figure 1. Table 2 shows the use of cartilage grafts for the laryngotracheal reconstructions.

DSI measurements were done in 38 out of 55 patients whose parents completed the pVHI. Seventeen patients could not comply with the DSI measurements, mostly due to mental retardation.

Table 1: Patient characteristics of study population for pVHI (n=55)

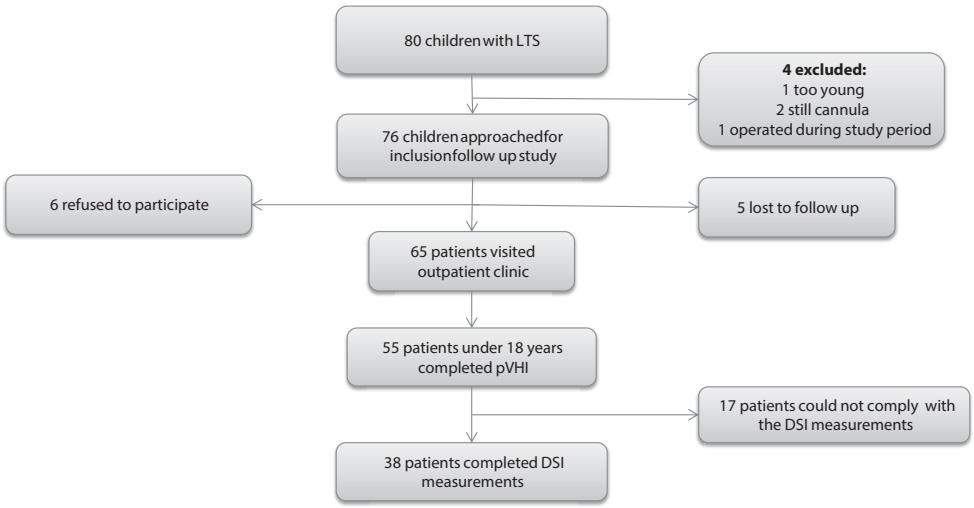
Female	30
Median age; range (in years)	11 (4-17)
Median follow-up after surgery; range (in years)	7 (2-16)
Tracheostomy present pre-operatively	44
Grade of stenosis (Myer-Cotton)	
Grade I	1
Grade II	16
Grade III	37
Grade IV	1
Site of stenosis	
Only subglottic	33
Glottic involvement	22
Number of patients with comorbidities[a]	31
Bronchopulmonary Dysplasia (BPD)	10
Tracheomalacia	9
Congenital syndrome	9
Congenital heart disease	4
Other [b]	8
Type of surgery	
Single stage laryngotracheal reconstruction (SS-LTR)	53
Double stage laryngotracheal reconstruction (DS-LTR)	1
Cricotracheal Resection (CTR)	1
Median age at surgery; range (in years)	2 (0-12)

pVHI = pediatric voice handicap index. [a] 7 patients had more than one comorbidity. [b] Other include: mental retardation, reflux disease and OSAS (obstructive sleep apnoea syndrome).

Table 2: Types of graft used for laryngotracheal reconstruction (n=54)

Only anterior graft	1
Only posterior graft	3
Anterior graft + posterior split	2
Anterior + posterior graft	48
Total laryngotracheal reconstruction	54

Figure 1: Flow chart of in– and exclusion



LTS = laryngotracheal stenosis, pVHI = pediatric Voice Handicap Inventory, DSI = Dysphonia Severity Index

Voice measurements outcome

Pediatric Voice Handicap Index (pVHI)

Parents judged their child's talkativeness with a median score of 5 (range 1-7).

The median (range) total pVHI questionnaire score was 17 (0-68). Median (range) scores for the subscales were 7 (0-18) for the functional subscale, 8 (0-32) for the physical subscale and 2 (0-26) for the emotional subscale.

Parents judged the quality of their child's voice with a median VAS score of 3,5 (0-9,6)

Dysphonia Severity Index (DSI)

Median total DSI score was -0.03 (-6.57 to 5.78). In thirty-six out of forty-seven (77%) patients with DSI measurements, the score was lower than 2,0

Univariate associations between pre-operative factors and long-term voice outcome

Table 3 shows the univariate associations (β) between the voice measurements total pVHI questionnaire, VAS, total DSI and baseline characteristics, operative factors and follow-up health status. Univariate associations were also calculated for the different DSI parameters (data not shown). Only the MPT had a significant positive relation with the age at time of follow-up indicating higher MPT with increasing age.

Table 3: Univariate analysis of associations (β) between baseline characteristics, pre–operative factors, post–operative factors and total pVHI, VAS and total DSI outcome.

	pVHI	**VAS**	**DSI**
Biographical data			
Age at time of follow-up (years)	-0.101	0.164	***0.321***
Gender[a]	-0.028	-0.018	0.136
Operative factors			
Age at time of surgery (years)	-0.116	-0.047	***0.436***
Tracheostomy present?[b]	***-0.320***	-0.265	0.149
Comorbidities present?[b]	***0.359***	0.180	-0.257
Glottic involvement?[b]	***0.489***	***0.352***	0.001
Myer-Cotton grade stenosis[c]	-0.934	-0.051	-0.237
Congenital syndrome[b]	0.057	0.021	0.079
Posterior graft used[b]	0.211	0.242	-0.076
Post-operative health status			
Stridor[b]	***0.554***	***0.406***	-0.271
Bruce treadmill test, SD score	-0.264	-0.160	0.007
FIV1/VCmax in %	***-0.539***	***-0.413***	0.004
VCmax SD	0.170	0.139	0.082
PEF SD	-0,317	-0,137	0,067
FEV1 SD	-0,145	-0,194	0,015

[a] female =0, male = 1. [b] no = 0, yes = 1. [c] MC grade I & II = 0, MC grade III & IV = 1.Significant associations (p<0.05) are given in bold italics, SD = standard deviation. FIV1 = forced inspiratory volume in 1 second, VCmax = maximum vital capacity, PEF = peak expiratory flow, FEV1 = forced expiratory volume in 1 second.

Multiple linear regression analysis

Table 4 shows the results for the multivariate linear regression model. The presence of comorbidities and glottic involvement of the stenosis are significant factors for higher total score on the pVHI questionnaire. For the follow-up health status, the presence of stridor and worse inspiratory pulmonary function tests (FIV1/VCmax) were significantly associated with a higher total score on pVHI questionnaire.

Presence of stridor at follow-up outpatient visit was significantly associated with a higher parent reported VAS.

Table 4: Results from multivariate linear regression model.

Operative factors	**Constant**	**Unstandardised**	**SE**	**Standardised**	***p*-value**	**R^2**
Total pVHI (n=55)						
glottic involvement[a]	2.857	4.826	1.284	0.426	<.01	0.33
comorbidity[a]		4.152	1.268	0.371	<.01	
Follow-up health status	**Constant**	**Unstandardised**	**SE**	**Standardised**	***p*-value**	**R^2**
Total pVHI score (n=35)						
Audible stridor[a]	13.49	4.88	1.50	0.44	<.01	0.45
FIV1/VCmax in %		-0.13	0.04	-0.42	<.01	
pVHI VAS (n=35)						
FIV1/VCmax in %	0.87	-0.01	-0.00	-0.42	0.01	0.18

pVHI = pediatric voice handicap inventory, VAS = Visual Analogue scale, FIV1 = forced inspiratory volume in 1 second, VCmax = Maximum vital capacity. [a] no = 0, yes = 1.

Discussion

In this study, we report the long-term voice outcome and voice-related quality of life after surgery for acquired laryngotracheal stenosis (LTS). We found high values for total pVHI questionnaire, VAS and low values for total DSI, indicating significant voice disturbance at long-term follow-up. After multivariate analysis, we found that the presence of comorbidities and glottic involvement of the stenosis are significant factors associated with a higher total score on the pVHI questionnaire. Presence of stridor at time of follow-up and poor inspiratory pulmonary function testing are significant factors for higher VAS and higher total score on pVHI questionnaire.

Airway surgery is always a balance between creating an adequate airway for life-long ventilation while at the same time maintaining an acceptable voice and swallowing function. While most studies focus on the airway aspect, reporting decannulation rates as outcome measure, only a small number of studies have reported on voice outcome after surgery. All report a worryingly high incidence of voice disturbance, abnormal laryngeal features and phonation characteristics like ventricular band phonation, vocal cord immobility and anterior commissure blunting.[5,6,17,18]

Since laryngotracheal stenosis is a rare condition, most of these studies have small numbers and fail to identify significant factors associated with voice outcome. Pooling of data is not feasibly due to the strong heterogeneity of the studies and of the methods used.

The objective measurement of voice quality in children proves to be a challenge and there is no consensus on the best tool for this purpose. We have used the dysphonia severity index

(DSI) in an attempt to quantify the voice quality of our subjects. A large number of children could not comply with the study protocol and interpretation of outcome is difficult because no norm values exist for pediatric population.

A small number of studies have reported on DSI outcome in children. The normal DSI values for children differ strongly in these studies. This is also due to the fact that the use of different analysis software influences the total DSI score. Considering the published studies and our own experience with the DSI as an outcome measure for voice quality, we have determined a score higher than 2,0 to be normal for the pediatric population.[13-16] Of our study population, no less than 77% of the patients had a clinically significant voice disturbance with a DSI score below 2,0.

The pVHI is a validated and easy to use tool in assessing voice-related quality of life in the pediatric population.[9] It has successfully been used in a number of studies on voice outcome after pediatric airway surgery. [9,19] Using the pVHI, we were able to identify significant factors for poor pVHI questionnaire outcome after long-term follow-up: glottic involvement of the stenosis and presence of comorbidities in which BPD, tracheomalacia and congenital syndromes were the most common.

Presence of glottic stenosis and of comorbidities were also the most important factors in our previous reports on functional outcome and health-related quality of life.[2,3] These findings have triggered us to reconsider the single stage LTR approach in cases where glottic involvement of the stenosis is apparent. One could argue the use of post-operative stents in cases of extensive glottic scarring in order to keep the glottis abducted in the healing phase after laryngeal reconstruction.[20] While this could work for a more patent airway, this could have a worsening effect on voice quality. Unfortunately, data on the influence of stenting on post-operative voice quality is lacking.

Our study cohort predominately consists of grade II and III stenoses for which a single stage laryngotracheal reconstruction was performed using posterior grafts. Subsequently, our results reflect mainly voice outcome in patients with grade II and III stenosis treated with an ss-LTR and posterior graft.

Using a posterior cartilage graft could very well influence the quality of the voice. Since we have used a posterior graft in almost all of our patients (51 out of 55 cases), an honest evaluation on the effect of the posterior graft on voice outcome cannot be made with our data. To our opinion, however, it is more likely that the extensive scarring of the glottis predominates a bad voice after surgery. In this regard, it would be very interesting to have a series of pre- and postoperative voice measurements in order to identify the true influence an airway reconstruction has on the quality of the voice. This will be the subject of future research.

Strengths and limitations

This study is the first to evaluate long-term voice outcome in a cohort of patients after airway surgery regardless of their subjective voice complaints. We have identified operative factors associated with poor voice-related quality of life after surgery. These findings have important implications for the counseling of patients and parents suffering from pediatric laryngotracheal stenosis. Our results indicate that there is a clear need for an assessment of the voice quality and voice-related quality of life at long-term follow-up. We have used the DSI as an objective measure for voice quality and found a low DSI score in a large portion of our study cohort.

As for limitations, this is still a relatively small cohort for assessing such a heterogenic patient population. There is a significant difference in severity of the stenosis between the complete cases and non-complete cases. However, we feel that this is of no influence on the voice outcome analysis and conclusions. The demographical and operative data was collected retrospectively from the hospital records, carrying the risk of incomplete data.

The use of the DSI as a means to quantify voice quality in children is difficult since no norm values exist for this age group and we encountered a large number of patients who could not comply with the protocol. This underlines the difficulty when trying to quantify voice quality in the pediatric population. We have determined a DSI score lower than 2,0 to correlate to significant voice disturbance. Although there is no robust evidence for this, we feel that it is a very prudent estimate and that the actual norm score will be higher than two.

Conclusions

After surgery for pediatric laryngotracheal stenosis, significant voice disturbance is a common finding. Pre-operative glottic involvement of the stenosis and presence of comorbidities are important factors for poorer voice-related quality of life outcome. Voice quality and voice-related quality of life should be part of the standard pre- and postoperative assessment in patients suffering from laryngotracheal stenosis.

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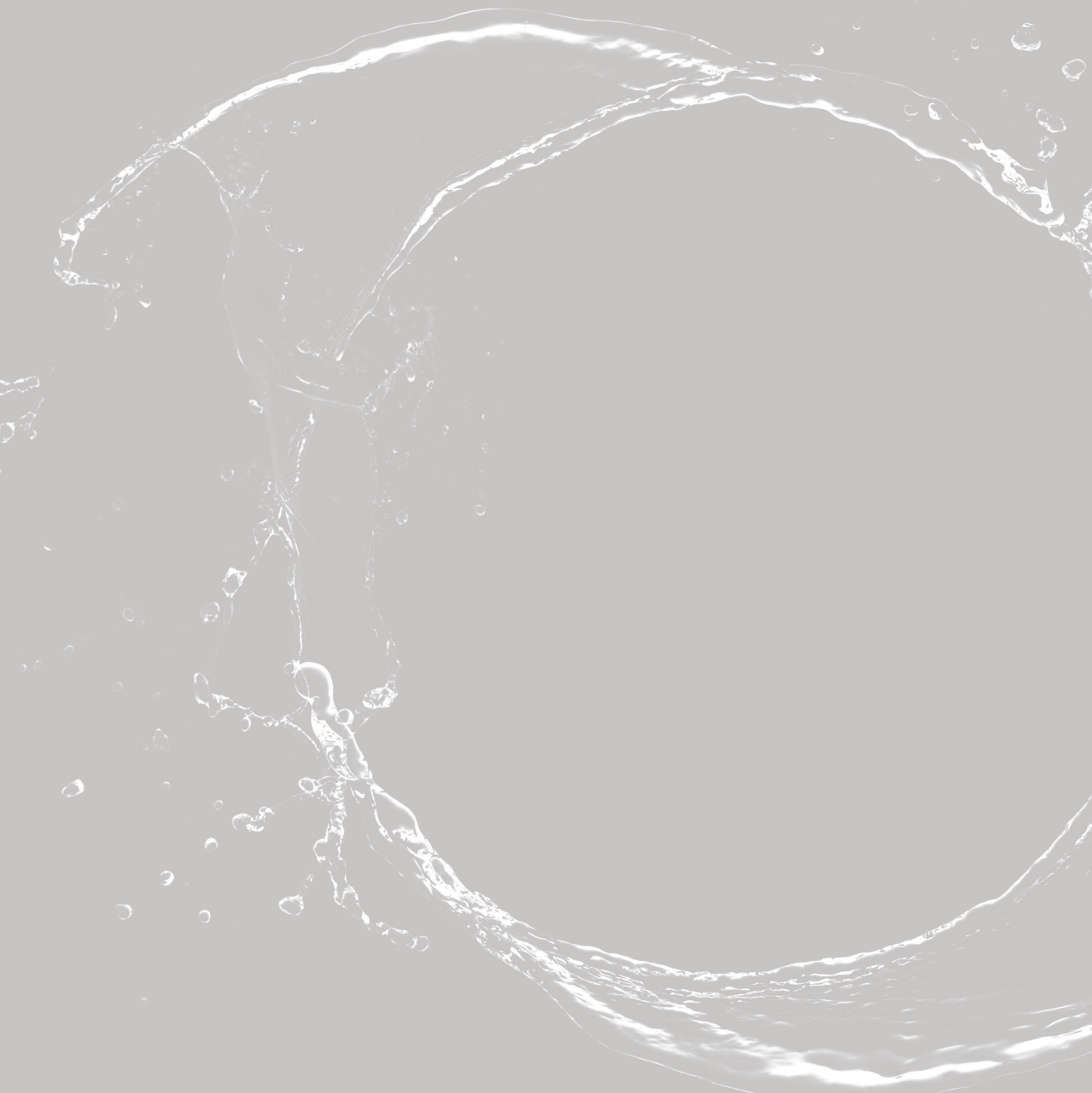


chapter 7

Summary

Summary

This thesis describes the long-term outcome of children surgically treated for acquired laryngotracheal stenosis (LTS). Acquired LTS is usually secondary to injury caused by long-term intubation which causes scar tissue formation and narrowing (stenosis) of the airway in the glottic and/or subglottic area. The stenosis can be so severe that a tracheostomy tube is necessary for these children to survive. Surgery aims to relieve the child of his or her tracheostomy (so-called decannulation) and to create a sufficiently patent airway for respiration while maintaining voice and swallowing function.

Chapter One
The incidence, pathophysiology and development in surgical treatment for acquired LTS is described in chapter one. We provide an overview of the current reports on surgical outcome for acquired LTS and address the knowledge which is lacking in international literature and a short outline of the different chapters of this thesis is given.

Chapter Two
When retrospectively reviewing our data over an 18 year period, we found excellent decannulation results in 98 infants surgically treated for acquired LTS. An overall decannulation rate (ODR) of 95% and an operation specific decannulation rate (OSDR) of 92% is reported, which is very high when compared to other centres. The children who failed decannulation (n=6) were all treated with an LTR (5 single stage, 1 double stage), suffered from a grade III stenosis, and 5 out of 6 patients had presence of comorbidities, although these observations were not statistically significant when compared to the group with successful decannulation.

When analysing our surgical cohort we found children with extensive medical histories, in accordance with other published series. A large number of children treated for LTS are of preterm birth with a great number of comorbidities and congenital syndromes. The most common comorbidities in our study population were bronchopulmonary dysplasia and tracheomalacia.

With the exception of the grade IV Myer-Cotton stenosis (managed by a cricotracheal resection (CTR)), the use of the single stage laryngotracheal reconstruction (ss-LTR) for the treatment of severe LTS was always preferred. In our studied cohort, 91 out of 98 patients were treated with an ss-LTR, even for grade III stenosis (n=65) with glottic involvement and comorbidities. This is markedly different than other centres who advocate a double stage procedure with post-operative stenting or a CTR to treat more severe cases of LTS. When reviewing the 91 ss-LTRs in our cohort, we have an excellent decannulation rate of 93%.

The single stage approach is more challenging in the post-operative period. In twenty percent of our ss-LTRs a complicated post-operative course was seen, requiring interventions such as

temporary re-intubation or temporary re-tracheostomy. This indicates that the use of an ss-LTR for severe LTS mandates a well-equipped and experienced PICU department.

Follow–up research on long–term outcome

We have undertaken a large follow-up study to determine our long-term outcome. Included were children who were treated for acquired laryngotracheal stenosis by an LTR or CTR in a 15 year time period, without tracheostomy and older than four years at time of follow-up. We have sent a number of questionnaires and invited all patients for a follow-up visit in our outpatient clinic. A total of 80 children were operated in this time period. One patient still had a tracheal cannula, one was operated in the study period and two children were under four years at time of follow-up study, leaving 76 children eligible for inclusion. Five of these could not be contacted and were lost to follow-up and six refused to participate. This left 65 patients who were included in this follow-up study.

Out of the 65 patients, 55 visited the outpatient clinic; 10 patients refused this visit because of distance issues, but did fill out the questionnaires. The total group of 65 patients had a median age of 11 years (range 4-24) and median follow-up time of 7 years (range 2-17) after surgery.

The patients who visited the outpatient clinic were subject to a number of examinations and measurements in order to assess general health, respiratory status, endurance, health-related quality of life (HRQoL), voice quality and voice-related quality of life. The results of these measurements are discussed in the following chapters.

Chapter Three

Airway surgery is primarily aimed to create an airway with sufficient lumen for respiration, growth and exercise. Therefore, an important part of outcome research is aimed at the patency of the recreated airway. As an objective non-invasive airway measure we have introduced pulmonary function testing (PFT) with forced expiratory and inspiratory flow-volume loops. Maximum endurance was tested through the validated Bruce treadmill test.

We found that both tests are non-invasive and feasible in children from the age of 5 when able to comply with the study protocol; patients with mental retardation being the largest non-compliant group. In our follow-up cohort, 78% of patients were able to adequately perform PFT and 80% of patients were able to perform the treadmill test.

When analysing our results we found that more than half of the patients had PFT outcomes indicating significant airway obstruction which was predominately inspiratory. One third of the studied patients had impaired exercise tolerance. Presence of inspiratory stridor had a positive predictive value for impaired inspiratory flow deficits of 70%. On the other hand, the judgement of parents of their child's exercise capacity had a poor predictive value (40%) for the actual exercise tolerance on the treadmill.

After statistical analysis, we found that glottic involvement of the stenosis was associated with inspiratory flow impairment on PFT. Presence of comorbidities was associated with expiratory flow deficits, poor endurance on the treadmill and below average height for age (HFA).

Chapter Four

We are the first centre to report on health-related quality of life (HRQoL) after surgery for pediatric LTS. We have used the Child Health Questionnaire (CHQ) to assess HRQoL with a parent proxy version (Child Health Questionnaire Parent Form (CHQ-PF50, age 4-18 yrs.)) and a patient self-reporting version (Child Health Questionnaire Child Form (CHQ-CF87, age 11-18 yrs.). We found that at long-term follow-up, deficits in HRQoL exist in a great deal of patients.

When reviewing the parent proxy results, the outcome on QoL resembles that of the QoL outcome in children with asthma, indicating the impact shortness of breath has on quality of life. On the other hand, when reviewing the patient self-report the outcome hardly differs from the norm population. When comparing parent proxy and child self-assessment, we found significant differences on six out of eleven corresponding subscales. On all of these subscales, the parents judged their children's QoL scores lower than their children. This difference between parent reporting and child reporting is not unusual and is important for clinicians when assessing quality of life in their post-operative cohort. Both the parent-proxy and child self-reported questionnaires shed a different light on the overall quality of life of the child and should be taken into account.

We found a significant association between a number of factors and lower scores on HRQoL. The most important factors were glottic involvement of the stenosis and the presence of comorbidities. The functional outcomes on the Bruce treadmill test and pulmonary function test correlate with the outcomes of the HRQoL. This indicates that QoL outcome might be improved when optimizing airway patency, improving endurance and optimizing care for existing comorbidities.

Chapter Five

In order to use the pediatric Voice Handicap Inventory (pVHI) in our study cohort, we have translated the English pVHI into Dutch and validated it for the Dutch population. For the validation, questionnaires were filled out by the parents of children who visited our outpatient dysphonia clinic and their results were compared to a control group of asymptomatic children who were recruited from a nearby school. This resulted in a dysphonia group of 79 children and a control group of 122 children. There was a significant difference between both groups with an excellent internal consistency. In 32 children who participated in voice outcome at long-term follow-up after surgery for LTS (Chapter six) the pVHI was filled out twice in order to assess the test-retest reliability. We found a high test-retest reliability with moderate to almost perfect correlation.

Because objective assessment of voice quality remains very challenging and norm values are lacking for the pediatric population, we have used ROC curve analysis to determine the cut-off point of the score on the total pVHI questionnaire for dysphonic children. At a total pVHI score of 7, we found a specificity of 93% and a sensitivity of 100%, indicating significant disturbance of voice-related quality of life.

Chapter Six

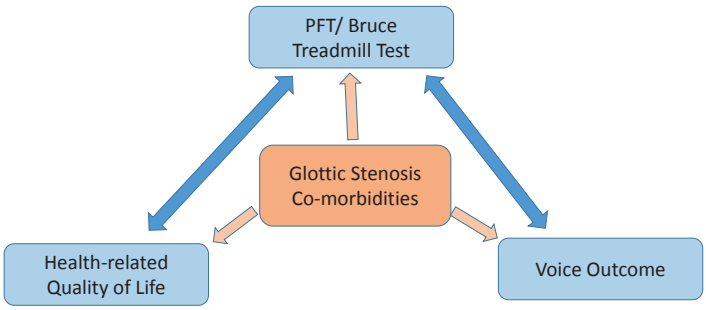
To objectively assess the quality of the children's voices, we have used the dysphonia severity index (DSI), a validated tool for objective measurement of voice quality in the adult population. Unfortunately, no norm values exist for the DSI in the pediatric population, which makes interpretation of these results difficult. We estimated that a total DSI score under 2,0 represents significant voice disturbance in children. To our opinion, this is still a very cautious estimate and the cut off value for voice disturbance in children on the total DSI score is probably higher than 2,0. The median DSI score was -0,03 and in no less than 77% of children the DSI score was under 2,0. However, 17 out of 55 children could not provide adequate voice samples for the DSI and this underlines one of the difficulties in voice assessment in the pediatric population.

We also used the pediatric voice handicap inventory (pVHI), a validated tool on voice-related QoL which has proven a valuable and easy-to-use instrument in the pediatric population. The median pVHI score was 17 and in 75% of children the pVHI score was 7 or higher, indicating significant disturbance of voice-related quality of life. After multivariate analysis, the presence of comorbidities and glottic stenosis are significantly associated with poor pVHI outcome, as was reduced inspiratory flow on PFT and presence of inspiratory stridor.

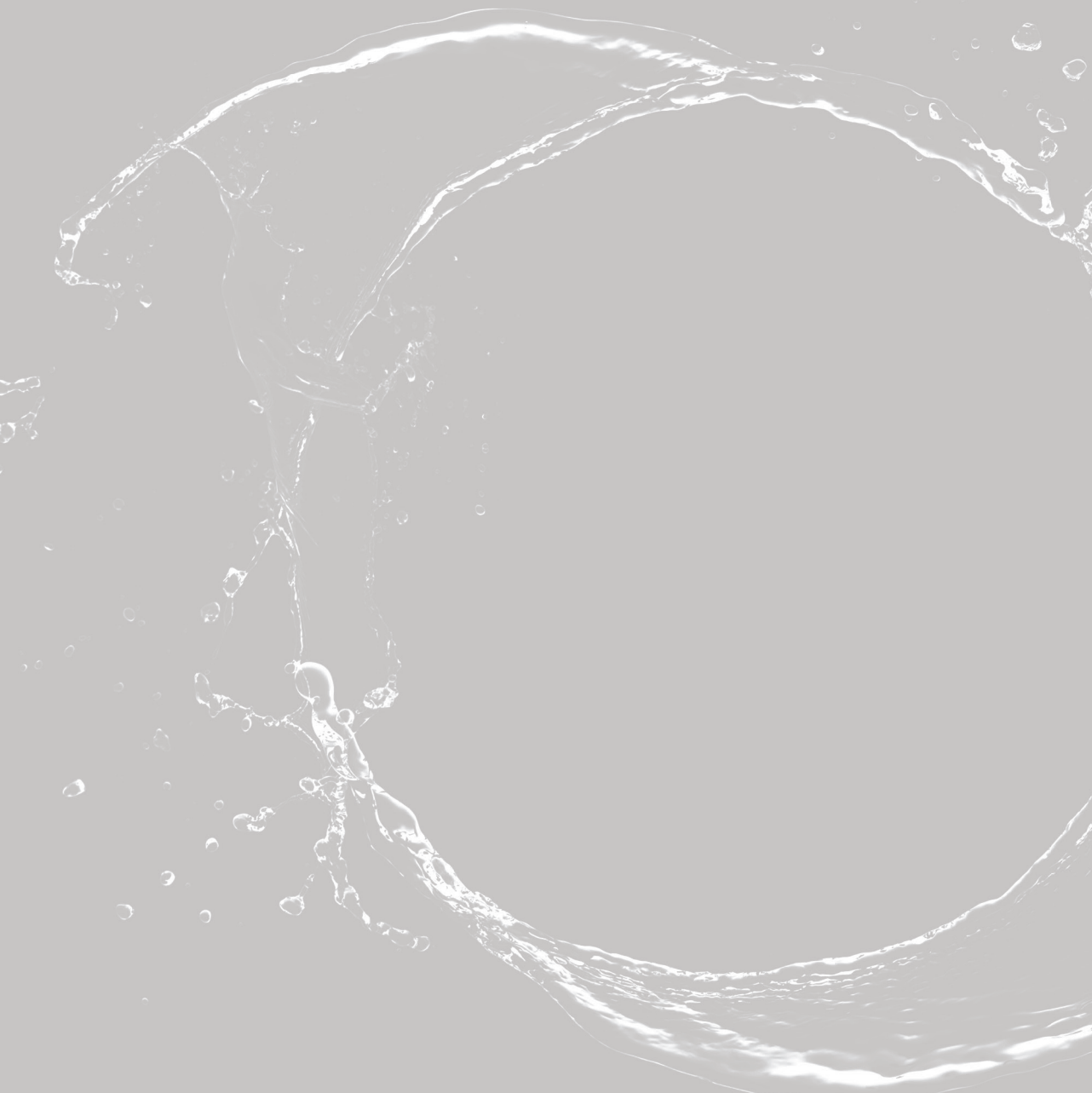
Relationship between different outcome measures

The different outcome parameters PFT/Bruce treadmill, HRQoL and voice outcome are correlated to each other. The connection between the different outcome parameters is depicted in figure 1.

Figure 1: Connection between different outcome parameters



Double arrows indicate significant correlations between outcome parameters, single arrows indicate significant factors associated with outcome parameters. PFT = pulmonary function test.



chapter 8

General Discussion

Introduction

This thesis focuses on long-term functional outcome of surgery for acquired pediatric laryngotracheal stenosis (LTS). The goal of this research project was to evaluate the long-term outcome of a large cohort of children surgically treated for acquired LTS. By evaluating outcome, we hope to draw conclusions for our own clinical practice as well as to add data and insight to the existing knowledge on surgery for acquired LTS.

Preparations for this research project started in 2008 when the research protocol was written, consent was obtained from the ethics committee, and the patient data was extracted from the hospital records. We have approached all children who were surgically treated for acquired laryngotracheal stenosis (LTS) in a 15 year time period (1994 until 2009) for a follow-up visit. Evaluation of patients started in 2011 when patients visited the outpatient clinic. During this visit, a number of questionnaires and functional tests were done to assess the current medical status.

Where we were when we started our research in 2011

Surgery for laryngotracheal stenosis

In the field of pediatric otorhinolaryngology, the surgical treatment of acquired pediatric laryngotracheal stenosis had already improved greatly until 2011. Most cases of pediatric laryngotracheal stenosis could be treated and children relieved of their tracheostomy. Nonetheless, there was still uncertainty and debate on a number of issues regarding the best treatment in certain clinical situations. A number of leaders in the field of LTS surgery had tried to provide clinical guidelines on the timing of surgery, type of surgical intervention and indications to use post-operative stents. When our research project started, there was no scientific evidence to support any of these guidelines.[1-5]

Our institution has followed the international developments in the field of airway surgery for LTS. All possible surgical procedures including endoscopic procedures, laryngotracheal reconstruction (LTR) and cricotracheal resection (CTR) are performed in our institution. We have experience with single stage (ss) and double stage (ds) procedures. For the latter we have used the Berkovits silicone laryngotracheal stent with great satisfaction for many years.[6]

We started using the single stage LTR in 1995 and from that moment on this was the preferred surgical approach in our institution. The use of a single stage procedure for LTS necessitates an intensive collaboration with pediatric anesthetists and the pediatric intensive care ward and a sound peri-operative medical protocol. Since the late 80s, we have used prophylactic antibiotics and proton pump inhibitors in all patients with LTS and surgery is typically carried out when the stenotic airway is free of active inflammation and edema. The post-operative protocol has seen its share of alterations over the last 20 years, the most prominent change being the shortened duration of intubation after surgery since 1998. From that moment on, we used a protocol of sedation without muscle relaxants and a relatively short period of intubation (see box 1) of three or four days.

Box 1: Post–operative protocol after SS–LTR

Nasal intubation for 3-4 days; admission to the IC ward
Spontaneous breathing, under sedation, when possible. No muscle relaxants
Standard antibiotics (1 week therapeutic dosage, 5 weeks prophylactic dosage) & PPI's for 6 weeks
Dexamethasone is routinely administered 6 hrs. and 1 hr. prior to extubation
Extubation and endoscopy under general anesthesia, spontaneous breathing in OR
Post-operative nebulization of adrenaline or corticosteroids when stridor is present

Decannulation rate

Internationally, the decannulation rate is the major outcome parameter when reporting on respiratory outcome for laryngotracheal stenosis. This seems logical, since it is the easiest objective outcome measure and is readily available when reviewing the hospital records. When we started our research project high decannulation rates have been reported in international literature despite differences in surgical strategies.[2,4,7-11] However, when reviewing the previously published data, two different methods of calculation were used for the decannulation rate. In method A, the number of patients successfully decannulated after surgery are divided by the total number of patients with a pre-operative tracheostomy. In method B, the number of decannulated patients are divided by the total number of operated patients with and without a pre-operative tracheostomy. The decannulation rate will be higher when using method B than when using method A. In the published literature, there seems to be no international consensus on how the decannulation rate is calculated. Pooling of the published studies is not feasible due to the heterogeneity in outcome reporting, patient groups, types of surgeries and study methods.

We feel that a successful decannulation only marginally depicts the true patency of the recreated airway. This is especially true for the growing child. Since most children are operated and decannulated at a young age (median 2 yrs., see ch. 2), it seems sensible to have a long-term follow-up on the patency of the reconstructed airway up until adulthood when the child is fully grown.

With this research project, we hope to provide a convincing argument on which method of calculation is best for the decannulation rate. We hope to prove that decannulation rate, however important at time of surgery, should be considered a short-term outcome measure and long-term measurements on respiratory outcome are necessary.

Respiratory outcome

When reviewing the published studies at the start of our research project, there was a lack of long-term outcome reporting and a lack of objective outcome measurements other than decannulation that reflect the quality of the airway after surgery. Furthermore, using the decannulation rate as an outcome measure in children without a preoperative tracheostomy seems incorrect. Some studies have tackled this problem by reporting subjective outcome like improvement of complaints after surgery, presence of breathiness or stridor, or have done repeat endoscopies to assess the recreated airway. However, these are all subjective, non-standardized measures and are therefore unfit as an objective outcome measure.[4, 8, 9, 12]

We have sought an objective assessment tool for respiratory outcome in our surgical cohort. Preferably, this tool should be non-invasive and easily performed in all centers who deal with pediatric LTS in order to pool data and compare outcome of different surgical strategies. Next

to this, we felt it would be sensible to objectively evaluate exercise capacity as an outcome measure for LTS.

A possible tool for the assessment of respiratory outcome could be pulmonary function testing (PFT) which has the potential to measure inspiratory and expiratory airflow. Until now, PFT in children has mainly been used by pediatric pulmonologist to assess airflow of the lower trachea and lungs.[13] The Bruce treadmill test was evaluated as an outcome measure for endurance.

Quality of life

Until 2011, reports on quality of life outcome after surgery for pediatric LTS were lacking. This in striking contrast to several patient groups with other chronic pediatric diseases, where quality of life is main parameter in outcome assessments.[14-17] A possible explanation for this lack of reporting is that pediatric LTS is not considered to be a chronic illness after surgery and successful decannulation. Given the fact that these children usually have a background of critical illness, this may be untrue and there may be a place for the assessment of quality of life in these patients. We are the first to address the quality of life in a large surgical cohort for pediatric LTS at long-term follow-up.

Voice outcome

As far as voice is concerned, it was generally accepted that a large number of children with LTS suffer from dysphonia although robust data on prevalence are lacking.[18-22] It was also unknown what factors contributed to a bad voice after surgery for LTS. The influence of surgical factors like LTR versus CTR approach, complete laryngofissure, the use of posterior cartilage grafts or the effect of long-term postoperative laryngotracheal stenting on the quality of the voice was unknown. Possible patient factors that could influence voice outcome are vocal cord dysfunction, glottic scarring and ankylosis of the crico-arytenoid joint.

In current practice, children are usually operated at a young age with a tracheostomy in situ. At this stage, voice quality seems less important than the creation of an adequate airway and decannulation. Furthermore, children with a severe LTS who depend on a tracheostomy are often aphonic and even a poor voice after successful airway surgery will be an improvement of the pre-operative situation.[18, 19]

Everyone involved in pediatric voice research was facing the same problem: there is no internationally established method to objectively assess voice quality in children. None of the available objective voice assessment tools in adults had been validated for children. Validation of these tools is complicated by the fact that voices in children change a great deal as the child ages, especially in males. Second, objective voice measurements can reasonably be done from the age of 5 years. Since most children are operated on in the first few years of

life, objective assessment of voice quality requires standardized long-term follow-up and this is lacking in most centers.[19, 21, 23]

We set out to improve our knowledge on voice-related quality of life and quality of voice outcome after surgery for LTS. The dysphonia severity index (DSI) was used as a means to objectively evaluate voice quality in the pediatric population and factors associated with voice outcome were identified.

What we have learned

Decannulation rate

When reviewing our surgical results, we can report excellent decannulation outcome; our results can compete with those of other large airway centers. The decannulation results of our outcome research essentially show the results one can achieve with an ss-LTR approach. Although there is a degree of selection bias (all Myer-Cotton grade IV stenosis are treated with a CTR, for example), we have demonstrated that complex grade III Myer-Cotton stenosis can be adequately treated with a ss-LTR. A complicated post-operative course with temporary re-intubation or re-tracheostomy was seen in twenty percent of ss-LTR cases.

We have used method A for the calculation of the decannulation rate; dividing the number of patients successfully decannulated after surgery by the total number of patients with a pre-operative tracheostomy. In our opinion this is the only valid method of calculating the decannulation rate; it makes no sense to use decannulation as an outcome parameter for patients without a pre-operative tracheostomy to begin with. The decannulation rate should only be used for patients with a pre-operative tracheostomy and this can only be considered a short-term outcome measure for airway patency. The latter is confirmed by the fact that children in our cohort present with deficits in respiratory outcome, despite being successfully decannulated.

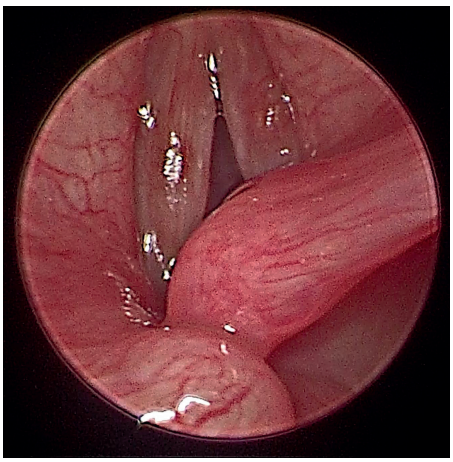
Respiratory outcome

In our experience, the pulmonary function test (PFT) is an excellent non-invasive tool to assess the patency of the recreated airway. Inspiratory flow on the PFT outcome is directly associated with the patency of the upper airway, which explains why glottic stenosis is such an important factor for inspiratory PFT outcome at long-term follow-up. In our current practice, we use PFT as a measurement of pre- and post-operative airway patency in children without a tracheostomy (figure 1). Improvement of airway caliber can accurately be measured by the increase in numerical value of the airflow.

The use of PFT in children is common for pediatric pulmonologists and can be performed easily in any specialized pediatric center. It is customary, however, for pediatric pulmonologists to focus on the expiratory values of the PFT since their main area of interest is the lower airways (distal trachea and lungs). For pediatric LTS, we are most interested in the upper, extra thoracic airway which means that a forced inspiratory flow volume loop must be added to the spirometry protocol. This poses a problem: unlike the expiratory values, there are no norm values for the inspiratory values in the pediatric population; there is a need to establish these for peak inspiratory flow (PiF) and forced inspiratory volume in 1 second (FIV1). To overcome this problem in our analysis, we used the FIV1 as percentage of the Maximum Vital Capacity (FIV1/VCmax), in which 80% or higher was considered normal. The

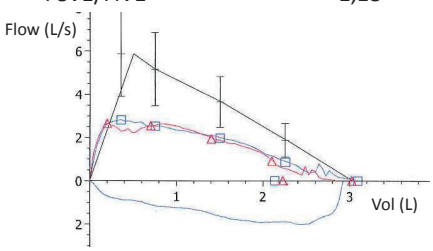
Figure 1: typical results of spirometry in a patient with a fixed upper airway stenosis

Pre-operative image

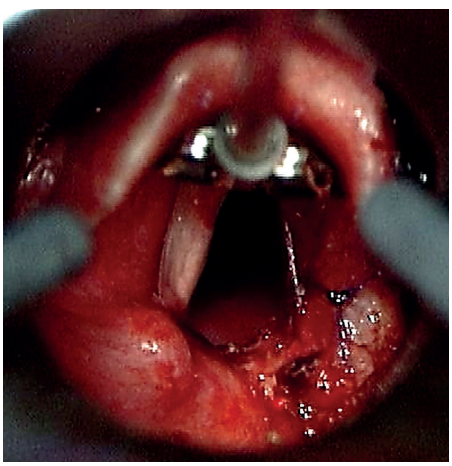


Pre-operative PFT

VC max (L)	3,09
FeV1 (L)	2,14
FeV1%VC (%)	69,08
PEF (L/s)	2,80
FiV1 (L)	1,82
FiV1%VCmax (%)	58,75
FeV1/FiV1	1,18

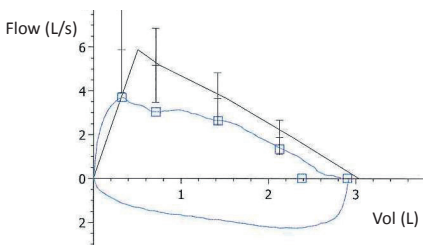


Post-operative image



Post-operative PFT

VC max (L)	2,91
FeV1 (L)	2,38
FeV1%VC (%)	81,73
PEF (L/s)	3,68
FiV1 (L)	2,09
FiV1%VCmax (%)	71,79
FeV1/FiV1	1,14



Top image: pre-operative situation. This patient suffered from a posterior glottic stenosis with extensive scarring of the right arytenoid after a prolonged period of neonatal intubation. On PFT, note the normal maximum vital capacity (VCmax), but severely disturbed expiratory and inspiratory flows. The ratio FEV1/FIV1 = 1,18, suggesting an inspiratory obstruction. FIV1/VCmax is 59%. Bottom image: post-operative situation after CO2 laser resection of the arytenoid with preservation and suturing of a mucosal flap. Post-op PFT shows marked improvement of inspiratory and expiratory flows; FIV1/VCmax = 72%. PFT = pulmonary function test, VC max = maximum vital capacity, FeV1 = forced expiratory volume in 1 second, PEF = peak expiratory flow, FiV1 = Forced inspiratory volume in 1 second, L/s = liter per second, L = liter.

ratio FEV1/FIV1, normally between 0,8 and 1,0 is useful in estimating whether the obstruction is predominately inspiratory (ratio > 1,0) or expiratory (ratio < 0,8).[13]

To assess endurance, we used the Bruce treadmill test. As we expected, the performance on the treadmill is influenced by multiple factors, which is why the presence of comorbidities is such an important factor. Although the Bruce treadmill test proved very valuable in our research setting, it is quite a time-consuming and specialized tool to assess endurance. Other tools like the 6-minute walk test seem more appropriate as a standardized outcome measure in the outpatient clinic.[24, 25]

The respiratory deficits we encountered in our cohort at long-term follow-up proves that the decannulation rate is not suitable as a long-term outcome measure. PFT and the Bruce treadmill test may add relevant information to the decannulation rate and are feasible in children from the age of 5 when able to comply with the study protocol; patients with mental retardation being the largest non-compliant group. In our follow-up cohort, around 80% of patients were able to adequately perform these tests. These measures give objective numerical data with established norm values for the pediatric population. This opens up possibilities to compare outcome data between different centers if they were to adhere to the same protocol.

Quality of life outcome

Despite the fact that QoL in laryngotracheal stenosis did not receive much attention in current literature, our results indicate that QoL is a significant issue in these patients. This is partly due to co-existing comorbidities. We have found a correlation between QoL and the presence of glottic stenosis, the outcomes on the Bruce treadmill test and the outcomes on PFT, implying a direct link between airway patency and QoL. Our findings imply that QoL may be improved when improving airway patency, endurance and optimizing care for existing comorbidities.

There is a marked difference in reporting of QoL between the parent-proxy questionnaires and child self-reporting questionnaires. This is not an unusual finding but is an important message to clinicians when assessing quality of life in their post-operative cohort. The parent-proxy and child self-reported questionnaires shed a different light on the overall quality of life of the child and both should be taken into account.[26, 27]

We have shown that the assessment of quality of life has a place in the long-term outcome after LTS but the CHQ tool we have used is quite lengthy for repeated assessment of QoL. Furthermore, the results of the CHQ need processing through a complex syntax before the actual score can be given to the patients, so this is not a good QoL assessment tool in an outpatient clinic setting where parents would want direct feedback on how their child is doing.[28, 29] The EQ5D and a simple VAS score seem more appropriate, but are still not disease specific quality of life tools. Given the impact of quality of life after surgery for pediatric LTS,

there is a clear need for a practical disease-specific quality of life instrument. A first attempt at this is made by Nouraei et al. Their recent study on the validation of a disease specific Airway-Dyspnoea-Voice-Swallow (ADVS) scale and Patient-Reported Outcome Measure (PROM) for pediatric LTS shows promise, although larger numbers are needed to assess its validity for different patient groups. We will deploy this tool in our long-term follow-up and aim to pool our data with other centers.[30]

Voice outcome

We have shown that a worryingly large number of children present with poor voice quality and voice-related quality of life after surgery for LTS. The dysphonia severity index (DSI) was used to objectively assess voice outcome. With this tool, we have encountered the same problems that other centers have; objective voice assessment in children is very difficult and no norm values exist. We have also experienced difficulties in obtaining voice samples of sufficient quality for evaluation; 17 out of 55 children could not comply with the DSI protocol.

The pediatric Voice Handicap inventory (pVHI) proved an easy-to-use instrument in this population and all parents were able to fill out this questionnaire. We have translated and validated the Dutch pVHI and established norm values for the Dutch population. With this, we can now determine the prevalence of significant voice-related quality of life disturbance.

Pre-operative glottic stenosis is correlated to poor voices at follow-up. We feel that the pre-operative scarring of the vocal cords and/or the crico-arytenoid joints are the cause of this long-term voice disturbance, more than the surgical intervention. Unfortunately, we cannot prove this theory since we have not done any pre-operative voice assessments. This will be part of our ongoing outcome research.

We still do not know whether an LTR, CTR, or post-operative stenting are associated with poorer voice outcome, since nearly all our patients were treated with an ss-LTR. Pooling of data from others centers with other surgical strategies and post-operative stenting could help answer these questions.

Given the large prevalence of voice deficits and poor voice-related quality of life, we have shown that long-term voice assessment is an important parameter when assessing outcome of surgery. In a very young child voice quality may not seem an important outcome factor, but it is likely that this increases over time when dysphonia has a bigger impact in one's personal and professional life, limiting social interactions and career opportunities.

Factors associated with long–term outcome

Glottic involvement of the stenosis and the presence of comorbidities are by far the most important factors associated with long-term outcome on all measured parameters in this thesis. Both of these factors are correlated with worse respiratory, voice and HRQoL outcome. The Myer-Cotton grade of stenosis, traditionally seen as an important factor associated with outcome for pediatric airway surgery, plays no role of importance in our long-term outcome.

In all centers, pediatric LTS is associated with a high prevalence of comorbidities. In our study cohort, no less than 55% of patients presented with comorbidities of which bronchopulmonary dysplasia (BPD) and tracheomalacia were the most common. Children with comorbidities performed less on respiratory outcome, voice outcome, quality of life outcome and presented with poor nutritional status (poor height for age, indicating chronic malnutrition). Given these findings, we feel that multiple medical disciplines should be involved in the long-term follow-up and management of these children. We advocate a multidisciplinary team of an ENT (airway) surgeon, a specialized pediatrician, a pediatric pulmonologist, and a swallow and speech therapist. We feel that improvement in the care for comorbidities can have a positive influence on the well-being of these patients.

The fact that pre-operative glottic stenosis is associated with poorer long-term outcome poses a difficult dilemma. Airway wise, one could advocate a more aggressive approach to the scarred glottis with (laser) microlaryngeal surgery or the use of stents to allow the reconstructed glottis to heal in a maximally abducted position. On the other hand, this could induce a closing defect of the posterior commissure with a worsening effect on voice quality and swallowing/aspiration. We feel that more attention should be given to the scarred glottis in outcome reports, since long-term outcome will be determined by the way the glottic stenosis is dealt with. In that regard, it would be very interesting to be able to compare our outcome data with other centers who have used other surgical strategies for glottic stenosis.

What we have learned: Conclusions from our outcome analysis

- Despite successful decannulation, a large number of children still present with deficits in functional outcome at long-term follow-up;
- The decannulation rate is of limited value for long-term outcome and addition of PFT, endurance tests, quality of life and voice assessment is important;
- Glottic stenosis and comorbidities are the most important factors for unfavorable long-term functional outcome.

What we have learned: changes in future practice

- We have started a standardized follow-up program after treatment for LTS with follow-up until adulthood;
    - We have added PFT, height and weight measurements and will add endurance tests, voice and QoL measurements as standardized outcome parameters in our follow-up program;
    - We have started a multidisciplinary outpatient clinic to improve long-term care for our patients after surgery. The multidisciplinary team exists of a pediatric ENT surgeon, a pediatric intensivist, a pediatric pulmonologist, a swallow and speech therapist, a physician assistant and specialized nurses.
- We have increased the use microlaryngeal (laser) surgery and/or post-operative stents when glottic stenosis is apparent.

What we have added to the literature

We are the first to report on long-term functional outcome in a large cohort of children treated for acquired LTS. We have shown that the decannulation rate alone is not a suitable outcome measure for long-term outcome. We have identified glottic stenosis and the presence of comorbidities as the most important factors associated with surgical outcome. Although the importance of these factors has been recognized by other authors[1, 3], this thesis is the first to confirm this through statistical analysis in a surgical cohort. In our long-term outcome, these factors are far more important than the Myer-Cotton grade of stenosis, which until now was considered one of the most important factors in international literature.

We have demonstrated that pulmonary function testing is an excellent tool for the objective assessment of the patency of the reconstructed airway. This outcome measure can be easily adopted by other centers where pediatric pulmonary function testing is done. In this way, we will be able to pool the data in order to determine which surgical strategy is best in certain clinical situations.

We are the first to assess the HRQoL in children treated for acquired LTS. We have shown that HRQoL has a place in outcome assessment for LTS and that, next to existing comorbidities, the patency of the reconstructed airway is directly associated with QoL outcome on the long-term.

We are the first to describe the prevalence of voice disturbance in a large surgical cohort for LTS and are the first to use the dysphonia severity index in a population of children.

We have translated and validated the Dutch pediatric Voice Handicap Inventory (pVHI). We have identified a cut-off point for the pVHI for the pediatric population.

We have shown that long-term multidisciplinary follow-up is necessary in children treated for LTS since long-term deficits still exist, despite successful decannulation.

What is lacking in this research

We have not investigated swallow outcome and/or feeding difficulties in our cohort. Surgery on the larynx and/or trachea has the potential to influence swallowing function. This is lacking in our reports. Like assessment of voice, quantification of swallowing or feeding deficits is difficult and we are currently developing and validating a questionnaire on pediatric swallow and feeding status. At the moment, standardized swallow and feeding assessments are part of our multidisciplinary outpatient clinic and we will report on these outcomes in the future.

We do not have pre-operative voice data of our surgical cohort of children. Subsequently, we cannot be sure that children with glottic involvement of the stenosis have worse voice outcome because of the pre-operatively scarred glottis or because of the fact that we performed airway surgery. We are currently incorporating voice assessment and the pVHI as a standardized pre-operative measurement for all children undergoing surgery.

Plans and recommendations

- Achieve international consensus on which method is used to calculate the decannulation rate;
- There is a definite need to compare our data with that of other centers dealing with pediatric LTS. We urge other centers to adhere to our follow-up protocol in order to compare different surgical strategies on respiratory, QoL and voice outcome;
- When glottic stenosis is apparent, consider using microlaryngeal (laser) surgery to address the glottis or do a double stage reconstruction with a period of stenting. We will assess whether this change in strategy has different outcomes on voice and quality of life.
- Use pulmonary function testing as a standard objective measure to assess airway outcome;
- Development of an easy-to-use disease specific quality of life instrument or incorporation of the recently published disease specific outcome measure;
- Validation of a tool for objective assessment of voice quality in children.

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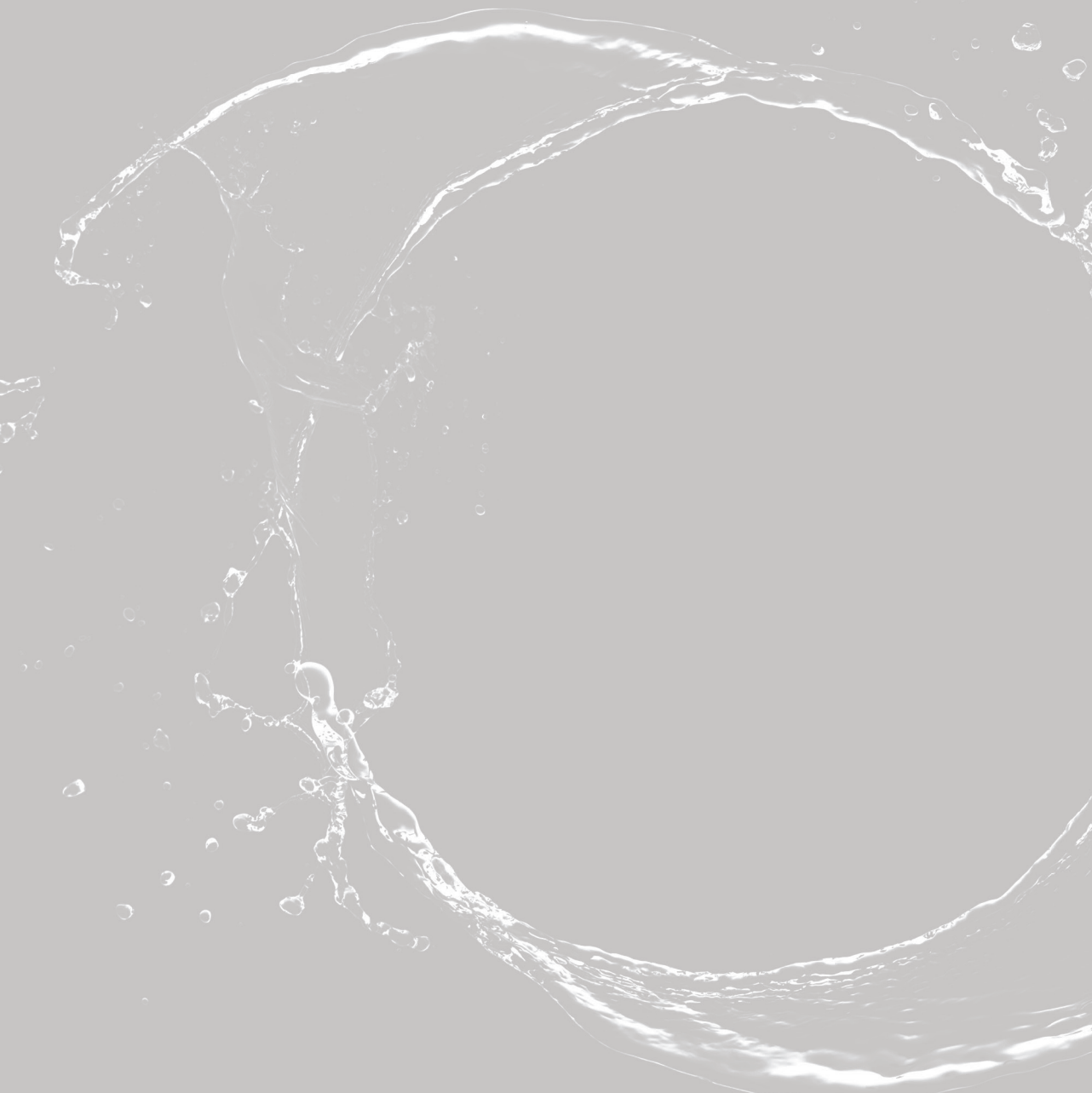


chapter 9

Nederlandse Samenvatting

Nederlandse samenvatting

Dit proefschrift beschrijft de lange-termijnresultaten van de chirurgische behandeling van verworven laryngotracheale stenose (LTS) bij kinderen. Verworven LTS is meestal secundair aan beschadiging veroorzaakt door langdurige intubatie. Dit kan littekenvorming in en vernauwing (stenose) van de luchtweg veroorzaken op het niveau van de stemplooien en/of de subglottis. De stenose kan zo ernstig zijn dat deze kinderen een tracheotomie nodig hebben om te overleven. Operaties in dit gebied hebben als doel om het kind te verlossen van zijn of haar tracheotomie (zogenaamde decanulatie) en om een voldoende open luchtweg te creëren voor ademhaling, waarbij de stem en slikfunctie gespaard blijven.

Hoofdstuk Een

De incidentie, pathofysiologie en ontwikkeling van de chirurgische behandeling van verworven LTS worden in hoofdstuk Een beschreven. We geven een overzicht van de huidige studies over de chirurgische resultaten van verworven LTS en benoemen de ontbrekende kennis in de internationale literatuur. Een korte beschrijving van de verschillende hoofdstukken van dit proefschrift wordt gegeven.

Hoofdstuk Twee

Na retrospectieve analyse van onze data over een tijdsperiode van 18 jaar bleken we uitstekende resultaten te hebben geboekt als we kijken naar de decanulatie bij 98 kinderen die geopereerd werden voor verkregen LTS. De “overall decannulation rate (ODR)” was 95% en de “operation specific decannulation rate (OSDR)” was 92%, wat in vergelijking met andere grote centra erg hoog is. De zes kinderen bij wie decanulatie mislukt was, waren behandeld met een laryngotracheale reconstructie (LTR, 5 “single stage”, 6 “double stage”), hadden allen een graad III stenose en vijf van de zes hadden een of meerdere comorbiditeiten. Deze factoren waren in vergelijking met de succesvol gedecanuleerde groep niet significant.

Na analyse van ons chirurgische cohort vonden we dat veel kinderen met LTS een uitgebreide medische voorgeschiedenis hadden, vergelijkbaar met andere studies over pediatrische LTS. Een groot aantal van de kinderen in onze groep was prematuur geboren en velen hadden comorbiditeiten en congenitale syndromen. De meest voorkomende comorbiditeit in onze studiepopulatie was bronchopulmonaire dysplasie en tracheomalacie.

Met uitzondering van de graad IV Myer-Cotton stenose (behandeld met een cricotracheale resectie (CTR)) werden kinderen met ernstige LTS bij voorkeur behandeld met een single stage laryngotracheale reconstructie (ss-LTR). In onze studiegroep werden 91 van de 98 kinderen met een ss-LTR behandeld, zelfs voor graad III stenose (n=65) met glottische verlittekening en comorbiditeiten. Dit is duidelijk anders dan andere centra die een double stage aanpak met postoperatief stenten of een CTR bepleiten om ernstige gevallen van LTS te behandelen.

Als we alleen naar de 91 ss-LTRs in ons cohort kijken, hebben we nog altijd een uitstekende decanulatie van 93%.

De single stage aanpak bleek uitdagend in de postoperatieve periode. Bij 20% van de kinderen die behandeld werden met een ss-LTR trad een gecompliceerd postoperatief beloop op, waarbij interventies als tijdelijke her-intubatie of tijdelijke her-tracheotomie noodzakelijk waren. Dit geeft aan dat een goed uitgeruste en ervaren PICU noodzakelijk is bij het gebruik van de ss-LTR voor ernstige LTS.

Vervolgonderzoek naar lange–termijnresultaten

We hebben een grote vervolgstudie gestart naar onze lange-termijnresultaten. Kinderen die gedurende een tijdsperiode van 15 jaar door middel van een LTR of CTR behandeld werden voor LTS werden geïncludeerd, zolang ze geen tracheotomie hadden en ouder waren dan vier jaar. Een aantal vragenlijsten werd verstuurd en alle patiënten die geschikt waren voor inclusie werden uitgenodigd voor een vervolgbezoek aan de polikliniek. In totaal werden 80 kinderen in eerder genoemde tijdsperiode geopereerd. Eén patiënt had nog steeds een tracheotomie, één patiënt werd tijdens de onderzoeksperiode geopereerd en twee patiënten waren jonger dan vier jaar ten tijde van het vervolgonderzoek. Uiteindelijk bleven er 76 patiënten over die benaderd werden voor deze studie. Vijf patiënten konden niet worden bereikt (“lost to follow-up”) en zes patiënten weigerden mee te doen aan het onderzoek. Uiteindelijk konden 65 patiënten worden geïncludeerd in deze studie.

Van de 65 geïncludeerde patiënten bezochten er 55 de polikliniek; tien patiënten weigerden dit bezoek in verband met lange reisafstanden, maar vulden wel de toegezonden vragenlijsten in. De totale geïncludeerde groep van 65 patiënten had een mediane leeftijd van elf jaar (4-24 jaar) en een mediane follow-up na chirurgie van zeven jaar (2-17 jaar).

De patiënten die de polikliniek bezochten, werden onderworpen aan een aantal onderzoeken en metingen om algemene gezondheidstoestand, respiratoire status, uithoudingsvermogen, kwaliteit van leven, stemkwaliteit en stem-gerelateerde kwaliteit van leven te evalueren. De resultaten van deze metingen worden beschreven in de volgende hoofdstukken.

Hoofdstuk Drie

Het primaire doel van luchtwegchirurgie is het creëren van voldoende lumen voor ademhaling, groei en lichaamsbeweging. Een belangrijk deel van onderzoek naar uitkomsten van chirurgie is dan ook gericht op de kwaliteit van de gereconstrueerde luchtweg.

Als objectieve maat voor de luchtweg hebben we longfunctieonderzoek geïntroduceerd met geforceerde inspiratoire en expiratoire flow-volume loops. Het maximale uithoudingsvermogen werd getest door middel van de gevalideerde Bruce loopband test. Beide tests bleken non-invasief en goed uitvoerbaar bij kinderen vanaf vijf jaar, mits de

kinderen in staat waren tot het opvolgen van het onderzoeksprotocol. Bij kinderen die dit niet konden was meestal sprake van mentale retardatie. In onze studiegroep was 78% van de patiënten in staat tot het volbrengen van het longfunctieonderzoek en 80% van de patiënten volbracht de loopbandtest.

Na analyse van de resultaten bleek dat meer dan de helft van de patiënten longfunctie-uitkomsten had die duidden op significante, voornamelijk inspiratoire obstructie van de luchtweg. Eén derde van de patiënten had een verminderd uithoudingsvermogen. Aanwezigheid van inspiratoire stridor had een positief voorspellende waarde van 70% voor beperkte inspiratoire flow. De ouderlijke inschatting van het uithoudingsvermogen van hun kind had een positief voorspellende waarde van slechts 40%.

Na statistische analyse vonden we dat glottische betrokkenheid van de stenose geassocieerd was met inspiratoire flow beperking bij longfunctie onderzoek. Aanwezigheid van comorbiditeit was geassocieerd met expiratoire flow beperking, verminderd uithoudingsvermogen en te lage lengte voor het gewicht.

Hoofdstuk Vier

Wij zijn het eerste centrum dat gezondheid-gerelateerde kwaliteit van leven na chirurgie voor LTS bij kinderen heeft gemeten. Om de kwaliteit van leven te meten gebruikten we de Child Health Questionnaire (CHQ) met een ouder volmacht versie (child health questionnaire parent form (CHQ-PF50, 4-18 jaar)) en een kind versie (child health questionnaire child form (CHQ-CF87, 11-18 jaar)). In veel gevallen was sprake van verminderde kwaliteit van leven na lange-termijn follow-up.

Na analyse bleken de uitkomsten van de ouder volmacht vragenlijsten overeen te komen met die van kinderen met astma, wat impliceert dat benauwdheid een zekere impact heeft op kwaliteit van leven. Het was echter opvallend dat uitkomsten van de kwaliteit van leven die de patiënten over zichzelf invulden nauwelijks verschilden van de normale populatie. Als we de uitkomsten van de ouders en van de patiënten zelf vergeleken vonden we significante verschillen op zes van de elf corresponderende sub-schalen, waarbij ouders de kwaliteit van leven van hun kinderen lager inschatten dan de kinderen zelf.

Het is bij kwaliteit van leven onderzoek niet ongebruikelijk dat ouders een andere kijk hebben op de kwaliteit van leven van hun kinderen dan die kinderen zelf en dit is een belangrijk gegeven voor clinici die kwaliteit van leven onderzoeken in hun postoperatieve cohort. Beide visies werpen een ander licht op de kwaliteit van leven van het kind en beiden moeten meegenomen worden in de evaluatie van kwaliteit van leven.

We vonden een aantal factoren dat een significante relatie had met lagere scores op de kwaliteit van leven uitkomsten. De belangrijkste factoren waren glottische betrokkenheid van de stenose en de aanwezigheid van comorbiditeit. De uitkomsten van de Bruce

loopbandtest en de longfunctietest correleerden met de uitkomsten van de kwaliteit van leven vragenlijsten. Dit betekent dat kwaliteit van leven mogelijk verbeterd kan worden door de kwaliteit van de luchtweg, het uithoudingsvermogen of de zorg voor comorbiditeiten te verbeteren.

Hoofdstuk Vijf

Om de pediatric Voice Handicap Inventory (pVHI) te kunnen inzetten in onze populatie werd de Engelse pVHI vertaald in het Nederlands en gevalideerd voor de Nederlandse populatie. Ten behoeve van de validatie werden de pVHI vragenlijsten ingevuld door ouders van kinderen die op ons dysfonie spreekuur voor kinderen kwamen. De resultaten werden vergeleken met die van een controlegroep van kinderen van een nabijgelegen school zonder stemklachten. Dit leverde een dysfoniegroep van 79 kinderen en een controlegroep van 122 kinderen op. Er was een significant verschil tussen beide groepen met een uitstekende interne consistentie. De pVHI werd met een tussenpose tweemaal ingevuld door een groep van 32 kinderen die werden onderzocht na chirurgie voor LTS (hoofdstuk Zes), waardoor de test-retest betrouwbaarheid kon worden geëvalueerd. De test-retest betrouwbaarheid was hoog met matige tot bijna perfecte correlatie.

Objectieve beoordeling van stemkwaliteit bij kinderen is zeer uitdagend en normaalwaarden ontbreken. We hebben de ROC curve analyse gebruikt om normaalwaarden te bepalen voor de pVHI in de Nederlandse populatie. Een totale pVHI score van zeven of hoger wijst op een significante verstoring van de stem-gerelateerde kwaliteit van leven met een specificiteit van 93% en een sensitiviteit van 100%.

Hoofdstuk Zes

De “Dysphonia Severity Index” (DSI), een gevalideerd instrument voor objectieve stem meting bij volwassenen, werd gebruikt om de kwaliteit van de stem te evalueren in ons cohort. Normaalwaarden voor de DSI bij kinderen ontbraken helaas en dit bemoeilijkte de interpretatie van onze resultaten. We schatten dat een totale DSI score lager dan 2,0 overeenkwam met significante stemafwijkingen bij kinderen. Naar onze mening was dit een erg voorzichtige schatting en de afkapwaarde voor dysfonie lag waarschijnlijk hoger dan 2,0. De mediane score op de DSI in ons cohort was -0,03 en bij maar liefst 77% van de kinderen was de DSI score onder 2,0. De moeilijkheid van de objectieve meting van stemkwaliteit bij kinderen werd onderstreept door het feit dat 17 van de 55 kinderen niet konden voldoen aan het protocol voor de DSI meting.

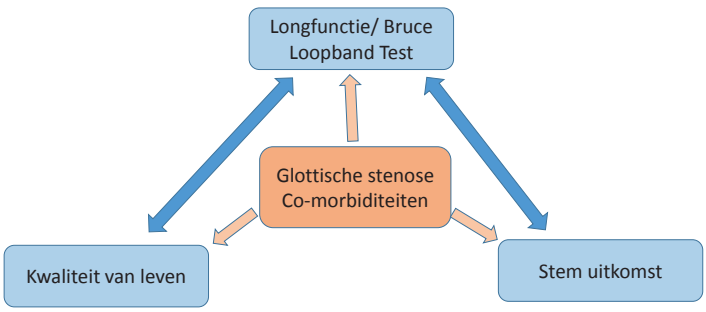
Daarnaast werd de pVHI ingezet om de stem-gerelateerde kwaliteit van leven te beoordelen. De pVHI is een gevalideerd instrument (hoofdstuk Vijf) voor de Nederlandse pediatrische populatie dat eenvoudig in gebruik is.

De mediane score van de totale pVHI was 17 en bij 75% van de kinderen was de pVHI score zeven of hoger, wat overeenkomt met een significante verstoring van de stem-gerelateerde kwaliteit van leven. Na multivariate analyse bleken de glottische betrokkenheid van de stenose en aanwezigheid van comorbiditeiten significant geassocieerd met een slechtere pVHI uitkomst. Ook de verminderde inspiratoire flow bij de longfunctietest en inspiratoire stridor waren geassocieerd met slechtere pVHI.

Relatie tussen verschillende uitkomst metingen

De verschillende uitkomstparameters longfunctie en Bruce loopband, kwaliteit van leven en stemuitkomst zijn alle gecorreleerd aan elkaar. De connectie tussen de verschillende uitkomstparameters is weergegeven in figuur 1.

Figuur 1: Connectie tussen verschillende uitkomstparameters



Dubbele pijlen geven significante correlaties tussen uitkomstparameters, enkele pijlen geven significante associaties weer tussen preoperatieve factoren en uitkomstparameters.

List of abbreviations

AUC	Area under the curve
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CAPE-V	Consensus auditory-perceptual evaluation of voice
CCG	Costal cartilage graft
CHQ	Child health questionnaire
- CHQ-CF87	Child health questionnaire – child form
- CHQ-PF50	Child health questionnaire – parent form
CTR	Cricotracheal resection
- ss-CTR	single stage cricotracheal resection
- ds-CTR	double stage cricotracheal resection
DSI	Dysphonia severity index
ENT	Ear-nose-throat
FEV1	Forced expiratory volume in 1 second
FIV1	Forced inspiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastro-oesophageal reflux disease
HFA	Height for age
HRQoL	Health-related quality of life
LTP	Laryngotracheoplasty
LTR	Laryngotracheal reconstruction
- ss-LTR	single stage laryngotracheal reconstruction
- ds-LTR	double stage laryngotracheal reconstruction
LTS	Laryngotracheal stenosis
MEF25%	Maximum expiratory flow at 25% of vital capacity
MC	Myer-Cotton
MPT	Maximum phonation time
OSAS	Obstructive Sleep Apnoea Syndrome
OSDR	Operation specific decannulation rate
ODR	Overall decannulation rate
OR	Operating room
PEF	Peak expiratory flow
PFT	Pulmonary function test
(P)IC(U)	(Pediatric) intensive care (unit)
PIF	Peak inspiratory flow
PPI	Proton-pump inhibitor
PROM	Patient reported outcome measure
pVHI	Pediatric voice handicap inventory
PVOS	Pediatric voice outcome survey

QoL	Quality of Life
ROC	Receiver operating characteristics
SD	Standard deviation
VAS	Visual analogue scale
VCmax	Maximum vital capacity
VHI	Voice handicap inventory
VIF	Variance inflation factor
WFA	Weight for age
WFH	Weight for height

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: B Pullens
PhD period: 2011-2016
Erasmus MC Department: KNO-heelkunde
Promotor: Prof.dr. R.J. Baatenburg de Jong

1. PhD training	**Year**	**Hours/ECTS**
Specific courses (e.g. Research school, Medical Training)		
- Journal clubs tijdens opleiding	2006-2011	1
- Evidence based medicine cursus tijdens opleiding		1
- Nascholing "evidence based medicine	2011	0.5
Presentations		
- Tracheal stenosis: diagnosis and treatment AMC	2013	2
- KNO vergadering April	2014	2
- ESPO Dublin	2014	2
- KNO vergadering April	2015	2
- KNO vergadering November	2015	2
- ESPO Lissabon 2x	2016	4
- Openingssymposium kinderthoraxcentrum	2016	2
(Inter)national conferences		
- ASPO Chicago	2011	1
- KNO vergadering (2/jaar)	2011>	1
- ESPO Amsterdam	2012	1
- Groninger Endoscopie cursus	2012	1
- Tracheal stenosis: diagnosis and treatment AMC	2013	1
- ESPO Dublin	2014	1
- Surgery of the laryngotracheal junction,	2015	1
- Lausanne airway course	2016	1
- ESPO Lissabon	2016	1
2. Teaching	**Year**	**Hours/ECTS**
Lecturing		
- Pediatrische KNO voor jeugdartsen in opleiding 4x	2011-2016	1
- Symposium "stridor"	2013	1
Other		
- Afscheidssymposium Hans Hoeve	2013	4
- Jaarverslagen kinderluchtweg team	2014 & 2015	2
- Workshop "Scopie bij een benauwd kind" 5x	2015 & 2016	4

Dankwoord

Niemand schrijft een proefschrift in zijn eentje en dat geldt zeker ook voor mij. Zonder het harde werken, de wijze raad en de aanmoedigingen van velen zou dit niet mogelijk zijn geweest.

Allereerst mijn grote dank aan en respect voor alle patiënten en hun ouders die hebben meegewerkt aan dit promotieonderzoek. Zij hebben zich door meerdere vragenlijsten moeten worstelen en vaak lange afstanden moeten reizen voor dit vervolgonderzoek. Mijn dank is groot.

Geachte Professor doctor Baatenburg de Jong, beste Rob. Hartelijk dank voor de mogelijkheid te promoveren op dit onderwerp, dat perfect past bij mijn dagelijkse werkzaamheden. Ik ben dankbaar voor de steun die ik van je krijg om me te ontplooien in het Sophia Kinderziekenhuis en als KNO-arts. Bij jou staat kwaliteit altijd voorop en ik bewonder de manier waarop je de afdeling runt.

Geachte doctor Joosten, beste Koen. Jij bent de motor achter het schrijven van dit proefschrift geweest; zonder jouw niet aflatende enthousiasme en begeleiding was het nooit geworden wat het nu is. Jouw soms meedogenloze tempo zorgde ervoor dat dit proefschrift nooit in het slop kwam. We hebben vaak aan één blik voldoende en ik prijs me gelukkig met de gedachte dat we nog vele jaren zullen samenwerken.

Geachte doctor Hoeve, beste Hans. In feite onderzoeken we de patiënten die door jou zijn geopereerd. Je resultaten zijn indrukwekkend. Ik hoop ooit op een dergelijk niveau te opereren. Dank je wel voor alles wat je me hebt geleerd op gebied van de kinderluchtweg. Jouw opmerkingen tilden het onderzoek telkens naar een hoger niveau.

Hooggeachte promotiecommissie. Hartelijk dank voor uw kritische blik op mijn proefschrift en de tijd die u genomen heeft om het op zijn wetenschappelijke waarde te toetsen.

Hooggeachte oppositieleden. Dank dat u met mij van gedachten heeft willen wisselen over mijn proefschrift. Uw komst betekent veel voor me.

Beste Marieke. Dit had eigenlijk jouw boekje en jouw moment moeten zijn. Helaas liep het anders maar ik besef me terdege dat ik dit werk nooit had kunnen doen zonder het werk dat reeds door jou verricht was toen ik aan dit onderzoek begon. Ik wens je veel succes en plezier toe als huisarts.

Beste co-auteurs Laura, Marc, Mariëlle, Marieke, Corrine en Karolijn. Hartelijk dank voor jullie hulp met het schrijven van de artikelen. Ik ben veel wijzer geworden over longfuncties, stemonderzoeken en kwaliteit van leven. Ik hoop op meer vruchtbare samenwerking in de toekomst.

Beste Marja, Wil, Esther en Janneke. Jullie zijn de spil van de kinder-KNO en jullie belang kan niet genoeg benadrukt worden. Dank voor jullie hulp bij de voorbereidingen van het symposium en de festiviteiten op deze voor mij belangrijke dag. Janneke, jou wil ik in het bijzonder bedanken voor de inspanningen die je elk jaar weer levert voor het prachtige jaarverslag van het kinderluchtwegteam.

Beste collega SKZ'ers. Ik heb de leukste baan die er is, in het leukste ziekenhuis en met de leukste collega's. Dank voor het overnemen van (nog) meer klinische taken zodat ik meer tijd had voor het vervolmaken van dit proefschrift. Ik zal het goedmaken de komende tijd.

Beste collega KNO-artsen. Ik waardeer de fijne sfeer en samenwerking die we hebben en het wederzijds respect waarmee we met elkaar omgaan. Ik weet dat dat niet vanzelfsprekend is.

Beste AIOS en ANIOS KNO. Jullie zijn de toekomst van KNO Nederland en jullie kennende gaat dat helemaal goed komen. Dank dat ik ondanks mijn vorderende leeftijd en grijze haren nog steeds mee mag naar jullie feestjes.

Beste leden van het kinderluchtwegteam en het kinderthorax centrum. Wij zijn met iets heel moois bezig. Laten wij niet vergeten waar het allemaal om te doen is: de allerbeste kwaliteit van zorg voor onze complexe patiënten. Doe geen concessies, doe wat nodig is en laat je vooral niet tegenhouden door ogenschijnlijke onmogelijkheden.

Beste paranimfen Marc en Hendrik. Het betekent veel voor me dat jullie mij op deze iconische dag willen flankeren. Hendrik, we hebben altijd contact gehouden na onze opleiding en ik koester onze vriendschap, al zien we elkaar natuurlijk veel te weinig. Ik maak me wel een beetje zorgen om je Bossche Bollen consumptie nu je je hebt gevestigd in het prachtige Brabant. Marc, ik ben dagelijks getuige van jouw jaloersmakende efficiëntie en toewijding op het wetenschappelijk vlak. In dit tempo hebben we binnenkort weer een feestje en moet ik u tegen je gaan zeggen. Tot die tijd ben ik natuurlijk nog gewoon jouw baas.

Lieve ouders, schoonouders, zussen, schoonzus en zwagers. Dank voor jullie liefde en steun van de afgelopen jaren.

Lieve Carlijn. Ik kan me geen betere, lievere en mooiere vrouw voorstellen dan jou. Het werk dreigt regelmatig de overhand te nemen en jij trekt dan gelukkig volkomen terecht aan de noodrem. Blijf dat alsjeblieft doen; ik wil samen oud en rimpelig worden.

Lieve Siem, Lieve Janne. Wat ben ik gelukkig met jullie. Elke dag geniet ik van jullie en ik prijs me gelukkig dat ik jullie mag zien opgroeien. Jaag je dromen na, en maak er een mooi feest van!

Curriculum vitae

Bas Pullens werd geboren op 23 juni 1978 in ’t Harde, gemeente Elburg. In 1996 haalde hij zijn eindexamen aan het Gymnasium Celeanum te Zwolle. In hetzelfde jaar begon hij aan de studie Geneeskunde aan de Universiteit Utrecht. Tijdens het doorlopen van de co-schappen raakte hij geïnteresseerd voor de KNO-heelkunde en in februari 2006 begon hij met de opleiding keel-, neus-, en oorheelkunde aan het Universitair Medisch Centrum Utrecht na eerst een aantal maanden als ANIOS werkzaam te zijn geweest in het Centraal Militair Hospitaal te Utrecht. Opleiders in het UMC waren achtereenvolgens wijlen professor dr. F.W.J. Albers, dr. A.F. van Olphen en professor dr. W. Grolman. De perifere opleiding doorliep Bas in het Gelre ziekenhuis te Apeldoorn onder begeleiding van professor dr. P.P.G. van Benthem. Tijdens de opleiding tot KNO-arts groeide de interesse voor wetenschappelijk onderzoek en zagen meerdere publicaties het licht met als voornaamste onderwerp de ziekte van Ménière. In 2011 voltooide Bas met succes de KNO opleiding.

Direct aansluitend begon Bas als KNO-arts in het Erasmus MC-Sophia Kinderziekenhuis waar dr. L.J. Hoeve hem de fijne kneepjes van de pediatrisch KNO bijbracht. Naast zijn werkzaamheden als KNO-arts begon in 2013 zijn promotietraject onder begeleiding van professor dr. R.J. Baatenburg de Jong, dr. K.F.M. Joosten en dr. L.J. Hoeve. Bas trouwde in januari 2015 met Carlijn Agterberg. Samen hebben zij twee kinderen: Siem (04-03-2011) en Janne (17-02-2013).

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