# The Air that we Breathe: Respiratory Morbidity in Children with Congenital Pulmonary Malformations

## Luchtwegproblemen bij kinderen met aangeboren longafwijkingen

Marjolein Spoel

The studies presented in this thesis were financially supported by:

Stichting Swart-van Essen

Fonds NutsOhra

ISBN: 978-94-6169-252-8



Photography: Perry van der Hoek (www.theycallmepierre.nl)

Printed by: Optima Grafische Communicatie Rotterdam

# The Air that we Breathe: Respiratory Morbidity in Children with Congenital Pulmonary Malformations

## Luchtwegproblemen bij kinderen met aangeboren longafwijkingen

**Proefschrift**

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam,

Op gezag van de rector magnificus Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

vrijdag 15 juni 2012 om 13.30 uur

door

**Marjolein Spoel**

geboren te Rotterdam

ERASMUS UNIVERSITEIT ROTTERDAM

**Promotiecommissie**

| | |
|---|---|
| Promotoren: | Prof.dr. D. Tibboel |
| | Prof.dr. J.C. de Jongste |
| Co-promotor: | Dr. H. Meijers-IJsselstijn |
| Overige leden: | Prof.dr. H. Tiddens |
| | Prof.dr. I. Reiss |
| | Prof.dr. R.M.H. Wijnen |

**Contents**

## Proloog

November 1992: Direct na de coschappen naar de afdeling kinderchirurgie van het Sophia kinderziekenhuis, toen nog aan de Gordelweg te Rotterdam. Een zeer bewuste keuze om daar te willen werken. Toen: Van elke twee patiënten die kort na de geboorte met een congenitale hernia diafragmatica op de IC kinderchirurgie opgenomen worden, overleeft er uiteindelijk maar één. Na perfecte opvang, optimale beademing, inotropie en alles wat we verder te bieden hebben, en dat is veel met alle expertise en mogelijkheden die tot onze beschikking staan, redt slechts de helft het. Geen statistieken maar namen, gezichtjes, ouders en emoties. Het was maar aan een deel van deze kinderen gegund om uiteindelijk met twee dolblije, en doordrongen van het hun bespaarde leed, ouders huiswaarts te gaan. Die frustrerende, neerwaartse spiraal van pulmonale hypertensie met almaar toenemende hypoxie en acidose die tot aan de dood van een mooi, gaaf mensje kan leiden……

Juni 2012: Met alle huidige nieuwe mogelijkheden en protocollen is die overleving gestegen van 50% tot maar liefst 80%. Wat een winst en vreugde. Toch?? Zestig procent van de kinderen die destijds zouden zijn overleden redden het nu, anno 2012, wel dankzij voortschrijdend inzicht en de mogelijkheden op medisch gebied. ECMO, HFO en evidence-based protocollen, op Europees niveau gedragen, bieden optimale overlevingskansen voor kinderen met ernstiger vormen van hernia diafragmatica, longhypoplasie en pulmonale hypertensie. Fantastisch! Maar na alle klinische inspanningen gaan onze wonderkindjes het normale leven in. Hun ouders zijn vaak blij met alle cognitieve en motorische vaardigheden die zij zich, na het moeizame begin van hun leven, toch eigen maken. Op de polikliniek van de chirurgische lange termijn follow-up wordt dit vergeleken met datgene wat gezonde leeftijdgenoten kunnen. Kunnen onze ‘paradepaardjes’ zich wel meten met hun leeftijdgenoten? En zo niet, wat dan? Dat is onze verantwoordelijkheid, verbeterde overleving gaat niet gelijk op met een verbetering van de kwaliteit van leven. Een ernstiger vorm van deze, en andere, aangeboren longafwijkingen gaat logischerwijs samen met meer beperkingen in het dagelijks leven. Aan ons om te meten en weten wat de beperkingen zijn, en hoe we ook na ontslag deze kinderen in hun latere leven de meest optimale en complete zorg kunnen bieden.

Daarom; deze afdeling, deze loopbaan, dit proefschrift!

Met dank!

Marjolein, juni 2012


General introduction

# Introduction

## Preamble

Intensive care for children is one of the areas of medicine that have significantly matured in the past decades. New treatment modalities have been introduced, such as high frequency oscillation (HFO), inhaled nitric oxide (NO), and extracorporeal membrane oxygenation (ECMO), and minimally invasive surgery is an example of improvement in surgical techniques. These new modalities have reduced mortality rates, but sometimes at the cost of more morbidity. Not only the underlying disease itself, but also side effects of the treatment can cause morbidity. Aspects of short-term and long-term morbidity have therefore become a focus of attention [1-2]. Congenital anomalies that include abnormal lung development requiring neonatal intensive care treatment can result in pulmonary function impairment. These long-term pulmonary sequelae can be assessed by lung function measurement. Longitudinal evaluation of lung function can help identify infants and children at risk for respiratory impairment and elucidate the long-term consequences of congenital lung anomalies.

## Anatomical congenital anomalies

Annually some 5,500 newborns (about 3% of all births) in the Netherlands present with major anatomical congenital anomalies [3]. These children often need prolonged hospitalization with (multiple) surgical interventions in the neonatal period and thereafter. Improved antenatal detection, improved surgical techniques and peri-operative care have reduced the mortality rates of these anomalies [4]. The pediatric surgeon Ravitch classified six major anatomical congenital anomalies as "index" diagnoses [5]. Those are: congenital diaphragmatic hernia, esophageal atresia, intestinal atresia, Hirschsprung's disease, anorectal malformations, and abdominal wall defects. The causes of most of these anomalies are still unknown. They occur either in isolated form or as part of more complex syndromes. In the Netherlands, children with index diagnoses are to be treated in one of the six designated pediatric surgical centres. Survivors may show considerable morbidity and many will have to rely on the health care system for the rest of their life [6-10]. This thesis deals with long-term morbidity in three anatomical congenital anomalies with concomitant abnormal lung development; congenital diaphragmatic hernia, esophageal atresia, and congenital cystic lung lesions.

## Congenital diaphragmatic hernia

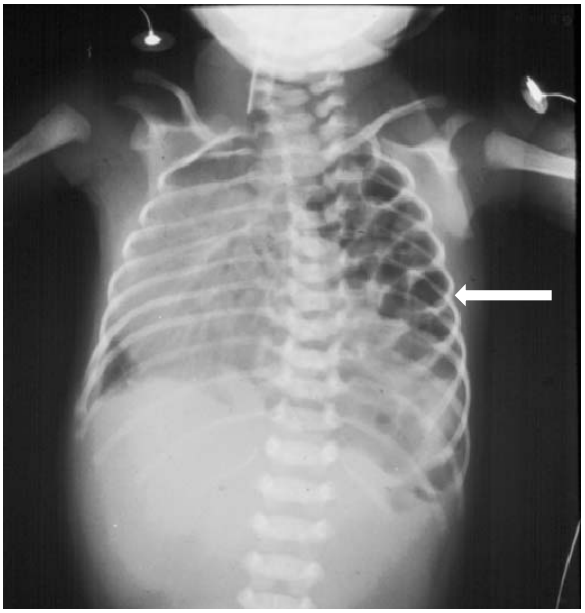
Congenital diaphragmatic hernia (CDH) is a rare congenital anomaly of the diaphragm with an incidence of approximately 1 per 2500 births. Typically, the abdominal organs will herniate into the chest cavity, with resulting maldevelopment of the alveoli and

pulmonary vessels [11]. The defect is usually – reported in 84% of the cases – located in the left hemidiaphragm. CDH can present as an isolated defect or in combination with other congenital anomalies, such as congenital heart disease or chromosomal anomalies [12]. The condition may be life-threatening and key determinants of mortality are the severity of pulmonary hypoplasia and the presence of therapy-resistant pulmonary hypertension [11]. Smaller number and generations of airways, thickened alveolar septa, and abnormal architecture of the respiratory acinus characterize pulmonary hypoplasia. Pulmonary hypertension may result from medial hyperplasia and adventitial thickening associated with under- and maldevelopment of the pulmonary vessels [13].

Although mortality rates have gone down over the years, mortality rates in live-born patients still range from 10-35%[14-19], depending on case selection. Moreover, survivors carry a substantial risk of developing secondary morbidity, such as cardiopulmonary, gastro-intestinal and neurological problems [20]. Approximately 30-50% of CDH survivors develop long-term pulmonary sequelae, including chronic lung disease, persistent pulmonary hypertension, asthmatic symptoms, and recurrent respiratory tract infections [11,21-24]. Pulmonary hypoplasia and lung damage due to mechanical ventilation predispose newborns with CDH to develop chronic pulmonary symptoms. Patients who receive ECMO and/or a patch repair are more likely to develop pulmonary complications [25]. Long-term pulmonary sequelae may range from full clinical recovery to impaired lung function, respiratory tract infections, cor pulmonale, and even death. Many studies report obstructive lung function abnormalities in CDH survivors; restrictive and combined obstructive/restrictive abnormalities are reported to a lesser extent [1,23-28]. Lung function abnormalities occur in 28-52% [25,28]. Longer duration of ventilation is associated with worse pulmonary function [23]. Furthermore, chest wall deformities, which occur in 46% of the patients, may be responsible for lung function anomalies [23-24]. CDH patients show higher rates of bronchial hyperreactivity after provocation tests than do controls [23-24]. This hyperreactivity is thought to be due to ventilation-induced lung damage rather than to pulmonary hypoplasia [23]. Apart from lung function anomalies, abnormalities on chest X-rays are reported in 33-80% of the patients [22,25]. These include hyperlucency, hyperinflation, persistent lung hypoplasia, decreased pulmonary vascularity, persistent lung opacities, mediastinal shift, and abnormal diaphragm configuration [21-22].

Lung function abnormalities in CDH survivors are relatively mild and usually improve over time, especially over the first six months [26]. This may well be due to compensatory growth of the lungs, as V/Q scans show no reduction in lung volume and a normal diffusion capacity [23]. Still, there is much to say for thorough pulmonary follow-up and lung function tests in CDH survivors beyond the neonatal period, especially those with severe chronic lung disease. In milder cases, monitoring of pulmonary problems is important to assess treatment strategies. Previous research on lung function abnormalities in CDH survivors was mostly retrospective and in small samples. These retrospective data also come from the era before ‘gentle’ ventilation strategies and ECMO were used and are therefore not representative for the present-day population of patients with CDH.

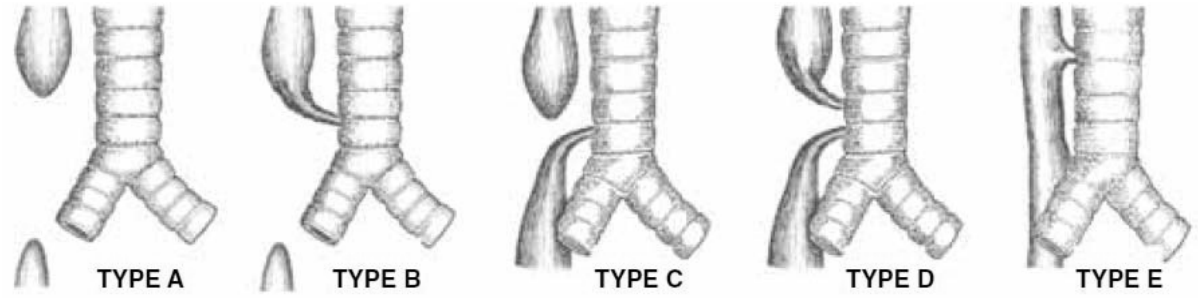
Research should therefore be directed towards prospective follow-up of lung function measurements starting from a very early age. This will eventually reveal the evolution and functional consequences of this anomaly during childhood and adolescence.



A newborn with left-sided congenital diaphragmatic hernia; abdominal organs protrude into the thoracic cavity.

## Esophageal atresia

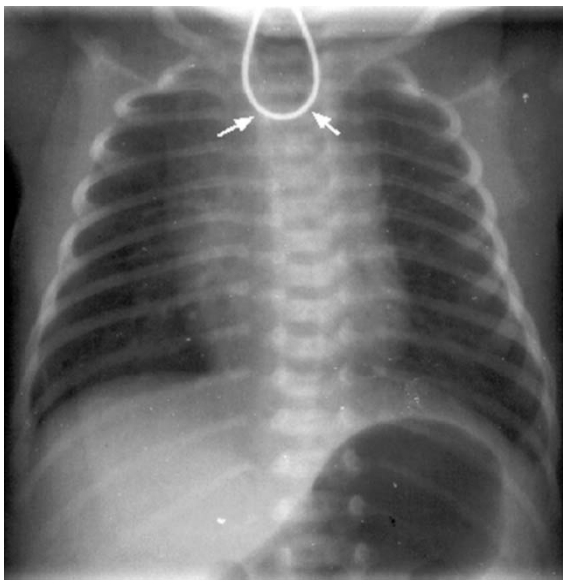
Esophageal atresia (EA) with or without tracheo-esophageal fistula (TEF) is an anatomical congenital anomaly of the gastrointestinal and respiratory tract characterized by absence of the normal continuity of the esophagus. TEF is a congenital connection between the proximal and/or distal esophagus and the airway. The great majority of the patients have both EA and TEF. The most common variant is EA with a distal TEF (type C), other types are pure EA without TEF (type A), EA with a proximal TEF (type B), EA with a distal and proximal fistula (type D), and a so-called H-type fistula (type E).




EA of any type occurs in approximately 1 in 3,500 live births. In about half of the cases there are associated anomalies, with cardiac malformations being the most common. Most children born with EA undergo surgical repair (end-to-end anastomosis) within a few days after diagnosis except for type A. EA-TEF is associated with tracheomalacia,

which is a condition of the trachea characterized by weakness of the supporting tracheal cartilage resulting in an abnormally wide posterior membranous wall [29]. This condition may cause the trachea to collapse, especially under increased transmural pressure such as during coughing, crying or feeding. Tracheomalacia most commonly affects the distal one-third of the trachea. Intervention is not always necessary; as the child grows the tracheal cartilage stiffens, and the airway widens, making the airway less vulnerable.

Since the first successful primary repair of EA and TEF in 1941 by Haight and Townsley [30], survival rates of infants with this condition have dramatically improved. Apart from advances in neonatal intensive care and surgical techniques, this may be ascribed to better anaesthetic management, early diagnosis and treatment of associated anomalies, recognition of anastomotic complications, dilation of anastomotic strictures, and aggressive treatment of gastro-esophageal reflux disease (GERD) [31].



Infant with esophageal atresia; nasogastric tube curls in the proximal part of the interrupted esophagus.

The improved survival has opened the eyes to the possibility of long-term complications of EA. Morbidity is often secondary to GERD, anastomotic strictures, disordered motility and tracheomalacia. In addition, children with EA-TEF may develop cough, wheeze, aspiration, pneumonia, vomiting, choking and feeding difficulties [32], which are most pronounced in the first 3 years of life and improve considerably after 8 years of age [33]. Respiratory symptoms may be multifactorial in origin and related to recurrent aspiration, bronchial obstruction and tracheomalacia. Variable respiratory and gastrointestinal symptoms can continue into adulthood and may be associated with abnormal pulmonary function tests. A more restrictive lung function pattern seen at school age is hypothesized to be the result of suboptimal lung growth in the early years of life [32]. It has also been suggested that recurrent pneumonia, due to retention of secretions from squamous

metaplasia of the tracheal mucosa and ineffective cough, may contribute to smaller lung volumes [34]. Thoracotomy itself may also result in restrictive pulmonary function impairment. Long-term outcome after thoracoscopic repair has not yet been described, but is expected to be better than after conventional surgery [35].

## Congenital lung lesions

Congenital malformations of the lung are relatively rare with an estimated prevalence of 1:11.000-35.000 pregnancies and vary widely in their presentation and severity [36-38]. Advances in diagnostic techniques have improved the antenatal detection and characterisation of congenital lung lesions [39]. Consequently, the incidence of these lesions has increased considerably. The differential diagnosis of an antenatally detected lung malformation includes congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration, bronchogenic cyst, and congenital lobar emphysema. Regarding the origin of CCAM, some consider it to be a hamartomous lesion of the bronchial tree; others favor a localized arrest in the development of the fetal bronchial tree [38]. CCAM usually presents on prenatal ultrasound as a cystic or solid intrapulmonary mass, usually confined to one lobe. A bronchopulmonary sequestration is a mass of non-functioning lung tissue with a blood supply originating from the systemic vasculature. Two types are distinguished: intralobar and extralobar. A bronchogenic cyst results from abnormal budding of the foregut, is usually unilocular, mostly located in the mediastinum and does not communicate with the airway [40]. Congenital lobar emphysema is a term used to describe a distended hyperlucent lobe, usually the left upper or right middle lobe. The pathogenesis remains unclear but transient bronchial obstruction in utero or bronchial valve stenosis have been suggested [41].

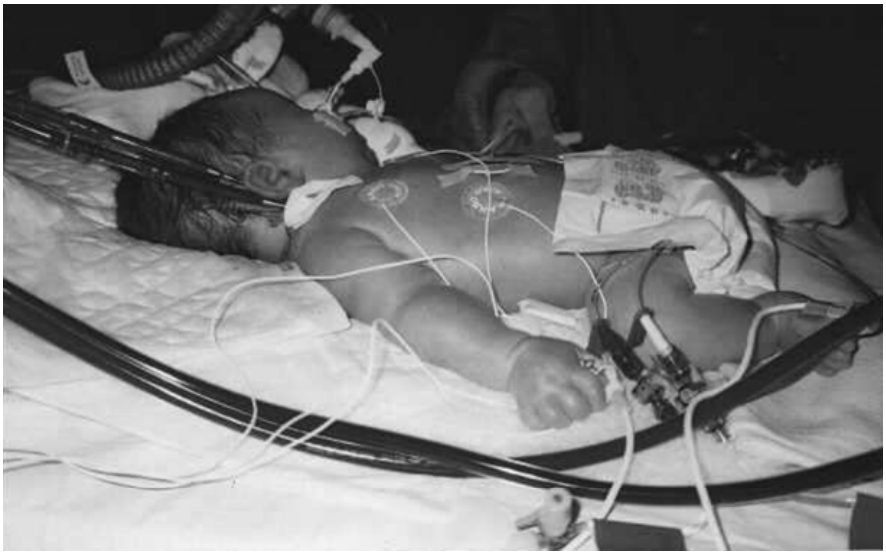
Most cases of congenital lung lesions are now diagnosed prenatally and it is possible to observe their natural courses in utero from severe hydrops to total regression. In the perinatal period, air trapping within the cystic component of CCAM can result in life-threatening respiratory distress requiring immediate surgical intervention. Later in life, communication of the cysts with the airways can result in recurrent pneumonia for which surgical resection of the affected lung part(s) is indicated. Controversy remains on postnatal surgical management in asymptomatic lesions, deferred surgery at 3-6 months to prevent possible late infection is suggested [36]. On the other hand, asymptomatic lesions may regress spontaneously and observation is warranted. To our knowledge, no studies on clinical course and respiratory outcome are available.

## Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) was first used to treat neonatal respiratory failure more than 30 years ago. It is a pulmonary bypass technique providing

life support in acute reversible cardiorespiratory failure when conventional management fails. It is thought that this prevents further injury from high oxygen concentration, volume trauma and barotrauma, and hence promotes lung healing [42]. The Erasmus MC-Sophia Children's Hospital Rotterdam and the Radboud University Medical Center Nijmegen are the only two ECMO centers in the Netherlands. In the Sophia Children's Hospital, more than 400 neonates have been treated with ECMO since 1992 and the overall survival rate of neonatal ECMO is stable around 70%.

In neonates, ECMO is used predominantly in CDH, meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, and sepsis. A large trial in the UK on neonatal ECMO conferred a survival advantage of ECMO over conventional management without a concomitant increase in severe disability [43-45]. Thus, ECMO may be of benefit to infants with severe respiratory dysfunction who otherwise would have died. Detailed assessment of long-term morbidity seems therefore essential to confirm the reported survival advantage [46].



Infant treated with neonatal extracorporeal membrane oxygenation.

## Follow-up

The departments of Pediatric Surgery and Pediatric Intensive Care in the Erasmus MC-Sophia Children's Hospital offer a multidisciplinary follow-up program for children born with major anatomical malformations and for their families since January 1999. The program aims to reduce the overall morbidity associated with these malformations, and to offer better care and lines of communication. From 2001 onwards, children treated with ECMO were included in the follow-up program as well. The follow-up team consists of: a pediatric surgeon, pediatricians, developmental psychologists, ICU nurses, a social worker, a clinical geneticist and pediatric physiotherapists. Children and their parents are evaluated when the child is 6, 12, and 24 months and 5, 8, 12 and 18 years of age.

Evaluation of growth and development up to age 24 months showed impaired growth and psychomotor developmental delay up to this age. Another study showed that early development was predictive of development at 5 years, which can guide individualized follow-up for this vulnerable group of children [2]. A study on lung function in the first year of life in patients treated with neonatal ECMO revealed airflow obstruction and signs of hyperinflation, especially in CDH patients [47]. In a nationwide evaluation of 5-year-olds following neonatal ECMO treatment, children presented with considerable morbidity [47,48]. In a study in 5- ,8- and 12-year-old children treated with neonatal ECMO, exercise capacity declined significantly over time irrespective of the primary diagnosis [48]. In the first 5 years of life patients with CDH and EA showed to be at risk for long-term respiratory morbidity, growth impairment, and disturbed maximal exercise performance [1]. These findings warrant a dedicated multidisciplinary follow-up team evaluating morbidity up till adolescence.

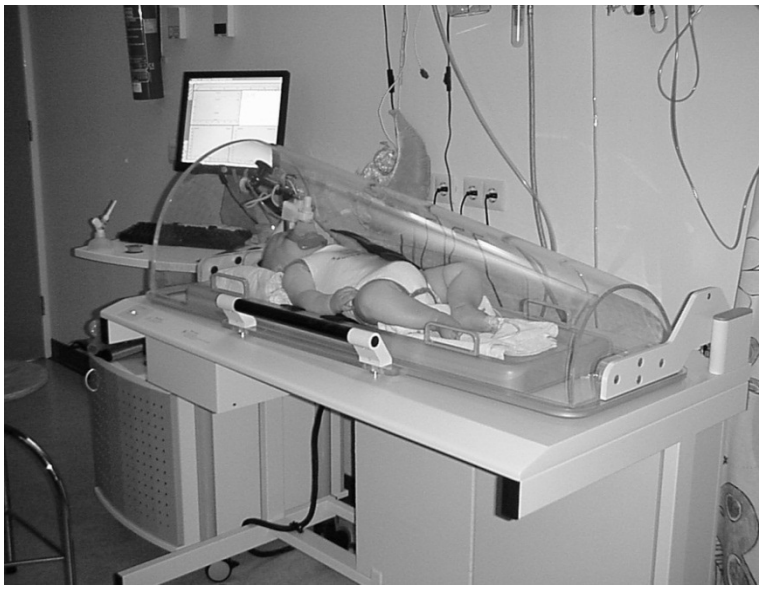
Because of the expected, considerable respiratory morbidity in the aforementioned patient groups, thorough follow-up should include lung function testing starting in the first year of life. In the first year of life we performed infant lung function testing, which of necessity is limited to functional residual capacity, tidal volume and maximal expiratory flow at functional residual capacity. At 5, 8, 12 and 18 years of age lung function tests also included measurement of dynamic and static lung volumes, and from 8 years onwards also diffusion capacity.

## Infant lung function testing

*Lung volume*

The only lung volumes that can be measured reliably and routinely in infants are the functional residual capacity (FRC) and tidal volume, based on the resting end-expiratory volume. FRC by plethysmography is also known as thoracic gas volume and measures all the compressible gas within the thoracic cage, including that which is not in direct communication with the airway opening. Therefore, values obtained with this method in healthy infants and young children are consistently some 15% higher than values obtained with gas dilution techniques [49-52]. This may reflect some degree of airway closure during tidal breathing, influence of air in the stomach and/or poor gas mixing[53]. Plethysmographic measurement of FRC under sedation is a time-consuming but noninvasive and repeatable technique for measurements of lung volume [54]. For the measurement of forced expiration during tidal breathing, we used the rapid thoracoabdominal compression technique with a non-elastic, inflatable jacket. This is a practical, non-invasive method to assess airway pathology which has been used for over 20 years at the department of respiratory medicine of the Erasmus MC-Sophia Children's Hospital. The maximal flow at FRC ($V'max_{FRC}$) is thought to reflect airway mechanics upstream to the airway segment subjected to flow limitation, and therefore is a measure

of airway patency that is relatively independent of the upper airway resistance [55-56]. Only a single study, in 29 patients with cystic fibrosis, attempted to relate lung function during infancy (at 6 months of age) to lung function in childhood (at 6 years of age) [57]. The measurement of $V'max_{FRC}$ was obtained at a lung volume close to $MEF_{25}$ and $MEF_{50}$, both of which can be used for comparison. However, no significant relationship between these parameters and $V'max_{FRC}$ was found.



Sedated infant during lung function testing.

## Aim and outline of this thesis

This thesis aims to improve the knowledge on pulmonary morbidity in infants with congenital lung anomalies such as CDH, EA and cystic lung lesions, children after ECMO treatment and young adults with CDH. We conducted the following prospective and longitudinal studies.

A cohort of CDH patients whose lung function previously had been studied in childhood [23] was now studied at young adult age in order to see if lung function had evolved since then. We now also studied exercise capacity.

In an earlier study, lung function testing in the first year of life after neonatal ECMO had revealed that CDH patients had more hyperinflation and airflow obstruction compared with infants treated with ECMO for other diagnoses [47]. We now studied CDH patients in the first year of life who either had received ECMO treatment or not in order to evaluate any differences between these 2 groups of CDH patients.

Furthermore, patients treated with neonatal ECMO were longitudinally studied at the ages of 5, 8 and 12 years to assess evolution of lung function in childhood. In addition,

analysis of diagnostic subgroups in this study identified lung function of ECMO-treated CDH patients during childhood.

Data on lung function in infants with EA [10,32,58-61] and CLL [62] are scarce and established in studies with a cross-sectional design. We assessed lung function in these infants longitudinally in the first year of life.

In Chapter 1 we describe the study comparing lung function in infants with CDH who either or not had received ECMO treatment and who either or not had developed chronic lung disease.

In Chapter 2 we report the study on lung function of infants with EA-TEF and the differences in outcome between thoracotomic and thoracoscopic surgical repair.

In Chapter 3 we evaluated respiratory morbidity and lung function in children with cystic lung lesions. Differences between infants needing resection and those who were treated conservatively were evaluated.

In Chapter 4 lung function in children with CDH, meconium aspiration syndrome and other diagnoses who underwent ECMO treatment in the neonatal period was evaluated at 5, 8 and 12 years of age.

In Chapters 5 and 6 we report the results of a study on lung function and exercise capacity in a cohort of young adults with CDH.

In Chapter 7 we describe lung function in 2 cases of recurrent CDH at the ages of 24 and 25 years respectively; lung function was tested before and after repair.

## References


1. Gischler SJ, van der Cammen-van Zijp MH, Mazer P, Madern GC, Bax NM, de Jongste JC, van Dijk M, Tibboel D, IJsselstijn H. A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. J Pediatr Surg 2009;44(9):1683-1690.

2. Mazer P, Gischler SJ, MH VDC-VZ, Tibboel D, Bax NM, IJsselstijn H, M VAND, Duivenvoorden HJ. Early developmental assessment of children with major non-cardiac congenital anomalies predicts development at the age of 5 years. Developmental medicine and child neurology 2010;52(12):1154-1159.

3. Anthony S SY, Jacobusse GW, van der Pal-de Bruin KM. Aangeboren afwijkingen in Nederland. Leiden: TNO, kwaliteit van leven 2006.

4. Hazebroek FW, Bouman NH, Tibboel D. The neonate with major malformations: experiences in a university children's hospital in the Netherlands. Semin Pediatr Surg 2001;10(4):222-229.

5. Ravitch MM, Barton BA. The need for pediatric surgeons as determined by the volume of work and the mode of delivery of surgical care. Surgery 1974;76(5):754-763.

6. Delacourt C, Hadchouel A, Toelen J, Rayyan M, de Blic J, Deprest J. Long term respiratory outcomes of congenital diaphragmatic hernia, esophageal atresia, and cardiovascular anomalies. Semin Fetal Neonatal Med 2012.

7. Peetsold MG, Heij HA, Kneepkens CM, Nagelkerke AF, Huisman J, Gemke RJ. The long-term follow-up of patients with a congenital diaphragmatic hernia: a broad spectrum of morbidity. Pediatr Surg Int 2009;25(1):1-17.

8. Peetsold MG, Kneepkens CM, Heij HA, H IJ, Tibboel D, Gemke RJ. Congenital diaphragmatic hernia: long-term risk of gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2010;51(4):448-453.

9. Poley MJ, Stolk EA, Tibboel D, Molenaar JC, Busschbach JJ. Short term and long term health related quality of life after congenital anorectal malformations and congenital diaphragmatic hernia. Arch Dis Child 2004;89(9):836-841.

10. Sistonen SJ, Pakarinen MP, Rintala RJ. Long-term results of esophageal atresia: Helsinki experience and review of literature. Pediatr Surg Int 2011;27(11):1141-1149.

11. Lally KP. Congenital diaphragmatic hernia. Curr Opin Pediatr 2002;14(4):486-490.

12. de Buys Roessingh AS, Dinh-Xuan AT. Congenital diaphragmatic hernia: current status and review of the literature. Eur J Pediatr 2009;168(4):393-406.

13. Rottier R, Tibboel D. Fetal lung and diaphragm development in congenital diaphragmatic hernia. Semin Perinatol 2005;29(2):86-93.

14. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. J Pediatr Surg 2002;37(3):357-366.

15. Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. Prenat Diagn 2008;28(7):592-603.

16. Frenckner B, Ehren H, Granholm T, Linden V, Palmer K. Improved results in patients who have congenital diaphragmatic hernia using preoperative stabilization, extracorporeal membrane oxygenation, and delayed surgery. J Pediatr Surg 1997;32(8):1185-1189.

17. Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. J Perinatol 2007;27(9):535-549.

18. Reyes C, Chang LK, Waffarn F, Mir H, Warden MJ, Sills J. Delayed repair of congenital diaphragmatic hernia with early high-frequency oscillatory ventilation during preoperative stabilization. J Pediatr Surg 1998;33(7):1010-1014; discussion 1014-1016.

19. van den Hout L, Schaible T, Cohen-Overbeek TE, Hop W, Siemer J, van de Ven K, Wessel L, Tibboel D, Reiss I. Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. Fetal Diagn Ther 2011;29(1):55-63.

20. American Academy of Pediatrics Section on S, American Academy of Pediatrics Committee on F, Newborn, Lally KP, Engle W. Postdischarge follow-up of infants with congenital diaphragmatic hernia. Pediatrics 2008;121(3):627-632.

21. Bagolan P, Morini F. Long-term follow up of infants with congenital diaphragmatic hernia. Semin Pediatr Surg 2007;16(2):134-144.

22. Bos AP, Hussain SM, Hazebroek FW, Tibboel D, Meradji M, Molenaar JC. Radiographic evidence of bronchopulmonary dysplasia in high-risk congenital diaphragmatic hernia survivors. Pediatr Pulmonol 1993;15(4):231-234.

23. IJsselstijn H, Tibboel D, Hop WJ, Molenaar JC, de Jongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. Am J Respir Crit Care Med 1997;155(1):174-180.

24. Trachsel D, Selvadurai H, Bohn D, Langer JC, Coates AL. Long-term pulmonary morbidity in survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2005;39(5):433-439.

25. Muratore CS, Kharasch V, Lund DP, Sheils C, Friedman S, Brown C, Utter S, Jaksic T, Wilson JM. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. J Pediatr Surg 2001;36(1):133-140.

26. Koumbourlis AC, Wung JT, Stolar CJ. Lung function in infants after repair of congenital diaphragmatic hernia. J Pediatr Surg 2006;41(10):1716-1721.

27. Stefanutti G, Filippone M, Tommasoni N, Midrio P, Zucchetta P, Moreolo GS, Toffolutti T, Baraldi E, Gamba P. Cardiopulmonary anatomy and function in long-term survivors of mild to moderate congenital diaphragmatic hernia. J Pediatr Surg 2004;39(4):526-531.

28. Vanamo K, Rintala R, Sovijarvi A, Jaaskelainen J, Turpeinen M, Lindahl H, Louhimo I. Long-term pulmonary sequelae in survivors of congenital diaphragmatic defects. J Pediatr Surg 1996;31(8):1096-1099; discussion 1099-1100.

29. Mair EA, Parsons DS. Pediatric tracheobronchomalacia and major airway collapse. Ann Otol Rhinol Laryngol 1992;101(4):300-309.

30. Haight C TH. Congenital atresia of the esophagus and tracheoesophageal fistula. Extrapleural ligation of fistula and end to end anastomosis of esophageal segments. Surg Gyneacol Obstet 1943;76:672-688.

31. Spitz L, Kiely E, Brereton RJ. Esophageal atresia: five year experience with 148 cases. J Pediatr Surg 1987;22(2):103-108.

32. Agrawal L, Beardsmore CS, MacFadyen UM. Respiratory function in childhood following repair of oesophageal atresia and tracheoesophageal fistula. Arch Dis Child 1999;81(5):404-408.

33. Dudley NE, Phelan PD. Respiratory complications in long-term survivors of oesophageal atresia. Arch Dis Child 1976;51(4):279-282.

34. Benjamin B, Cohen D, Glasson M. Tracheomalacia in association with congenital tracheoesophageal fistula. Surgery 1976;79(5):504-508.

35. van der Zee DC, Bax KN. Thoracoscopic treatment of esophageal atresia with distal fistula and of tracheomalacia. Semin Pediatr Surg 2007;16(4):224-230.

36. Chen HW, Hsu WM, Lu FL, Chen PC, Jeng SF, Peng SS, Chen CY, Chou HC, Tsao PN, Hsieh WS. Management of congenital cystic adenomatoid malformation and bronchopulmonary sequestration in newborns. Pediatr Neonatol 2010;51(3):172-177.

37. Kumar B, Agrawal LD, Sharma SB. Congenital bronchopulmonary malformations: a single-center experience and a review of literature. Ann Thorac Med 2008;3(4):135-139.

38. Laberge JM, Puligandla P, Flageole H. Asymptomatic congenital lung malformations. Semin Pediatr Surg 2005;14(1):16-33.

39. Witlox RS, Lopriore E, Oepkes D, Walther FJ. Neonatal outcome after prenatal interventions for congenital lung lesions. Early Hum Dev 2011;87(9):611-618.

40. Tran H, Fink MA, Crameri J, Cullinane F. Congenital cystic adenomatoid malformation: monitoring the antenatal and short-term neonatal outcome. Aust N Z J Obstet Gynaecol 2008;48(5):462-466.

41. Olutoye OO, Coleman BG, Hubbard AM, Adzick NS. Prenatal diagnosis and management of congenital lobar emphysema. J Pediatr Surg 2000;35(5):792-795.

42. Bartlett RH, Andrews AF, Toomasian JM, Haiduc NJ, Gazzaniga AB. Extracorporeal membrane oxygenation for newborn respiratory failure: forty-five cases. Surgery 1982;92(2):425-433.

43. Bennett CC, Johnson A, Field DJ, Elbourne D. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. Lancet 2001;357(9262):1094-1096.

44. McNally H, Bennett CC, Elbourne D, Field DJ. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. Pediatrics 2006;117(5):e845-854.

45. UK. UK collaborative randomised trial of neonatal extracoporeal membrane oxygenation. Lancet 1996;348:75-82.

46. Beardsmore CS, Westaway J, Killer H, Firmin RK, Pandya H. How does the changing profile of infants who are referred for extracorporeal membrane oxygenation affect their overall respiratory outcome? Pediatrics 2007;120(4):e762-768.

47. Hofhuis W, Hanekamp MN, IJsselstijn H, Nieuwhof EM, Hop WC, Tibboel D, de Jongste JC, Merkus PJ. Prospective longitudinal evaluation of lung function during the first year of life after extracorporeal membrane oxygenation. Pediatr Crit Care Med 2011;12(2):159-164.

48. van der Cammen-van Zijp MH, Gischler SJ, Hop WC, de Jongste JC, Tibboel D, IJsselstijn H. Deterioration of exercise capacity after neonatal extracorporeal membrane oxygenation. Eur Respir J 2011;38(5):1098-1104.

49. Gappa M, Fletcher ME, Dezateux CA, Stocks J. Comparison of nitrogen washout and plethysmographic measurements of lung volume in healthy infants. Am Rev Respir Dis 1993;148(6 Pt 1):1496-1501.

50. McCoy KS, Castile RG, Allen ED, Filbrun DA, Flucke RL, Bar-Yishay E. Functional residual capacity (FRC) measurements by plethysmography and helium dilution in normal infants. Pediatr Pulmonol 1995;19(5):282-290.

51. Society ATSERS. Respiratory mechanics in infants: physiologic evaluation in health and disease. Am Rev Respir Dis 1993;147(2):474-496.

52. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J 1995;8(3):492-506.

53. Stocks J MR, Kraemer P, Gutkowski E, Bar-Yishay E, Godfrey S. Plethysmographic assessment of functional residual capacity and airway resistance. Infant Respiratory Testing 1996;John Wiley-Liss & Sons Inc. New York.:190-240.

54. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. Eur Respir J 2001;17(2):302-312.

55. Gappa M, Ranganathan SC, Stocks J. Lung function testing in infants with cystic fibrosis: lessons from the past and future directions. Pediatr Pulmonol 2001;32(3):228-245.

56. Taussig LM, Landau LI, Godfrey S, Arad I. Determinants of forced expiratory flows in newborn infants. J Appl Physiol 1982;53(5):1220-1227.

57. Beardsmore CS. Lung function from infancy to school age in cystic fibrosis. Arch Dis Child 1995;73(6):519-523.

58. Beardsmore CS, MacFadyen UM, Johnstone MS, Williams A, Simpson H. Clinical findings and respiratory function in infants following repair of oesophageal atresia and tracheo-oesophageal fistula. Eur Respir J 1994;7(6):1039-1047.

59. Chetcuti P, Phelan PD, Greenwood R. Lung function abnormalities in repaired oesophageal atresia and tracheo-oesophageal fistula. Thorax 1992;47(12):1030-1034.

60. Malmstrom K, Lohi J, Lindahl H, Pelkonen A, Kajosaari M, Sarna S, Malmberg LP, Makela MJ. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. The Journal of pediatrics 2008;153(3):396-401.

61. Sistonen S, Malmberg P, Malmstrom K, Haahtela T, Sarna S, Rintala RJ, Pakarinen MP. Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. Eur Respir J 2010;36(5):1106-1112.

62. Keijzer R, Chiu PP, Ratjen F, Langer JC. Pulmonary function after early vs late lobectomy during childhood: a preliminary study. J Pediatr Surg 2009;44(5):893-895.


# Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia

Marjolein Spoel*, Lieke van den Hout*, Saskia J Gischler, Wim CJ Hop, Irwin Reiss, Dick Tibboel, Johan C de Jongste, Hanneke IJsselstijn.
*both authors contributed equally

Pediatr Crit Care Med. 2011 Jun 9. doi: 10.1097/PCC.0b013e3182231872 [Epub ahead of print]

## Abstract

*Objective*:
To evaluate lung function and respiratory morbidity prospectively during the first year of life in patients with congenital diaphragmatic hernia (CDH) and to study the effect of extracorporeal membrane oxygenation therapy (ECMO).
*Design*:
Prospective longitudinal cohort study
*Setting*:
Outpatient clinic of a tertiary level pediatric hospital
*Patients*:
The cohort of 43 infants included 12 patients treated with ECMO. Evaluation was at 6 and 12 months; 33 infants were evaluated at both time points.
*Interventions*:
None
*Measurements*:
Maximal expiratory flow at functional residual capacity ($V'max_{FRC}$) and functional residual capacity ($FRC_p$) were measured with Masterscreen Babybody (Viasys). SD-scores were calculated for $V'max_{FRC}$.
*Main results*:
Mean $V'max_{FRC}$ values at 6 and 12 months were significantly below the expected values (mean SD-scores -1.4 and -1.5, respectively) without a significant change between both time points. Values did not significantly differ between ECMO and non-ECMO-treated patients. $FRC_p$ values were generally high, 47% were above the suggested normal range, and did not change significantly over time. Mean $FRC_p$ values in ECMO patients were significantly higher than in non-ECMO patients ($p=0.006$). The difference (5.1 mL/kg ± 1.8 SE) did not change significantly between the two time points. Higher mean airway pressure and longer duration of ventilation were associated with higher $FRC_p$. None of the perinatal characteristics was associated with $V'max_{FRC}$. Mean weight SD-scores were significantly below zero at both time points ($p<0.001$). Mean weight SD-scores in ECMO patients were lower than in non-ECMO patients ($p=0.046$).
*Conclusions*:
Infants with CDH have decreased expiratory flows and increased functional residual capacity within the first year of life. ECMO-treated CDH patients may have more respiratory morbidity and concomitant growth impairment. Close follow-up beyond the neonatal period is therefore required.

## Introduction

Congenital diaphragmatic hernia (CDH) occurs in 1 in 3000 live births and accounts for 8% of all major congenital anomalies [1]. Many patients show lung hypoplasia and pulmonary hypertension requiring ventilatory support of variable duration. Conventional management includes different forms of mechanical ventilation (SIMV, IPPV, high-frequency oscillatory ventilation (HFOV), with or without inhaled nitric oxide). Infants with severe respiratory failure and high mortality risk will receive extracorporeal membrane oxygenation (ECMO) therapy in specialized centers. ECMO provides a cardiopulmonary bypass using minimal ventilator settings, potentially avoiding ongoing lung damage. Surgical repair of the diaphragmatic defect is delayed until stabilization is achieved and cardio respiratory condition has been optimized [2]. These strategies have raised survival rates of CDH patients to almost 80% [3-4]. However, survivors have high risk of respiratory morbidity through different stages of life. For example, ventilator induced lung injury and high concentrations of oxygen predispose newborns to develop bronchopulmonary dysplasia (BPD) [5].

Previous studies showed that ventilated CDH patients' lung volume was reduced during the immediate perioperative period and that their respiratory system compliance was low [6-7]. A retrospective study in infants with CDH showed abnormal lung function indices in the first 6 months, which gradually normalized by 24 months [8]. Recently, our group reported significantly higher lung volumes in the first year in ECMO-treated CDH patients than in infants who received ECMO for meconium aspiration syndrome [9]. Results of studies investigating pulmonary sequelae of non-ECMO patients in late childhood and adolescence were indicative of persistent airway obstruction and increased airway responsiveness [10-12].

We prospectively evaluated CDH patients' lung function at 6 and 12 months of age and looked for a possible effect of ECMO treatment on respiratory morbidity. We also studied possible associations between clinical characteristics and lung function parameters and other factors contributing to respiratory morbidity.

## Methods

A prospective longitudinal follow-up was conducted in all surviving patients with CDH admitted to the intensive care unit of the Erasmus MC - Sophia Children's Hospital between November 2004 and November 2008. (Flow chart, Figure 1). All patients were ventilated according to the principles of permissive hypercapnia and ventilatory support was provided either by conventional ventilation (Babylog 8000, Dräger Medical, Lübeck, Germany) or high-frequency oscillatory ventilation (Sensormedics, Bilthoven, the Netherlands). All infants were treated according to a standardized treatment protocol [13]. ECMO treatment was applied in case of reversible severe respiratory failure as

described by Reiss et al [13]. ECMO treatment always was of the veno-arterial type. Procedures and in- and exclusion criteria were described previously [9].
We recorded gestational age, birth weight, sex, side of the diaphragmatic defect, lung-to-head ratio (if available in case of a prenatal diagnosis) [14], position of the liver (intrathoracic or intra-abdominal, if available in case of a prenatal diagnosis), place of birth (inborn or outborn), initial ventilation mode (HFOV or conventional ventilation) and type of repair (primary or patch). Furthermore we recorded several indicators of illness severity: SNAP-II score during the first 12 hours [15], use of inotropics, use and maximal dose of inhaled nitric oxide (iNO), use of sildenafil, ECMO treatment, highest mean airway pressure (MAP), and duration of ventilatory support and supplemental oxygen provision. The presence and severity of BPD were determined as described by Bancalari [16].
The study was part of a follow-up programme for CDH patients in which lung function, growth and developmental parameters are regularly assessed until 18 years of age [17]. The assessment protocol is the standard of care in the Netherlands. The Medical Ethical Review Board Erasmus MC stated that “Medical Research in Human Subjects Act (also known by its Dutch abbreviation "WMO”) does not apply to this research proposal, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed”. Therefore IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes. Lung function data were evaluated at the end of 2009.

*Lung function*

Lung function was measured at the ages of 6 and 12 months (corrected for prematurity), provided there were no signs of infection or acute respiratory symptoms. Patients were not mechanically ventilated and were independent of supplemental oxygen at the time of lung function measurement. Infants were sedated with chloral hydrate (50-75 mg/kg). Forced expiratory flow at $FRC_p$ ($V'max_{FRC}$), a measure of airway patency and compressibility, was determined by the end-tidal rapid thoracoabdominal compression technique (Masterscreen Babybody, Viasys, Hochberg, Germany). The mean $V'max_{FRC}$ (mL/kg) of 3 to 5 technically acceptable measurements was calculated. All equipment and procedures complied with the guidelines of the ERS/ATS Task force on standards for infant respiratory testing [18]. Regarding $V'max_{FRC}$, we used the reference values provided by Hoo and colleagues [19]. SD-scores were calculated as the difference between observed and predicted value divided by the residual standard deviation from the reference values for $V'max_{FRC}$. Functional residual capacity ($FRC_p$) was measured by whole body plethysmography (Masterscreen Babybody, Viasys, Hochberg, Germany). The mean $FRC_p$ (mL/kg) of 3 to 5 technically acceptable measurements was calculated.
$FRC_p$ was expressed in mL/kg as suggested by Hülskamp et al [20]. The normal range suggested by those authors was 13 to 26 mL/kg.
$V'max_{FRC}$ SD-scores and $FRC_p$ (mL/kg) were the primary outcome measures.

*Respiratory morbidity and physical growth*

The infants were physically examined at both follow-up visits. Examination included measurement of height and weight, pulmonary auscultation, and neurological examination. Respiratory rate (RR) was measured during lung function assessment. The following factors were recorded: supplemental oxygen provision, episodes of wheezing, number of respiratory tract infections (RTI), therapeutic and prophylactic courses of antibiotic treatment, and use of inhaled bronchodilators and corticosteroids.
Dutch population data served as reference values for physical growth [21]. SD-scores for weight and height were calculated using Growth Analyser version 3.5 (Dutch Growth Foundation). SD-scores < -1.96 ($2.5^{th}$ percentile of the reference population) were considered abnormally low; SD-scores > 1.96 ($97.5^{th}$ percentile of the reference population) were considered abnormally high. SD-scores for patients treated with ECMO were calculated separately.
The above-mentioned factors were the secondary outcome measures.

*Data Analysis*

Patient characteristics are presented as number of patients (percentage) or median (range). Univariate analyses were performed, using Chi-squared and Mann-Whitney U tests where appropriate, to evaluate differences between ECMO and non-ECMO patients. Anthropometric and lung function data are presented as mean (SD).
In this longitudinal study, the data are composed of repeated lung function measurements obtained in different individuals at two time points (six and twelve months of age). In the majority of patients, assessment at both time points was performed whereas in others only measurements at one time point were obtained. Since repeated measurements ANOVA allows for missing data at one time point, $FRC_p$, $V'max_{FRC}$, $V'max_{FRC}$ SD-scores and SD-scores for weight and length were evaluated longitudinally using repeated measurements ANOVA [22].
Possible associations between clinical characteristics and lung function parameters were also analysed using ANOVA. For this purpose, highest MAP and the duration of ventilation were transformed logarithmically to reduce the effect of outlying observations. To evaluate a possible influence of ECMO treatment on $FRC_p$, $V'max_{FRC}$ SD-scores and SD-scores for weight and length, we specifically performed ANOVA analyses adjusting for ECMO treatment. Possible associations between clinical characteristics between ECMO treated and-non ECMO treated patients were also evaluated in an ANOVA adjusting for age (6 and 12 months).
The significance level was set at $p < 0.05$. SPSS 17.0 (Chicago, Illinois) was used for the analyses.

## Results

Between November 2004 and November 2008, 62 newborns with CDH had been admitted, of whom 48 had survived (77%). Two were lost to follow-up and 3 were clinically unstable or needed supplemental oxygen at the time of lung function assessment. Thus, 43 infants with CDH were included (Figure 1).

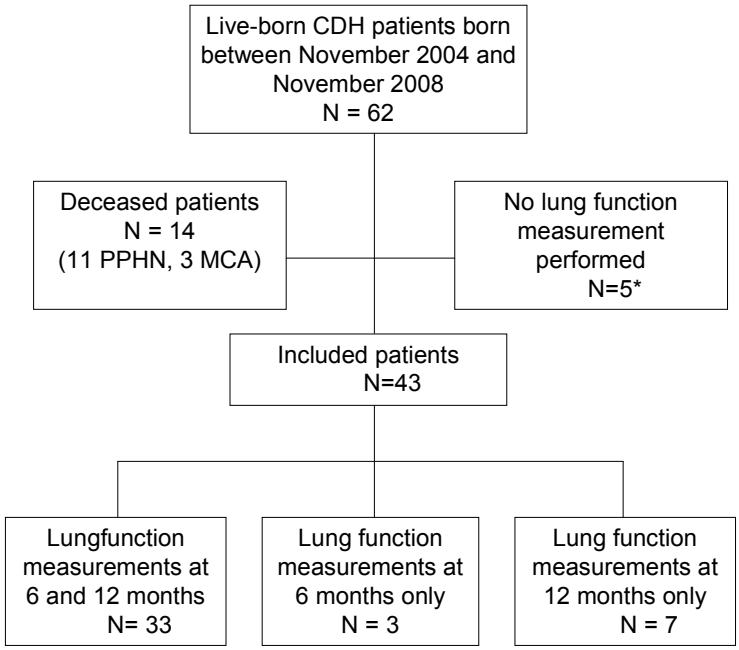



**Figure 1.** *Flowchart showing two patients were lost to follow up; three patients still had oxygen therapy at the time of lung function assessment and therefore measurements could not be performed. CDH: congenital diaphragmatic hernia, PPHN: therapy resistant persistent pulmonary hypertension of the neonate, MCA: multiple congenital anomalies.*

Thirty-three infants were measured both at 6 and 12 months of age. Reasons for not completing both measurements were being awake during one of the measurements (n= 4), loss to follow-up (n=1), recurrent RTI (n=1). Furthermore, 4 infants whose first measurement was performed with different equipment were excluded. Baseline characteristics of the 43 infants are shown in Table 1.

**Table 1**. **Baseline characteristics (n=43)**

| Variables | Total (n=43) | ECMO (n=12) | Non-ECMO (n=31) | p-value |
|---|---|---|---|---|
| Males | 30 (70) | 10 (83) | 20 (65) | 0.290 |
| Left-sided defect | 39 (91) | 11 (92) | 28 (90) | 1.000 |
| Prenatal diagnosis | 27 (63) | 4 (33) | 23 (74) | 0.032 |
| Lung-to-head ratio | 2 (0.9-3.5) | 1.5 (1.3-2.4) | 1.7 (0.9-3.5) | 0.689 |
| Intrathoracic liver position | 9 (21) | 2 (17) | 7 (23) | 0.702 |
| Inborn | 27 (63) | 4 (33) | 23 (74) | 0.032 |
| Gestational age, weeks | 38.7 (33.6-41.4) | 39.2 (36.9-41.4) | 38.4 (33.6-41) | 0.022 |
| Birth weight, kilograms | 3.0 (1.7-4.7) | 3.0 (2.3-4.6) | 3.0 (1.7-3.7) | 0.524 |
| High risk (intubated ≤ 6 hrs after birth) | 41 (95) | 12 (100) | 29 (94) | 1.000 |
| SNAPP-II score | 21 (0-52) | 37 (12-52) | 16 (0-41) | 0.095 |
| Treatment with HFO ventilation | 30 (75) | 12 (100) | 18 (58) | 0.019 |
| Patch repair | 28 (65) | 9 (75) | 19 (61) | 0.719 |
| Treatment with iNO | 24 (56) | 12 (100) | 12 (39) | <0.001 |
| iNO maximum dose, ppm | 20 (10-30) | 20 (15-30) | 20 (10-20) | 0.574 |
| Maximal mean airway pressure,cm $H_2O$ | 17 (10-29) | 20 (17-29) | 16 (10-20) | <0.001 |
| Treatment with inotropics | 39 (91) | 12 (100) | 27 (87) | 0.563 |
| Treatment with sildenafil | 7 (16) | 6 (50) | 1 (3) | 0.001 |
| Bronchopulmonary dysplasia | 16 (41) | 7 (64) | 9 (32) | 0.150 |
| Duration of mechanical ventilation, days | 10.3 (0.7-53.4) | 22.2 (8.5-53.4) | 8.1 (0.7-51.6) | 0.002 |
| Duration of oxygen dependence, days | 19.0 (3.0-141.3) | 37.0 (9.6-141.3) | 18.5 (3.0-104.5) | 0.171 |

*ECMO, extracorporeal mebrane oxygenation therapy. Data from the total group (n=43) and the subgroups of ECMO-patients (n=12) and non-ECMO patients (n=31). P-values are given for differences between the ECMO and non-ECMO group. Data are demonstrated as number (%) or median (range).*Data from the subgroups of infants measured at 6 months (n= 36) and at 12 months (n=40) did not differ significantly and are not shown. iNO: inhaled Nitric Oxide, ppm: parts per million.*

### *Lung function measurements*

The median postnatal age at the two lung function tests was 29.9 weeks (range 26.0-37.7, n=36) and 56.1 weeks (range 49.3-66, n=40). The corresponding median age corrected for prematurity was 28.4 weeks (range 25-37.7) and 54.4 weeks (range 50.1-66.9). Reliable $V'max_{FRC}$ measurements were obtained in 29 patients at 6 months and in 38 patients at 12 months. Reliable $FRC_p$ measurements were obtained in 35 patients at 6 months and in 38 patients at 12 months. At 6 months 24 infants (73%) had a RR ≥ 35 breaths/min, of whom 17 (52%) ≥ 40 breaths/min. At 12 months 18 infants (47%) had a RR of ≥ 35 breaths/min, of whom 7 (18%) ≥ 40 breaths/min.

Forty-seven percent of $FRC_p$ measurements were > 26 mL/kg (39% at 6 months and 55% at 12 months). The mean $FRC_p$ and mean SD-score of $V'max_{FRC}$ did not change significantly over time. The results of the ANOVA analysis are presented in Table 2.

| | 6 months | 12 months | P-value comparing the 2 time points |
|---|---|---|---|
| $FRC_p$ (mL/kg) | 28.1 (1.1) | 28.7 (0.8) | 0.518 |
| $V'max_{FRC}$ (SD-score)$^{\dagger}$ | -1.4 (0.1)$^{\dagger}$ | -1.5 (0.1)$^{\dagger}$ | 0.573 |
| $V'max_{FRC}$ (ml/sec) | 108.0 (7.9) | 153.9 (8.9) | <0.001 |
| RR (breaths/min) | 39.1 (1.2) | 34.0 (1.2) | <0.001 |

**Table 2. Mean values of lung function parameters at 6 and 12 months**
*Mean (SE) values from ANOVA are shown. $FRC_p$: functional residual capacity. RR: respiratory rate. $V'max_{FRC}$ (SD-score) $^{\dagger}$: p<0.001below the reference value (Z=0).*

*Associations between lung function parameters and clinical characteristics*
Overall, a longer duration of ventilation was associated with higher $FRC_p$ values at both 6 and 12 months (p=0.001). Doubling of the ventilation time resulted in a mean 1.9 mL/kg increase in $FRC_p$. Higher MAP was also significantly associated with higher $FRC_p$ values at both time points (p=0.002). Furthermore, $FRC_p$ values were significantly higher (p=0.049) and $V'max_{FRC}$ SD-scores were significantly lower (p=0.048) in patients who received treatment with iNO (p=0.049).
Other significant associations between clinical characteristics and $FRC_p$ values or $V'max_{FRC}$ SD-scores were not found.

*Lung function in ECMO patients*
A total of twelve patients received ECMO therapy (Table 1) for a median of 7.1 days (range 3-12.1).The median day on which ECMO was started was the second day of life (range 1-4 days).
Table 1 lists clinical characteristics for both ECMO and non-ECMO patients. The former were less often prenatally diagnosed (p=0.032), less often inborn (p=0.032), had a higher median gestational age at birth (p=0.022), were more often treated with iNO (p<0.001) and sildenafil (p=0.001), had a higher median maximal mean airway pressure (p<0.001), were more often treated with HFO (p=0.019) and were ventilated for a longer time (p=0.002) than non-ECMO patients.
At both time points, mean $FRC_p$ values differed significantly between ECMO- and non-ECMO-treated patients (p=0.006, Figure 2). This difference (5.1 mL/kg ± 1.8 SE) did not significantly change between the two time points (p=0.625). In ECMO patients, mean (SE) $V'max_{FRC}$ SD-scores at 6 and 12 months were -1.52 (0.31) and -1.54 (0.25) respectively. Mean (SE) $V'max_{FRC}$ SD-scores at 6 and 12 months were -1.41 (0.14) and -1.49 (0.15) in patients who did not receive ECMO therapy. These did not differ significantly (p=0.781).
To further evaluate possible effects of clinical characteristics and ECMO therapy on $FRC_p$ values, these characteristics were entered in the ANOVA models together with the

factor ECMO. When adjusted for duration of ventilation or highest mean airway pressure, the difference in $FRC_p$ values between ECMO and non-ECMO patients was not significant anymore (p=0.108 and p=0.369 respectively). No other significant associations between baseline characteristics and $FRC_p$ values were found when adjusted for ECMO.

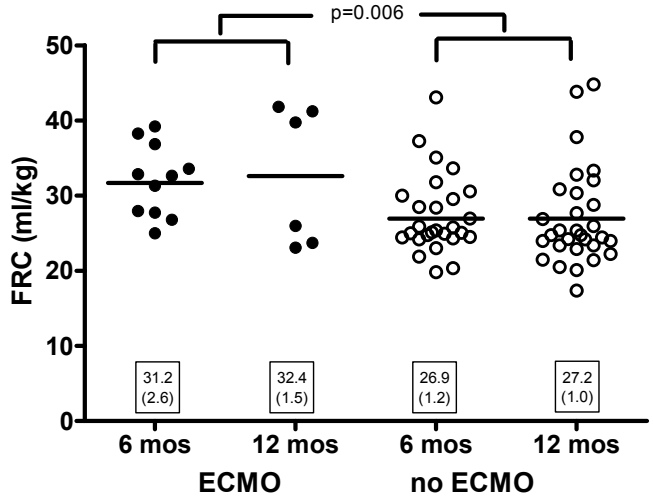



**Figure 2 :** *$FRC_p$ (mL/kg) measurements in CDH patients who were treated with ECMO (2 panels left side; ECMO) and in those who were not treated with ECMO (2 panels right side; no ECMO) at the age of 6 and 12 months. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with standard error (SE) between parentheses. Mean levels at both 6 and 12 months did not significantly differ between ECMO and non-ECMO treated patients (both p>0.60).*

*ECMO and BPD*

Sixteen patients developed BPD (41%, missing=4, see table 1). At both time points, BPD patients' mean $FRC_p$ was significantly higher than that of the non-BPD patients (p<0.001, Figure 3). This difference (6.2 ml/k kg ± 1.5 SE) did not significantly change between the two time points (p=0.585). ANOVA did not reveal a significant effect of BPD on $V'max_{FRC}$ SD-scores (p=0.159).

Seven of the 11 ECMO-treated patients developed BPD (1 missing) versus 9 of the 28 non-ECMO patients (3 missing, p=0.15, see table 1). Simultaneous evaluation of BPD and ECMO resulted in a significant effect of BPD on $FRC_p$ (p=0.001, difference: 3.2 mL/kg lower in no BPD). The effect of ECMO was larger in this combined analysis (difference: 5.4 mL/kg lower in no ECMO) but did not reach statistical significance (p=0.066).

In Figure 4, individual $FRC_p$ measurements are shown for the 4 combinations of ECMO/non-ECMO and BPD/non-BPD. Data obtained at 6 and 12 months were clustered because there were no significant differences between the 2 time points.

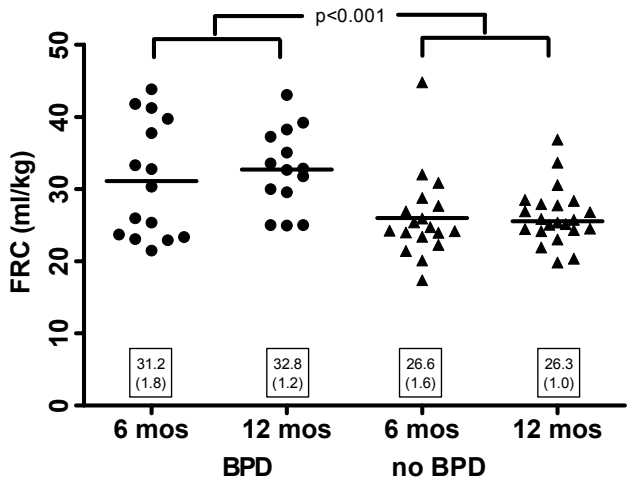



**Figure 3:** *$FRC_p$ (mL/kg) measurements in CDH patients who developed BPD (2 panels left side; BPD) and those who did not develop BPD (2 panels right side; no BPD) at the age of 6 and 12 months. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with SE between parentheses. Mean levels at both 6 and 12 months did not significantly differ between patients with and without BPD (both p>0.30).*

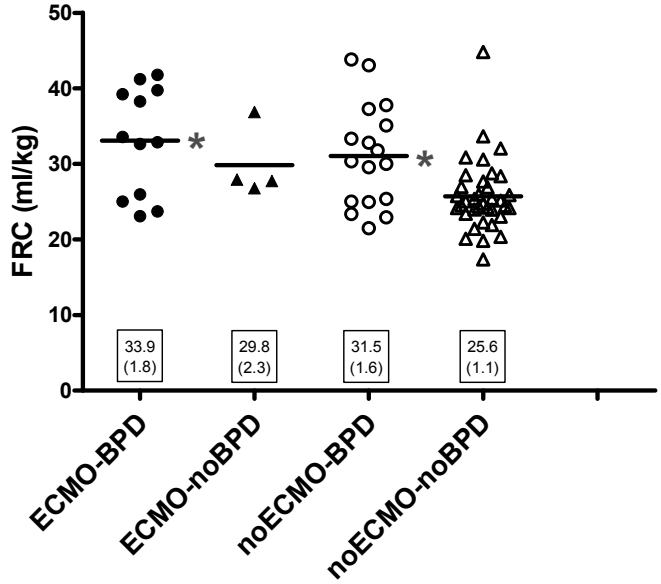



**Figure 4:** *$FRC_p$ (mL/kg) measurements of CDH at 6 and 12 months. Closed symbols represent ECMO-treated newborns; open symbols represent non-ECMO treated patients. BPD is indicated as circles; no-BPD as triangles. Thus, 4 different groups are shown. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with SE between parentheses. * mean level in this group significantly differed from that in the no ECMO/no BPD group (both p≤0.003). Other differences between groups were not significant.*

*Respiratory morbidity and physical growth*

At 6 months, 4 patients (12%) had received at least one therapeutic course of antibiotics; the same was true for 7 patients (19%) at 12 months. One child used antibiotics daily for 12 months to prevent recurrent respiratory tract infections. Two (6%) and 5 (14%) patients used bronchodilators and/or inhaled corticosteroids at 6 and 12 months, respectively. At 6 and 12 months, 12 (28%) and 6 patients (14%) respectively had an abnormally low weight. Mean weight SD-scores were -1.01 (0.22) and -1.10 (0.18) at 6 and 12 months, respectively, significantly below the norm ($Z$=0, $p < 0.001$ at both time points). At both 6 and 12 months, weight SD-scores in ECMO-treated patients (6 months:-1.61 (0.37) and 12 months: -1.59 (0.32)) were significantly lower than in patients without ECMO (6 months: -0.83 (0.22) and 12 months: -0.82 (0.20), p=0.047). Mean height SD-scores were 0.02 (0.18) and 0.07 (0.16) at 6 and 12 months, respectively. Height SD-scores were not significantly different from normal at 6 and 12 months (p= 0.9 and p=0.6 respectively). At both time points, height SD-scores did not differ significantly between patients with and without ECMO.

## Discussion

This prospective longitudinal study revealed that $FRC_p$ in patients with CDH was generally above the expected range and did not change significantly from 6 to 12 months. Forced expiratory flows were below the expected value and also did not change. ECMO-treatment was associated with significantly higher $FRC_p$. Presence of BPD, higher MAP and longer duration of ventilation were associated with higher $FRC_p$. None of the perinatal characteristics was associated with $V'max_{FRC}$.

Two studies by other groups reported reduced forced vital capacity and impaired maximal expiratory flows in neonates with CDH who were still on mechanical ventilation during lung function assessment [6-7]. In these studies, measurements were taken within the first weeks of life and the findings therefore cannot be compared to our findings in older and spontaneously breathing infants. A retrospective evaluation in 56 CDH patients showed that $FRC_p$ SD-scores, measured with the nitrogen washout technique, were initially below average but increased after the first 6 months of life; $V'max_{FRC}$ was below average throughout the first year of life [8]. A study using the sulphur hexafluoride wash-in/wash-out technique found similar $FRC_p$ levels in 13 CDH patients and in age-matched healthy controls [23]. Earlier, our group found higher $FRC_p$ levels in ECMO-treated CDH patients than in infants who needed ECMO-support for meconium aspiration syndrome [9]. These findings on $FRC_p$ are in line with the present findings.

In the present study, $FRC_p$ values were generally above the expected range. This is likely to be due to the lung hypoplasia that is inherent to CDH [24-27]. Repair of CDH is usually followed by compensatory hyperinflation of the ipsilateral and/or the contralateral lung to fill the space previously occupied by abdominal organs [8]. Helms and Stocks, however, found normal to low $FRC_p$ in infants aged up to 8 weeks after operative repair

of CDH [28]. They argued that normal lung volume does not necessarily imply normal intrauterine lung development. Indeed, normal lung volume later in infancy [29] may be the result of alveolar distension and even of destructive emphysema of a hypoplastic lung [24,30]. Nagaya and co-workers, using computed tomography scans and perfusion scintigrams in infants following surgical repair of CDH and ECMO treatment, found ipsilateral lung volumes that were 61% of contralateral lung volumes at 3 months and had increased to 88% at 3 years of age [31]. Perfusion of the affected side remained low, or decreased to below the initial value. These authors concluded that the ipsilateral lung apparently may have little ability to develop arterial branches and that enlargement of lung volume may depend on overexpansion or progressive emphysema, rather than on an increase in lung tissue [31]. Hayward and co-workers suggested that expansion of already existing alveoli and not an increase in the number of alveoli explained most of the lung growth in their CDH population 0.1-13 years[32]. Thus, the normal, near-normal or elevated $FRC_p$ values in our study are more likely to reflect hyperinflation than true lung tissue growth. $FRC_p$ values did not increase from 6 to 12 months, so there seems to be no progressive hyperinflation. Indeed, studies in older children after repair of CDH showed mildly increased residual volume and mild airway obstruction [10-12].

The question remains whether increased $FRC_p$ levels in CDH result from abnormal lung development or from lung damage due to barotrauma and hyperoxia. Most studies on lung function in BPD patients without CDH concern prematurely born neonates. As CDH patients are mainly born at term, findings are hard to compare. Studies on term born infants with BPD are scarce. However, Hofhuis and co-workers found that $FRC_p$ levels at 6 and 12 months in in ECMO-treated CDH patients were significantly higher than those in neonates treated with ECMO for meconium aspiration syndrome (MAS) [9]. Fifteen of the 25 MAS patients (60%) in that studied developed BPD (personal communication). This suggests that the elevated $FRC_p$ values in our population resulted from abnormal lung development in CDH patients rather than from the neonatal intensive care treatment. This assumption is supported by the study of Beardsmore and co-workers who found similar $FRC_p$ levels in term born neonates treated with ECMO or with conventional ventilation [33].

It could be argued that plethysmography in CDH patients with or without BPD in the present study may not be suitable to evaluate alveolar functional recovery. On the other hand, gas dilution FRC measurements also has limitations, and underestimates lung volumes as gas diffusion is suboptimal in airways with an elevated resistance. Hence, we propose that follow-up should include both lung function studies and lung imaging to evaluate the evolution of lung volume in CDH patients.

In the present study, $FRC_p$ in ECMO-treated patients was higher than in the other patients. We may speculate that ECMO treatment increases the chance of survival in case of CDH with more severe lung hypoplasia and/or persistent pulmonary hypertension, and consequently a higher respiratory morbidity and more hyperinflation of the lungs [9]. Indeed, after failure of conventional ventilation, HFO ventilation was used more frequently in the ECMO treated group. Also, total ventilation time and MAP were

significantly higher in the ECMO treated group. In the ECMO treated group, 64% developed BPD versus 32% in the non-ECMO treated group and although this difference did not reach statistical significance, it indicates more severe respiratory problems which is associated with higher $FRC_p$. A study by Bernbaum et al. reported a 63% incidence of BPD at discharge in survivors of CDH who underwent ECMO-procedure [34]. This incidence is the same as we found in our study. Also ECMO-treated patients received more often iNO and sildenafil in order to reduce pulmonary hypertension.

The decreased maximal expiratory flows in our study are in agreement with findings from similar studies in CDH patients [6-8,35]. Abnormal airway size or alveolar architecture may play a role here together with airway damage from mechanical ventilation. We found neither significant differences in forced expiratory flows between patients treated conservatively or with ECMO, nor between patients who did or did not develop BPD. Therefore, it seems that differences in $FRC_p$ cannot be explained by differences in airway obstruction only.

Although 41% of the patients developed BPD, only few suffered from respiratory tract infections requiring antibiotic treatment. Only few patients had wheezing and/or dyspnea requiring inhaled medication. We speculate that an increased airflow obstruction is indicative of abnormal airway structure and fibrosis as a result of lung injury rather than of increased airway responsiveness. All patients showed impaired growth during the first year of life, especially the ECMO-treated patients with weight SD-scores below average.

A potential limitation of our study was that we were not allowed to examine healthy controls, as sedation of healthy infants for research purposes is not permitted in the Netherlands. Therefore, we had to use reference values published by others. We expressed $FRC_p$ values in mL/kg. The earlier reference equations to compute $FRC_p$ into SD-scores are perhaps not entirely appropriate for data obtained with the newer equipment. We therefore expressed results as mL/kg, which is acceptable in the neonatal period, as the regression of $FRC_p$ on weight is relatively linear and passes close to the origin [36]. Until new reference data are available, users of new equipment would do well to interpret results cautiously. The normal range of FRC, suggested by Hülskamp et al, is 13-26 mL/kg, mean 19.6, SD 3.4 [20]. Regarding $V'max_{FRC}$, we used the references values provided by Hoo and colleagues. These reference values are based on a large representative population of healthy infants [19] and have been used by others using similar equipment as we did [37]. Another limitation was the lack of well defined parameters to assess the severity of pulmonary hypertension and the effect on cardiac function by cardiac ultrasound retrospectively. A possible relation between lung function parameters in the first year of life and severity of pulmonary hypertension shortly after birth could therefore not be established. Also, we did not evaluate pulmonary hypertension and a possible effect on lung function by cardiac ultrasound during follow-up.

In summary, we found evidence of lung hyperinflation and impaired lung growth in CDH survivors after ECMO-treatment. Long-term monitoring of these patients' lung function evolution is recommended.

## References


1. Brownlee EM, Howatson AG, Davis CF, Sabharwal AJ. The hidden mortality of congenital diaphragmatic hernia: a 20-year review. J Pediatr Surg 2009;44(2):317-320.

2. Bryner BS, West BT, Hirschl RB, Drongowski RA, Lally KP, Lally P, Mychaliska GB. Congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: does timing of repair matter? J Pediatr Surg 2009;44(6):1165-1171; discussion 1171-1162.

3. Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. J Perinatol 2007;27(9):535-549.

4. Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. Prenat Diagn 2008;28(7):592-603.

5. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723-1729.

6. Nakayama DK, Motoyama EK, Mutich RL, Koumbourlis AC. Pulmonary function in newborns after repair of congenital diaphragmatic hernia. Pediatr Pulmonol 1991;11(1):49-55.

7. Boas SR, Kurland G, Greally PG, Motoyama EK. Evolution of airway hyperresponsiveness in infants with severe congenital diaphragmatic hernia. Pediatr Pulmonol 1996;22(5):295-304.

8. Koumbourlis AC, Wung JT, Stolar CJ. Lung function in infants after repair of congenital diaphragmatic hernia. J Pediatr Surg 2006;41(10):1716-1721.

9. Hofhuis W, Hanekamp MN, IJsselstijn H, Nieuwhof EM, Hop WC, Tibboel D, de Jongste JC, Merkus PJ. Prospective longitudinal evaluation of lung function during the first year of life after extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2011 Mar;12(2):159-64.

10. Basek P, Bajrami S, Straub D, Moeller A, Baenziger O, Wildhaber J, Bernet V. The pulmonary outcome of long-term survivors after congenital diaphragmatic hernia repair. Swiss Med Wkly 2008;138(11-12):173-179.

11. IJsselstijn H, Tibboel D, Hop WJ, Molenaar JC, de Jongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. Am J Respir Crit Care Med 1997;155(1):174-180.

12. Peetsold MG, Heij HA, Nagelkerke AF, IJsselstijn H, Tibboel D, Quanjer PH, Gemke RJ. Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia. Eur Respir J 2009;34(5):1140-1147.

13. Reiss I, Schaible T, van den Hout L, Capolupo I, Allegaert K, van Heijst A, Gorett Silva M, Greenough A, Tibboel D. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. Neonatology 2010;98(4):354-364.

14. Jani JC, Benachi A, Nicolaides KH, Allegaert K, Gratacos E, Mazkereth R, Matis J, Tibboel D, Van Heijst A, Storme L, Rousseau V, Greenough A, Deprest JA, Antenatal CDHRg. Prenatal prediction of neonatal morbidity in survivors with congenital diaphragmatic hernia: a multicenter study. Ultrasound Obstet Gynecol 2009;33(1):64-69.

15. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. J Pediatr 2001;138(1):92-100.

16. Bancalari E, Claure N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. Semin Perinatol 2006;30(4):164-170.

17. Gischler SJ, Mazer P, Duivenvoorden HJ, van Dijk M, Bax NM, Hazebroek FW, Tibboel D. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 2009;44(7):1382-1389.

18. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R, Society EATFoSfIRFTERSAT. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. Eur Respir J 2001;17(2):302-312.

19. Hoo AF, Dezateux C, Hanrahan JP, Cole TJ, Tepper RS, Stocks J. Sex-specific prediction equations for Vmax(FRC) in infancy: a multicenter collaborative study. Am J Respir Crit Care Med 2002;165(8):1084-1092.

20. Hulskamp G, Hoo AF, Ljungberg H, Lum S, Pillow JJ, Stocks J. Progressive decline in plethysmographic lung volumes in infants: physiology or technology? Am J Respir Crit Care Med 2003;168(8):1003-1009.

21. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47(3):316-323.

22. Fitzmaurice G, Laird N, Ware J. Applied Longitudinal Analysis. 1st ed John Wiley & Sons 2004.

23. Dotta A, Palamides S, Braguglia A, Crescenzi F, Ronchetti MP, Calzolari F, Iacobelli BD, Bagolan P, Corchia C, Orzalesi M. Lung volumes and distribution of ventilation in survivors to congenital diaphragmatic hernia (CDH) during infancy. Pediatr Pulmonol 2007;42(7):600-604.

24. Hislop A, Reid L. Persistent hypoplasia of the lung after repair of congenital diaphragmatic hernia. Thorax 1976;31(4):450-455.

25. Gosche JR, Islam S, Boulanger SC. Congenital diaphragmatic hernia: searching for answers. Am J Surg 2005;190(2):324-332.

26. Stefanutti G, Filippone M, Tommasoni N, Midrio P, Zucchetta P, Moreolo GS, Toffolutti T, Baraldi E, Gamba P. Cardiopulmonary anatomy and function in long-term survivors of mild to moderate congenital diaphragmatic hernia. J Pediatr Surg 2004;39(4):526-531.

27. Okuyama H, Kubota A, Kawahara H, Oue T, Kitayama Y, Yagi M. Correlation between lung scintigraphy and long-term outcome in survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2006;41(9):882-886.

28. Helms P, Stocks J. Lung function in infants with congenital pulmonary hypoplasia. J Pediatr 1982;101(6):918-922.

29. Landau LI, Phelan PD, Gillam GL, Coombs E, Noblett HR. Respiratory function after repair of congenital diaphragmatic hernia. Arch Dis Child 1977;52(4):282-286.

30. Thurlbeck WM, Kida K, Langston C, Cowan MJ, Kitterman JA, Tooley W, Bryan H. Postnatal lung growth after repair of diaphragmatic hernia. Thorax 1979;34(3):338-343.

31. Nagaya M, Akatsuka H, Kato J, Niimi N, Ishiguro Y. Development in lung function of the affected side after repair of congenital diaphragmatic hernia. J Pediatr Surg 1996;31(3):349-356.

32. Hayward MJ, Kharasch V, Sheils C, Friedman S, Dunleavy MJ, Utter S, Zurakowski D, Jennings R, Wilson JM. Predicting inadequate long-term lung development in children with congenital diaphragmatic hernia: an analysis of longitudinal changes in ventilation and perfusion. J Pediatr Surg 2007;42(1):112-116.

33. Beardsmore CS, Westaway J, Killer H, Firmin RK, Pandya H. How does the changing profile of infants who are referred for extracorporeal membrane oxygenation affect their overall respiratory outcome? Pediatrics 2007;120(4):e762-768.

34. Bernbaum J, Schwartz IP, Gerdes M, D'Agostino JA, Coburn CE, Polin RA. Survivors of extracorporeal membrane oxygenation at 1 year of age: the relationship of primary diagnosis with health and neurodevelopmental sequelae. Pediatrics 1995;96(5 Pt 1):907-913.

35. Trachsel D, Selvadurai H, Bohn D, Langer JC, Coates AL. Long-term pulmonary morbidity in survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2005;39(5):433-439.

36. Hulskamp G, Pillow JJ, Dinger J, Stocks J. Lung function tests in neonates and infants with chronic lung disease of infancy: functional residual capacity. Pediatr Pulmonol 2006;41(1):1-22.

37. Borrego LM, Stocks J, Leiria-Pinto P, Peralta I, Romeira AM, Neuparth N, Rosado-Pinto JE, Hoo AF. Lung function and clinical risk factors for asthma in infants and young children with recurrent wheeze. Thorax 2009;64(3):203-209.


# Lung function is similar in the first year after thoracotomy or thoracoscopic repair of esophageal atresia

Marjolein Spoel, Conny JHM Meeussen, Saskia J Gischler, Wim CJ Hop, Nikolaas MA Bax, Rene MH Wijnen, Dick Tibboel, Johan C de Jongste, Hanneke IJsselstijn.

Submitted

## Abstract

*Background:*

Lung function abnormalities have been described in patients who underwent repair of esophageal atresia at neonatal age. We aimed to compare the influence of thoracotomy or thoracoscopy on lung function.

*Methods*

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

*Results*

Repair was by thoracotomy in 21 cases (57%) and by thoracoscopy in 16 cases (43%). Lung function parameters did not differ between types of surgery ($FRC_p$; p=0.384 and $V'max_{FRC}$; p= 0.241). $FRC_p$ values were in the upper normal range and increased from 6 to 12 months (22.5 and 25.4 mL/kg respectively, p=0.010). Mean (SD) $V'max_{FRC}$ was below the norm without significant change in SD-scores from 6 to 12 months (-1.9 and -2.3 respectively, p=0.248). Lung function or type of repair were not associated with clinical evolution up to 5 years.

*Conclusion*

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

## Introduction

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

We report a prospective study that evaluated lung function longitudinally at 6 and 12 months after repair of EA, distinguished by type of surgery: via thoracotomy or thoracoscopy. Furthermore we evaluated whether lung function outcomes in the first year of life could predict respiratory symptoms at 2 and 5 years of age and studied possible associations between clinical characteristics, other factors contributing to respiratory morbidity and lung function parameters.

## Methods

The children included in this study all participated in a prospective longitudinal follow-up program for surviving patients with EA admitted to the intensive care unit of the Erasmus MC - Sophia Children's Hospital between January 2005 and March 2009. Five types of EA are distinguished depending on the presence or absence of a TEF and its location. Until 2006, surgical repair was always by thoracotomy. Then, in 2006 a pediatric surgeon broadly experienced in minimal invasive surgery introduced thoracoscopic procedures in our department [9-10]. As a consequence, learning curve was minimalised. After preoperative cardiac ultrasound showing a normal turning aorta a right-sided extrapleural posterolateral thoracotomy was performed under general anesthesia. Right-sided transpleural thoracoscopy was performed by insertion of 3 cannulae (2x3 mm, 1x5 mm)

and $CO_2$ insufflation at a pressure of 5 mm Hg and a flow of 0.5 L/min. No chest drainage tube was placed routinely, feeding and anti-reflux therapy by nasogastric tube was started at day 3. All patients received morphine intravenously as analgesic treatment with doses adjusted to validated pain assessment using the COMFORT-B scale as published before by our group [11].

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

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

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

*Lung function*

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

limitation, which indicates that maximal expiratory flow is achieved during tidal breathing, was recorded during lung function measurement[17].
$FRC_p$ (mL/kg) was the primary outcome measure. Standard deviation scores (SDS) $V'max_{FRC}$, respiratory symptoms and anthropometric SDS were the secondary outcome measures.

*Respiratory morbidity, gastro-intestinal morbidity and physical growth*

Before lung function testing, infants were physically examined at both follow-up visits. Examination included height and weight measurements, pulmonary auscultation, and neurological examination. Respiratory rate (RR) was measured during lung function assessment. Three respiratory outcome variables were recorded: the occurrence of one or more respiratory tract infections (RTI) necessitating therapeutic courses of antibiotic treatment over the last 6 months prior to assessment, use of prophylactic antibiotics, and the use of inhaled bronchodilators and/or corticosteroids. Gastro-esophageal reflux (GER) was evaluated by barium swallow X-ray and pH-metry as previously described by our team [18]. According to the criteria by Vandenplas [19-20], a gastro-esophageal reflux index of > 10% was considered pathological. Gastrointestinal symptoms, use of medication and surgical treatment for GER were recorded. Dutch population data served as reference values for physical growth [21]. Chest X-rays were examined retrospectively to evaluate the presence of rib fusions.

*Data Analysis*

Patient characteristics are presented as number of patients (percentage) or median (range). Mann Whitney U tests served to test differences in perinatal characteristics between included and excluded patients and between patients with a thoracotomic and thoracoscopic surgical repair. In this longitudinal study, the data are composed of repeated lung function measurement values obtained in different individuals at two time points (6 and 12 months of age). Most infants were assessed at both time points; some, however, only once. Differences between the subgroup of patients measured both times, the subgroup measured only at 6, and the subgroup measured only at 12 months were explored with the Chi-square and Kruskal-Wallis tests. Anthropometric and lung function data are presented as mean (SD). $V'max_{FRC}$ SDS were calculated as the difference between observed and predicted value divided by the residual standard deviation from the reference values for $V'max_{FRC}$. Since repeated measurements ANOVA allows for missing data at one time point, $FRC_p$, $V'max_{FRC}$, $V'max_{FRC}$ SDS and SDS for weight and length were evaluated by this method [13,22].
To set approximate normal distribution for $FRC_p$, data were log-transformed. Back transforming the resulting means resulted in geometric means, which are presented. We analyzed the following parameters as covariates in univariate Mixed Models to investigate if they had a significant influence on lung function parameters: gestational

age, birth weight, duration of ventilation, duration of supplemental oxygen, age at surgery and type of surgery (thoracotomy or thoracoscopy). The duration of supplemental oxygen was transformed logarithmically in order to reduce the effect of outlying values. All results are expressed as mean (SD, 95% CI) or median (range, IQR). The significance level was set at $p < 0.05$. SPSS 17.0 (Chicago, Illinois) was used for the analyses.

## Results

Between January 2005 and March 2009, 55 newborns with EA were admitted to the Intensive Care Unit of the Erasmus MC-Sophia Children's Hospital. Five children with severe other congenital and/or syndromal anomalies died during admission, from causes unrelated to EA (trisomy 18 in one, CHARGE syndrome in one, cardiac anomalies in three). Thirteen infants (24%) were not included for various reasons; upper airway obstruction (n = 4), parental refusal to join the follow-up program including lung function measurement (n = 5), failure to sleep during lung function measurement (n = 2), severe scoliosis (n = 1) and the presence of a nasogastric tube preventing lung function measurement (n = 1). Thus, 37 infants were included in this study (Figure 1).

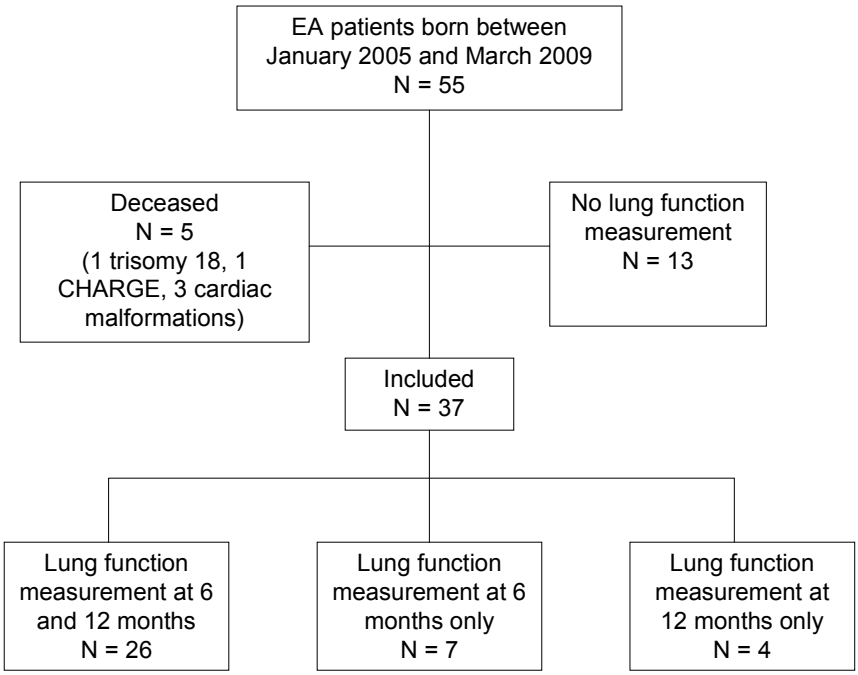



**Figure 1**: *Flowchart*

None of the perinatal characteristics differed significantly between included and excluded patients (not shown). Five patients had additional cardiac anomalies, all without hemodynamic consequences. These anomalies spontaneously resolved in 2 cases and remained without consequences in 2 other cases. One other patient was operated at the age of 2 weeks for coarctation of the aorta. Twenty-six infants were measured both at 6 and 12 months of age. Eleven were seen only once, either at 6 or at 12 months, for the following reasons: failure to sleep during one of the measurements (n = 5), respiratory tract infection at the time of measurement (n = 2), upper airway obstruction (n = 1), loss to follow-up (n = 1) and logistic reasons (n = 2). Thirty-five (95%) of all children were also seen at the age of 2 years, and 14 children (41%) at both 2 and at 5 years of age. The other participants in this study have not reached that age yet. Clinical characteristics of the 37 infants are shown in Table 1.The surgical procedure had been right-sided in all cases. In 1 patient, conversion to open thoracotomy was needed. Chest X-rays performed within the first 5 years of life (median 11, range 1.5-65 months) in 19/21 patients (90%) who underwent a thoracotomy revealed rib fusion at the ipsilateral side in 2/19 (10%). One other patient (5%) had a rib fusion at the contralateral side where formerly a thoracic drain had been placed. None of the 16 patients who underwent a thoracoscopic procedure showed rib fusions on chest X-rays within the first 3 years of life (median 8, range 1.5-36 months). At 5 years, 1/14 patients evaluated at this age had a stable lumbar scoliosis with a Cobb's angle of 18°. In none of the other patients a scoliosis was diagnosed at this age.

*Lung function measurements*

The median postnatal age at the first lung function test was 32 weeks (range 24-43 weeks; n = 33); at the second it was 57 weeks (range 51-66 weeks; n = 30). The corresponding median ages corrected for prematurity were 30 weeks (range 24-39 weeks) and 54 weeks (range 49-66 weeks), respectively. Reliable $V'max_{FRC}$ measurements were obtained in 25 patients at 6 months and in 27 patients at 12 months. Reliable $FRC_p$ measurements were obtained in 31 patients at 6 months and in 30 patients at 12 months. Reliable $FRC_p$ measurement with inability to measure SDS $V'max_{FRC}$ was caused by failure to sleep in 4 cases where the infant woke up during rapid inflation of the jacket, in 2 cases a gastrostomy drain needed for a severe anastomotic stricture prevented the infant from wearing the jacket. Two infants had tidal flow limitation and one had an irregular breathing pattern. At 6 months, 14 infants (44%) had a respiratory rate ≥ 35 breaths/min, of whom 6 (19%) had ≥ 40 breaths/min. At 12 months, 6 infants (19%) had a respiratory rate ≥ 35 breaths/min, of whom 3 (10%) had a respiratory rate ≥ 40 breaths/min.

Tidal flow limitation was observed seven times (six cases at 6 months and one at 12 months).

| Variables | Total group | Thoracotomy | Thoracoscopy | p |
|---|---|---|---|---|
| N | 37 | 21 (57) | 16 (43) | |
| Males, n (%) | 20 (54) | 12 (57) | 8 (50) | 0.670 |
| Gestational age (wks) | 38.3 (28.9-42.3) | 38.1 (33.7-42.3) | 38.0 (28.9-41.9) | 0.878 |
| Prematures, n (%) | 10 (27) | 7 (33) | 3 (19) | 0.166 |
| Birth weight (kg) | 2.70 (1.08-3.81) | 2.54 (1.18-3.81) | 2.89 (1.08-3.52) | 0.471 |
| Type of EA (n) | | | | 0.845 |
| A | 2 (5) | 1 (5) | 1 (7) | |
| C | 35 (95) | 20 (95) | 15 (93) | |
| Age at surgery (days) | 2 (0-121) | 2 (0-47) | 2 (1-121) | 0.192 |
| Duration of ventilation (days) | 2 (1-7) | 2 (1-5) | 1 (1-7) | 0.166 |
| Duration of oxygen dependence (days) | 2 (1-35) | 2 (1-10) | 1 (1-35) | 0.222 |
| Nissen fundoplication, n (%) | 4 (11) | 2 (10) | 2 (13) | 0.776 |
| Age at Nissen fundoplication (weeks) | 16 (11-19) | 14 (11-17) | 17 (14-19) | 0.439 |
| Aortopexy, n (%) | 2 (5) | 1 (5) | 1 (6) | 0.845 |
| Age at aortopexy (weeks) | 9 (7-11) | 7 | 11 | 0.317 |
| Anastomotic stricture, n (%) | 17 (46) | 9 (43) | 8 (50) | 0.548 |
| Number of dilatation procedures | 3 (1-15) | 3 (1-5) | 3 (1-15) | 0.230 |
| Additional anorectal malformation, n (%) | 5 (14) | 3 (14) | 2 (13) | 0.827 |
| Cardiac anomaly, n (%) | 5 (14) | 3 (14) | 2 (13) | 0.827 |
| Repaired by right sided thoracotomy | 1 | 1 | | |
| Age at repair (weeks) | 2 | 2 | | |

**Table 1:** *EA: esophageal atresia. Type A = esophageal atresia without tracheo-esophageal fistula, type C = esophageal atresia with distal tracheo-esophageal fistula. Data are shown as number (%) or median (range). Characteristics of the 3 subgroups – measured both times (n=26), only at 6 (n=7) and only at 12 months (n=4) – did not differ significantly (data not shown).*

Neither at 6 nor at 12 months $FRC_p$ values were ≤ 13 mL/kg. Twenty-five percent of $FRC_p$ measurements were > 26 mL/kg (19% at 6 months and 30% at 12 months). The mean $FRC_p$ increased significantly from 6 to 12 months (p=0.010). SDS V'$max_{FRC}$ did not change significantly over time (p=0.248). The results are presented in Table 2 and Figure 2. Results from analyses excluding the two patients with a long-gap-type EA (type A) were not significantly different (data not shown). Five $FRC_p$ measurements in 4 patients were >30 mL/kg (Figure 2). All four had airflow obstruction with SDS V'$max_{FRC}$ between

-2.08 and -3,57. Tidal flow limitation was observed in two of them; another patient had clinical evidence of tracheomalacia. None of the patients underwent a bronchoscopy as a routine pre- or postoperative diagnostic procedure to confirm the extent of tracheomalacia.

| | 6 mos | 12 mos | p-value |
|---|---|---|---|
| $FRC_p$, mL/kg | 22.5 (20.7-24.6) | 25.4 (23.2-27.7) | 0.010 |
| $V'max_{FRC}$, SDS | -1.9 (-2.5 to -1.3)* | -2.3 (-2.7 to -1.8)* | 0.248 |
| $V'max_{FRC,}$ mL/sec | 79.8 (52.8-106.8) | 109.1 (81.4-136.8) | 0.023 |
| RR, breaths/min | 34.2 (31.6-36.7) | 30.6 (27.6-33.6) | 0.005 |

**Table 2**: *$FRC_p$: functional residual capacity. $V'max_{FRC}$: maximal expiratory flow at functional residual capacity. RR: respiratory rate. * p< 0.001 below the reference value (SDS = 0). Mean (95% CI) values from analysis of variance are shown.*

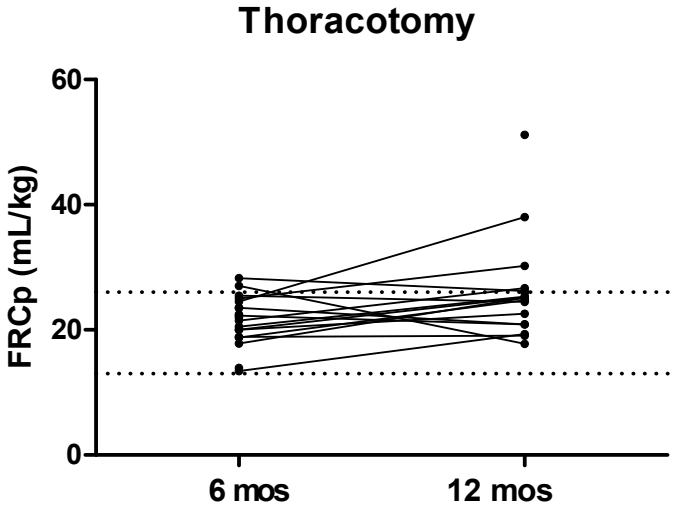



**Figure 2a:** *$FRC_p$ (mL/kg) at 6 and 12 months in patients with thoracotomic type of repair. Repeated measurements are indicated by closed dots and a connecting line. The range of normal values (beween 13 and 26 mL/kg) is indicated by dotted horizontal lines.*

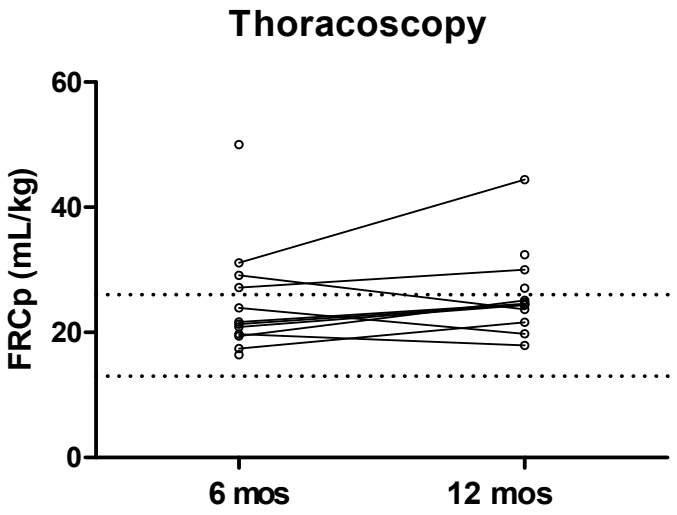



**Figure 2b:** *$FRC_p$ (mL/kg) at 6 and 12 months in patients with thoracoscopic type of repair. Repeated measurements are indicated by open dots and a connecting line. The range of normal values (beween 13 and 26 mL/kg) is indicated by dotted horizontal lines.*

*Associations between lung function parameters and clinical characteristics*

Perinatal characteristics did not differ significantly between patients undergoing a thoracotomic and a thoracoscopic type of repair (Table 1). $FRC_p$ and SDS $V'max_{FRC}$ were not associated with type of surgery (p=0.384 and p=0.241 respectively, Table 3). A longer duration of the log supplemental oxygen days was associated with higher SDS $V'max_{FRC}$ only at 12 months (p=0.020). A two-fold longer duration of supplemental oxygen days resulted in a mean increase of 0.4 SDS $V'max_{FRC}$ at both time points. Other significant associations between clinical characteristics and $FRC_p$ values or SDS $V'max_{FRC}$ were not found. When analyses were repeated after exclusion of the 2 patients with a long gap type esophageal atresia (type A), results did not change significantly (not shown).

| | Thoracotomy (n=21) | Thoracoscopy (n=16) | p-value |
|---|---|---|---|
| $FRC_p$, mL/kg | 23.2 (20.9-25.8) | 24.9 (22.0-28.2) | 0.384 |
| $V'max_{FRC}$, SDS | -1.9 (-2.4 to -1.3)* | -2.3 (-3.0 to -1.7)* | 0.241 |
| $V'max_{FRC,}$ mL/sec | 101.6 (68.9-134.3) | 85.8 (48.5-123.1) | 0.520 |
| RR, breaths/min | 33.3 (29.9-36.6) | 31.2 (27.4-35.1) | 0.425 |

**Table 3**: *$FRC_p$: functional residual capacity. $V'max_{FRC}$: maximal expiratory flow at functional residual capacity. RR: respiratory rate. * p< 0.001 below the reference value (SDS = 0). Mean (95% CI) values from analysis of variance are shown.*

*Respiratory morbidity at 6 and 12 months, 2 years and 5 years of age*

All infants had been ventilated conventionally. One was born prematurely at 29 weeks and developed CLD according to the definition by Jobe and Bancalari [23]. Two suffered from tracheomalacia with life-threatening incidents requiring an aortopexia at the ages of 7 and 11 weeks, respectively. Respiratory morbidity at the various ages is specified in Table 4. One case of atopic eczema occurred; the family history of 8 patients was positive for atopic symptoms.

| | 6 mos (n=34) | 12 mos (n=35) | 2 yrs (n=35) | 5 yrs (n=14) |
|---|---|---|---|---|
| RTI with AB treatment, n (%) | 10 (29.4) | 15 (42.9) | 11 (31.4) | 4 (28.6) |
| Profylactic AB | | | | |
| Airway, n (%) | 4 (11.8) | 3 (8.6) | 5 (14.3) | 3 (21.4) |
| Urologic, n (%) | 2 (5.9) | 3 (8.6) | 5 (14.3) | 1 (7.1) |
| Use of bronchodilators, n (%) | 6 (17.6) | 7 (20.0) | 1 (2.9) | NA |
| Use of inhaled steriods, n (%) | 2 (5.9) | 3 (8.6) | 2 (5.7) | NA |
| Ausculatory abnormalities | | | | |
| Wheezing | NA | NA | NA | NA |
| Mucus | 7 (20.6) | 6 (17.1) | 4 (11.4) | 1 (7.1) |

**Table 4:** *RTI: ≥ 1 respiratory tract infection in the past 6 months requiring a therapeutic dose of AB; AB = antibiotics.NA=not applicable.*

*Associations between lung function parameters and respiratory morbidity at different ages*

$FRC_p$ values and SDS $V'max_{FRC}$ at 6 and 12 months were not associated with the occurrence of RTI requiring therapeutic antibiotic treatment in the previous 6 months. Two infants at 6 months and three at 12 months were being treated with prophylactic antibiotics for urologic reasons (both had an anorectal malformation as well). $FRC_p$ at 12 months was significantly higher in these five children (p=0.006, airway and urologic prophylaxis). At 12 months, the use of bronchodilators and inhaled corticosteroids was

not associated with lower $FRC_p$ or SDS $V'max_{FRC}$. At 6 months, the use of bronchodilators and inhaled corticosteroids was associated with higher log $FRC_p$ (p=0.031). At 2 and 5 years of age, neither number of RTI within the past 6 months nor the use of prophylactic antibiotics was associated with lung function parameters during the first year of life.

*Gastro-intestinal morbidity*

A barium swallow X-ray was performed in 36 infants at a median age of 10 (IQR 6-13) weeks. Eight infants had no signs of reflux, three showed reflux only at abdominal compression, and 25 had spontaneous reflux. A 24-hrs pH-metry was performed in 35 infants at a median age of 9 (IQR 8-17) weeks. Thirty-three of them were measured during 24 hours without the use of anti-reflux medication; 27 of them were measured another 24 hours longer with the use of anti-reflux medication. Pathological GER was found in 3 of the former (3/33; 9.1%) and in 2 of the latter (2/27; 7.4%). Four patients who suffered from severe tracheomalacia with life-threatening events underwent a surgical anti-reflux procedure before the age of 6 months (normal pH-metry n=2, pathological GER n=1, no pH-metry available n=1).

*Physical growth*

At all ages SDS height and weight for height were significantly below the norm (SDS=0) except for height at 5 years. Height and weight data at 6 and 12 months, 2 and 5 years are shown in Figure 3.

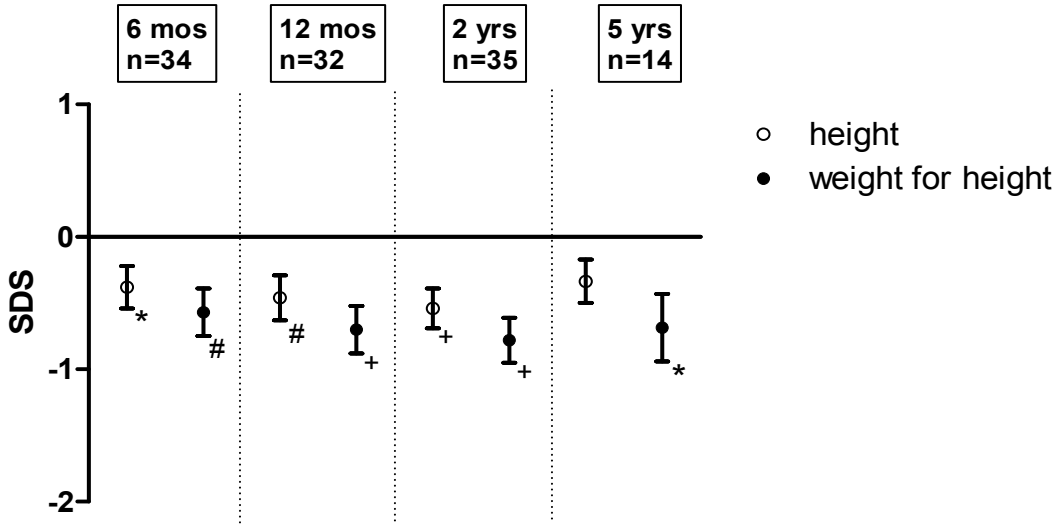



**Figure 3:** *Mean (SE) SDS height and weight for height at 6 and 12 months and 2 and 5 years. At all ages SDS height and weight for height were significantly below the norm (SDS=0) except for height at 5 years. * p ≤ 0.05, # p ≤ 0.01, + p ≤ 0.001*

## Discussion

In this study we longitudinally evaluated lung function during the first year of life in 37 infants after thoracotomic or thoracoscopic repair of EA. Thirty-five patients had type C EA and 2 type A. Furthermore we evaluated possible relationships between lung function, perinatal characteristics and respiratory morbidity. Lung function did not differ by type of surgery. $FRC_p$ values, referring to intrathoracic lung volume [24], were in the upper normal range and had significantly increased from 6 to 12 months. SDS $V'max_{FRC}$ was significantly below the norm without a significant change from 6 to 12 months. Flow limitation, which may reflect severe airway malacia, was observed in 7 patients (19%).

Lung function abnormalities in patients with EA with obstructive as well as restrictive patterns have been described at different ages from infancy [3,5] and childhood [3,6-7] to adulthood [6,8,25]. Sistonen and colleagues reported restrictive lung function in 57% of 101 adult EA patients (aged 22-56 years), for which thoracotomy-induced rib fusion was a significant risk factor [25]. Thirty percent of these adult EA patients had rib fusions in the previous thoracotomy area [26]. In the present study only 3 patients show rib fusion in the first year of life, all after thoracotomy. A thoracoscopic repair might contribute to a reduction of rib fusion and later concomitant restrictive ventilatory defects but we did not find a significant difference in lung function yet in the first year of life. Maybe differences in lung function between the 2 types of repair may become manifest later in life. $FRC_p$ corrected for body weight increased significantly from 6 to 12 months suggesting an increase in lung volume. There is no reason to assume that this is based on extensive lung growth during the first year of life after repair of EA. It might well be that persistent higher airway obstruction caused by tracheomalacia, together with recurrent RTI, caused a mild form of hyperinflation, reflected by $FRC_p$ values in the upper normal range. Indeed, 4 patients with $FRC_p$ values far above the normal range also had low SDS $V'max_{FRC}$ values and 3 of them had clinical signs of substantial tracheomalacia with tidal flow limitation.

SDS $V'max_{FRC}$ was significantly below the norm without a change during the first year of life. Beardsmore et al. also found abnormal lung function at various time-points during the first year of life in 9 of 16 EA-TEF patients [5]. These patients' functional abnormalities were related with severity of persistent symptoms. Other studies have reported airway obstruction in 30- 41% of older EA patients [6-7]. A longer duration of log supplemental oxygen days was associated with higher $V'max_{FRC}$. This may be a false positive, type 1 error, however in view of the multiple tests performed. Recurrent RTI were reported in 30-40% of our patients, in line with findings from other studies in EA patients [27-28]. Recurrent RTI, as seen in patients with cystic fibrosis and primary ciliary dyskinesia, are associated with significantly diminished flows [29-30] and hyperinflation and air trapping [29].

Tidal flow limitation was observed in 7 patients (19%). Van der Wiel and colleagues showed that tidal flow limitation was 100% predictive of airway malacia, as diagnosed by bronchoscopy; although only half of 32 wheezy infants with airway malacia had tidal flow

limitation [31]. Turner and colleagues found an association between tidal flow limitation early in the first year of life and reduced lung function later in life [32]. Thus, absence of tidal flow limitation does not rule out airway malacia but presence of tidal flow limitation may identify an at-risk group in these EA patients. At both ages in our study, 19% of the infants had a RR above the normal median at that age while asleep [33].

The decreased morbidity with increasing age in EA patients appears considerably higher for the respiratory symptoms than for gastrointestinal symptoms [34], suggesting no clear direct causal relation between gastrointestinal and respiratory complications [2]. In the present study only 2 patients who were treated with anti-reflux medication showed pathological GER. We therefore assume that GER did not substantially affect lung function results in our study.

Like subjects in comparable studies, physical growth of or subjects was impaired [4,28]. As $FRC_p$ in mL/kg and SDS $V'max_{FRC}$ are corrected for weight and length respectively, we assume this impaired growth did not influence the lung function results. On the other hand, impaired nutritional status can influence the prevalence of RTI.

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

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

Another limitation is the lack of lung function measurements at the age of 5 years. In a previous study we found that only few 5-year-old EA-patients could successfully perform flow-volume measurement testing [4]. In the present cohort we will therefore evaluate lung function, including measurement of static and dynamic lung volumes, at the age of 8 years.

In conclusion, there were no differences in lung function in the first year of life after thoracotomic or thoracoscopic type of repair of EA and the influence of ribfusion is low. We did not find arguments in this study for the pro- and con-discussion of thoracotomy vs thoracoscopically treated patients with EA. The results of infant lung function testing were of limited predictive value for respiratory morbidity at older age. Clinical care should especially consist of frequent monitoring focused on nutritional status and RTI

prevention. Low-threshold use of antibiotics, prophylactic antibiotics and vaccination for respiratory syncytial and influenza virus is recommended in case of recurrent RTI.

## References


1. Lopez PJ, Keys C, Pierro A, Drake DP, Kiely EM, Curry JI, Spitz L. Oesophageal atresia: improved outcome in high-risk groups? J Pediatr Surg 2006;41(2):331-334.

2. Delacourt C, de Blic J. Pulmonary outcome of esophageal atresia. J Pediatr Gastroenterol Nutr 2011;52 Suppl 1:S31-32.

3. Agrawal L, Beardsmore CS, MacFadyen UM. Respiratory function in childhood following repair of oesophageal atresia and tracheoesophageal fistula. Arch Dis Child 1999;81(5):404-408.

4. Gischler SJ, van der Cammen-van Zijp MH, Mazer P, Madern GC, Bax NM, de Jongste JC, van Dijk M, Tibboel D, IJsselstijn H. A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. J Pediatr Surg 2009;44(9):1683-1690.

5. Beardsmore CS, MacFadyen UM, Johnstone MS, Williams A, Simpson H. Clinical findings and respiratory function in infants following repair of oesophageal atresia and tracheo-oesophageal fistula. Eur Respir J 1994;7(6):1039-1047.

6. Chetcuti P, Phelan PD, Greenwood R. Lung function abnormalities in repaired oesophageal atresia and tracheo-oesophageal fistula. Thorax 1992;47(12):1030-1034.

7. Malmstrom K, Lohi J, Lindahl H, Pelkonen A, Kajosaari M, Sarna S, Malmberg LP, Makela MJ. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. J Pediatr 2008;153(3):396-401.

8. Sistonen SJ, Pakarinen MP, Rintala RJ. Long-term results of esophageal atresia: Helsinki experience and review of literature. Pediatr Surg Int 2011;27(11):1141-1149.

9. Bax KM, van Der Zee DC. Feasibility of thoracoscopic repair of esophageal atresia with distal fistula. J Pediatr Surg 2002;37(2):192-196.

10. van der Zee DC, Bax NM. Thoracoscopic repair of esophageal atresia with distal fistula. Surg Endosc 2003;17(7):1065-1067.

11. Ceelie I, van Dijk M, Bax NM, de Wildt SN, Tibboel D. Does minimal access major surgery in the newborn hurt less? An evaluation of cumulative opioid doses. Eur J Pain 2011;15(6):615-620.

12. Gischler SJ, Mazer P, Duivenvoorden HJ, van Dijk M, Bax NM, Hazebroek FW, Tibboel D. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 2009;44(7):1382-1389.

13. Spoel M, van den Hout L, Gischler SJ, Hop WC, Reiss I, Tibboel D, de Jongste JC, IJsselstijn H. Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia. Pediatr Crit Care Med 2011.

14. Hulskamp G, Hoo AF, Ljungberg H, Lum S, Pillow JJ, Stocks J. Progressive decline in plethysmographic lung volumes in infants: physiology or technology? Am J Respir Crit Care Med 2003;168(8):1003-1009.

15. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R, Society EATFoSfIRFTERSAT. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. Eur Respir J 2001;17(2):302-312.

16. Hoo AF, Dezateux C, Hanrahan JP, Cole TJ, Tepper RS, Stocks J. Sex-specific prediction equations for Vmax(FRC) in infancy: a multicenter collaborative study. Am J Respir Crit Care Med 2002;165(8):1084-1092.

17. Koulouris NG, Hardavella G. Physiological techniques for detecting expiratory flow limitation during tidal breathing. Eur Respir Rev 2011;20(121):147-155.

18. Bergmeijer JH, Hazebroek FW. Prospective medical and surgical treatment of gastroesophageal reflux in esophageal atresia. J Am Coll Surg 1998;187(2):153-157.

19. Salvatore S, Hauser B, Vandemaele K, Novario R, Vandenplas Y. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr 2005;40(2):210-215.

20. Vandenplas Y, Salvatore S, Hauser B. The diagnosis and management of gastro-oesophageal reflux in infants. Early Hum Dev 2005;81(12):1011-1024.

21. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47(3):316-323.

22. Fitzmaurice G LN, Ware J. Applied Longitudinal Analysis. . 1st ed John Wiley & Sons 2004.

23. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr 2011;23(2):167-172.

24. Hulskamp G, Pillow JJ, Dinger J, Stocks J. Lung function tests in neonates and infants with chronic lung disease of infancy: functional residual capacity. Pediatr Pulmonol 2006;41(1):1-22.

25. Sistonen S, Malmberg P, Malmstrom K, Haahtela T, Sarna S, Rintala RJ, Pakarinen MP. Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. Eur Respir J 2010;36(5):1106-1112.

26. Sistonen SJ, Helenius I, Peltonen J, Sarna S, Rintala RJ, Pakarinen MP. Natural history of spinal anomalies and scoliosis associated with esophageal atresia. Pediatrics 2009;124(6):e1198-1204.

27. Chetcuti P, Phelan PD. Respiratory morbidity after repair of oesophageal atresia and tracheo-oesophageal fistula. Arch Dis Child 1993;68(2):167-170.

28. Lacher M, Froehlich S, von Schweinitz D, Dietz HG. Early and long term outcome in children with esophageal atresia treated over the last 22 years. Klin Padiatr 2010;222(5):296-301.

29. Marthin JK, Petersen N, Skovgaard LT, Nielsen KG. Lung function in patients with primary ciliary dyskinesia: a cross-sectional and 3-decade longitudinal study. Am J Respir Crit Care Med 2010;181(11):1262-1268.

30. Peterson-Carmichael SL, Harris WT, Goel R, Noah TL, Johnson R, Leigh MW, Davis SD. Association of lower airway inflammation with physiologic findings in young children with cystic fibrosis. Pediatr Pulmonol 2009;44(5):503-511.

31. van der Wiel EC, Hofhuis W, Holland WP, Tiddens HA, de Jongste JC, Merkus PJ. Predictive value of infant lung function testing for airway malacia. Pediatr Pulmonol 2005;40(5):431-436.

32. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Young S, Landau LI, Le Souef PN. Infants with flow limitation at 4 weeks: outcome at 6 and 11 years. Am J Respir Crit Care Med 2002;165(9):1294-1298.

33. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, Maconochie I, Tarassenko L, Mant D. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377(9770):1011-1018.

34. Little DC, Rescorla FJ, Grosfeld JL, West KW, Scherer LR, Engum SA. Long-term analysis of children with esophageal atresia and tracheoesophageal fistula. J Pediatr Surg 2003;38(6):852-856.

35. Borrego LM, Stocks J, Leiria-Pinto P, Peralta I, Romeira AM, Neuparth N, Rosado-Pinto JE, Hoo AF. Lung function and clinical risk factors for asthma in infants and young children with recurrent wheeze. Thorax 2009;64(3):203-209.


# Lung function of infants with congenital lung lesions in the first year of life

Marjolein Spoel, Kees P van de Ven, Harm AWM Tiddens, Titia E Cohen-Overbeek, Wim CJ Hop, Rene MH Wijnen, Lex PWM Maat, Dick Tibboel, Hanneke IJsselstijn.

Submitted

**Abstract**

*Background:*

Several studies have evaluated short-term neonatal outcome in infants with congenital lung lesions (CLL) but clinical course and lung function on the longer term have not yet been documented.

*Objective:*

To evaluate respiratory symptoms and lung function longitudinally in the first year of life in infants with CLL and analyse differences herein between infants managed by observation only and infants whose affected lung parts were resected; the surgical group.

*Methods:*

In 30 patients with CLL we evaluated respiratory symptoms and lung function at 6 and 12 months. Functional residual capacity ($FRC_p$) and maximal expiratory flow at functional residual capacity ($V'max_{FRC}$) were measured with body plethysmography. SD-scores were calculated for $V'max_{FRC}$.

*Results:*

Prevalence of respiratory symptoms did not differ between the observation and surgical group. Mean (95%CI) $FRC_p$ values were in the upper or above normal range without a significant change in time (25.4 (23.7-27.1) and 26.8 (25.1-28.5) mL/kg, p=0.195 at 6 and 12 months respectively). SDS $V'max_{FRC}$ was significantly below normal without a change in time (SDS -1.39 (-1.70 to -1.09) and -1.72 (-2.21 to -1.24), p=0.209 at 6 and 12 months respectively). Mean $FRC_p$ values and SDS $V'max_{FRC}$ did not differ between the observation and surgical groups.

*Conclusion:*

Respiratory morbidity and lung function were not significantly different between the observation and surgical groups. We recommend prolonged pulmonary follow-up of all CLL patients into adulthood to further identify the long term effects of CLL and observation or surgery.

## Introduction

Congenital malformations of the lung are rare with a reported estimate prevalence of one in 11.000-35.000 pregnancies and vary widely in their presentation and severity [1-3]. Advances in antenatal diagnostic techniques have improved the detection and characterisation of congenital lung lesions (CLL) [4]. The differential diagnosis of lung lesion includes congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), bronchogenic cyst (BC) and congenital lobar emphysema (CLE). CCAMs are characterised by hamartomous growth of terminal respiratory structures deriving their blood supply from the pulmonary vasculature. BPSs are masses of non-functioning lung tissue, either in intralobar or extralobar form. BCs result from abnormal budding of the foregut, are usually unilocular, mostly located in the mediastinum and do not communicate with the airway [5]. CLE is a term used to describe a distended hyperlucent lobe, usually the left upper or right middle lobe, perhaps resulting from transient bronchial obstruction in utero [6].

Natural courses of CLL in utero from severe hydrops to total regression have been observed [7]. In the perinatal period, air trapping within the cystic component of CCAM can result in life-threatening respiratory distress requiring immediate surgical intervention. Later in life, communication of the cysts with the airways can result in recurrent pneumonia for which surgical resection of the affected lung part(s) is indicated. Controversy remains whether asymptomatic lesions should be resected. Some centers prefer elective resection at 3-6 months to reduce the risk of infection [1]; others prefer observation only because asymptomatic lesions may regress spontaneously [8-9].

Several studies evaluated short-term neonatal outcome but to our knowledge, lung function in the first year of life has not yet been documented. We report a prospective study in in infants with CLL in which we established the clinical course, respiratory symptoms, and lung function halfway and at the end the first year of life. Furthermore we analysed differences between infants with asymptomatic lesions, the observation group, and those after resection of the affected lung part(s), the surgical group. We also studied possible associations between clinical characteristics and lung function parameters.

## Methods

Of all CLL patients born in our center between May 2005 and September 2010 we recorded data on antenatal ultrasound, gestational age, birth weight, gender, type of lung anomaly, duration of post-operative ventilation and supplemental oxygen. In the group of infants that underwent resection of the affected lung part(s), the surgical group, surgical procedure (lobectomy, pneumonectomy or non-anatomical resection) was recorded. The indication for resection was respiratory distress in all cases. Asymptomatic infants, the observation group, were observed only.

The study was part of a routine follow-up program for CLL patients in which lung function, growth and developmental parameters are regularly assessed until 18 years of age [10-11]. The Medical Ethical Review Board Erasmus MC stated that "the Medical Research in Human Subjects Act does not apply to this research proposal, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed". Therefore approval was waived. All parents were informed and provided permission to use the data for research purposes. Lung function data were evaluated at the end of 2011.

*Respiratory morbidity and physical growth*

The infants were physically examined at the ages of 6 and 12 months. Examination included anthropometry and pulmonary auscultation. Respiratory rate (RR) was measured during lung function assessment. The following factors were recorded: respiratory tract infections (RTI) with a need of therapeutic courses of antibiotic treatment in the 6 months prior to the visit, use of prophylactic antibiotics and the use of inhaled bronchodilators and/or corticosteroids. Dutch population data served as reference values for physical growth [12].

*Infant lung function tests*

Infant lung function test were done at the ages of 6 and 12 months (corrected for prematurity), when children were clinically stable. Infants were sedated with chloral hydrate (50-75 mg/kg). Functional residual capacity ($FRC_p$) was measured by whole body plethysmography (Masterscreen Babybody, Viasys, Hochberg, Germany) as described previously [13]. $FRC_p$ was expressed in mL/kg as suggested by Hülskamp et al [14]. Forced expiratory flow at $FRC_p$ ($V'max_{FRC}$), a measure of airway patency and compressibility, was determined by the end-tidal rapid thoracoabdominal compression technique (Masterscreen Babybody, Viasys, Hochberg, Germany). All equipment and procedures complied with the guidelines of the ERS/ATS [15]. Regarding $V'max_{FRC}$, we calculated standard deviation scores (SDS) according to Hoo [16]. $FRC_p$ (mL/kg) was the primary outcome measure. SDS $V'max_{FRC,}$ respiratory symptoms and anthropometric SDS were the secondary outcome measures.

*Imaging*

Antenatal ultrasound scan data of infants with an antenatal diagnosis were collected if available and evolution of the CLL in the prenatal period was described. These data were not available for all infants because in the Netherlands the 20 week anomaly scan was not introduced until 2007. Data included gestational age at diagnosis, type of CLL, and size measured from 2D images as two perpendicular measurements of the CLL.

*Data analysis*

Group comparisons were made with Mann Whitney U tests. In a minority of patients, lung function was measured only at one of the two time points. Since repeated measurements ANOVA allows for missing data at one time point, mean (95% CI) $FRC_p$, SDS $V'max_{FRC}$ and SDS for weight and height were evaluated longitudinally using this method [17]. The following parameters were entered as covariates in univariate Mixed Models to investigate their influence on lung function parameters: gestational age at birth, birth weight, duration of ventilation, duration of supplemental oxygen, and management – either observation or surgery. The durations of ventilation and supplemental oxygen were transformed logarithmically to reduce the effect of outlying values. All results are expressed as number (percentage), mean (SD) or median (range) where appropriate.The significance level was set at $p < 0.05$. SPSS 17.0 (Chicago, Illinois) was used for the analyses.

## Results

Between May 2005 and December 2010, 55 of 57 newborns with a CLL survived (96%). One died from persistent pulmonary hypertension after pneumectomy for CCAM; one from intracranial hemorrhage after bowel resection for complicating necrotizing enterocolitis. For logistic reasons the infants were gradually included in the follow-up program. Seventeen (31%) patients had been included after the first year of life and were therefore excluded from this study. Two other, asymptomatic, patients had serious neurological co-morbidity (1 with a chromosomal anomaly and 1 with a muscular disease due to Filamin A deficiency) as contraindication for lung function testing. Parents of 5 patients refused follow-up including lung function testing. One patient was awake during the first measurement en suffered from a RTI at the second occasion. Eventually, 30 patients with a congenital lung lesion participated in the follow-up program including lung function and 27 did not participate (Figure 1).

Participants' birth weight was significantly lower than that of the non-participants (median 2930 (1650-4200) g vs.median 3580 (2450-4505) g; p=0.005). Other perinatal characteristics did not significantly differ between participants and non-participants (data not shown). Fifteen participants were measured at both time-points, 5 at 6 months only and 10 at 12 months only (Figure 1). Reasons for not completing both measurements were delayed inclusion (n=7), RTI (n=3), being awake (n=2), and logistic reasons (n=3). Clinical characteristics of participants are shown in Table 1. Thirteen (43%) developed respiratory symptoms and underwent resection of the lung lesion at a median age of 3 weeks (range 0-39 weeks). All patients were ventilated post-operatively; two were extubated on the day of surgery. One patient underwent pneumonectomy and was treated with veno-arterial extracorporeal membrane oxygenation (ECMO) for 5 days due to respiratory failure of conventional mechanical ventilation.

*Respiratory morbidity and physical growth*

In all 13 patients who underwent resection (surgical group), respiratory distress necessitated surgery. Significantly more therapeutic courses of antibiotics in case of infection had been prescribed between 0-6 months than between 6-12 months. This difference between the 2 time point did not reach statistical significance in the observation and the surgical group separately. Number of courses of antibiotics for RTI or respiratory symptoms did not differ between these two periods (Table 2). Prevalences of respiratory symptoms for the whole population did not significantly differ at 6 and 12 months, Table 2) nor between the observation and surgical groups (data not shown).

Overall, SDS weight at 12 months was significantly below normal (Table 2). There were no significant differences in SDS weight and SDS height between both groups (data not shown).

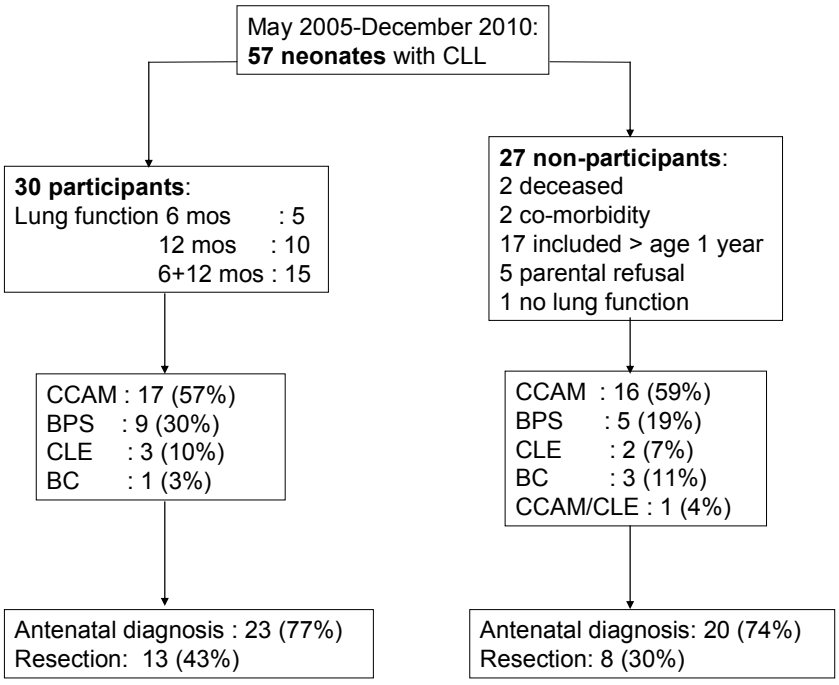



**Figure 1: Flowchart**

| Variables | Total | Observational group | Surgical group | Between groups p |
|---|---|---|---|---|
| N | 30 | 17 | 13 | |
| Males | 21 (70) | 13 (76) | 8 (62) | 0.385 |
| Gestational age (wks) | 39.1 (38.0-41.0) | 39.6 (37.1-41.6) | 40.0 (34.7-41.7) | 0.950 |
| Birth weight (grams) | 3490 (3000-4505) | 3585 (2450-4200) | 3730 (2925-4505) | 0.601 |
| Type lung lesion | | | | 0.887 |
| CCAM | 17 (57) | 10 (59) | 7 (54) | |
| BPS | 9 (30) | 5 (29) | 4 (31) | |
| CLE | 3 (10) | 2 (12) | 1 (8) | |
| BC | 1 (3) | 0 | 1 (8) | |
| Duration ventilation (days) | 0 (0-40) | 0 (0-10) | 2 (0-40) | <0.001 |
| Conventional | 0 (0-38) | 0 (0-10) | 2 (0-38) | <0.001 |
| HFO | 0 (0-11) | 0 | 0 (0-11) | 0.016 |
| Duration oxygen supply (days) | 4 (0-42) | 0 (0-10) | 5 (0-42) | <0.001 |
| Type of surgery | | | | |
| Lobectomy | 8 (62) | | 8 (62) | |
| Pneumectomy | 2 (15) | | 2 (15) | |
| N-A resection | 3 (23) | | 3 (23) | |
| Age at surgery (wks) | 3 (0-39) | | 3 (0-39) | |

**Table 1**: *CCAM: congenital cystic adenomatoid malformation, BPS: bronchopulmonary sequestration, BC: bronchogenic cyst, CLE: congenital lobar emphysema. HFO: high frequency oscillatory ventilation. N-A resection:non-anatomical resection. P values are given for the differences between patients in the observation and surgical groups. Data demonstrated as number (%), median (range) or mean (SD) where appropriate. One asymptomatic CCAM patient had a laryngeal cyst causing upper airway compression, after resection of this specific lesion 10 days of mechanical ventilation were necessary. * significantly below normal (SDS=0), one sample t-test was used.*

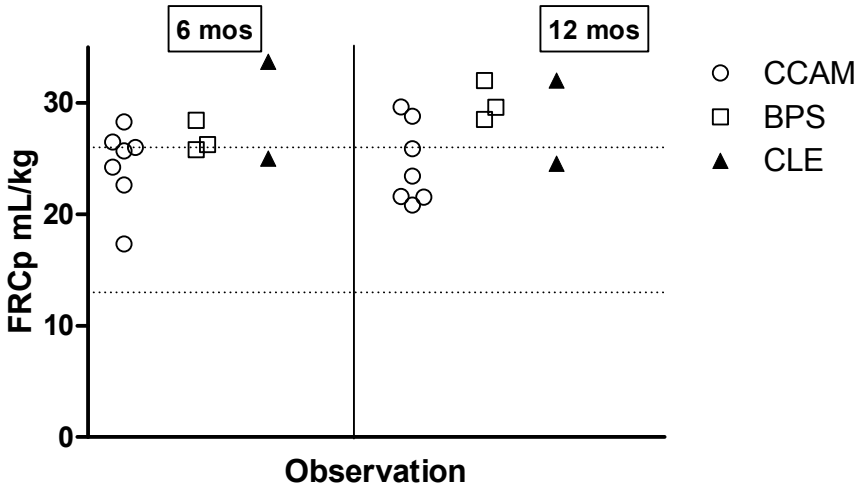
| | 6 mos | 12 mos | p-value |
|---|---|---|---|
| RTI with AB treatment | | | |
| None | 15/26 (58%) | 25/29 (86%) | |
| 1 | 9/26 (35%) | 4/29 (14%) | |
| 2 | 1/26 (4%) | 0 | |
| 3 | 1/26 | 0 | 0.018 |
| Inhalation medication | | | |
| No | 25/28 (89%) | 29/30 (97%) | |
| Yes | 3/28 (11%) | 1/30 (3%) | 0.500 |
| Admitted for RTI | | | |
| No | 28/30 (93%) | 29/30 (97%) | |
| Yes | 2/30 (7%) | 1/30 (3%) | 1.000 |
| Auscultatory findings | | | |
| Normal | 25/26 (96%) | 28/30 (93%) | |
| Wheezing | 1/26 (4%) | 2/30 (7%) | 1.000 |
| SDS height | 0.32 (0.85) | 0.11 (1.0) | 0.451 |
| SDS weight | -0.20 (1.04) | -0.36 (1.05)* | 0.409 |
| $FRC_p$, mL/kg | 25.4 (23.7-27.1) | 26.8 (25.1-28.5) | 0.112 |
| $V'max_{FRC}$, SDS | -1.39 (-1.70 to -1.09)* | -1.72 (-2.21 to -1.24)* | 0.113 |
| RR, breaths/min | 35.4 (32.4-38.4) | 30.4 (28.7-32.1) | 0.009 |

**Table 2:** *Respiratory symptoms: n= number of respiratory tract infections (RTI) in the past 6 months requiring treatment with antibiotics (AB). SDS weight height are expressed as mean (SD). Lung function: $FRC_p$: functional residual capacity. $V'max_{FRC}$: maximal expiratory flow at functional residual capacity. RR: respiratory rate. * p< 0.001 below the reference value (SDS = 0). Mean (95% CI) values from analysis of variance are shown.*

*Infant lung function tests*

The median postnatal age at the two respective time points was 30 weeks (range 23-40 weeks, n= 20) and 54 weeks (range 49-72 weeks, n=25). Reliable $V'max_{FRC}$ measurements were obtained in 19 patients at 6 months and 25 patients at 12 months. Reliable $FRC_p$ measurements were obtained in 20 patients at 6 months and 24 patients at 12 months. Results are shown in Figures 2a-b and 3a-b.

All $FRC_p$ values were > 13 mL/kg. Fifty percent of $FRC_p$ measurements were > 26 mL/kg; i.e. in 8/20 patients at 6 months and 14/24 patients at 12 months. Mean SDS $V'max_{FRC}$ was below normal at both time points in both groups. Mean $FRC_p$ and mean SDS $V'max_{FRC}$ did not change significantly over time (Table 2) and did not significantly differ between the groups: mean (95%CI) $FRC_p$ was 25.3 (23.3-27.3) in the observation group vs. 27.3 (25.1-29.6) in the surgical group (p=0.149); mean (95%CI) SDS $V'max_{FRC}$ was -1.45 (-1.84 to -1.06) vs. -1.41 (-1.90 to -0.91) (p=0.892).



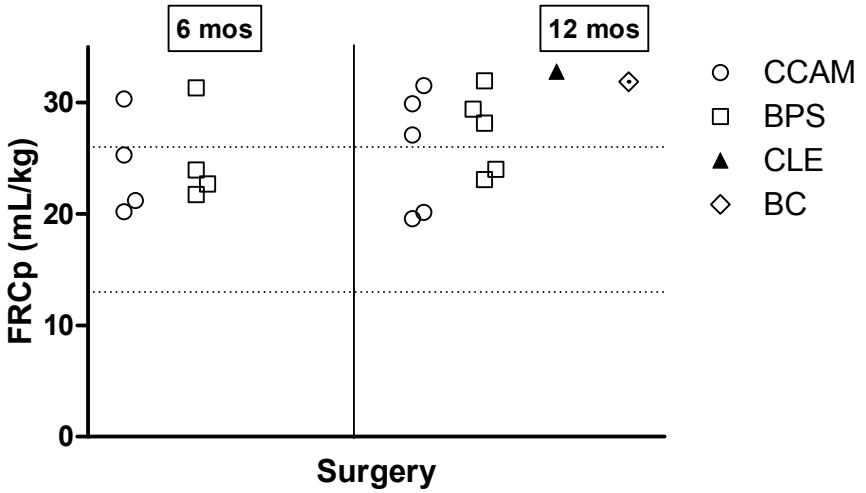
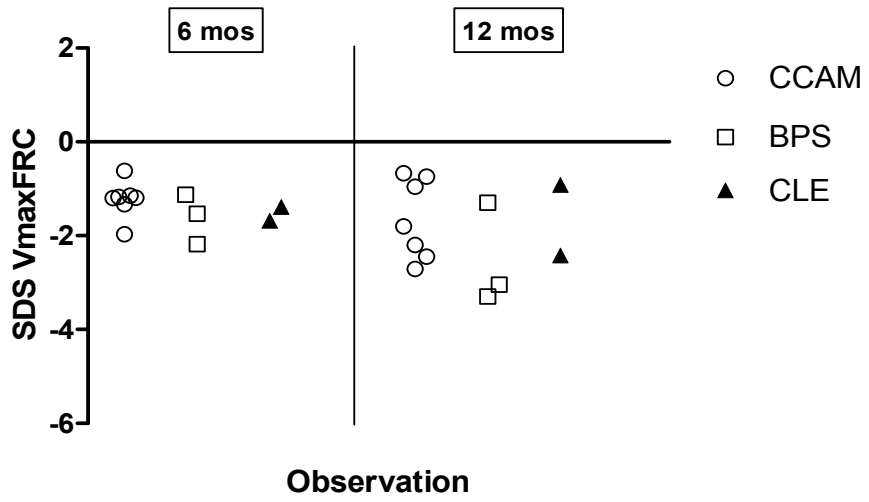




**Figure 2a/2b**: *$FRC_p$ in observation and surgical group. $FRC_p$ (mL/kg) at 6 and 12 months (observation group; Figure 2a, surgical group 2; Figure 2b). The range of normal values (beween 13 and 26 mL/kg) is indicated by dotted horizontal lines. Open circles represent CCAM: congenital cystic adenomatoid malformation, open squares represent BPS: bronchopulmonary sequestration, closed triangles represent CLE: congenital lobar emphysema, open diamonds represent BC: bronchogenic cyst.*



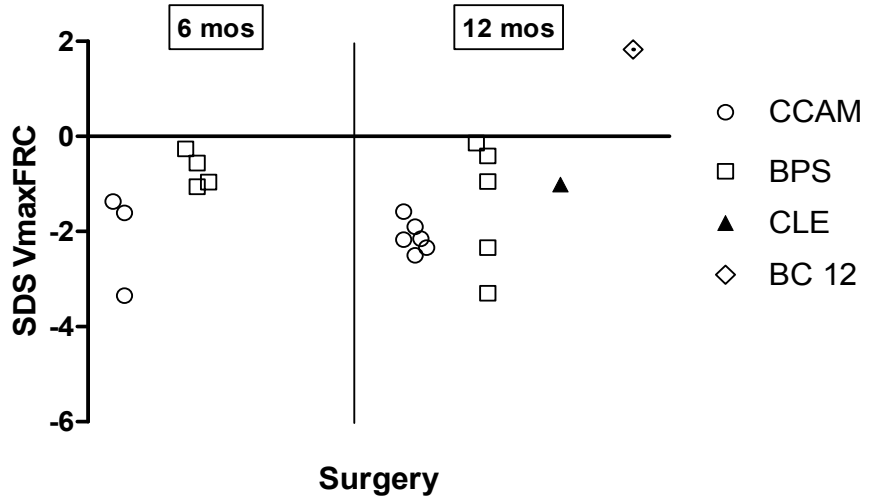




**Figure 3a/3b**: *V'max$_{FRC}$ in observation and surgical group. SDS V'max$_{FRC}$ at 6 and 12 months (observation group; Figure 3a, surgical group: Figure 3b). Open circles represent CCAM: congenital cystic adenomatoid malformation, open squares represent BPS: bronchopulmonary sequestration, closed triangles represent CLE: congenital lobar emphysema, open diamonds represent BC: bronchogenic cyst.*

*Antenatal ultrasound*

In 23/30 patients (77%) the lung lesion had been identified by antenatal ultrasound scan. Serial antenatal ultrasonographic monitoring showed partial regression in 7 cases (47%), complete regression in 2 cases (13%), and progression in 6 cases (40%) in the observation group, and partial regression in 4 cases (50%), stable lesion in 1 case (13%), and progression in 3 cases (37%) in the surgical group.

*Associations between lung function parameters and clinical characteristics*

We found no significant associations between $FRC_p$ and SDS $V'max_{FRC}$ and gestational age, birth weight, log duration of ventilation, log duration of supplemental oxygen and observation or surgery at both time points. $FRC_p$ and SDS $V'max_{FRC}$ did not significantly differ between the observation and surgical group (p=0.796 and p=0.553 respectively).

## Discussion

To our knowledge this is the first longitudinal study that evaluated lung function and respiratory morbidity in the first year of life in infants with a CLL. We found that $FRC_p$ values were in the upper or above normal range without a significant change from 6 to 12 months. SDS $V'max_{FRC}$ was significantly below normal at 6 and 12 months without a significant change from 6 to 12 months. Both $FRC_p$ and $V'max_{FRC}$ did not differ significantly between infants in the observation or surgical group. We found no significant associations between clinical characteristics and lung function parameters.

Several studies on CLL describe antenatal observations and perinatal outcome. Malignant transformation was described but this issue remains controversial [3]. The management of initially asymptomatic lesions deserves attention because complications like pneumonia, pneumothorax, hemoptysis and hemothorax may arise [3]. Some centers recommend early surgical intervention to prevent these complications; this would also stimulate compensatory lung growth [1,18-19]. On the other hand, early resection of pulmonary lesions is associated with higher morbidity and mortality[20]. Observational management may be warranted because asymptomatic lesions may remain asymptomatic or regress spontaneously. In the present study we looked beyond the perinatal period at outcome parameters in the first year of life because these are very important to justify a policy of observation only in asymptomatic patients. Compensatory lung growth has been described in several (animal) studies after extensive resection of lung tissue [21-23]. However, our results do not testify to compensatory lung growth taking place during this first year of life. $FRC_p$ measurements were in the upper normal or above normal range in both groups and did not change significantly from 6 to 12 months. $FRC_p$ is considered to represent lung volume during quiet breathing. We assume that $FRC_p$ is a poor estimate of the volume of functional lung parenchyma in infants with CLL, as we observed before [13]. Enlarged, air filled spaces in the lung parenchyma cause hyperinflation with consequently an increase of $FRC_p$. Also, $FRC_p$ values did not signicantly differ between patients in the observation and surgical groups. We speculate this might be due to hyperinflation of the remaining lung tissue or to the presence of residual abnormal lung tissue. Airway patency as measured by $V'max_{FRC}$ was significantly below normal at both 6 and 12 months, and to the same extent in the observation as in the surgical group. We assume, therefore, that this may be a consequence of the anatomical anomaly itself and not of surgical treatment and/or the

subsequent mechanical ventilation. The hyperinflated cystic, or in some cases more solid, lesions can compress the surrounding structures which can result in a mediastinal shift observable on a chest X-ray or CT scan [19]. In 2009, Keijzer et al. performed pulmonary function tests in 14 CLL children (mean age 10 years) who all had undergone lobectomy. Test results pointed at mild airflow obstruction in all, irrespective of surgery having been performed before or after the 2nd year of life [24]. In our study, respiratory morbidity was not significantly different between infants who underwent resection and those managed by observation. Only a minority of patients needed inhalation medication ( 11% and 3% at 6 and 12 months respectively) or hospital admission for RTI (7% and 3% at 6 and 12 months respectively).

A limitation of our study was the heterogeneity in the types of CLL and the consequently small numbers per type. Four different types of CLL were included with CCAM and BPS as the largest groups. However, to evaluate the differences between infants in the observation and surgical groups, the type of CLL seemed to be of lesser importance as this was not our primary research question. Another potential limitation was that we were not allowed to examine healthy controls, as sedation of healthy infants for research purposes is not permitted in the Netherlands. Therefore, we had to use lung function reference values published by others. We expressed $FRC_p$ values in mL/kg as described previously. The normal range of $FRC_p$, suggested by Hülskamp et al, is 13-26 mL/kg, mean 19.6, SD 3.4 [14]. Regarding $V'max_{FRC}$, we used the references values provided by Hoo and colleagues, which are based on a large representative population of healthy infants and have been used by others using similar equipment as we did [16].

In conclusion, we found no significant differences in respiratory morbidity and infant lung function parameters between the observation and surgical groups. Mild airflow obstruction is common in patients with any type of CLL. We assume that $FRC_p$ does not accurately reflect lung volume and is not suitable to assess possible compensatory lung growth in the first year of life after resection of lung part(s). There may be a role for standardized pre- and postnatal imaging in this respect. For the future we recommend prolonged pulmonary follow-up of lung structure and function.

## References


1. Chen HW, Hsu WM, Lu FL, Chen PC, Jeng SF, Peng SS, Chen CY, Chou HC, Tsao PN, Hsieh WS. Management of congenital cystic adenomatoid malformation and bronchopulmonary sequestration in newborns. Pediatr Neonatol 2010;51(3):172-177.

2. Kumar B, Agrawal LD, Sharma SB. Congenital bronchopulmonary malformations: a single-center experience and a review of literature. Ann Thorac Med 2008;3(4):135-139.

3. Laberge JM, Puligandla P, Flageole H. Asymptomatic congenital lung malformations. Semin Pediatr Surg 2005;14(1):16-33.

4. Witlox RS, Lopriore E, Oepkes D, Walther FJ. Neonatal outcome after prenatal interventions for congenital lung lesions. Early Hum Dev 2011;87(9):611-618.

5. Tran H, Fink MA, Crameri J, Cullinane F. Congenital cystic adenomatoid malformation: monitoring the antenatal and short-term neonatal outcome. Aust N Z J Obstet Gynaecol 2008;48(5):462-466.

6. Olutoye OO, Coleman BG, Hubbard AM, Adzick NS. Prenatal diagnosis and management of congenital lobar emphysema. J Pediatr Surg 2000;35(5):792-795.

7. Hadchouel A, Benachi A, Revillon Y, Rousseau V, Martinovic J, Verkarre V, Dumez Y, Delacourt C. Factors associated with partial and complete regression of fetal lung lesions. Ultrasound Obstet Gynecol 2011;38(1):88-93.

8. Aziz D, Langer JC, Tuuha SE, Ryan G, Ein SH, Kim PC. Perinatally diagnosed asymptomatic congenital cystic adenomatoid malformation: to resect or not? J Pediatr Surg 2004;39(3):329-334; discussion 329-334.

9. Langston C. New concepts in the pathology of congenital lung malformations. Semin Pediatr Surg 2003;12(1):17-37.

10. Gischler SJ, van der Cammen-van Zijp MH, Mazer P, Madern GC, Bax NM, de Jongste JC, van Dijk M, Tibboel D, IJsselstijn H. A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. J Pediatr Surg 2009;44(9):1683-1690.

11. Gischler SJ, Mazer P, Duivenvoorden HJ, van Dijk M, Bax NM, Hazebroek FW, Tibboel D. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 2009;44(7):1382-1389.

12. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47(3):316-323.

13. Spoel M, van den Hout L, Gischler SJ, Hop WC, Reiss I, Tibboel D, de Jongste JC, IJsselstijn H. Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia. Pediatr Crit Care Med 2011.

14. Hulskamp G, Hoo AF, Ljungberg H, Lum S, Pillow JJ, Stocks J. Progressive decline in plethysmographic lung volumes in infants: physiology or technology? Am J Respir Crit Care Med 2003;168(8):1003-1009.

15. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R, Society EATFoSfIRFTERSAT. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. Eur Respir J 2001;17(2):302-312.

16. Hoo AF, Dezateux C, Hanrahan JP, Cole TJ, Tepper RS, Stocks J. Sex-specific prediction equations for Vmax(FRC) in infancy: a multicenter collaborative study. Am J Respir Crit Care Med 2002;165(8):1084-1092.

17. Fitzmaurice GM. Applied Longitudinal Analysis 1st ed John Wiley & Sons 2004.

18. Adzick NS. Management of fetal lung lesions. Clin Perinatol 2003;30(3):481-492.

19. Laje P, Liechty KW. Postnatal management and outcome of prenatally diagnosed lung lesions. Prenat Diagn 2008;28(7):612-618.

20. Marshall KW, Blane CE, Teitelbaum DH, van Leeuwen K. Congenital cystic adenomatoid malformation: impact of prenatal diagnosis and changing strategies in the treatment of the asymptomatic patient. AJR Am J Roentgenol 2000;175(6):1551-1554.

21. Hsia CC, Herazo LF, Fryder-Doffey F, Weibel ER. Compensatory lung growth occurs in adult dogs after right pneumonectomy. J Clin Invest 1994;94(1):405-412.

22. Takeda S, Hsia CC, Wagner E, Ramanathan M, Estrera AS, Weibel ER. Compensatory alveolar growth normalizes gas-exchange function in immature dogs after pneumonectomy. J Appl Physiol 1999;86(4):1301-1310.

23. Yilmaz C, Ravikumar P, Dane DM, Bellotto DJ, Johnson RL, Jr., Hsia CC. Noninvasive quantification of heterogeneous lung growth following extensive lung resection by high-resolution computed tomography. J Appl Physiol 2009;107(5):1569-1578.

24. Keijzer R, Chiu PP, Ratjen F, Langer JC. Pulmonary function after early vs late lobectomy during childhood: a preliminary study. J Pediatr Surg 2009;44(5):893-895.


# Diagnosis-related deterioration of lung function after extra-corporeal membrane oxygenation

Marjolein Spoel*, Roxanne Laas*, Saskia J Gischler, Wim JC Hop, Dick Tibboel, Johan C de Jongste, Hanneke IJsselstijn.

* both authors contributed equally

Eur Respir J. 2012 Apr 10 [Epub ahead of print]

**Abstract**

*Objective:*

To assess lung function longitudinally after neonatal ECMO, and to identify any effects of diagnosis and perinatal characteristics.

*Patients and methods*:

121 neonatal ECMO-treated children (70 meconium aspiration syndrome, 20 congenital diaphragmatic hernia, 31 other diagnoses) performed altogether 191 lung function measurements at 5, 8 and/or 12 years. We assessed dynamic and static lung volumes, reversibility of airway obstruction and diffusion capacity.

*Results:*

Mean SDS $FEV_1$ at 5 years before and after bronchodilation (-0.51 and 0.07) was significantly higher than at 8 (-0.79 and -0.4, $p<0.04$) and 12 years (-1.10 and -0.52, $p<0.003$). Mean SDS for all spirometric parameters before and after bronchodilation were significantly lower in the congenital diaphragmatic hernia group compared the other diagnostic groups (all $p\leq0.025$). A significant volume of trapped air was observed in 86% patients with congenital diaphragmatic hernia, 50% with meconium aspiration syndrome and 58% with other diagnoses. After bronchodilation mean SDS $FEV_1$ and FVC were negatively influenced by duration of ventilation (both $p<0.001$) and duration of ECMO ($p=0.003$ and $p=0.02$ respectively).

*Conclusion:*

Long-term pulmonary sequelae after neonatal ECMO-treatment mainly occur in congenital diaphragmatic hernia patients and tend to deteriorate over time.

## Introduction

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique providing life support when conventional treatment for severe respiratory failure is not enough. Underlying diagnoses include meconium aspiration syndrome, congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension of the newborn (PPHN), sepsis and pneumonia. Ventilator settings are low during ECMO so the lungs can rest. Lung healing is promoted by reducing barotrauma and hyperoxia [1]. The collaborative UK ECMO trial showed improved survival of term infants with severe respiratory failure who were treated with ECMO [2-5]. The long-term pulmonary sequelae of neonatal ECMO have hardly been studied. Cross-sectional studies during or shortly after ECMO all reported reduced lung function, perhaps due to severity of the underlying respiratory disease [6-10]. We report a study in which we longitudinally evaluated residual lung function in neonatal ECMO-treated children now between 5 and 12 years of age, distinguished by underlying diagnosis. Furthermore we related perinatal characteristics to lung function.

### Methods

*Participants*

A prospective longitudinal follow-up study was conducted in children who received veno-arterial (VA) ECMO support within the first week of life between February 1991 and August 2004 at the Intensive Care Unit of the Erasmus MC-Sophia Children's Hospital. The cohort was supplemented with 5 children who received VA ECMO in two other ECMO centers (Nijmegen, The Netherlands: n=4 and Leuven, Belgium: n=1). Inclusion criteria and treatment protocols in those centers were the same as ours. ECMO was initiated in case of reversible severe respiratory failure and an estimated mortality risk of higher than 80% using the entry criteria of Stolar et al [11]. We reported our entry criteria and exclusion criteria earlier [10] and these did not change during the study period. The study was embedded in a structured prospective post-ECMO follow-up program initiated in 2001 that provides for regular assessments of lung function, growth and developmental parameters until 18 years of age [12]. Based on the national consensus on neonatal follow-up and the Dutch Ministry of Health's requirement to provide relevant data, the assessment protocol is the standard of care in the Netherlands following ECMO. As a consequence IRB approval was waived. The parents received information about the study and gave written informed consent for analysis of data collected during routine care. Background data were obtained from the charts, including diagnosis, gestational age, birth weight, age at onset of ECMO, duration of ECMO support, duration of mechanical ventilation, highest mean airway pressure (MAP) and highest oxygenation index (OI) prior to ECMO, total duration of mechanical ventilation (including ECMO), and duration of oxygen dependency.

Following Jobe and Bancalari, we defined chronic lung disease (CLD) as oxygen dependency at day 28 and classified it as as mild, moderate or severe, based on the amount of oxygen needed at day 56 or at discharge, whichever comes first [13].

*Lung function*

Pulmonary function tests were performed at 5, 8, and 12 years if children were in a clinically stable condition.
We obtained flow-volume curves; forced expiratory volume in 1 sec ($FEV_1$), forced vital capacity (FVC), and maximum midexpiratory phase ($FEF_{25-75}$) were determined from the best of three reproducible maneuvers. At 8 and 12 years we also determined total lung volume, functional residual capacity, and residual volume by helium dilution spirometry ($TLC_{spiro}$ , $FRC_{spiro}$ and $RV_{spiro}$, respectively) and by bodyplethysmography ($TLC_{pleth}$, $FRC_{pleth}$ and $RV_{pleth}$), and carbon monoxide diffusion capacity ($D_{LCO}$) corrected for alveolar volume ($K_{CO}$) using a single breath method (all equipment: Jaeger Masterlab, Viasys, Hoechberg, Germany). Equipment and procedures were all according to European Respiratory Society (ERS) criteria [14].

*Respiratory morbidity*

At 5, 8, and 12 years a medical history was taken including the presence of atopic and respiratory symptoms, and prescription of prophylactic antibiotics, bronchodilators and inhaled corticosteroids medication for pulmonary disease.

*Analysis*

The OI was calculated as: [(Mean airway pressure x $FiO_2$)/$PaO_2$] x 100 [11]. $FEV_1$, FVC, $FEV_1$/FVC, and $FEF_{25-75}$ were expressed as SDS calculated from the reference values of Stanojevic [15]. Volume of trapped air is considered significant when the ratio of plethysmographic to spirometric FRC is larger than 1.10 [16]. Post bronchodilator changes of $FEV_1$ were calculated as a simple percentage of the prebronchodilator value: 100x (post-pre)/post. A >11% bronchodilator change in $FEV_1$ was considered significant, reflecting reversible airflow obstruction [17].
The null hypothesis that the SDS of lung function parameters did not differ from those of the reference population (SDS=0) was tested with the one sample Student's T-test.
Mixed-model ANOVA, which allows for missing data, was applied for the longitudinal evaluation of the spirometric SDS at 5, 8 and 12 years and RV/TLC ratios, and the ratio of $FRC_{pleth}$ to $FRC_{spiro}$ and SDS of $D_{LCO}$ at 8 and 12 years [18].
Values for the two largest diagnostic subgroups (CDH and MAS) were analyzed separately. The other subgroups were but small and we grouped these as "other diagnoses". Correlation coefficients between lung function parameters and gestational

age, birth weight and duration of ventilation, supplemental oxygen and ECMO were established with Spearman‘s correlation test.
Possible associations between lung function parameters and CLD were explored by univariate analyses. All results are expressed as mean (SD) or median. P-values of <0.05 were considered significant. Statistical analysis was performed using SPSS 17.0.

**Results**

238 children received ECMO support within the first week of life between February 1991 and August 2004 in the Erasmus MC - Sophia Children’s Hospital; 166 survived (70%) (Figure 1). Twenty children could not perform reproducible lung function tests. Five children could not be traced, 4 were followed in another ECMO center, parents of 15 children gave no consent, and 6 children had not been tested for logistic reasons. Hence, the study population included 121 ECMO survivors (including the aforementioned 5 from other centers) who altogether performed 191 pulmonary function tests between February 2002 and March 2011 in Erasmus MC Rotterdam. Seventy children (58%) had been diagnosed with MAS; 20 (17%) with CDH. Smaller subgroups received ECMO for: persistent pulmonary hypertension of the newborn (PPHN; n=17), sepsis (n=8), pneumonia (n=4) and cardio respiratory failure (n=2). The characteristics at birth are shown in Table 1. The tested children did not differ from the non-tested children in gestational age, birth weight, underlying diagnosis, highest MAP, highest OI, age at onset of ECMO or duration of ECMO (data not shown). Atopic symptoms were reported in 7 (9.7%), 9 (11.7%) and 9 (21.4%) children at 5, 8 and 12 years respectively. One child at age 5 (1.4%) and 1 child at age 8 years (1.3%) took antibiotic prophylaxis to prevent recurrent airway infections. At 5 years, 10 children (13.9%) used bronchodilators (4 with additional inhaled steroids). At 8 years, 8 children (10.4%) used bronchodilators (5 with additional inhaled steroids). At 12 years, 4 children (9.8%) used bronchodilators (2 with additional inhaled steroids).

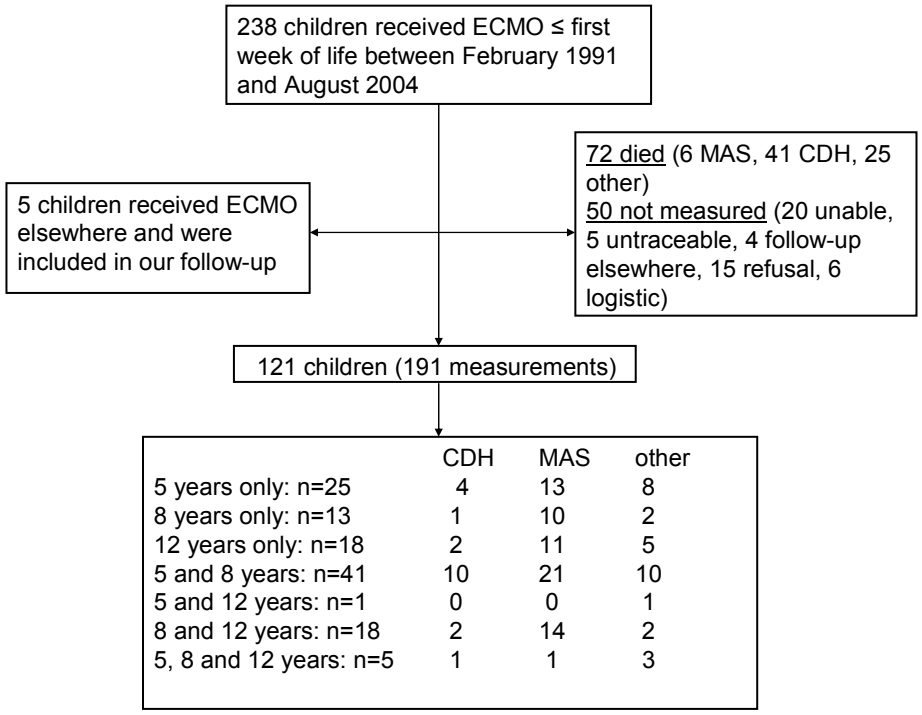



**Figure 1:** *Flowchart: children included in follow-up program.*

| | All participants | MAS | CDH | Other |
|---|---|---|---|---|
| N (male) | 121 (65) | 70 (33) | 20 (15) | 31 (17) |
| Gestational age (wk) | 40 (34.7-43.3) | 40.6 (36.6-43.3) | 39 (36-40.9) | 38.5 (34.7-42.3) |
| Birth weight (g) | 3380 (2160-4980) | 3400 (2300-4980) | 3500 (2160-3810) | 3280 (2375-4880) |
| Age at onset ECMO (hours) | 25 (5-168) | 23 (6-73) | 16 (5-168) | 40 (15-152) |
| Duration of ECMO (hours) | 132 (24-369) | 126 (24-345) | 192 (68-369) | 122 (53-288) |
| Duration of ventilation (days) | 10 (1-70) | 10 (1-34) | 28 (11-70) | 9.5 (2-30) |
| Highest MAP prior to ECMO (cm H2O) | 20 (12-45) | 20 (14-30) | 19 (12-45) | 19 (13-26) |
| Highest OI prior to ECMO | 43 (15-143) | 44 (27-143) | 44 (15-130) | 40 (21-106) |
| NO treated newborns, n (%) | 80 (66) | 42 (60) | 13 (65) | 25 (81) |
| CLD, n (%) | 22 (18.2) | 12 (17.2) | 10 (50.0) | - |
| Mild CLD | 11 (9.1) | 10 (14.3) | 1 (5.0) | - |
| Moderate CLD | 1 (0.8) | - | 1 (5.0) | - |
| Severe CLD | 10 (8.3) | 2 (2.9) | 8 (40.0) | - |

**Table 1:** *Clinical perinatal characteristics of neonatal ECMO-treated patients. Data are expressed as median (range) unless otherwise indicated. Shown are the total group and the subgroups of infants. ECMO: Extracorporeal membrane oxygenation. MAS: meconium aspiration syndrome. CDH: congenital diaphragmatic hernia. MAP: mean airway pressure. OI: oxygenation index. NO= nitric oxide therapy. CLD: chronic lung disease, classified according to Jobe and Bancalari* [13]

## Lung function

*Spirometry*

The results of spirometry after bronchodilation (BD) are shown in Table 2. Significant differences from the norm (SDS=0) are indicated in the table. Significant reversibility of $FEV_1$ was observed in 34 measurements (18%). The median change in $FEV_1$ after BD was 5% (IQR 1 to 10%).

Mean SDS $FEV_1$ before and after BD significantly changed within time: at 5 years it was significantly higher than at 8 years (p=0.039 before and p=0.001 after BD) and at 12 years (p=0.003 before and p=0.001 after BD). It did not significantly change between 8 and 12 years.

Mean SDS FVC before and after BD did not change significantly within time (p-values not shown).

Mean SDS $FEV_1$/FVC at 5 years was higher than at 8 and 12 years, both before and after BD (all p-values < 0.001). After BD mean SDS $FEV_1$/FVC did not change significantly between 8 and 12 years; before BD it was higher at 8 years (p=0.033).

Mean SDS $FEF_{25-75}$ after BD was higher at 5 years than at 8 years (p=0.02); it did not change significantly before BD or from 8 to 12 years before and after BD.

Figures 2 and 3 show the SDS $FEV_1$ at 5, 8, and 12 years for the three subgroups and the whole group, before and after BD. Initial diagnosis was a significant determinant in the mixed model: all spirometric parameters before BD in the CDH group were significantly lower than those in the other two subgroups. The parameters did not significantly differ between the MAS group and the other diagnoses group (data not shown). Individual measurements of $FEV_1$ before and after BD in CDH patients are shown in Figures 4 and 5.

We analysed spirometric values in children with repeated measurements separately. After bronchodilation, SDS $FEV_1$ was significantly higher at 5 year compared with 8 and 12 years (p=0.002 and p=0.005 respectively). $FEV_1$/FVC was significantly higher at 5 years compared with 8 and 12 years (both p<0.001). $FEF_{25-75}$ was significantly higher at 5 years compared with 8 years (p=0.028), there was no significant difference with 12 years. This is similar to the analysis of the whole group, including children with only one measurement. For all lung function parameters, differences between the different subgroups were independent of age.

| | 5 yrs (n=72) | 8 yrs (n=77) | 12 yrs (n=42) |
|---|---|---|---|
| SDS $FEV_1$ | | | |
| All participants | 0.07 (0.14) | -0.40 (0.15)† | -0.52 (0.16)† |
| MAS | 0.49 (0.17)‡ | 0.12 (0.14) | 0.01 (0.23) |
| CDH | -0.71 (0.40) | -2.27 (0.36)* | -2.73 (0.61)† |
| Other | 0.01 (0.23) | 0.08 (0.31) | -0.49 (0.25) |
| SDS FVC | | | |
| All participants | -0.08 (0.15) | -0.22 (0.13) | -0.29 (0.16) |
| MAS | 0.40 (0.18)† | 0.01 (0.15) | 0.12 (0.27) |
| CDH | -0.69 (0.43) | -1.48 (0.35)* | -1.28 (0.98) |
| Other | -0.01 (0.29) | 0.19 (0.25) | -0.17 (0.33) |
| SDS $FEV_1$/FVC | | | |
| All participants | 0.32 (0.15) | -0.53 (0.12)* | -0.63 (0.15)* |
| MAS | 0.22 (0.19) | -0.19 (0.11) | -0.32 (0.19) |
| CDH | 0.11 (0.35) | -1.47 (0.39)‡ | -2.16 (0.30)‡ |
| Other | 0.21 (0.35) | -0.37 (0.28) | -0.61 (0.34) |
| SDS $FEF_{25-75}$ | | | |
| All participants | -0.56 (0.19)‡ | -1.02 (0.18)* | -0.97 (0.20)* |
| MAS | -0.12 (0.25) | -0.34 (0.14)† | -0.67 (0.21)‡ |
| CDH | -1.76 (0.42) ‡ | -3.07 (0.46)* | -3.28 (0.54)‡ |
| Other | -0.82 (0.38) | -0.71 (0.42) | -0.93 (0.30)† |

**Table 2:** *Longitudinal results of spirometry after neonatal ECMO, after bronchodilation. ECMO: extracorporeal membrane oxygenation. CDH: congenital diaphragmatic hernia. Mean SDS (± SE) are shown for FEV1, FVC, FEV1/FVC, and FEF25-75. Number of patients studied in each group: MAS: 35, 46 and 26 at 5, 8 and 12 years, CDH: 15, 14 and 5 at 5, 8 and 12 years. other: 22, 17 and 11 at 5, 8 and 12 years.SDS significantly below normal (SDS=0; one-sample Student T-test): †: $p < 0.05$; ‡: $p < 0.01$;*: $p \leq 0.001$*

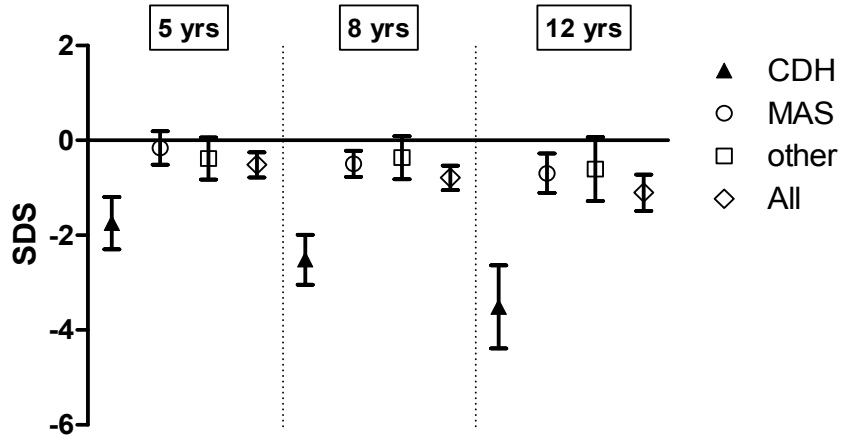



**Figure 2.** *SDS $FEV_1$ (mean, 95%CI) before bronchodilation at 5, 8 and 12 years for the different subgroups. Triangles represent CDH patients (n = 14, 13 and 5 at 5, 8, and 12 years respectively); circles represent children with MAS (n = 34, 46, and 24 at 5, 8, and 12 years respectively), squares represent children who underwent neonatal ECMO for other diagnoses (n = 22, 16 and 9 at 5, 8, and 12 years respectively). A summary of all cases is shown as diamond.*

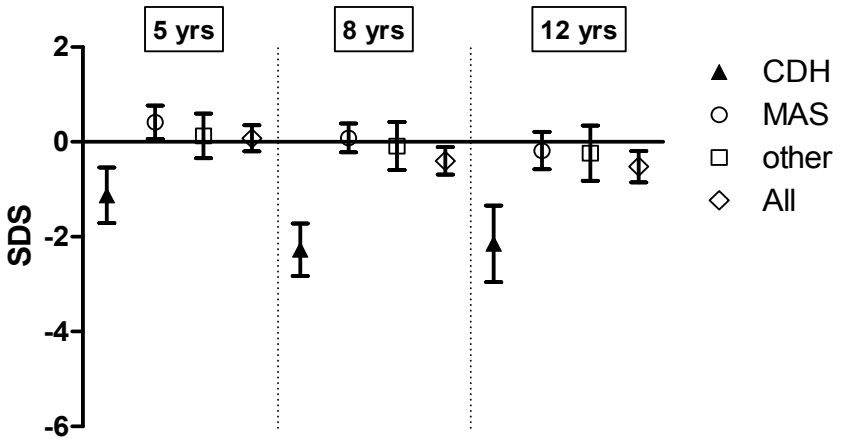



**Figure 3.** *SDS $FEV_1$ (mean, 95%CI) after bronchodilation at 5, 8 and 12 years for the different subgroups. Triangles represent CDH patients (n= 10, 14 and 5 at 5, 8, and 12 years respectively); circles represent children with MAS (n=26, 46 and 23 at 5, 8, and 12 years respectively), squares represent children who underwent neonatal ECMO for other diagnoses (n= 16, 15 and 11 at 5, 8, and 12 years respectively). A summary of all cases is shown as diamond.*

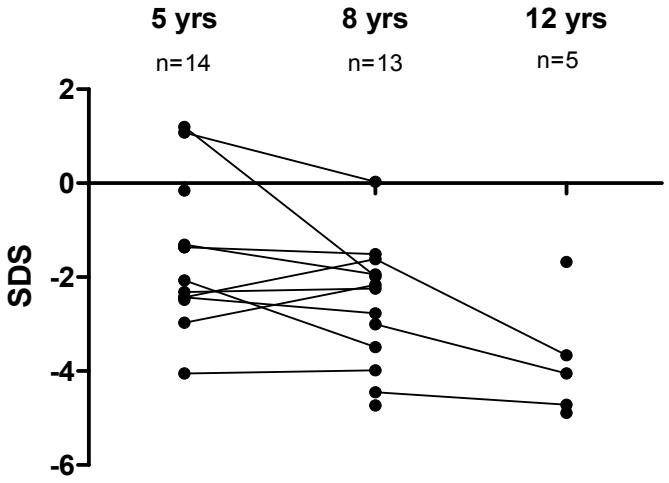



**Figure 4.** *Change of SDS $FEV_1$ before bronchodilation in CDH patients from 5 to 12 years. Each dot respresents a measurement of an individual patient.*

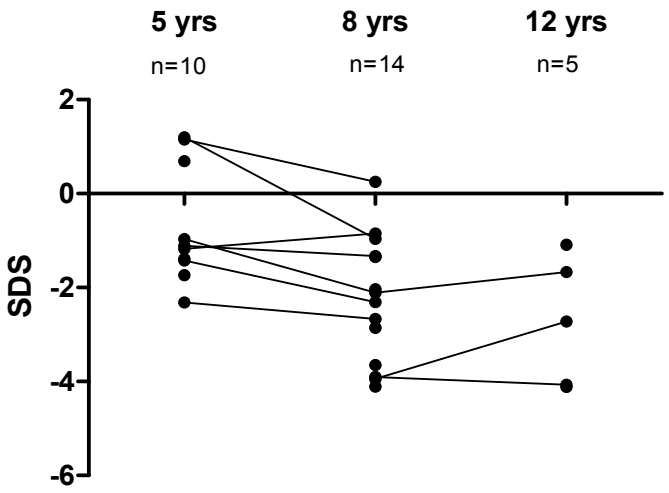



**Figure 5.** *Change of SDS $FEV_1$ after bronchodilation in CDH patients from 5 to 12 years. Each dot respresents a measurement of an individual patient.*

*Helium dilution spirometry, bodyplethysmography, and diffusion capacity at 8 and 12 years.*

The mean (SD) $RV\%TLC_{spiro}$ at 8 years was 22.1 (8.3); at 12 years it was 21.1 (7.0). The mean (SD) $RV\%TLC_{pleth}$ at 8 years was 29.4 (8.2); at 12 years it was 26.5 (6.8) (Table 3). The mean $FRC_{pleth/spiro}$ was 1.22 (0.22) at 8 years and 1.09 (0.11) at 12 years. A significant volume trapped air (defined as $FRC_{pleth/spiro}$>1.10)[137] was observed in 32 (64%) and 13 (46%) of children at 8 and 12 years, respectively. This concerned 12/14 measurements in the CDH group (86%), 26/52 in the MAS group (50%), and 7/12 in the other diagnoses group (58%). Total diffusion capacity did not differ from the norm population at 8 and 12 years (p=0.286 and p=0.392 respectively). However, after correction for alveolar volume the diffusion capacity was significantly below the norm at the age of 8 (p<0.001) but not at 12 years (p=0.172).

| | 8 years | n | 12 years | n |
|---|---|---|---|---|
| RV%TLCspiro | 22.1 (8.3) | 56 | 21.1 (7.0) | 30 |
| RV%TLCpleth | 29.4 (8.2) | 40 | 26.5 (6.8) | 25 |
| $FRC_{pleth/spiro}$ | 1.22 (0.22) | 50 | 1.09 (0.11) | 28 |
| VTA, n (%) | 32 (64) | | 13 (46) | |
| DLCOc (SDS) | 0.32 (1.6) | 29 | -0.28 (1.5) | 22 |
| KCOc (SDS) | -0.95 (1.1)* | 22 | -0.41 (1.2) | 18 |

**Table 3.** *Static lung volumes and diffusion capacity at 8 and 12 years. $DL_{CO}c$: diffusion capacity corrected for Hb. $K_{CO}c$: diffusion capacity corrected for alveolar volume and Hb.*
*$RV\%TLC_{spiro}$, $RV\%TLC_{pleth}$: mean (SD) %. $FRC_{pleth/spiro}$, Diffusion capacity: mean (SD).*
*VTA: volume trapped air; number (%) of patients with significant VTA (defined as $FRC_{pleth/spiro}$ > 1.10) is shown.*
**: significantly below normal (SDS-score = 0) (p<0.001 at 8 years).*

### Other determinants of lung function parameters

Beside the effects of age and initial diagnosis we evaluated the influence of other determinants on spirometric parameters. Before BD, mean SDS $FEV_1$ and SDS FVC were negatively influenced by duration of ventilation (both parameters $p<0.001$), duration of ECMO support ($p\leq0.001$ for both parameters), and the presence of CLD (both $p\leq0.001$). Both parameters were positively correlated to birth weight (both $p\leq0.001$); SDS $FEV_1$ only was positively correlated to gestational age ($p=0.001$). After BD, mean SDS $FEV_1$, SDS FVC and SDS $FEF_{25-75}$ were negatively influenced by duration of ventilation (all parameters $p<0.001$), duration of ECMO support (all $p<0.03$), and the presence of CLD (all $p\leq0.001$). Mean SDS $FEV_1$, SDS FVC, SDS $FEV_1$/FVC and SDS $FEF_{25-75}$ were positively influenced by birth weight (all $p<0.05$); mean SDS $FEV_1$ and SDS $FEF_{25-75}$ were also positively influenced by gestational age (both $p<0.01$). In univariate analysis doubling of the logarithm ventilation time resulted in a mean decrease of -0.415 SDS $FEV_1$ at 5 years, -0.782 SDS $FEV_1$ at 8 years, and -1.35 SDS $FEV_1$ at 12 years (all $p\leq0.001$). $RV\%TLC_{pleth}$ and $FRC_{pleth/spiro}$ were positively correlated to duration of ventilation ($p<0.001$), duration of ECMO support ($p<0.02$), and birth weight ($p<0.04$). Highest MAP and OI before ECMO did not correlate with any of the lung function parameters.

## Discussion

Residual lung function of the studied 121 children – in terms of mean SDS $FEV_1$ and SDS $FEF_{25-75}$ before BD – had significantly decreased between 5 and 12 years of age. CDH was associated with significantly lower spirometric values and higher frequency of a significant volume of trapped air compared to other diagnoses. Mean SDS $FEV_1$,FVC, and $FEF_{25-75}$ were negatively influenced by duration of ventilation, and the presence of CLD.

Long-term pulmonary function abnormalities such as hyperinflation and airway obstruction are well recognized after neonatal respiratory failure secondary to lung injury from MAS, CDH and neonatal pneumonia [10,19-20]. Treatment modalities such as supplemental oxygen and mechanical ventilation contribute to the pathogenesis of CLD [21]. Avoiding continued exposure to high inspired oxygen concentration and barotrauma during the course of ECMO has reduced mortality and encouraged lung healing and recovery. To our knowledge this is the first longitudinal study on the impact of neonatal ECMO on lung function in children between 5 and 12 years of age. Beardsmore et al. in 2000 cross-sectionally studied 51 ECMO patients at age 1 year and found few differences in lung function compared with conventionally ventilated controls. This provided reassurance that in addition to decreased mortality respiratory function following ECMO was no worse [6]. In addition, another study by Beardsmore et al. showed

that when children were categorized according to the underlying reason for ECMO, those treated for RDS and those treated beyond the first 3 weeks for bronchiolitis or pneumonia had poorer pulmonary function 12 months later. However, only few CDH patients were included in this studied population of 106 subjects [22]. Hofhuis and colleagues found below-average but normal lung volumes and stable forced expiratory flows during the first year of life in 64 infants following ECMO. At 12 months, only the CDH patients showed signs of hyperinflation with plethysmographic FRC significantly above normal [10]. In an earlier study we found significantly impaired expiratory flows and increased FRC levels in 12 ECMO and 31 non-ECMO treated CDH patients during the first year of life. The ECMO-treated CDH patients had significantly higher FRC levels, thus reflecting more hyperinflation [20]. In a cross-sectional study in 54 eight-year-old patients after severe neonatal respiratory failure, Majaesic and coworkers found a poorer pulmonary outcome in the subgroup of ECMO treated CDH patients [23]. In 2004 Hamutcu and coworkers cross-sectionally studied 50 children after neonatal ECMO treatment. At a mean age of 11 years they had significantly lower $FEV_1$ and $FEF_{25-75}$ and hyperinflation with higher RV compared to healthy matched controls. Single breath diffusion capacity for carbon monoxide was within the normal range [19]. When children with congenital heart disease (8%) and CDH (12%) were excluded from analysis, no significant differences in lung function were observed. Boykin and coworkers reported signs of air trapping and mild lower airway obstruction in 17 ECMO-treated MAS patients [7].

The strength of the present study is the longitudinal aspect, as most other studies were performed cross-sectionally. A potential weakness is the lack of appropriate reference values for longitudinal spirometric measurements and the lack of a healthy control group in our study. Up-to-date reference data are needed to reflect evolving measurement techniques and equipment and changes in population characteristics. In 2008, Quanjer and co-workers compared 5 commonly used reference equation sets to serial measurements and found that Stanojevic's equations performed best and are suitable for longitudinal data analysis as they cover a wide age range and account for a gradual transition from childhood into adulthood. In another study they compared 30 spirometry datasets and concluded that the use of local controls to validate reference equations will rarely be practical due to the numbers required and that the use of reference equations derived from large or collated datasets is recommended [24]. Therefore we computed SDS of spirometric values using those equations, which distinguish between the effects of disease and those of growth and development [25]. As treatment protocols improve over time, results from earlier studies may not just be applicable to patients treated with ECMO today. This is, albeit to a lower extent, also a limitation of our study. Not all patients were tested at all 3 time points, which created an unfavorable but unavoidable heterogeneity in the age distribution. Our ventilation strategies and ECMO treatment protocols have indeed been adjusted over the past decade, resulting in better survival in CDH patients [26]. Recent protocols based on meta-analysis of retrospective studies

provide guidelines for the use of ECMO in CDH patients [27]. These could well lead to better long-term pulmonary outcome and lung function.
In our study, the SDS for all spirometric parameters in the CDH group were significantly lower than those in the MAS or other diagnoses patients. This finding is in line with findings from other studies. While infants with MAS have normal lung development, CDH is associated with lung hypoplasia and PPHN. The severity of lung hypoplasia and PPHN in CDH patients covers a wide range. ECMO-treated CDH patients are regarded as the most severe cases [20,26]. Their improved survival might be counterbalanced by increased morbidity. Maldevelopment of the alveoli and pulmonary vessels with disturbed lung growth may be responsible for the deterioration of lung function. Also, prolonged ventilatory support and supplemental oxygen after ECMO treatment may result in CLD. Recurrent respiratory tract infections can further compromise lung function over time.
Our group has recently reported a significant decline of exercise capacity in a cohort of ECMO survivors which overlaps with the population described in the present study. [28]. Interestingly, this decline was irrespective of the underlying diagnosis and we were unable to show an association between maximal exercise capacity and SDS of $FEV_1$ and $FEV_1$/FVC. For all patients, we advocate an active lifestyle and healthy eating pattern as sports participation interacts positively and BMI negatively with exercise capacity [29].
Adequate treatment of recurrent respiratory tract infections, close monitoring and treatment of asthma could perhaps halt deterioration of exercise capacity and lung function, especially in CDH patients. The use of prophylactic bronchodilators, e.g. during exercise, should not be advised routinely.

From our results it can be concluded that lung function is compromised after neonatal ECMO treatment and seems to deteriorate over time in CDH patients only. Airway patency in patients with all other diagnoses was within the normal range and remained stable over time. Therefore we assume that the underlying condition and not ECMO itself is responsible for the compromised lung function post-ECMO. ECMO may even reduce the harmful effects of high pressure ventilation and high doses of oxygen. Although the severity of pulmonary hypertension diminishes during ECMO and later in CDH patients, sequelae of abnormal lung development will still be present as reflected by compromised lung function in this patient group.

We recommend prolonged follow-up, especially of patients with CDH, to further elucidate the increased respiratory morbidity that occurs with better survival and changing treatment protocols.

## References


1. Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. Cochrane Database Syst Rev 2008(3):CD001340.

2. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. UK Collaborative ECMO Trail Group. Lancet 1996;348(9020):75-82.

3. The collaborative UK ECMO (Extracorporeal Membrane Oxygenation) trial: follow-up to 1 year of age. Pediatrics 1998;101(4):E1.

4. Bennett CC, Johnson A, Field DJ, Elbourne D, Group UKCET. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. Lancet 2001;357(9262):1094-1096.

5. McNally H, Bennett CC, Elbourne D, Field DJ, Group UKCET. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. Pediatrics 2006;117(5):e845-854.

6. Beardsmore C, Dundas I, Poole K, Enock K, Stocks J. Respiratory function in survivors of the United Kingdom Extracorporeal Membrane Oxygenation Trial. Am J Respir Crit Care Med 2000;161(4 Pt 1):1129-1135.

7. Boykin AR, Quivers ES, Wagenhoffer KL, Sable CA, Chaney HR, Glass P, Bahrami KR, Short BL. Cardiopulmonary outcome of neonatal extracorporeal membrane oxygenation at ages 10-15 years. Crit Care Med 2003;31(9):2380-2384.

8. Garg M, Kurzner SI, Bautista DB, Lew CD, Ramos AD, Platzker AC, Keens TG. Pulmonary sequelae at six months following extracorporeal membrane oxygenation. Chest 1992;101(4):1086-1090.

9. Greenspan JS, Antunes MJ, Holt WJ, McElwee D, Cullen JA, Spitzer AR. Pulmonary sequelae in infants treated with extracorporeal membrane oxygenation. Pediatr Pulmonol 1997;23(1):31-38.

10. Hofhuis W, Hanekamp MN, IJsselstijn H, Nieuwhof EM, Hop WC, Tibboel D, de Jongste JC, Merkus PJ. Prospective longitudinal evaluation of lung function during the first year of life after extracorporeal membrane oxygenation. Pediatr Crit Care Med 2011;12(2):159-164.

11. Stolar CJ, Snedecor SM, Bartlett RH. Extracorporeal membrane oxygenation and neonatal respiratory failure: experience from the extracorporeal life support organization. J Pediatr Surg 1991;26(5):563-571.

12. Hanekamp MN, Mazer P, van der Cammen-van Zijp MH, van Kessel-Feddema BJ, Nijhuis-van der Sanden MW, Knuijt S, Zegers-Verstraeten JL, Gischler SJ, Tibboel D, Kollee LA. Follow-up of newborns treated with extracorporeal membrane oxygenation: a nationwide evaluation at 5 years of age. Crit Care 2006;10(5):R127.

13. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723-1729.

14. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.

15. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008;177(3):253-260.

16. Eber E ZM. Pediatric pulmonary function testing. Prog Respir Res, Basel, Karger 2005;33:94-102.

17. Casan P, Roca J, Sanchis J. Spirometric response to a bronchodilator. Reference values for healthy children and adolescents. Bull Eur Physiopathol Respir 1983;19(6):567-569.

18. Fitzmaurice G LN, Ware J. Applied Longintudinal Analysis. 1st ed John Wiley & Sons 2004.

19. Hamutcu R, Nield TA, Garg M, Keens TG, Platzker AC. Long-term pulmonary sequelae in children who were treated with extracorporeal membrane oxygenation for neonatal respiratory failure. Pediatrics 2004;114(5):1292-1296.

20. Spoel M, van den Hout L, Gischler SJ, Hop WC, Reiss I, Tibboel D, de Jongste JC, IJsselstijn H. Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia. Pediatr Crit Care Med 2011.

21. Stocks J, Godfrey S. The role of artificial ventilation, oxygen, and CPAP in the pathogenesis of lung damage in neonates: assessment by serial measurements of lung function. Pediatrics 1976;57(3):352-362.

22. Beardsmore CS, Westaway J, Killer H, Firmin RK, Pandya H. How does the changing profile of infants who are referred for extracorporeal membrane oxygenation affect their overall respiratory outcome? Pediatrics 2007;120(4):e762-768.

23. Majaesic CM, Jones R, Dinu IA, Montgomery MD, Sauve RS, Robertson CM. Clinical correlations and pulmonary function at 8 years of age after severe neonatal respiratory failure. Pediatr Pulmonol 2007;42(9):829-837.

24. Quanjer PH, Stocks J, Cole TJ, Hall GL, Stanojevic S, Global Lungs I. Influence of secular trends and sample size on reference equations for lung function tests. Eur Respir J 2011;37(3):658-664.

25. Quanjer PH, Borsboom GJ, Kivastik J, Merkus PJ, Hankinson JL, Houthuijs D, Brunekreef B, Ihorst G, Kuhr J. Cross-sectional and longitudinal spirometry in children and adolescents: interpretative strategies. Am J Respir Crit Care Med 2008;178(12):1262-1270.

26. van den Hout L, Schaible T, Cohen-Overbeek TE, Hop W, Siemer J, van de Ven K, Wessel L, Tibboel D, Reiss I. Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. Fetal Diagn Ther 2011;29(1):55-63.

27. Reiss I, Schaible T, van den Hout L, Capolupo I, Allegaert K, van Heijst A, Gorett Silva M, Greenough A, Tibboel D, Consortium CE. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. Neonatology 2010;98(4):354-364.

28. van der Cammen-van Zijp MH, Gischler SJ, Hop WC, de Jongste JC, Tibboel D, IJsselstijn H. Deterioration of exercise capacity after neonatal extracorporeal membrane oxygenation. Eur Respir J 2011;38(5):1098-1104.

29. van der Cammen-van Zijp MH, van den Berg-Emons RJ, Willemsen SP, Stam HJ, Tibboel D, H IJ. Exercise capacity in Dutch children: new reference values for the Bruce treadmill protocol. Scand J Med Sci Sports 2010;20(1):e130-136.


# Lung function in young adults with congenital diaphragmatic hernia; a longitudinal evaluation

Marjolein Spoel, Monique HM van der Cammen-van Zijp, Wim CJ Hop, Dick Tibboel, Johan C de Jongste, Hanneke IJsselstijn.

Pediatr Pulmonol. 2012 Mar 26. doi: 10.1002/ppul.22557. [Epub ahead of print]

## Abstract

*Background*

Survival rates of patients with congenital diaphragmatic hernia (CDH) have improved to up to 80%. Little is known about long-term consequences of the disease and its treatment. We evaluated lung function and respiratory symptoms longitudinally in a previously studied cohort of CDH patients and age-matched non-CDH patients who underwent similar neonatal intensive care treatment.

*Study Design*

We tested 27 young adults (mean (SD) age: 26.8 years (2.9)) with CDH and 30 non-CDH patients. Dynamic and static lung volumes, midexpiratory flows and diffusion capacity were expressed as mean (SD) standard deviation scores (SDS). Prevalence of respiratory symptoms was evaluated with the European Community Respiratory Health Survey.

*Results*

All data are expressed as mean (SD). $FEF_{25-75}$ in CDH patients had slightly deteriorated since childhood (CDH: -0.7 (1.4) vs. -1.6 (1.5), p<0.001; non-CDH patients: 0.2 (1.4) vs. -0.3 (1.6), p=0.038, ns). Diffusion capacity decreased in both groups (CDH: $DL_{CO}c$ 0.2 (1.1) vs. -1.5 (1.1), p <0.001; non-CDH: $DL_{CO}c$ 0.1 (0.4) vs. -1.1 (1.1), p<0.001). Lung volumes were normal in both groups. The prevalence of asthma was higher than in the normal population (27.6% in CDH patients and 30% in non-CDH patients, p<0.001).

*Conclusions*

Airflow obstruction and diffusion capacity deteriorated mildly from childhood into adulthood in survivors of congenital diaphragmatic hernia. The improved survival of patients with more severe forms of diaphragmatic hernia calls for long-term follow-up of lung function.

## Introduction

Congenital diaphragmatic hernia (CDH) combines a developmental defect of the diaphragm with pulmonary hypoplasia, abnormal pulmonary vascular development and vaso-reactivity [1]. Postnatal survival rates are now approaching 80% [2].The focus of research has therefore shifted from mortality to morbidity [3]. Neonates with CDH are at risk of developing bronchopulmonary dysplasia (BPD) due to ventilator induced injury and high concentrations of oxygen [4-5]. Respiratory morbidity through different stages of life of CDH patients was reported in several cross-sectional studies [6-12]. In 1997 we published data on lung function in 7 to18-year-old CDH patients and age-matched controls without CDH and lung hypoplasia who underwent similar neonatal treatment. We found mild airway obstruction in both groups and more peripheral airway obstruction in CDH than in non-CDH patients. Both groups had normal lung volume and a high prevalence of increased airway responsiveness [9]. To our knowledge, no study has evaluated lung function longitudinally from childhood to adulthood in CDH. The primary objective of this study was to evaluate longitudinal development of pulmonary function and respiratory symptoms in the above mentioned cohort of CDH patients and non-CDH patients with normal lung development who as neonates underwent similar intensive care treatment The secondary objective was to compare lung function and respiratory symptoms at adult age between groups as this would allow for estimating if and to what extent neonatal intensive care treatment contributes to the sequelae of CDH.

## Methods

*Participants*

The original study by IJsselstijn et al [9] concerned 40 children at a mean (SD) age of 11.8 (2.6) years who as neonates had been operated on for CDH in the Erasmus MC-Sophia Children's Hospital, could perform lung function tests reproducibly, and had been clinically stable for at least 3 weeks prior to the lung function tests. The study excluded children who had undergone previous thoracic surgery for other reasons than CDH, suffered from non-CDH lung hypoplasia or other lung anomalies, or were unable to perform reproducible lung function tests. Setting out to include 2 controls for each CDH patient, IJsselstijn et al. were able to recruit 65 non-CDH patients from the 3 academic centres in question in the Netherlands with the best possible match for age at follow-up, gestational age, birth weight, duration of mechanical ventilation, supplemental oxygen and sex. In the present study we contacted all 40 participants (CDH) and their individually matched controls (non-CDH) in the original study. Exclusion criterion for the present study was severe neurological co-morbidity preventing lung function measurement. The Medical Ethical Review Board Erasmus MC approved the study (MEC-2007-150) and all patients provided written informed consent.

*Medical assessment*

Medication for pulmonary disease was discontinued 24 hours prior to the tests. Height (cm) and weight (kg) were measured. Body mass index (BMI) was calculated and the Dutch Growth Analyser, version 3.0 (Dutch Growth Foundation, Rotterdam, the Netherlands) served to calculate standard deviation score (SDS) for height on the basis of Dutch reference values [13]. This was done to correct for sex-specific differences. We classified smoking habits and calculated "pack years": ((number of cigarettes smoked per day x number of years smoked) / 20). Presence of scoliosis was determined by a standardized physical examination.

*Lung function measurement*

Spirometry was performed with a dry rolling seal spirometer (Jaeger, Wurzburg, Germany). To assess potential airway obstruction, spirometry was repeated after inhalation of 12 mcg of formoterol. Forced expiratory volume in 1 sec ($FEV_1$) and $FEV_1$/ forced vital capacity (FVC) and forced expiratory flows between 25% and 75% of vital capacity ($FEF_{25-75}$) were expressed as SDS [14]. To compare the lung function parameters longitudinally and to correct for sex, we calculated SDS from the absolute data using the reference equations according to Stanojevic [15]. Total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC) were determined by whole body plethysmography (Masterscreen PFT, Carefusion, San Diego, USA) and expressed as SDS [16].
Diffusion capacity for carbon monoxide ($DL_{CO}$) was measured by the single-breath method using a multigas analyzer (Jaeger, Wurzburg, Germany). Reference values for $DL_{CO}$ and $DL_{CO}$ corrected for alveolar volume ($K_{CO,}$) were based on the modified reference equations by Stam [17], (extended dataset, as recommended by the manufacturer). $DL_{CO}$ and $K_{CO}$ were corrected for hemoglobin concentration ($DL_{CO}c$ and $K_{CO}c$). The fraction of exhaled NO ($FE_{NO}$) was measured online using the NIOX analyzer (Aerocrine, Solna, Sweden) according to previously described guidelines [18]. Equipment and procedures all fulfilled ERS criteria [19].

*Questionnaires*

The European Community Respiratory Health Survey (ECRHS) questionnaire was administered to assess the prevalence of respiratory symptoms and asthma [20]. A validated screening questionnaire was used to assess the prevalence of atopic symptoms [21].

*Data analysis*

Differences in perinatal characteristics between participants and non-participants were established with Mann Whitney U tests. One-sample t-tests were used to test whether mean SDS height and lung function parameters differed from normal (SDS=0). The prevalence of respiratory symptoms from the ECRHS questionnaire among CDH and non-CDH patients was compared with that of the general population with the Chi-square test. Longitudinal differences in lung function between childhood and adulthood in CDH and non-CDH patients were tested with paired sample T-tests. Only childhood data from the participating CDH and non-CDH patients in the current study were used. Adulthood data of normally distributed variables were compared between CDH and non-CDH patients in using Mixed Model ANOVA taking account of the pairing of individuals. In case 2 non-CDH patients were available for one CDH patient, mean value of 2 non-CDH patients was used for the paired analysis. RV/TLC was expressed as percentage. A post bronchodilator change in $FEV_1$ of > 12% was considered clinically significant, thus reflecting reversible airflow obstruction [19,22]. We analyzed the following components in a Mixed Model as covariates to investigate if they had a significant influence on lung function parameters: neonatal ventilatory support, neonatal supplementary oxygen, SDS height at follow up, atopy, doctor-diagnosed asthma, smoking habits and parental smoking habits. Data were shown as mean (SD) unless stated otherwise. In view of the multiple comparisons made, statistical significance was accepted at two-tailed 1% level for all tests. Statistical analyses were performed using SPSS 15.0 for Windows.

## Results

In CDH patients, 27 of the 40 patients in the original study of IJsselstijn [9] (68%) participated fully (mean (SD) age 26.8 (2.9) years). Two others only completed the questionnaires. Two of them had not undergone lung function testing in childhood (one refused and one suffered from neurodevelopmental impairment which improved over the years). Eleven CDH patients did not participate at all for the following reasons: refusal (n=9), acquired serious neurological co-morbidity (n=1) and lost to follow-up (n=1). For these 27 CDH patients 48 previously matched patients were available; two others had died (from causes unrelated to neonatal problems). Sixteen patients refused and 2 were lost to follow-up. Thus, the non-CDH group consisted of 30 patients (63%) at a mean (SD) age of 26.6 (2.4) years. Eighteen CDH patients each had one matched patient and 6 CDH patients each had 2 matched patients. Matched patients were not available for the 3 remaining CDH patients.

In non-CDH patients the 30 participants had received neonatal intensive care for: meconium aspiration (n=12), persistent pulmonary hypertension (n=5), respiratory

distress syndrome (n=5), asphyxia (n=4), pneumonia (n=3) and sepsis (n=1). Perinatal characteristics (age at follow-up, gestational age, birth weight, duration of ventilation, supplemental oxygen and sex) did not significantly differ between participants and non-participants (data not shown). In CDH patients the mean SDS height was significantly lower than that of the non-CDH patients (p=0.002), between groups p-value). Participants' characteristics are listed in Table 1.

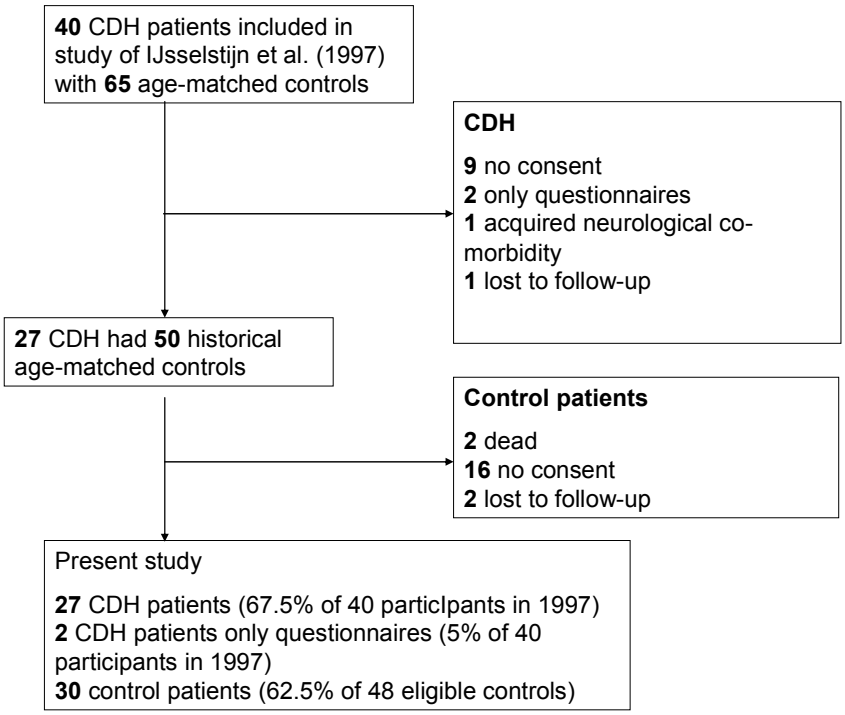



**Figure 1:** *Flowchart. CDH: congenital diaphragmatic hernia*

| | CDH | Non-CDH |
|---|---|---|
| Number | 27 | 30 |
| Male n (%) / female n (%) | 16 (59) / 11 (41) | 20 (67) / 10 (33) |
| Birth weight, kg ; mean (SD) | 3.2 (0.6) | 3.0 (0.6) |
| Gestational age, weeks (median, range) | 40 (28-43) | 38 (29-40) |
| Left-sided diaphragm defect | 26 (96%) | - |
| Patch repair n (%) | 10 (37%) | - |
| Duration of ventilation, days (median, range) | 4 (0-143) | 4.5 (0-25) |
| Duration of oxygen supply, days (median, range) | 6 (0-60) | 5 (0-19) |
| CLD n (%)(O2 > 28 days) | 5 (18.5) | 0 (0) |
| History of asthma; n(%) * | 8 (29.6) | 9 (30.0) |
| Family history lung disease positive; n(%) * | 7 (25.9) | 5 (16.7) |
| Family history atopy positive (n%) * | 12 (44.4) | 10 (33.3) |
| Atopic symptoms (≥ 1); n (%) † | 17 (63) | 15 (50) |
| Smoking * | | |
| Yes: n (%) | 12 (44.4) | 8 (26.7) |
| Pack years of smokers: median (range) | 10.4 (3.5-30.0) | 8.8 (0.1-22.5) |
| Maternal smoking during pregnancy * | | |
| Yes: n (%) | 4 (15) | 3 (10) |
| Parental smoking during childhood * | | |
| Yes: n (%) | 18 (67) | 19 (63) |
| Age at assessment, years; mean (SD) | 26.8 (2.9) | 26.6 (2.4) |
| SDS height; mean, (SD) ‡ (n=27) | -0.9 (1.1) | 0.0 (0.9) |
| BMI, m/kg$^2$; mean (SD) (n=27) | 23.8 (4.4) | 24.3 (3.8) |
| Scoliosis: n (%)(n=27) | | |
| Mild | 5 (18.5) | 0 (0) |
| Severe | 2 (7) | 0 (0) |

**Table 1:** *Characteristics of all participants studied in adulthood. CDH = congenital diaphragmatic hernia, CLD = chronic lung disease. Patch repair: diaphragm defect repaired with a patch (Teflon, Lyodura), in 1 patient primary or patch repair unknown. BMI = body mass index.*

**items from ECRHS questionnaire † item from atopy questionnaire ‡ between groups p = 0.002, (mixed model ANOVA)*

### *Change in lung function from childhood to adulthood*

In CDH patients all spirometry parameters before BD did not change significantly over time. In non-CDH patients mean (SD) SDS $FEV_1$/FVC improved significantly over time (-0.8 (1.0) in childhood and -0.3 (1.3) in adulthood; p<0.001). The other spirometry values before BD were unchanged in non-CDH patients (data not shown). In CDH patients mean values of SDS $FEF_{25-75}$, SDS $DL_{CO}c$ and SDS $K_{CO}c$ after BD in were significantly lower in adulthood than in childhood (Table 2a). In non-CDH patients mean SDS $DL_{CO}c$, $K_{CO}c$ and SDS $K_{CO}c$ were significantly lower in adulthood than in childhood (Table 2b).

Results of lung function measurements after BD are shown in Table 2, Figure 1 and 2. Bronchodilator responsiveness, defined as improvement of SDS $FEV_1$ after bronchodilation, was statistically significant in both groups in childhood and adulthood (in CDH patients mean difference 0.53 ($p<0.001$) and 0.26 ($p=0.001$) respectively, in non-CDH patients 0.58 ($p<0.001$) and 0.31 ($p<0.001$)). The improvement of SDS $FEV_1$ after bronchodilation decreased significantly from childhood to adulthood in both groups ($p<0.003$).

| Mean (SD) | Childhood (n=27) | Adulthood (n=27) | p-value |
|---|---|---|---|
| SDS $FEV_1$ | -0.8 (1.2) * | -1.3 (1.4) * | 0.046 |
| SDS FVC | -0.4 (1.0) | -0.7 (1.2) * | 0.051 |
| SDS $FEV_1$/FVC | -0.6 (1.2) * | -0.9 (1.2) * | 0.222 |
| SDS $FEF_{25-75}$ | -0.7 (1.4) | -1.6 (1.5) * | <0.001† |
| $RV/TLC_{pleth}$ % | 29.3 (5.1) | 27.0 (5.6) | 0.028† |
| $DL_{CO}c$ (µmol/s/kPa) | 95.3 (20.8) | 147.2 (38.6) | 0.001† |
| SDS $DL_{CO}c$ | 0.2 (1.1) | -1.5 (1.1) * | <0.001† |
| $K_{CO}c$ (µmol/s/kPa/L) | 32.0 (4.2) | 26.3 (4.0) | <0.001† |
| SDS $K_{CO}c$ | -0.1 (0.6) | -0.5 (0.7) * | 0.622 |

**Table 2a***: Longitudinal lung function from childhood to adulthood in CDH patients. Results of Spirometry, Lung volume measurement and Diffusion Capacity in CDH patients after bronchodilation in childhood and adulthood*

| Mean (SD) | Childhood (n=30) | Adulthood (n=30) | p-value |
|---|---|---|---|
| SDS $FEV_1$ | -0.1 (1.3) | -0.4 (1.7) | 0.132 |
| SDS FVC | -0.1 (1.1) | -0.4 (1.4) | 0.031 |
| SDS $FEV_1$/FVC | -0.2 (1.1) | 0.0 (1.2) | 0.413 |
| SDS $FEF_{25-75}$ | 0.2 (1.4) | -0.3 (1.6) | 0.038 |
| $RV/TLC_{pleth}$ % | 25.6 (4.9) | 23.9 (4.3) | 0.106 |
| $DL_{CO}c$ (µmol/s/kPa) | 109.8 (23.5) | 173.6 (31.3) | <0.001† |
| SDS $DL_{CO}c$ | 0.1 (0.4) | -1.1 (1.1) * | <0.001† |
| $K_{CO}c$ (µmol/s/kPa/L) | 32.1 (3.2) | 26.1 (3.4) | <0.001† |
| SDS $K_{CO}c$ | 0.1 (0.6) | -0.4 (0.9) | 0.007† |

**Table 2b:** *Longitudinal lung function from childhood to adulthood non-CDH patients. Results of Spirometry, Lung volume measurement and Diffusion Capacity in non-CDH patients after bronchodilation in childhood and adulthood*

** one sample t-test: mean value significantly below the norm (SDS=0)*

*†: significantly lower, paired sample T test ($p < 0.01$)*

*Childhood data only from the participating CDH and non-CDH patients were used.*

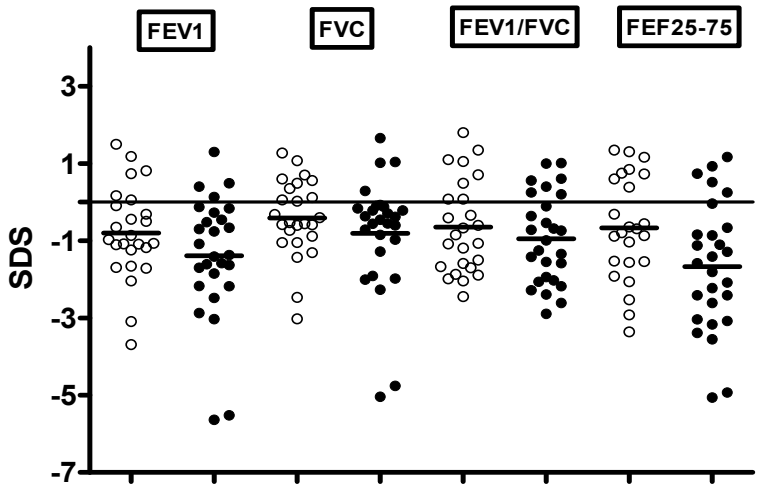



**Figure 1:** *CDH patients: Spirometric values (SDS) after bronchodilation. Open circles represent values in childhood, closed circles represent adult values. Bars per panel indicate mean value.*

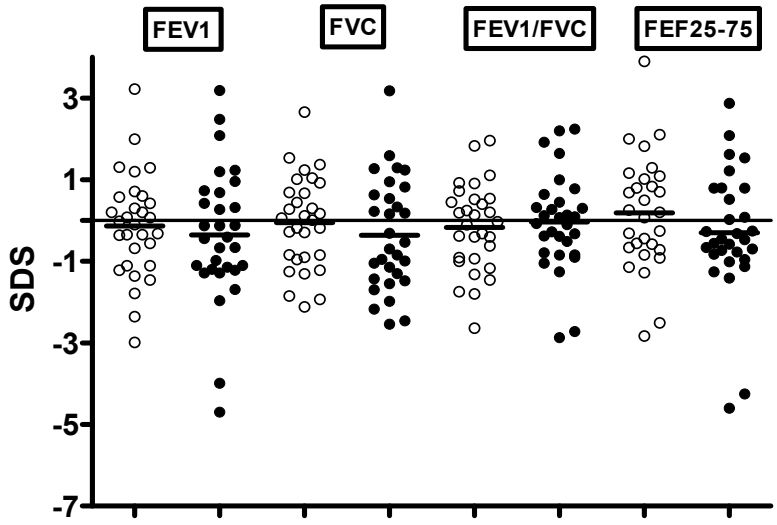



**Figure 2:** *non-CDH patients with normal lung development and similar neonatal intensive care treatment: Spirometric values (SDS) after bronchodilation. Open circles represent values in childhood, closed circles represent adult values. Bars per panel indicate mean value.*

*Differences in lung function in adulthood between CDH and non-CDH patients*

The mean SDS $FEF_{25-75}$ before BD in CDH patients was significantly lower than that in non-CDH patients (-1.6 (1.5) vs. -0.6 (1.3); p=0.008). Clinically reversible airflow obstruction with > 12% individual post bronchodilator change in $FEV_1$ occurred in 5/27 (18.5%) CDH patients and in 1/30 (3.3%) non-CDH patients. The mean (SD) SDS $FEV_1$/FVC and SDS $FEF_{25-75}$ after BD in CDH patients were significantly lower than those

in non-CDH patients (Table 3). In adult CDH patients all spirometric values, before and after BD, and SDS $DL_{CO}c$ and SDS $K_{CO}c$ were significantly below normal ($p<0.009$) for all parameters, within groups one sample t-test). In adult non-CDH patients mean SDS $FEV_1$ and SDS $FEF_{25-75}$ before BD, and $DL_{CO}c$ after BD were significantly below normal ($p\leq0.006$, Table 3).

| Mean (SD) | CDH (n=27) | non-CDH (n=30) | p-value |
|---|---|---|---|
| SDS $FEV_1$ | -1.2 (1.4)* | -0.2 (1.5) | 0.071 |
| SDS FVC | -0.7 (1.1) * | -0.3 (1.3) | 0.243 |
| SDS $FEV_1$/FVC | -0.8 (1.2) * | 0.0 (1.0) | 0.008† |
| SDS $FEF_{25-75}$ | -1.5 (1.6) * | -0.2 (1.3) | 0.006† |
| Reversibility $FEV_1$(ml) | 101 (150) | 158 (124) | 0.154 |
| % $FEV_1$ change after BD | 3.4 (5.5) | 3.7 (2.9) | 0.855 |
| SDS $TLC_{pleth}$ | 0.1 (1.1) | 0.1 (1.1) | 0.977 |
| SDS $RV_{pleth}$ | 0.3 (0.9) | -0.1 (0.9) | 0.071 |
| SDS $FRC_{pleth}$ | -0.1 (1.1) | -0.1 (1.1) | 0.960 |
| $RV/TLC_{pleth}$ (%) | 27 (5.8) | 24 (4.4) | 0.015 |
| SDS $DL_{CO}c$ | -1.5 (1.1) * | -1.1 (1.0) * | 0.145 |
| SDS $K_{CO}c$ | -0.5 (0.7) * | -0.3 (0.9) | 0.349 |
| NO ppb (median, range) | 9.9 (4.0-33.7) | 18.4 (5.9-37.8) | 0.025 |

**Table 3:** *Comparison of lung function between both groups in adulthood. * : significantly below normal (SDS = 0). One sample t-test was used. †: significantly lower, p-values from mixed model ANOVA*

*Questionnaires*

In CDH patients, 3 (10.3%) reported shortness of breath when walking at their own pace on level ground (Table 4). This proportion was significantly larger than that in the general population ($p < 0.001$). The prevalences of doctor-diagnosed asthma in CDH and non-CDH patients were significantly higher compared to reference values ($p<0.001$ in both groups). The prevalence of atopic symptoms did not significantly differ between groups (in CDH patients: 63%; in non-CDH patients: 50%; $p=0.471$; Table 1).

*Associations*

In CDH patients, a longer duration of supplementary oxygen was associated with lower SDS FVC ($R= -0.60$, $p=0.001$). ANOVA showed no other significant associations between clinical characteristics and and lung function parameters.

| Symptom | CDH (n=29) Yes, % | Non-CDH (n=30) Yes, % | General pop. (n=1310) Yes, % | CDH p | Non-CDH p |
|---|---|---|---|---|---|
| • Have you had wheezing in your chest at any time in the last 12 months? | 31 | 10 | 20.4 | 0.242 | 0.241 |
| • Have you had this wheezing when you did not have a cold? | 13.8 | 3.3 | 12.2 | 1.00 | 0.232 |
| • Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill? | 13.8 | 0 | 13.1 | 1.00 | 0.042 |
| • Do you get short of breath walking with other people of your own age on level ground? | 10.3 | 0 | 1.6 | 0.004 * | 1.00 |
| • Do you have to stop for breath when walking at your own pace on level ground? | 10.3 | 0 | 0.4 | <0.001 * | 1.00 |
| • Have you ever had asthma? | 27.6 | 30 | 4.5 | <0.001 * | 0.001 * |
| • Have you had an attack of asthma in the last 12 months? | 0 | 3.3 | 1.3 | 1.00 | 0.338 |
| • Do you use asthma medication now? | 6.9 | 3.3 | 2.1 | 0.128 | 0.473 |
| • Do you have hay fever? | 17.2 | 13.3 | 18.7 | 1.000 | 0.617 |
| • Do you have eczema? | 27.6 | 36.7 | 36.2 | 0.458 | 1.00 |

**Table 4:** *Prevalence of symptoms established with the ECRHS questionnaire. General population from the Dutch part of the European Community Respiratory Health Survey (ECRHS) questionnaire 20. Prevalences of symptoms in CDH and non-CDH patients were compared with prevalences in the general population using crosstabs and Chi-square/Fisher exact test. Questionnaires were completed by 29 CDH patients. * : significantly higher prevalence compared with general population*

## Discussion

In this study we evaluated the course of lung function and respiratory symptoms from infancy until adulthood in a cohort of CDH patients and matched non-CDH patients with normal lung development who underwent similar neonatal intensive care treatment. In both groups airflow obstruction increased from childhood into adulthood, being still mild to moderate in CDH patients, and mild in non-CDH patients. Several cross-sectional studies showed peripheral airway obstruction in infants with CDH [23], in childhood [6,9,11] and adulthood [24-25] but evolution of this airway obstruction has never been assessed. In 2009 Filippone reported that $V'max_{FRC}$ values in seventeen 2-year old BPD survivors correlated with $FEV_1$ values at 9 and 15 years of age. This suggested that early lung injury may influence long-term lung function and respiratory health [26]. The limited differences between CDH and non-CDH patients in this study suggest that it is not residual lung hypoplasia but mainly neonatal intensive care treatment that contribute to long-term pulmonary sequelae. Bronchodilator response decreased from childhood into adulthood but remained significant. This indicates that the observed airway obstruction due to increased airway responsiveness was still present and that a reduced distal

airway diameter is not only due to fibrotic changes. Although airway obstruction improved after bronchodilation, all spirometric values were still reduced in CDH patients. Indeed, the prevalences of asthma in CDH and non-CDH patients were significantly higher than that in the general population. Static lung volumes were normal in adult patients in both groups, consistent with the observations of others [11]. The RV/TLC ratio was higher and tended to be significantly higher in CDH than in non-CDH patients, which might be due to obstructive lung disease. As the number of alveoli may be reduced, we also measured diffusion capacity as a measure of the alveolar surface. Significantly decreased levels of $DL_{CO}c$ in both groups in adulthood, and decreased levels of $K_{CO}c$ in CDH patients suggest a decreased diffusion surface area. Although a normal TLC suggests the absence of residual lung hypoplasia in CDH, it cannot differentiate between normal lungs and hyperinflated hypoplastic lungs. Increased RV/TLC and reduced $K_{CO}c$ are suggestive of persisting abnormal lung structure. Indeed, several reports on lung morphology after neonatal repair of CDH describe an increase in alveolar size [27] and chest radiographs are frequently abnormal in CDH survivors [28]. A recent study comparing MRI-based functional pulmonary measurements in 12 CDH patients and healthy matched controls revealed normal volumes on pulmonary function testing and increased ipsilateral lung volume on MRI in CDH [29]. Those CDH patients had a smaller cross-sectional area and lower flow parameters of the left pulmonary artery. Earlier scintigraphic studies also showed reduction of the entire pulmonary vascular bed [30]. From ventilation–perfusion data Hayward and colleagues suggested that most of the lung growth in their CDH population 0.1-13 years was caused by the expansion of already existing alveoli and not by increasing numbers of alveoli [31]. Our findings suggest dysanaptic lung growth with normal lung volumes, a decreasing RV/TLC ratio from childhood into adulthood and decreased $D_{LCO}c$ and $K_{CO}c$, – consistent with findings in these aforementioned studies. Asthma appeared to be highly prevalent in both groups. This is in line with findings from previous studies and we previously documented increased airway responsiveness in this group [32] [9]. In the general population, wheezing and shortness of breath was reported more frequently than doctor-diagnosed asthma. With a registered (RIVM, National Institute for Health and Environment) asthma prevalence of 2.3% in the age group 20-29 years in the Dutch population, we assume the crux of the matter is overestimation of (non-asthma) wheezing and exercise induced (normal) shortness of breath in the ECRHS population rather than underestimation of doctor-diagnosed asthma. Many CDH patients smoked. Smoking can cause a slightly faster decline in $FEV_1$ with age [33] and a lower diffusion capacity [34]. In our study smoking was not associated with spirometric parameters. Diffusion capacity however, was negatively related to pack years. This might (partly) explain the significantly below-normal $K_{CO}c$ value in CDH patients. When using the data from the ECRHS questionnaire, the prevalence of smoking in CDH patients was not significantly different. However, the ECRHS questionnaire was published in 1996 and during this period the prevalence of smoking in the Netherlands decreased from 35% to 23% in the period 2007-2009 when our study was performed (Statistics Netherlands).

A potential weakness of our study was the lack of appropriate reference values for longitudinal spirometric measurements. As techniques, equipment and population characteristics evolve, up-to-date reference data to reflect these changes are needed. In 2008, Quanjer and co-workers compared different reference equations. Importantly, they concluded that Stanojevic's reference equations covered the widest age range (4-80 years) with a gradual transition from childhood into adulthood [15]. This is why we computed SDS of spirometric values at both ages using these equations. Also, longitudinal reference data for static lung volumes and diffusion capacity are lacking. For diffusion capacity, we used reference data from Stam et al. for 6-18 year-olds and those for adults from 18 years old [17,35]. We could not longitudinally compare our lung volume data collected during childhood and adulthood.

In conclusion, both CDH patients and non-CDH patients who as neonates underwent similar intensive care treatment had mild airflow obstruction and reduced diffusion capacity at adult age, both of which conditions had deteriorated mildly but significantly since childhood in CDH patients. Differences between groups were only minor, indicating that not only residual sequelae of CDH but mainly intensive care treatment contributed to the outcome. For children born from the early 1990s onwards, improved ventilation techniques such as high frequency oscillation and extracorporeal membrane oxygenation therapy can reduce lung injury. This evolution may be counterbalanced by the rise in CDH survival rate from 50 to 80%, with survivors showing more severe lung hypoplasia and persistent pulmonary hypertension [36-37]. As collective data have recently documented a 41% incidence of BPD [38], there is every reason to advocate long-term follow-up of lung function in CDH patients. Education and early intervention may be important to reduce the harmful effects of smoking on lung function.

## References


1. Stevens TP, van Wijngaarden E, Ackerman KG, Lally PA, Lally KP. Timing of delivery and survival rates for infants with prenatal diagnoses of congenital diaphragmatic hernia. Pediatrics 2009;123(2):494-502.

2. van den Hout L, Schaible T, Cohen-Overbeek TE, Hop W, Siemer J, van de Ven K, Wessel L, Tibboel D, Reiss I. Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. Fetal Diagn Ther 2011;29(1):55-63.

3. Lally KP, Engle W. Postdischarge follow-up of infants with congenital diaphragmatic hernia. Pediatrics 2008;121(3):627-632.

4. Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. J Perinatol 2007;27(9):535-549.

5. Bancalari E, Claure N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. Semin Perinatol 2006;30(4):164-170.

6. Basek P, Bajrami S, Straub D, Moeller A, Baenziger O, Wildhaber J, Bernet V. The pulmonary outcome of long-term survivors after congenital diaphragmatic hernia repair. Swiss Med Wkly 2008;138(11-12):173-179.

7. Bhandari A, Panitch HB. Pulmonary outcomes in bronchopulmonary dysplasia. Semin Perinatol 2006;30(4):219-226.

8. Greenough A. Bronchopulmonary dysplasia--long term follow up. Paediatr Respir Rev 2006;7 Suppl 1:S189-191.

9. IJsselstijn H, Tibboel D, Hop WJ, Molenaar JC, de Jongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. Am J Respir Crit Care Med 1997;155(1):174-180.

10. Pal K, Gupta DK. Serial perfusion study depicts pulmonary vascular growth in the survivors of non-extracorporeal membrane oxygenation-treated congenital diaphragmatic hernia. Neonatology 2010;98(3):254-259.

11. Peetsold MG, Heij HA, Nagelkerke AF, IJsselstijn H, Tibboel D, Quanjer PH, Gemke RJ. Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia. Eur Respir J 2009;34(5):1140-1147.

12. Wong PM, Lees AN, Louw J, Lee FY, French N, Gain K, Murray CP, Wilson A, Chambers DC. Emphysema in young adult survivors of moderate-to-severe bronchopulmonary dysplasia. Eur Respir J 2008;32(2):321-328.

13. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47(3):316-323.

14. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008;177(3):253-260.

15. Quanjer PH, Borsboom GJ, Kivastik J, Merkus PJ, Hankinson JL, Houthuijs D, Brunekreef B, Ihorst G, Kuhr J. Cross-sectional and longitudinal spirometry in children and adolescents: interpretative strategies. Am J Respir Crit Care Med 2008;178(12):1262-1270.

16. Zapletal A, Paul T, Samanek M. [Significance of contemporary methods of lung function testing for the detection of airway obstruction in children and adolescents (author's transl)]. Z Erkr Atmungsorgane 1977;149(3):343-371.

17. Stam H, Hrachovina V, Stijnen T, Versprille A. Diffusing capacity dependent on lung volume and age in normal subjects. J Appl Physiol 1994;76(6):2356-2363.

18. Baraldi E, de Jongste JC. Measurement of exhaled nitric oxide in children, 2001. Eur Respir J 2002;20(1):223-237.

19. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.

20. Rijcken B, Kerkhof M, de Graaf A, Boezen H, Droste JHJ, Kremer AM. Europees Luchtweg Onderzoek Nederland, Rijksuniversiteit Groningen Epidemiologie 1996:29-33.

21. Lakwijk N, Van Strien RT, Doekes G, Brunekreef B, Gerritsen J. Validation of a screening questionnaire for atopy with serum IgE tests in a population of pregnant Dutch women. Clin Exp Allergy 1998;28(4):454-458.

22. Society AT. Lung Function Testing: selection of reference values and interpretatative strategies. Am Rev Respir Dis 1991;144:1202-1218.

23. Koumbourlis AC, Wung JT, Stolar CJ. Lung function in infants after repair of congenital diaphragmatic hernia. J Pediatr Surg 2006;41(10):1716-1721.

24. Arena F, Baldari S, Centorrino A, Calabro MP, Pajno G, Arena S, Ando F, Zuccarello B, Romeo G. Mid- and long-term effects on pulmonary perfusion, anatomy and diaphragmatic motility in survivors of congenital diaphragmatic hernia. Pediatr Surg Int 2005;21(12):954-959.

25. Peetsold MG, Vonk-Noordegraaf A, Heij HH, Gemke RJ. Pulmonary function and exercise testing in adult survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2007;42(4):325-331.

26. Filippone M, Bonetto G, Cherubin E, Carraro S, Baraldi E. Childhood course of lung function in survivors of bronchopulmonary dysplasia. JAMA 2009;302(13):1418-1420.

27. Thurlbeck WM, Kida K, Langston C, Cowan MJ, Kitterman JA, Tooley W, Bryan H. Postnatal lung growth after repair of diaphragmatic hernia. Thorax 1979;34(3):338-343.

28. Bagolan P, Morini F. Long-term follow up of infants with congenital diaphragmatic hernia. Semin Pediatr Surg 2007;16(2):134-144.

29. Abolmaali N, Koch A, Gotzelt K, Hahn G, Fitze G, Vogelberg C. Lung volumes, ventricular function and pulmonary arterial flow in children operated on for left-sided congenital diaphragmatic hernia: long-term results. Eur Radiol 2010;20(7):1580-1589.

30. Ritter L, Otto HJ, Huhnerbein J, Thal W, Sollich V, Schuster R. [Findings of combined ventilation/perfusion scintigraphy in children with abnormalities of the bronchi, the lung and lung blood vessels] Befunde der kombinierten Ventilations-/Perfusionsszintigraphie bei Kindern mit Fehlbildungen der Bronchien, der Lungen und Lungengefasse. Kinderarztl Prax 1993;61(1):12-18.

31. Hayward MJ, Kharasch V, Sheils C, Friedman S, Dunleavy MJ, Utter S, Zurakowski D, Jennings R, Wilson JM. Predicting inadequate long-term lung development in children with congenital diaphragmatic hernia: an analysis of longitudinal changes in ventilation and perfusion. J Pediatr Surg 2007;42(1):112-116.

32. Trachsel D, Selvadurai H, Bohn D, Langer JC, Coates AL. Long-term pulmonary morbidity in survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2005;39(5):433-439.

33. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. Am Rev Respir Dis 1988;138(4):837-849.

34. Van Ganse WF, Ferris BG, Jr., Cotes JE. Cigarette smoking and pulmonary diffusing capacity. Chest 1971;59:Suppl:33S.

35. Stam H, van den Beek A, Grunberg K, Stijnen T, Tiddens HA, Versprille A. Pulmonary diffusing capacity at reduced alveolar volumes in children. Pediatr Pulmonol 1996;21(2):84-89.

36. Azarow K, Messineo A, Pearl R, Filler R, Barker G, Bohn D. Congenital diaphragmatic hernia--a tale of two cities: the Toronto experience. J Pediatr Surg 1997;32(3):395-400.

37. Wilson JM, Lund DP, Lillehei CW, Vacanti JP. Congenital diaphragmatic hernia--a tale of two cities: the Boston experience. J Pediatr Surg 1997;32(3):401-405.

38. van den Hout L, Reiss I, Felix JF, Hop WC, Lally PA, Lally KP, Tibboel D. Risk factors for chronic lung disease and mortality in newborns with congenital diaphragmatic hernia. Neonatology 2010;98(4):370-380.


# Exercise capacity, daily activity and severity of fatigue in term born young adults after neonatal respiratory failure

Monique HM van der Cammen-van Zijp, Marjolein Spoel, Roxanne Laas, Wim CJ Hop, Johan C de Jongste, Dick Tibboel, Rita JG van den Berg-Emons, Hanneke IJsselstijn.

Submitted

**Abstract**

Little is known about long-term effects of neonatal intensive care on exercise capacity, physical activity, and fatigue in term borns.

We determined these outcomes in 57 young adults, treated for neonatal respiratory failure; 27 of them had congenital diaphragmatic hernia with lung hypoplasia (group 1) and 30 had normal lung development (group 2). Patients in group 2 were age-matched, with similar gestational age and birth weight, and similar neonatal intensive care treatment as patients in group 1. All patients were born before the era of extracorporeal membrane oxygenation, nitric oxide administration and high frequency ventilation. Exercise capacity was measured by cycle ergometry; daily physical activity with an accelerometry-based activity monitor; and fatigue by the Fatigue Severity Scale.

Median (range) $VO_2$ peak in mL/kg/min was 35.4 (19.6-55.0) in group 1 and 37.6 (15.7-52.7) in group 2. There was a between groups p-value of 0.65 for exercise capacity. Daily activity and fatigue was also similar in both groups. So, residual lung hypoplasia did not play an important role in this cohort . There were no significant associations between exercise capacity and perinatal characteristics.

Future studies need to elucidate whether exercise capacity is impaired in patients with more severe lung hypoplasia who nowadays survive.

## INTRODUCTION

Long-term pulmonary sequelae and exercise tolerance in term born patients following neonatal respiratory failure are under-documented. Airflow obstruction and hyperinflation have been reported in 8- and 11-year-old children following neonatal intensive care treatment [1-2]. Hamutcu (2004) reported that both oxygen saturation levels at maximal exercise and peak oxygen consumption in 11-year-olds who had undergone neonatal extracorporeal membrane oxygenation (ECMO) treatment were lower than those in healthy controls.

Congenital diaphragmatic hernia (CDH) patients form an interesting subgroup of term born neonates with respiratory failure. In CDH, a developmental defect of the diaphragm is combined with pulmonary hypoplasia, abnormal pulmonary vascular development and vaso-reactivity [3]. The focus of research interest has gradually shifted from mortality to morbidity [4]. Cross-sectional studies have documented a range of long-term complications at childhood and adolescent ages, including ventilation-perfusion mismatch and airflow obstruction [5-11].

We previously reported pulmonary sequelae in CDH patients (median age 11.7 years) and age-matched patients who underwent similar neonatal intensive care treatment [7]. This cohort was born before the era of ECMO, nitric oxide administration and high frequency ventilation. In other words, the concepts of treatment and the therapeutic possibilities were quite different than nowadays. In childhood, we found increased bronchial responsiveness, normal carbon monoxide diffusion capacity ($DL_{CO}$) and mild airway obstruction in both groups, with more peripheral airway obstruction in CDH patients. Exercise capacity was not determined then. Re-evaluation of lung function in the same cohort in young adulthood, revealed a slight but significant deterioration of airflow obstruction in CDH patients and deterioration of $DL_{CO}$ in both groups. The prevalence of asthma was – for both groups – higher than in the normal population [12].

Another cohort of patients with neonatal respiratory failure who all had to be treated with neonatal ECMO was studied at 5-12 years. In that cohort we observed decreased exercise capacity deteriorating over time [13].

Little is known about exercise capacity and health status in adult survivors after neonatal surgical repair of CDH [14]. Moreover, it is unclear whether CDH and lung hypoplasia influence level of physical activity or severity of fatigue. The aims of the present study therefore were:

- To assess exercise capacity, level of physical activity, severity of fatigue, health status and participation in our previously studied cohort of CDH survivors (group 1) in comparison with a group of age-matched non-CDH patients with normal lung development who underwent similar neonatal treatment (group 2); and so to

investigate if and to what extent residual lung hypoplasia affects the above-mentioned parameters in young adults after neonatal respiratory failure.

- To investigate correlations between exercise capacity and perinatal characteristics, and between exercise capacity and outcome parameters, i.e. lung function, smoking habits, fatigue, health status and participation at young adult age.

## METHODS

### *Participants*

All patients described in a study by IJsselstijn et al.[7] were regarded as potential participants. In that study, efforts had been made to match each CDH patient with two non-CDH patients. The non-CDH had been matched for age at follow-up and were further selected to obtain the best possible match for gestational age, birth weight, duration of artificial ventilation, duration of supplemental oxygen, and gender. We screened all participants with the Physical Activity Readiness Questionnaire [15-16] and participants had to be clinically stable > 3 weeks. Any medication for pulmonary disease was discontinued 24 hours prior to testing. Patients with serious comorbidity, such as serious neurological impairment, were excluded. Except for daily physical activity testing, which was done at home, all assessments were performed in our outpatient clinic on a single morning between 9 and 12 am.
The Medical Ethical Review Board Erasmus MC approved the study (MEC-2007-150) and all patients provided written informed consent.

### *Medical assessment*

Height (cm) and weight (kg) were measured. Body mass index (BMI) and standard deviation scores (SDS) for height were calculated as described previously [12]. Sports participation, paid employment and smoking habits were recorded. Smoking was quantified in terms of “pack years”. The presence of scoliosis was determined by a standardized physical examination; it was considered severe if referral to an orthopaedic surgeon was required.

### *Lung function*

Spirometry was performed with a dry rolling seal spirometer (Jaeger, Wurzberg, Germany) and repeated after inhalation of 12 mcg of formoterol. Forced expiratory volume in 1 s ($FEV_1$), forced vital capacity (FVC), and $FEV_1$/FVC were expressed as standard deviation scores (SDS) [17]. In addition $DL_{CO}$ was measured using a single-

breath method. Reference values for $DL_{CO}$ and $DL_{CO}$ corrected for alveolar volume ($DL_{CO}/V_A$ ) were based on modified equations according to Stam et al. [18]. For males: $DL_{CO}$ (μmol.s$^{-1}$.kPa$^{-1}$) = 271 - (2.1 x age) (SD 25); for females: $DL_{CO}$ = 187 - (1.3 x age) (SD 19). For males and females: $DL_{CO}/V_A$ (μmol.s$^{-1}$.kPa$^{-1}$.L$^{-1}$) = 31.5 - (0.17 x age) (SD 3.4).

*Exercise testing*

All exercise tests were performed after spirometry, and therefore 1-2 hrs after inhalation of formoterol. Maximal cardiopulmonary exercise testing (CPET) was performed on an electrically braked cycle ergometer (ER800, Jaeger Toennies, Breda, The Netherlands) according to ATS/ACCP guidelines [19]. Resistance was increased every minute (min) with a variable load according to Wasserman et al [20]. Pedal frequency was maintained between 50 - 70 revolutions/min. Heart rate (HR) was monitored with a pulse oximeter (MARS (motion artifact reduction system), type 2001, Respironics Novametrix, Murrysville (PA)). Respiratory gas was monitored on a breath-by-breath basis using a Jaeger Oxycon Pro (Care Fusion, Houten, the Netherlands). Cardio-respiratory fitness was defined as the mean oxygen uptake during the last 30 seconds (s) of exercise ($VO_2$peak expressed as ml/min and relative to body weight as ml/min/kg). The ventilatory anaerobic threshold (VAT, expressed as percentage of the $VO_2$peak) was estimated [20-21]. The $VE/VCO_2$ slope was calculated from a regression line of minute ventilation and carbon dioxide production. Peak workload ($W_{peak}$) was defined as the mean highest workload maintained during 1 min. The CPET was considered to be maximal if one or more of the following conditions were met: achievement of maximal HR > 80% of pred; (pred = 220 beats per min (bpm) - age (years)), respiratory exchange ratio (RER = ratio of $VCO_2/VO_2$) > 1.15, or exhaustion [19]. The Borg scale for rating perceived exertion [22] was applied to measure subjective strain. $VO_2$peak was reported as absolute value and was calculated as percentage of the predicted $VO_2$max for group comparisons because of the unequal distribution of men and females in the two groups [23]. We analyzed peripheral venous plasma lactate concentrations at rest and at 3 min after peak exercise [24].

*Level of daily physical activity*

Level of physical activity was measured in a subgroup of both study groups with an accelerometry-based activity monitor (AM) during two consecutive weekdays (48 hours). We aimed at studying the first available 15 subjects in each study group for this measurement. To avoid measurement bias, we explained the principles of the AM only after the measurements were taken. All subjects agreed with this procedure. Level of daily physical activity was analyzed by: 1] duration of dynamic activities as percentage of a 24-h period; 2] mean motility representing both duration and intensity of daily physical activity; and 3] motility during walking, representing walking speed. Data were compared

with those of 45 age-matched healthy subjects, who were measured with the same AM and the same measurement protocol, obtained from a database of our institution. This reference population is representative for the Dutch population and comprises a wide range in profession, socioeconomic status, education, living situation, and activity level . Methodology and validity of the AM and the use of the reference population have been described previously [25-26].

*Fatigue, health status, and participation*

Severity of fatigue experienced in daily life was assessed with the Fatigue Severity Scale (FSS) [27]. The FSS is a nine items questionnaire, with a mean score of the nine questions that ranges from 1 (no sign of fatigue) to 7 (most disabling fatigue). "Fatigue" was defined as a score of > 1 SD (FSS ≥ 4); "severe fatigue" as a score of > 2 SD (FSS ≥ 5.1) above the mean score in healthy individuals [28]. The Dutch Life Habits Questionnaire (LIFE-H 3.0) was administered to evaluate functioning in daily activity and social participation. Scores for the two sub-domains (daily activity and social roles) and the Life Habit total score were calculated. A score < 8 indicated difficulty in performance [29]. Health status was measured with the Short Form (SF)-36 health survey, which consists of 36 questions organized into eight domains. Two summary scores can be derived: physical health and mental health [30]. SD scores were calculated using Dutch age-adjusted population norms (25-34 years) [31].

*Data analysis*

Mann Whitney U tests served to test differences in perinatal characteristics between participants and non-participants. The relationship between lung function and exercise capacity was analysed only from spirometric data after bronchodilation. One-sample t-tests served to test whether the mean SDS height, $FEV_1$, FVC, $FEV_1$/FVC, $DL_{CO}$ and $DL_{CO}/V_A$, within both groups differed from those of the norm population. Data of normally distributed variables were compared between groups using Mixed Model ANOVA taking into account the pairing of individuals. Other data were compared between groups with Wilcoxon's signed rank tests or Mc Nemar's tests. Correlation coefficients between perinatal characteristics and outcome parameters with the %pred $VO_2$peak were established using the Pearson‘s correlation test. Data of the AM measurement were calculated per day (24-h period) and averaged over the two measurement days because there were no differences between the first and the second day. Univariate analysis of variance served to compare data of AM measurements of group 1 with those of group 2 and those of healthy subjects. Continuous parameters with a lognormal distribution were transformed logarithmically to reduce the effect of outlying observations. Statistical significance was accepted at two-tailed 5% level. Statistical analyses were performed using SPSS 17.0.

## RESULTS

All 40 CDH patients from the previous study [7] were approached; 27 (68%) of them were included (group 1; Figure 1). For these 27 patients 48 previously matched patients were available; two others had died (from causes unrelated to neonatal problems). Thirty of them participated (63%). Eighteen CDH patients each had one matched patient; 6 CDH patients each had 2 matched patients. Matched patients were not available for 3 CDH patients. The 30 matched patients (group 2) had received neonatal intensive care for: meconium aspiration (n = 12), persistent pulmonary hypertension (PPH) (n = 5), respiratory distress syndrome (n = 5), asphyxia (n = 4), pneumonia (n = 3), and sepsis (n = 1) (see: Figure 1 and Table 1) Perinatal characteristics of participants and non-participants in both groups did not differ significantly (data not shown). Data on liver position at time of surgical repair of the diaphragmatic defect could be obtained in 21/26 CDH patients (81%). In 16/21 (76%) of CDH patients the liver was in the abdominal cavity, whereas in 5/21 (24%) of cases (part of) the liver was in the thoracic cavity.

| | group 1 | group 2 |
|---|---|---|
| number | 27 | 30 |
| male; n (%) | 16 (59) | 20 (67) |
| birth weight, kg; mean (SD) | 3.2 (0.6) | 3.0 (0.6) |
| ventilatory support, days; median (range) | 4 (0-142) | 4.5 (0-25) |
| supplementary oxygen, days; median (range) | 6 (0-60) | 5 (0-19) |

**Table 1**: *Perinatal characteristics of participants. group 1: congenital diaphragmatic hernia patients, group 2: non-CDH patients who underwent similar neonatal treatment.n = number, kg = kilogram, SD = standard deviation*

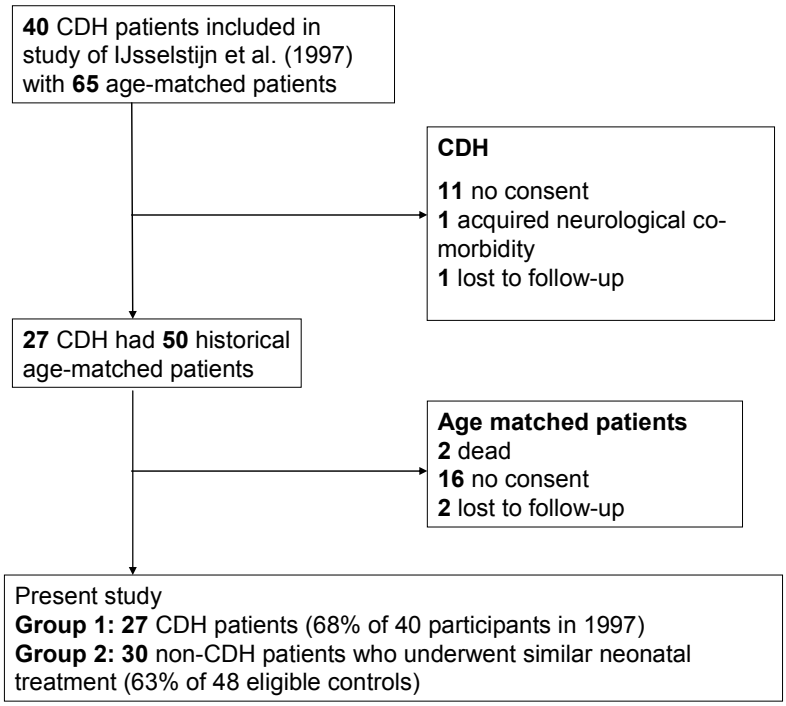



**Figure 1:** *Flowchart*

At examination, mean height in group 1 was significantly lower than that in group 2. The mean SDS $FEV_1$, SDS FVC, SDS $FEV_1$/FVC, SDS $DL_{CO}$ and SDS $DL_{CO}/V_A$ were all significantly below zero in group 1. In group 2 only the mean SDS $DL_{CO}$ was significantly below zero. Mean SDS $FEV_1$/FVC in group 1 was significantly lower than that in group 2. Scoliosis was seen only in CDH patients (group 1) (see: Table 2).

Three patients did not perform CPET: one in group 1 with unstable diabetes and two in group 2 with motor skill disorders. Technical problems led to unreliable data in one other patient in group 2. $VO_2$ peak in ml/min/kg had a median (range) of 35.4 (19.6-55.0) in group 1 and 37.6 (15.7-52.7) in group 2. Males and females were not equally distributed between the two groups; therefore we presented in table 3 separate values for males and females in both groups. Furthermore we recalculated the $VO_2$ peak as percentage predicted of the $VO_2$ max published by Wasserman to correct for gender influence on outcome. These mean (SD) values were not different between both groups: group 1: 96.4% (15.4) and group 2: 98.0% (14.0); between groups' p-value: 0.65. Furthermore the groups did not differ in peak HR (between groups' p-value: p=0.34), peak HR as percentage of predicted (between groups' p-value: p=0.35), VAT (between groups' p-value: p=0.66), $VE/VCO_2$ slope (between groups' p-value: p=0.43), RER (between groups' p-value: p=0.09), and Borg score (between groups' p-value: p=0.90)(Table 3). The mean (SD) venous lactate concentration at rest was 1.0 (0.4) $mmol.l^{-1}$ in both groups; peak levels 3 minutes after maximal exercise were 8.0 (2.9) and 8.7 (2.1) $mmol.l^{-1}$ in group 1 and group 2, respectively (between groups' p-value: p=0.29).

| | group1, n = 27 | group 2, n = 30 |
|---|---|---|
| age at examination, years | 26.8 (2.9) | 26.6 (2.4) |
| BMI | 23.8 (4.4) | 24.3 (3.8) |
| SDS length * | -0.9 (1.1) | 0.0 (0.9) |
| $FEV_1$ (l) | 3.4 (1.0) | 4.3 (1.0) |
| SDS $FEV_1$ | -1.4 (1.6)† | -0.4 (1.7) |
| FVC (l) | 4.5 (1.3) | 5.3 (1.1) |
| SDS FVC | -0.8 (1.5)† | -0.4 (1.4) |
| $FEV_1$/FVC ratio | 0.8 (0.1) | 0.8 (0.1) |
| SDS $FEV_1$/FVC ‡ | -0.9 (1.2)† | 0.0 (1.2) |
| $DL_{CO}$ ($\mu mol.s^{-1}.kPa^{-1}$) | 154.8 (39.6) | 176.2 (34.7) |
| SDS $DL_{CO}$ | -1.5 (1.1)† | -1.1 (1.0)† |
| $DL_{CO}/V_A$ ($\mu mol.s^{-1}.kPa^{-1}.L^{-1}$) | 25.4 (3.6) | 26.8 (3.2) |
| SDS $DL_{CO}/V_A$ | -0.5 (0.7)† | -0.2 (0.8) |
| Scoliosis; n (%) | | |
| mild | 5 (19) | 0 (0) |
| severe | 2 (7) | 0 (0) |
| Smoking | | |
| yes; n (%) | 12 (44) | 8 (27) |
| pack years of smokers: median (range) | 10.4 (3.5 - 30.0) | 8.8 (0.1 - 22.5) |
| Sports participation | | |
| no | 14 (52) | 10 (33) |
| 1 - 4 times weekly | 6 (22) | 14 (47) |
| ≥ 4 times weekly | 7 (26) | 6 (20) |
| Paid employment; n (%) | | |
| no | 3 (11) | 2 (7) |
| > 12 hours weekly | 24 (89) | 28 (93) |

**Table 2:** *Characteristics of the participants at young adult age*

*group 1: congenital diaphragmatic hernia patients,*

*group 2: non-CDH patients who underwent similar neonatal treatment.*

*BMI = body mass index; $FEV_1$ = forced expiratory volume in 1 s ; FVC = forced vital capacity; $DL_{CO}$ = diffusion capacity carbon monoxide; $V_A$ = alveolar volume*

** between groups P value = 0.002, ‡ between groups P value = 0.008*

*Level of physical activity*

Level of physical activity was measured in 28 patients (group 1: n=15; group 2: n=13). For both groups, perinatal characteristics did not significantly differ between the participants and non-participants (data not shown). AM testing resulted in a significant group and gender difference (p=0.02 and 0.01 respectively, independent of the group effect (p=0.36)) in duration of dynamic activities; duration was longer in women than in men. Duration of dynamic activities was longest in group 2 (p=0.02 in comparison with healthy subjects) (Table 4).

*Fatigue, health status, and participation*

Seven patients in group 1 (26%) and one in group 2 (3%) reported "fatigue" (FSS between 4 and 5.1); three in group 1 (11%) and three in group 2 (10%) reported "severe fatigue" (FSS ≥ 5.1). In group 1 the mean (SD) score on the FSS was 3.4 (1.5); in group 2 this was 2.9 (1.2) (p = 0.14, between groups p-value). Mean SDS physical and mental health scales of the SF-36 for both groups were not significantly different from zero: SDS SF-36 physical scale was 0.0 (0.7) and -0.1 (0.7) in group 1 and group 2, respectively (p=0.66, between groups p-value). For the SF-36 mental scale the SDS were -0.2 (0.9) and -0.2 (1.0) for group 1 and group 2, respectively (p=0.93, between groups p-value). On the LIFE-H questionnaire, five patients in group 1 (19%) and one in group 2 (3%) reported difficulties in daily activities (p=0.03, between groups p-value); six patients in group 1 (22%) and four in group 2 (14%) reported difficulties in social participation (p=0.42, between groups p-value) (see: table 4).

| | group 1<br>n=26 | | group 2<br>n=27 | |
|---|---|---|---|---|
| $VO_2$peak ml/min | 2160 (1442-4149) | | 3037 (1442-4168) | |
| $VO_2$peak ml/min/kg | 35.4 (19.7-55.0) | | 37.6 (15.7-52.7) | |
| $VO_2$ peak % pred | 96.4 (15.4) | | 98.0 (14.0) | |
| Peak Workload, W | 173 (113-338) | | 259 (135-338) | |
| Max. heart rate / min | 183 (146-207) | | 184 (162-203) | |
| Max. heart rate / min, % pred | 95 (77-106) | | 95 (83-103) | |
| VAT | 63.9 (14.1) | | 62.3 (10.7) | |
| VE/$VCO_2$ slope | 29.1 (3.3) | | 28.3 (4.1) | |
| Respiratory Exchange Ratio | 1.19 (SD 0.08) | | 1.22 (0.06) | |
| Borg Score | 8.7 (SD 1.1) | | 8.7 (SD 1.3) | |
| Additional information: | group 1 males<br>n=15 | group 1 females<br>n=11 | group 2 males<br>n=20 | group 2 females<br>n=7 |
| $VO_2$peak ml/min | 2974 (1459-4149) | 1908 (1442-2253) | 3281 (2557-4168) | 2160 (1442-2719) |
| $VO_2$peak ml/min/kg | 38.1 (29.6-55.0) | 30.5 (19.7-41.3) | 40.0 (30.5-52.7) | 30.5 (15.7-35.5) |
| Peak Workload, W | 250 (120 - 338) | 150 (113 - 180) | 281 (210 - 338) | 180 (135 - 225) |

**Table 3**: *Results on exercise testing .*

*Group 1: congenital diaphragmatic hernia patients,*

*Group 2: non-CDH patients who underwent similar neonatal treatment.*

*Data are presented as median (range), or as mean (SD). $VO_2$% pred = in comparison with $VO_2$ Wasserman (2005). Definition of abreviations: pred = predicted; W = Watt; VAT = ventilatory anaerobic threshold; VE/$VCO_2$ =relationship between minute ventilation and the rate of $CO_2$ elimination.VAT is presented as % of the $VO_2$peak ml/min.*

| | group 1 (n=15) | group 2 (n=13) | *reference data (n=45)* |
|---|---|---|---|
| male/female | n=8/n=7 | n=8/n=5 | *n=19/n=26* |
| age (yrs) | 27 (25-28) | 27 (26-29) | *27 (24 - 30) (n=38)* |
| BMI ($kg/m^2$) | 22.2 (19.7-28.0) | 24.4 (21.3-28.5) | *21.2 (19.6-23.0)* |
| duration dynamic activities (% of measurement day) | 10.6 (8.1-16.7) (n=15) | 13.0 (10.3-20.6)* (n=13) | *11.3 (8.1 - 12.7) (n=27)* |
| mean motility | 0.025 (0.021 - 0.029) (n=15) | 0.026 (0.022 - 0.048) (n=13) | *0.027 (0.022 - 0.032) (n=31)* |
| motility during walking | 0.188 (0.153 - 0.194) | 0.167 (0.146 - 0.183) | *0.171 (0.158 - 0.184)* |

**Table 4**: *Physical activity as measured with the Activity Monitor.*

*Group 1: congenital diaphragmatic hernia patients*

*Group 2: non-CDH patients who underwent similar neonatal treatment.*

*Reference data that were not obtained during this study but retrieved from a database in our institution are shown in italics. Data are presented as median (IQR)*

** p = 0.018, group difference between group 2 and reference data*

### *Correlations*

In the total study group (n=53), SDS $FEV_1$, SDS $_{DLCO}$, Life-H social participation and SF-36 SD physical health were positively related with $VO_2$peak %pred (see: table 5).

| | R | P-value |
|---|---|---|
| SDS $FEV_1$ | 0.39 | 0.004 |
| SDS $DL_{CO}$ | 0.34 | 0.015 |
| Life-H social participation | 0.31 | 0.028 |
| SD SF 36 physical health | 0.28 | 0.045 |

**Table 5:** *Significant associations with $VO_2$ peak % pred in total group (53 patients)*

R denotes Pearson correlation coefficient

$FEV_1$ = forced expiratory volume in 1 sec

$DL_{CO}$ = diffusion capacity carbon monoxide

Life-H = Life Habit

SF 36 = Short Form 36

## DISCUSSION

We aimed to assess exercise capacity, severity of fatigue, and level of physical activity in young adults who at neonatal age had been treated for respiratory failure: a cohort of patients with CDH and lung hypoplasia (group 1) and a cohort non-CDH patients matched for age and neonatal intensive care treatment (group 2). Levels of exercise capacity did not differ between both groups, which seems to indicate that residual lung hypoplasia does not affect this outcome.

In both groups the $VO_2$peak values did not deviate from norm values [23]. We found no significant relationships between $VO_2$peak % pred and perinatal characteristics. Interestingly, of the lung function parameters, only the SDS $FEV_1$ and the SDS $DL_{CO}$ correlated positively with $VO_2$peak % pred. The SDS $DL_{CO}/V_A$ did not correlate with $VO_2$peak % pred. The significantly lower mean SDS $FEV_1$/FVC in group 1 did not affect exercise capacity tolerance. Other factors than airway obstruction may play a role here. It has been speculated that reduced diffusion capacity of the lungs diminishes exercise capacity in CDH and lung hypoplasia. However, this assumption is not supported by our data.

There were no differences between both study groups in daily physical activity. However, there was a tendency towards a longer duration of dynamic physical activities in the group of patients with normal lung development. Overall the results imply that neonatal intensive care treatment does not lead to an inactive lifestyle in adulthood.

The proportion of patients reporting fatigue was slightly, but not significantly higher in group 1 compared to group 2. Difficulties with physical activities were significantly more often reported in group 1 than in group 2. We speculate that patients with CDH and lung hypoplasia may experience more fatigue and difficulties in performing physical activities. However, due to the small numbers studied – especially in daily activity testing – findings should be cautiously interpreted.
Interestingly, we found an association of the Life-H social participation scale and the scores on the physical scale of the SF-36 with the $VO_2$peak % pred.

The association between exercise capacity and sports participation was not statistically significant (p = 0.134 Spearman's Rho = 0.21). Further (longitudinal) research should investigate if higher sports participation indeed improves exercise capacity and leads to better self-perception after neonatal respiratory failure.
It could be argued that the reference values for $VO_2$ peak may not be appropriate for our population, because they were collected several years ago and in a different population. We chose the reference data by Wasserman et al [23] to compare our results with that from Peetsold et al. (2007) and Vrijlandt et al. (2006) and because the calculations of Wasserman et al. also took weight and height into account.
Peetsold et al. (2007) reported on exercise capacity in 12 young adult survivors of CDH (all non ECMO treated patients): the mean (SD) $VO_2$max % pred was 90.8% (18.9), a little lower than in our cohort. Vrijlandt et al. [32] reported that young Dutch adults born prematurely had a lower exercise level and $VO_2$ max % pred than healthy controls when analysed using the reference values of Wasserman et al. (2005). Healthy controls, however, had a mean (SD) $VO_2$ max % pred of 105 (20), so we may assume that values of Wasserman et al slightly underestimate exercise capacity of present-day healthy Dutch young adults.
To place our conclusions in perspective, we recalculated our results with reference values of [33-34]. Only with the use of the values of Wasserman et al. (2005) our groups scored within the normal range. However, none of the reference values yielded a significant difference between the groups (see Table 6). So the main conclusion that residual lung hypoplasia does not affect exercise capacity in young adults with CDH, is not influenced by the choice of reference values.
Scoliosis was noted in CDH patients only, but at a higher prevalence than previously described [35-36], possibly because we considered even very mild deviation of the spine as "mild scoliosis". We did not perform radiographic evaluation and referred two patients with severe scoliosis to an orthopaedic surgeon.
As a possible limitation**,** selection bias may have occurred. However, in the original study [7] the response rate was 40/45 (89%). In the present study there were no significant differences in perinatal characteristics between participants and non-participants.
The number of subjects studied is relatively small**.** However, in the previous study, we contacted all CDH survivors born between 1975 and 1986 who underwent surgical repair

in our hospital. We put a lot of effort in finding two non-CDH patients matched for age at follow-up, gestational age, birth weight, duration of ventilation and supplemental oxygen, and gender, for each participating CDH patient. As most neonates with respiratory insufficiency are prematurely borns, whereas only three CDH patients in the original study were born prematurely, we needed to recruit patients from three university hospitals in the Netherlands. As 68% of the CDH patients and 63% of the eligible controls were willing to participate in the present study, we performed our study with these relatively small numbers. It can be argued that the non-CDH patients are not suitable as controls because in that group the underlying diagnosis of acquired lung diseases leading to neonatal respiratory insufficiency is heterogeneous and the long-term outcome in these patients may be influenced by this. On the other hand, should we have chosen controls who did not suffer from neonatal respiratory failure, it would have become less clear to what extent long-term respiratory morbidity in CDH patients is caused by residual lung hypoplasia or by lung damage due to neonatal artificial ventilation.

Another limitation of our study is that cardiac performance was not evaluated. Therefore, we were not informed about ventilation/perfusion mismatch, which may occur in patients with CDH and lung hypoplasia [6]. Riley and colleagues (2000) reported reduced exercise capacity in patients with persistent pulmonary hypertension (PPH). In our study venous lactate concentrations did not differ between the both groups. Moreover, lactate concentrations after exercise correspond with the values measured by Riley et al (2000) in healthy controls. These observations suggest that our study population did not suffer from PPH. Furthermore, the $VE/VCO_2$ slope in both groups was not elevated, also suggesting that PPH did not play an important role here (Palange et al. 2007).

Recently we reported significantly decreased exercise capacity in 5-year-old children with CDH [5,37]. The children in those studies had the benefit of new treatment modalities such as ECMO. Nevertheless we believe that today's survivors of CDH might suffer from more severe residual pathology, and not necessarily do better than patients treated long ago. Actually, it could even be the other way around. Independent risk factors that may determine the need for ECMO or development of chronic lung disease in CDH are intrathoracic position of the liver and observed to expected lung-to-head ratios (Van den Hout et al. 2011). In the present study, antenatal data were not available, but the rate of intrathoracic liver position was 24%. In the cohort from Van den Hout et al. (2011) intrathoracic liver position had been observed in 41% of survivors. This, and the fact that the median duration of ventilation in our study cohort was only 4 days, suggests that disease severity was less in our population compared to CDH patients who nowadays survive.

In conclusion, in the present cohort we found no differences in exercise capacity between our study groups and only slightly increased airflow obstruction in CDH patients with lung hypoplasia. This suggests that residual lung hypoplasia in CDH doesn't seem to play a role in this group of young adults. The finding that exercise capacity is normal in

both groups has to be interpreted with caution because of the lack of more recent reference values.

**Perspectives:**

Based on the conclusions of this study it can be assumed that in patients with CDH no residual lung hypoplasia is present in adulthood. One can argue, however, that the young adults evaluated in the present study had less residual pulmonary sequelae than those born with CDH and lung hypoplasia in more recent years. Survival rates of neonates with severe respiratory failure, including CDH patients with more severe lung hypoplasia, have much improved owing to advancements in intensive care treatment and treatment modalities such as ECMO. We, therefore, conclude that the results of the present study confirm the necessity of intensive follow-up with recommendations about life-style, sports activities and physical activity level.

| | group 1 | group 2 | Paired samples test |
|---|---|---|---|
| $VO_2$peak | n = 26 | n = 27 | |
| % Pred Wasserman | 96.4 (15.4) | 98.0 (14.0) | p = 0.65 |
| % Pred Shvartz ml/min/kg | 84.0 (16.1)† | 84.7 (14.4)† | p = 0.95 |
| % Pred Jones | 91.6 (16.8)§ | 89.3 (13.7)† | p = 0.47 |
| % Pred Fairbarn | 75.3 (14.0)† | 78.5 (11.6)† | p = 0.53 |

**Table 6 Results Cardiopulmonary Exercise Testing using different reference values**

group 1: congenital diaphragmatic hernia patients

group 2: non-CDH patients who underwent similar neonatal treatment

† *One sample t-test p < 0.001 (patients versus norm scores)*

§ *One sample t-test p = 0.017 (patients versus norm scores)*

## References


1. Hamutcu R, Nield TA, Garg M, Keens TG, Platzker AC. Long-term pulmonary sequelae in children who were treated with extracorporeal membrane oxygenation for neonatal respiratory failure. Pediatrics 2004;114(5):1292-1296.

2. Swaminathan S, Quinn J, Stabile MW, Bader D, Platzker AC, Keens TG. Long-term pulmonary sequelae of meconium aspiration syndrome. The Journal of pediatrics 1989;114(3):356-361.

3. Sluiter I, van de Ven CP, Wijnen RM, Tibboel D. Congenital diaphragmatic hernia: still a moving target. Semin Fetal Neonatal Med 2011;16(3):139-144.

4. Lally KP, Engle W. Postdischarge follow-up of infants with congenital diaphragmatic hernia. Pediatrics 2008;121(3):627-632.

5. Gischler SJ, van der Cammen-van Zijp MH, Mazer P, Madern GC, Bax NM, de Jongste JC, van Dijk M, Tibboel D, IJsselstijn H. A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. J Pediatr Surg 2009;44(9):1683-1690.

6. Hayward MJ, Kharasch V, Sheils C, Friedman S, Dunleavy MJ, Utter S, Zurakowski D, Jennings R, Wilson JM. Predicting inadequate long-term lung development in children with congenital diaphragmatic hernia: an analysis of longitudinal changes in ventilation and perfusion. J Pediatr Surg 2007;42(1):112-116.

7. IJsselstijn H, Tibboel D, Hop WJ, Molenaar JC, de Jongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. Am J Respir Crit Care Med 1997;155(1):174-180.

8. Marven SS, Smith CM, Claxton D, Chapman J, Davies HA, Primhak RA, Powell CV. Pulmonary function, exercise performance, and growth in survivors of congenital diaphragmatic hernia. Arch Dis Child 1998;78(2):137-142.

9. Peetsold MG, Heij HA, Nagelkerke AF, IJsselstijn H, Tibboel D, Quanjer PH, Gemke RJ. Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia. Eur Respir J 2009;34(5):1140-1147.

10. Trachsel D, Selvadurai H, Adatia I, Bohn D, Schneiderman-Walker J, Wilkes D, Coates AL. Resting and exercise cardiorespiratory function in survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2006;41(6):522-529.

11. Zaccara A, Turchetta A, Calzolari A, Iacobelli B, Nahom A, Lucchetti MC, Bagolan P, Rivosecchi M, Coran AG. Maximal oxygen consumption and stress performance in children operated on for congenital diaphragmatic hernia. J Pediatr Surg 1996;31(8):1092-1094; discussion 1095.

12. Spoel M, van der Cammen-van Zijp MH, Hop WC, Tibboel D, de Jongste JC, IJsselstijn H. Lung function in young adults with congenital diaphragmatic hernia; a longitudinal evaluation. Pediatr Pulmonol 2012.

13. van der Cammen-van Zijp MH, Gischler SJ, Hop WC, de Jongste JC, Tibboel D, IJsselstijn H. Deterioration of exercise capacity after neonatal extracorporeal membrane oxygenation. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 2011;38(5):1098-1104.

14. Peetsold MG, Vonk-Noordegraaf A, Heij HH, Gemke RJ. Pulmonary function and exercise testing in adult survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2007;42(4):325-331.

15. Chisholm DM, Collis ML, Davenport W, Gruber N, Stewart GW. PAR-Q validation report: the evaluation of a self-administered pre-exercise screening questionnaire for adults. Victoria, BC: BC Ministry of Health and Health and Welfare Canada; 1978.

16. American College of Sports Medicine. ACSM's Guidelines for Exercise testing and Prescription: 8 th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2009.

17. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008;177(3):253-260.

18. Stam H, Hrachovina V, Stijnen T, Versprille A. Diffusing capacity dependent on lung volume and age in normal subjects. J Appl Physiol 1994;76(6):2356-2363.

19. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167(2):211-277.

20. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation. Philadelphia: Lippincott Williams & Wilkins; 2005.

21. Reinhard U, Muller PH, Schmulling RM. Determination of anaerobic threshold by the ventilation equivalent in normal individuals. Respiration 1979;38(1):36-42.

22. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-381.

23. Wasserman K, Hanssen J, Sue D, Stringer W, Whipp B. Principles of Exercise Testing and Interpretation: Philadelphia: Lippincott Williams & Wilkins; 2005.

24. Burtis C, Ashwood E, eds. Tietz Textbook of Clinical Chemistry. Philadelphia; 1994.

25. Nieuwenhuijsen C, van der Slot WM, Dallmeijer AJ, Janssens PJ, Stam HJ, Roebroeck ME, van den Berg-Emons HJ, Transition Research Group South West N. Physical fitness, everyday physical activity, and fatigue in ambulatory adults with bilateral spastic cerebral palsy. Scand J Med Sci Sports 2011;21(4):535-542.

26. van den Berg-Emons RJ, Bussmann JB, Stam HJ. Accelerometry-based activity spectrum in persons with chronic physical conditions. Arch Phys Med Rehabil 2010;91(12):1856-1861.

27. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep 2008;31(11):1601-1607.

28. Merkies IS, Schmitz PI, Samijn JP, van der Meche FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Neurology 1999;53(8):1648-1654.

29. Fougeyrollas P, Noreau L, Bergeron H, Cloutier R, Dion SA, St-Michel G. Social consequences of long term impairments and disabilities: conceptual approach and assessment of handicap. Int J Rehabil Res 1998;21(2):127-141.

30. Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. Pharmacoeconomics 2000;17(1):13-35.

31. Zee Klvd, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken RUG 1993.

32. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47(3):316-323.

33. Vrijlandt EJ, Gerritsen J, Boezen HM, Grevink RG, Duiverman EJ. Lung function and exercise capacity in young adults born prematurely. Am J Respir Crit Care Med 2006;173(8):890-896.

34. Fairbarn MS, Blackie SP, McElvaney NG, Wiggs BR, Pare PD, Pardy RL. Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. Chest 1994;105(5):1365-1369.

35. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. Am Rev Respir Dis 1985;131(5):700-708.

36. van der Cammen-van Zijp MH, van den Berg-Emons RJ, Willemsen SP, Stam HJ, Tibboel D, IJsselstijn H. Exercise capacity in Dutch children: new reference values for the Bruce treadmill protocol. Scandinavian journal of medicine & science in sports 2009.

37. Trachsel D, Selvadurai H, Bohn D, Langer JC, Coates AL. Long-term pulmonary morbidity in survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2005;39(5):433-439.

38. Vanamo K, Rintala R, Sovijarvi A, Jaaskelainen J, Turpeinen M, Lindahl H, Louhimo I. Long-term pulmonary sequelae in survivors of congenital diaphragmatic defects. J Pediatr Surg 1996;31(8):1096-1099; discussion 1099-1100.

39. van der Cammen-van Zijp MH, IJsselstijn H, Takken T, Willemsen SP, Tibboel D, Stam HJ, van den Berg-Emons RJ. Exercise testing of pre-school children using the Bruce treadmill protocol: new reference values. Eur J Appl Physiol 2010;108(2):393-399.


# Recurrent diaphragmatic hernia in two young adults: Lung function before and after repair.

Marjolein Spoel, John Vlot, Kees P van de Ven, Johan C de Jongste, Dick Tibboel, Hanneke IJsselstijn.

Submitted

## Abstract

We report 2 cases of recurrent CDH in young adult patients in whom we measured lung function before and after repair of the defect. Lung volumes and airway patency did not differ between the two measurements. Diffusion capacity had deteriorated slightly in both patients (SDS $DL_{CO}c$ from -4.29 to -5.06 and from -1.67 to -3.41; SDS $K_{CO}c$ from -2.16 to -3.50 and from -0.44 to -1.48). Our findings suggest that recurrence of the diaphragmatic defect had not measurably compromised lung function.

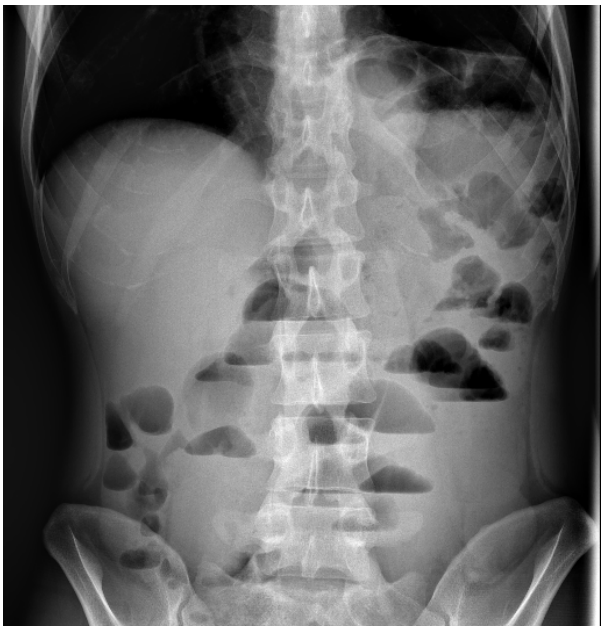

## Introduction

Survival rates of patients with congenital diaphragmatic hernia (CDH) have improved to up to 80% [1] and the focus of CDH research has therefore shifted from mortality to morbidity [2]. Recurrent congenital diaphragmatic hernia is a complication with a reported incidence between 3 and 22% [3-5]. Primary repair is applied in smaller defects; prosthetic materials are used in larger defects. Patch repair has been suggested to be a risk factor for recurrence [6]. We report 2 cases of young adult CDH patients who underwent lung function measurements in the course of a longitudinal follow-up study, and within 3 years after evaluation appeared to have a late recurrence of CDH. To determine whether lung function had changed after repair of the diaphragmatic defect, we repeated lung function tests postoperatively.

## Case reports

Patient 1

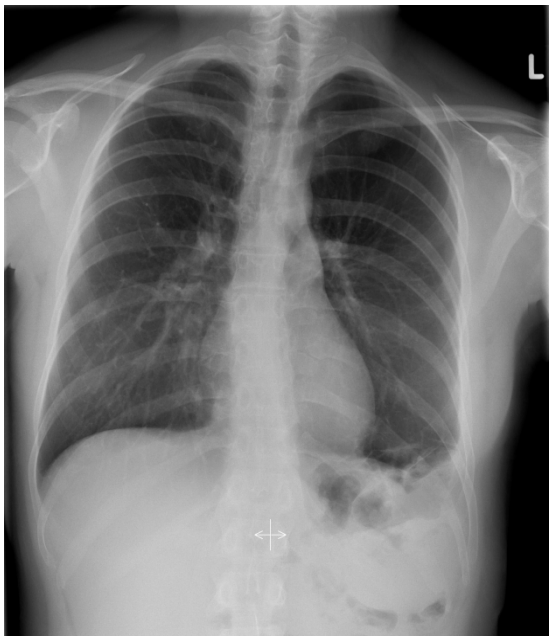
At 23-year-old male performed a lung function test in June 2008. He had been born with a left-sided diaphragmatic hernia at a gestational age of 40 weeks, birth weight 3500 g, and needed mechanical ventilation for 20 days and supplemental oxygen for 25 days in the neonatal period. The defect was closed in the neonatal period with a Lyodura patch (human cadaver, B. Braun Melsungen AG, Germany). At the day of lung function testing, he suffered from mild abdominal discomfort. On physical examination chest auscultation was normal, without bowel sounds. In May 2009 he was admitted to a regional hospital with intestinal obstruction signs which on CT-imaging appeared to be due to herniation of bowel loops into the thoracic cavity. Conservative therapy was successful and he was referred to our centre. Four months later he underwent surgical repair of a two-fist large posterolateral defect, which was closed using a Gore-tex® patch of 15x19 cm. Ten months postoperatively – in July 2010 – his lung function was re-evaluated. Test results are shown in the Table.



Abdominal X-ray patient 1: Recurrent CDH with bowel loops protruding in the left side of the thoracic cavity.

Patient 2

A 21-year-old female performed a lung function test also in February 2008. She had been born with a left-sided CDH and underwent Lyodura patch repair in the neonatal period as well. At the age of 19 years she underwent a Nissen fundoplication for therapy-resistant gastro-esophageal reflux (GER). On the day of lung function testing, she had had no symptoms at all. Physical examination revealed no abnormalities, with normal breathing sounds on chest auscultation. In January 2011, 35 months later, she developed progressive tenderness in the upper left abdomen. CT-imaging revealed that colon and spleen had herniated into the chest. Eight months later, she underwent surgical repair by thoracotomy of the recurrent diaphragmatic defect. Bowel loops protruded into the thoracic cavity and a large posterolateral defect in the diaphragm was closed using a Gore-tex® patch. In November 2011, 2 months after surgery, her lung function was re-evaluated. Test results are shown in the Table.




Chest X-ray patient 2: Recurrent CDH with bowel loops protruding in the left side of the thoracic cavity.

| | **Patient 1** | | **Patient 2** | |
|---|---|---|---|---|
| | 1st test | 2nd test | 1st test | 2nd test |
| Spirometry | | | | |
| $FEV_1$ | -1.61 | -1.43 | -0.13 | -0.71 |
| FVC | -1.91 | -1.76 | -0.46 | -1.14 |
| $FEV_1$/FVC | 0.20 | 0.29 | 0.25 | 0.57 |
| $FEF_{25-75}$ | -0.66 | -0.50 | 0.25 | -0.35 |
| $TLC_{He}$ | -2.27 | -2.19 | 0.56 | -0.28 |
| $RV_{He}$ | -0.90 | -1.12 | 0.78 | -0.14 |
| $FRC_{He}$ | -0.81 | -0.72 | 0.32 | -0.60 |
| $RV/TLC_{He}$ (%) | 22.86 | 20.85 | 30.86 | 27.19 |
| Plethysmography | | | | |
| $TLC_{pleth}$ | -1.63 | -1.56 | 0.65 | 0.38 |
| $RV_{pleth}$ | -0.53 | 0.24 | 0.91 | 1.27 |
| $FRC_{pleth}$ | -0.92 | 0.09 | 0.26 | 0.09 |
| $RV/TLC_{pleth}$ (%) | 23.31 | 27.87 | 31.41 | 35.18 |
| $FRC_{pleth}/FRC_{He}$ (%) | 0.97 | 1.16 | 0.99 | 1.15 |
| Diffusion capacity | | | | |
| $DL_{CO}c$ | -4.29 | -5.06 | -1.67 | -3.41 |
| $K_{CO}c$ | -2.16 | -3.5 | -0.44 | -1.48 |

**Table 1** *Lung function after bronchodilation at the first and second test in 2 patients. Standard deviation scores (SDS) for spirometry, plethysmography and diffusion capacity were calculated from the absolute data as described previously [7]. He: static volumes measured by helium spirometry; pleth: static lung volumes measured by bodyplethysmography; $D_{LCO}c$: diffusion corrected for haemoglobin concentration. $K_{CO}c$: diffusion corrected for haemoglobin concentration and alveolar volume.*

## Discussion

Recurrence of CDH may be asymptomatic and accidentally detected on chest X-ray performed for another reason. However, most recurrences present with symptoms that can be either respiratory with coughing and wheezing, or gastrointestinal with reflux and feeding difficulties or with pain due to obstruction [8]. The age at presentation varies considerably [6], but late recurrences after several years are rare [8]. Only one study has specifically evaluated risk factors for recurrence [6]. This study reported a 14% incidence of recurrence in CDH patients within 7 months after the initial repair and found that a right-sided defect, the use of a patch and extracorporeal membrane oxygenation (ECMO) accounted for a higher risk. Our patients both had a left-sided defect and were treated before ECMO was available in our institution. In both cases, the primary defect in the diaphragm had been repaired in the neonatal period by a Lyodura patch. Both patients have been free of symptoms until young adulthood. Prior to the diagnosis of recurrent CDH, these 2 patients participated in a study on long term pulmonary sequelae of CDH. Until then, none of the other patients (n=25) had presented with recurrent hernia. Lung function was re-evaluated 10 months (patient 1) and 2 months (patient 2) after repair of the recurrent CDH. As both patients had a large diaphragmatic defect with a considerable volume of bowel in the thoracic cavity during surgery, we assumed that lung volumes could have been compromised at the first test. Most studies in adult CDH patients, including our own, report normal TLC values with increased RV/TLC ratios and reduced KCOc, consistent with radiographically confirmed, hyperinflated and hypoplastic lungs [9]. In these 2 patients lung volume as reflected by TLC had not noticeably deteriorated between the first and second test. In both, diffusion capacity had deteriorated slightly over time. Patient 1 smoked 20 cigarettes/day, which might have contributed to this, although the elapsed time between the measurements was rather short to explain such a deterioration [10]. Patient 2 was a lifelong non-smoker and we found no explanation for the decrease in KCOc. She had suffered from GER, however, for which anti-reflux surgery was performed at the age of 19. Prolonged periods of (micro)aspirations may influence lung function negatively. Airflow obstruction could be due to compression of lung tissue by bowel loops in the thorax. This assumption was not supported by the spirometric findings in the second lung function test. In patient 1, airflow obstruction had slightly improved whereas in patient 2 it had slightly worsened. In patient 2, the relatively short time span since thoracotomy could have compromised a forced expiratory manoeuvre during spirometry.

We conclude that in 2 patients with recurrent CDH, the diffusion capacity of the lungs deteriorated after operative closure of the diaphragm defect without any changes in expiratory flows or lung volumes. We speculate that at the first evaluation abdominal organs had not yet herniated into the chest, or that any volume effect had been minimal. Although recurrence of CDH in adulthood is rare, thorough examination including chest X-ray, should be considered in case of suspect gastrointestinal symptoms.

## References

1. van den Hout L, Schaible T, Cohen-Overbeek TE, Hop W, Siemer J, van de Ven K, Wessel L, Tibboel D, Reiss I. Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. Fetal Diagn Ther 2011;29(1):55-63.

2. American Academy of Pediatrics Section on S, American Academy of Pediatrics Committee on F, Newborn, Lally KP, Engle W. Postdischarge follow-up of infants with congenital diaphragmatic hernia. Pediatrics 2008;121(3):627-632.

3. Cohen D, Reid IS. Recurrent diaphragmatic hernia. J Pediatr Surg 1981;16(1):42-44.

4. Koot VC, Bergmeijer JH, Molenaar JC. Lyophylized dura patch repair of congenital diaphragmatic hernia: occurrence of relapses. J Pediatr Surg 1993;28(5):667-668.

5. Simson JN, Eckstein HB. Congenital diaphragmatic hernia: a 20 year experience. Br J Surg 1985;72(9):733-736.

6. Hajer GF, vd Staak FH, de Haan AF, Festen C. Recurrent congenital diaphragmatic hernia; which factors are involved? Eur J Pediatr Surg 1998;8(6):329-333.

7. Spoel M, van der Cammen-van Zijp MHM HW, Tibboel D, de Jongste JC, IJsselstijn H. Lung function in young adults with congenital diaphragmatic hernia; a longitudinal evaluation. Pediatr Pulmonol. 2012 Mar 26. doi: 10.1002/ppul.22557. [Epub ahead of print]

8. Rowe DH, Stolar CJ. Recurrent diaphragmatic hernia. Semin Pediatr Surg 2003;12(2):107-109.

9. Peetsold MG, Heij HA, Nagelkerke AF, IJsselstijn H, Tibboel D, Quanjer PH, Gemke RJ. Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia. Eur Respir J 2009;34(5):1140-1147.

10. Van Ganse WF, Ferris BG, Jr., Cotes JE. Cigarette smoking and pulmonary diffusing capacity. Chest 1971;59:Suppl:33S.

# General discussion

## General discussion

The studies in this thesis generally deal with the short-term and long-term respiratory morbidity associated with severe congenital anomalies such as congenital diaphragmatic hernia, esophageal atresia and congenital lung lesions. After all, the better survival of children with these conditions achieved in the past decades coincides with increased morbidity, also due to adverse effects of intensive care treatment such as high inspiratory oxygen fraction, shear forces and high peak inspiratory pressures during mechanical ventilation. A role of neonatal ECMO-treatment herein has been suspected as well.

In January 1999 we started a multidisciplinary follow-up program aimed to evaluate and potentially reduce the overall morbidity associated with major anatomical anomalies, to offer better care and to improve lines of communication. In 2001 children treated with ECMO became a target group as well [1]. Many of the problems encountered in children with major congenital anomalies are also found in ECMO-treated patients and the patient populations partly overlap. In this follow-up program pulmonary function and/or respiratory morbidity are assessed routinely at the ages of 6, 12 and 24 months and at 5, 8, 12 and 18 years. At 18 years, transition to adult specialists and targeted genetic counselling is accomplished.

The most important aims of the studies presented in this thesis are:

- to evaluate lung function and respiratory morbidity in the first year of life in children with congenital diaphragmatic hernia who either received or not received ECMO treatment (Chapter 1).
- to evaluate lung function and respiratory morbidity in the first year of life in infants with esophageal atresia after thoracotomy or thoracoscopic surgery and in infants with congenital lung lesion, asymptomatic or after resection of the affected lung part(s) (Chapters 2 and 3).
- to study lung function and respiratory morbidity at 5, 8 and 12 years of age after neonatal ECMO treatment for congenital diaphragmatic hernia, meconium aspiration syndrome, and other diagnoses (Chapter 4).
- to assess lung function and exercise capacity in young adults with congenital diaphragmatic hernia and in matched controls, who underwent similar neonatal treatment (Chapter 5 and 6).
- to describe two patients in this cohort with a recurrent diaphragmatic defect presenting with gastrointestinal symptoms (Chapter 7).

Based on the findings of our studies and the literature so far, we will elaborate on the pulmonary morbidity in congenital diaphragmatic hernia, esophageal atresia and congenital lung lesions. Moreover, we give recommendations for future research.

## Congenital diaphragmatic hernia

Interference in early embryonic development of both the lungs and the diaphragm may lead to herniation of the abdominal organs in the thoracic cavity causing pulmonary hypoplasia and maldevelopment of the lungs [2]. This condition is termed congenital diaphragmatic hernia (CDH). Furthermore, either structural or functional abnormalities of pulmonary vasculature cause pulmonary hypertension [3-5]. The pulmonary artery density is decreased and the media and adventitia of the small arteries are thickened [6] causing reduced blood flow through the lungs and subsequent hypoxia. Directly after birth mechanical ventilation is started which in itself is associated with baro- and volutrauma and may cause ventilator-induced lung injury comprising alveolar septal damage, inflammation, fibrosis and pulmonary edema [7-8]. Besides intensive ventilation and oxygenation techniques, postnatal infections, such as sepsis and airway colonization, may also predispose for pulmonary injury [9].

During the last 20 years, 'gentle' ventilation and permissive hypercapnia [10-12], delayed surgery [13] and improved peri-operative care [14] have contributed most to bringing down mortality in this condition. As multicenter randomized controlled trials on CDH are lacking, only standardized treatment protocols may enable more valid comparisons of patient data in multicenter studies and identify areas for future research[15]. A collaboration of specialized CDH centers in Western Europe, the CDH-EURO consortium, has developed a consensus statement for the postnatal treatment of patients with CDH based on the recent literature and expert opinion [15]. After the implementation of a standardized treatment protocol the survival rates in CDH patients are now approaching 80% [14,16]. This forms the basis for the VICI trial which may provide further insight in ventilation strategies in CDH patients (NTR1310) [17].

### *ECMO treatment*

In case conventional treatment strategies fail, ECMO can be used as a form of cardiopulmonary bypass for severe, but reversible cardiopulmonary failure. ECMO improved survival rates in infants with respiratory failure due to meconium aspiration syndrome, respiratory distress syndrome or sepsis [18]. Its benefit for infants with CDH is still unclear [19]. Especially ECMO-treated CDH patients, who have the most severe form of lung hypoplasia and pulmonary hypertension, should herefore be followed thoroughly to asses long-term outcome and provide optimal care in their first years of life. Because of this evolution in the treatment of CDH in the last decades, there is a need for longitudinal follow-up of cohorts of CDH patients, treated in the same period. Respiratory morbidity and long-term outcome with respect to pulmonary function can not be extrapolated from today's adult CDH survivors to children who survived in recent years.

*Respiratory morbidity*

Several cross-sectional studies evaluated lung function in children with CDH and found peripheral airway obstruction in infancy [20], childhood [21-23] and adulthood [24-25]. Although pulmonary hypoplasia is present, restrictive impairment is not a common finding in CDH. Lung volumes in childhood and adulthood are usually within the normal range [22-23,25]. Most likely the hypoplasia has been compensated for by alveolar distension and consequently hyperinflation [26-27].

Prospective longitudinal studies in these patients are scarce. In 2011 our group reported on lung function in the first year of life in infants after neonatal ECMO treatment born between 2001-2005. They found significantly more hyperinflation, as reflected by higher $FRC_{p,}$ in CDH patients than in patiens with with meconium aspiration syndrome (MAS). Maximal expiratory flow at functional residual capacity ($V'max_{FRC}$) was significantly below the average in both groups without a change in the first year and did not differ between groups [28].

We conducted several longitudinal studies to evaluate lung function in more detail in CDH patients, with and without ECMO treatment.

In a group of CDH patients we found decreased expiratory flows and hyperinflation within the first year of life. Twenty-eight percent of these patients had received ECMO treatment. The $FRC_p$ in these patients was significantly higher than that in non-ECMO treated patients, especially in those who had developed chronic lung disease (CLD). $V'max_{FRC}$ did not differ between ECMO treated and non-ECMO treated patients (Chapter 1).

A second study concerned children who as neonates had received ECMO treatment for various conditions. Longitudinal evaluation of lung function between the ages of 5 to 12 years revealed significantly more airflow obstruction and higher prevalence of hyperinflation in CDH patients than in children with other conditions. Lung function in CDH patients tended to deteriorate over time (Chapter 4).

The third longitudinal study concerned a cohort of young adults with CDH who at a median age of 11.7 years had shown mild airflow obstruction and reduced diffusion capacity. Now, 15 years later, the airflow obstruction and diffusion capacity had slightly deteriorated. Taking into account similar findings – although less robust – in controls who as neonates also had received intensive care for respiratory problems, we concluded that neonatal intensive care treatment had contributed to the long-term pulmonary problems in CDH survivors [22] (Chapter 5).

In all above-mentioned studies, ventilation and/or supplemental oxygen time and $FRC_p$ levels in infancy correlated positively with extent of airflow obstruction in child- and adulthood. In childhood and adulthood, we found increased RV%TLC and $FRC_{pleth/spiro}$ > 1.10 in CDH patients, which may reflect hyperinflation caused by alveolar distension [29].

Importantly, the group of CDH survivors from the seventies and eighties had milder forms of lung hypoplasia and/or pulmonary hypertension than today's group of survivors. Their lung function had only slightly deteriorated since childhood. Both the anatomical anomaly itself and neonatal treatment could be responsible for deteriorated lung function. Among today's CDH survivors are patients with more severe disease requiring mechanical ventilation and supplemental oxygen for a longer time. Eventually we may be faced, therefore, with a population of adult CDH patients with much more respiratory problems and impaired lung function. This relative negative outcome may be counterbalanced nowadays by the increasing use of gentle ventilation and permissive hypercapnia to prevent triggering inflammatory responses resulting in chronic lung disease (CLD) [30]. Greenough showed that in premature infants without CDH respiratory morbidity was still present in adolescence [31]. Seeing that our studies also rather consistently found airflow obstruction and hyperinflation at different ages, we are concerned these CDH patients may develop clinically significant chronic obstructive pulmonary disease (COPD) and/or emphysema in the future. In a study on preterm infants ventilated for respiratory distress syndrome, 20% had radiological evidence of pulmonary interstitial emphysema [32]. The development of this condition was significantly associated with the use of high peak pressures.

Chronic pulmonary impairment may be associated with compromised exercise capacity [33]. Also, preterm born adults showed reduced pulmonary blood flow and gas transfer during exercise [34]. And then, exercise capacity of ECMO-treated patients aged 5 to 12 years, with or without CDH, was significantly worse than expected from reference data, and deteriorated over time [35]. Therefore we also examined exercise capacity in the earlier mentioned cohort of young adults with CDH. It was not significantly different from exercise capacity of a cohort of matched controls without CDH and lung hypoplasia. This finding suggests that residual lung hypoplasia did not affect outcome. For today's CDH survivors however, and especially those treated with ECMO and prolonged mechanical ventilation, we expect they are at serious risk for worsening lung function and exercise capacity in time [31,34,36]. Considerable impairment in daily life could be their perspective, unfortunately. Bronchopulmonary dysplasia (BPD) was originally characterized by airway injury, smooth muscle hypertrophy and lung parenchymal fibrosis with emphysematous changes [37]. The new BPD may occur with little acute lung injury and is believed to be affected by factors such as inflammation and the presence of a patent ductus ateriosus [38-39]. CLD encompasses both the classic and the new BPD but also recognizes that lung injury can occur not only in preterm infants but in term infants who need aggressive ventilatory support for severe lung disease and develop lung injury as a result [39]. We therefore defined oxygen dependence after 28 days of postnatal age as CLD and not as BPD in our population of, mostly term born, CDH patients.

## Esophageal atresia

Tracheomalacia and respiratory morbidity in esophageal atresia (EA) with tracheoesophageal fistula (TEF) have been described in multiple studies [1,40-41]. Lung function abnormalities with obstructive as well as restrictive patterns have been described at different ages in infancy [40,42], and childhood [40,43-44] to adulthood [43,45-46]. Restrictive lung function is supposed to result from reduced lung growth after surgery rather than being a concomitant feature of EA [46]. Thoracotomy-induced rib fusions and gastro-esophageal reflux disease (GERD) associated problems are considered major risk factors for restrictive ventilatory patterns in EA patients later in life [46]. Thoracoscopic repair might help reduce these restrictive lung function abnormalities [47]. The above-mentioned cross-sectional studies described lung function abnormalities at different ages. To our knowledge, we performed the first prospective, longitudinal evaluation of lung function and respiratory morbidity in a cohort of 37 infants with EA (Chapter 2). Lung volume was normal during the first year of life, and did not differ between those who had undergone a thoracotomic or a thoracoscopic type of repair. In contrast, $FRC_p$ values were in the upper normal range and increased from 6 to 12 months. There is no reason to assume that this higher $FRC_p$ value is based on catch-up lung growth during the first year of life after repair of EA. It might well be that persistent higher airway obstruction caused by tracheomalacia, together with recurrent respiratory tract infection, caused mild hyperinflation, reflected by $FRC_p$ values in the upper normal range. Rib fusions were present only in 3 patients (8%) in our study, but in around 30% in a study in adult EA patients [48]. Infant lung function testing (ILFT) was not associated with respiratory morbidity at 2 and 5 years of age in this patient group with EA-TEF. For clinical management, we consider ILFT in the first year of life of limited value. Clinical care should especially focus on GERD and active treatment, nutritional status and the prevention of respiratory tract infection. Low-threshold use of antibiotics, prophylactic antibiotics and vaccination for respiratory syncytial and influenza virus is recommended in case of recurrent respiratory tract infections.

## Congenital cystic lung lesions

The incidence of antenatally diagnosed congenital lung lesions (CLL) has increased. Studies on infants with CLL mostly focus on etiology, diagnosis, natural history of the lesions and neonatal survival. To our knowledge, no studies on clinical course and respiratory outcome are available (Chapter 3). It is likely to assume that the true incidence of CLL has not changed over the years but rather that prenatal ultrasound imaging has become more sensitive and that it is implemented as a routine procedure at 20 weeks of gestation from 2007 onwards. Especially congenital cystic adenomatoid malformations (CCAM) has resulted in growing doubt with regards to the prediction of the natural history during pregnancy. This results into major uncertainty by consultants and parents with significant burden for both groups. The ‘increasing’ incidence has

considerable implications for the management of CLL. If resection is advocated in these cases, many children will be undergoing lung surgery in the near future [49]. The management of asymptomatic CLL is still controversial. Some authors recommend observation, however most authors favor surgical resection, at least for CCAM, intralobar sequestration and bronchogenic cysts [50]. Finally, others recommend surgery for 'significant' lesions and observation of smaller ones [51-52]. Arguments for observation are the unknown natural history and possible regression and secondly the disadvantages and risks of thoracotomy and lung resection [50]. Arguments against prolonged observation are the risk of infection, pneumothorax or sudden cyst enlargement with respiratory compromise, cases of malignancy occurring in such lesions, faster post-operative recovery in a young asymptomatic child, and early resection allowing for compensatory lung growth [50]. We assume that $FRC_p$ does not accurately reflect lung volume, and there is less suitable to assess compensatory lung growth in the first year of life. This assumption is based, first, on our findings that both $FRC_p$ and $V'max_{FRC}$ did not significantly differ between the infants who underwent resection and those who did not, and, second, on the fact that we found no significant associations between clinical characteristics and lung function parameters.

## Limitations of the studies

*Infant lung function testing*

ILFT has progressed in the last decade and has contributed to the understanding of normal lung development as well as the mechanisms involved in lung disease [53]. Reference values for various populations are lacking, however. A potential limitation of our research was that we were not allowed to examine healthy controls, as sedation of healthy infants for research purposes is not permitted in the Netherlands. Therefore, we had to use reference values published by others. The earlier reference equations to compute $FRC_p$ into standard deviation scores (SDS) are perhaps not entirely appropriate for data obtained with the newer equipment. The more recent low deadspace equipment for plethysmographic measurements resulted at introduction in much lower SDS than predicted [54]. We expressed $FRC_p$ values in mL/kg. Earlier published prediction equations could not be used to interpret $FRC_p$ results obtained with our newer equipment. Expressing results as mL/kg, is acceptable when pertaining to neonates, as the regression of $FRC_p$ on weight is relatively linear and passes close to the origin [55]. Until new reference data are available, users of new equipment would do well to interpret results cautiously. There is therefore an urgent need for collaborative studies of healthy infants using the same equipment and carefully standardized protocols for data collection, analysis, and quality control, so that new reference data can be established as rapidly as possible. Collation of appropriate reference data in healthy infants, not only for lung volumes but also for all other parameters of lung function in infants, could be facilitated by the ERS/ATS taskforce by use of the improved and readily available

contemporary equipment. The normal range of $FRC_p$, suggested by Hülskamp et al. is 13-26 mL/kg, mean 19.6, SD 3.4 [54]. $FRC_p$ as measured by whole body plethysmography is based on Boyle's law and includes the volume of any gas trapped behind obstructed airways [55]. In case of normal anatomy of the lungs and normal peripheral airway diameter, $FRC_p$ reflects lung volume well. In case of hyperinflation and/or airway obstruction $FRC_p$ is overestimated and rather reflects airway pathology. These measurements depend on rapid equilibration of pressures during respiratory efforts against occlusions, so that pressure changes at the airway opening reflect those in the alveoli. In the presence of airway obstruction, this equilibration may not occur [55]. Assessments of FRC by gas dilution or washout are similarly non-invasive but require the infant to remain asleep for at least 10 minutes, whereas 5 measures of $FRC_p$ can be collected in less than 5 minutes. Furthermore, in the presence of airway obstruction and uneven ventilation, FRC may be seriously underestimated if insufficient time is allowed for complete equilibration of gas concentrations [56-57]. For all these reasons we chose the plethysmographic assessment of FRC. In our population of infants with CDH, EA, or CLL we find many cases of hyperinflation due to enlarged air filled spaces in the lung and/or and secondary to airway obstruction. Alveolar size may be increased in CDH,[58] and ventilation-perfusion data suggested that most of the lung growth from 0.1-13 years was caused by expansion of already existing alveoli and not by greater abundance of alveoli [59]. Significant inhomogeneity of ventilation was shown by lung clearance index measurement in CDH patients in the first year of life [60]. Also, in prematurely born BPD patients, our group found mean $FRC_p$ values in the upper normal range in a previously performed study [61]. In EA, airway malacia may cause airway obstruction and perhaps some hyperinflation. In CLL we also found mild airflow obstruction and $FRC_p$ measurements in the upper normal or above normal range we speculate this may be due to ventilation heterogeneity secondary to the cystic lesion, or disrupted anatomy due to resection. In CDH, EA and CLL we therefore assume that high and above normal $FRC_p$ rather reflects airway pathology than a beneficial high lung volume.

Interrupter technique measurements are feasible to assess airway function in infants and preschool children and proved to be sensitive in detecting airway calibre changes, monitoring the effect of interventions and identifying subgroups with mild respiratory symptoms among children from a general population [62-64]. However, the between-occasion repeatability is too poor for intra-individual detection of changes and therefore less suitable for longitudinal measurements in our studies [62].

Forced oscillation technique (FOT) provides information on the mechanical properties of the respiratory system and requires only normal tidal breathing without performance of respiratory manoeuvres. However, it is a sensitive measure for airway obstruction but it does not discriminate between obstructive and restrictive lung disorders [65], which is of particular interest in the population of children we studied.

*Reference values for longitudinal lung function testing*

Selecting an appropriate reference data set is essential for interpretation of lung function data and especially for longitudinal measurements in children of various ages, seeing that lung function increases 20-fold during the first 10 years of life [66]. Quanjer and Stanojevic compared 30 spirometry datasets worldwide in Caucasian subjects. They concluded that the use of local controls to validate reference equations will rarely be practical due to the high numbers required. Therefore, reference equations derived from large or collated datasets can be recommended. Differences between the largest datasets were small and clinically minimal [67]. In another study Quanjer et al. compared five commonly used reference equation sets to serial measurements in Dutch, German and Austrian children. They found that Stanojevic's equations performed best and are suitable for longitudinal data analysis as they cover a wide age range from 4-80 years and account for a gradual transition from childhood into adulthood [68]. Taking this into consideration, and to facilitate comparison of our study with other recent studies, we used Stanojevic's reference equations for longitudinal spirometry in our 5-, 8- and 12-year-old patients after neonatal ECMO treatment, and in young adult CDH patients [69].
Recently, researchers in the department of Paediatric Pulmonology in the University Medical Centre-Wilhelmina Children's Hospital, Utrecht, the Netherlands, published new Dutch reference data for spirometry, using age, height and sex as determinants for pulmonary function. They measured a healthy population of Dutch, Caucasian children aged 6-18 years using similar methods as in our study [70]. Therefore, we considered to use these new reference equations for spirometry, lung volumes and diffusion capacity, and recalculated standard deviation scores according to the new equations by Koopman et al. The results did not alter the main conclusions of our study. However, we decided not to use these new reference equations for the studied population of 5-, 8- and 12-year old ECMO-treated patients for several reasons: First, the Utrecht dataset only provides reference equations for spirometric values before bronchodilation. Second, reference equations for $FEV_1$/FVC are not available for 5-year-old children. Third, and perhaps most important, we encountered a number of ambiguities in the newly published reference equations which are currently being reassessed by the Utrecht research group. Although the main conclusions of our study were not altered by using their reference equations, differences between spirometric values expressed as SDS according to these reference equations and those by Stanojevic were striking. Especially spirometric values further below the normal range deviated to a greater extent.
Also, longitudinal reference data for static lung volumes and diffusion capacity are lacking. Longitudinal comparison of static lung volumes from childhood to adulthood was therefore not possible. For diffusion capacity, we used reference equations from Stam and colleagues for 6 to 18-year-olds and those for adults from the age of 18 years [71-72].

*Lung function testing; reflection of abnormal pulmonary development?*

As lung function testing in infants and children has progressed over the last 20 years, many research questions have been addressed and there is now consensus how the techniques should be applied [73-75]. However, lung function tests reveal mainly the physiological representation of abnormal pulmonary development. The anatomical substrate for lung function results, as well as questions concerning evolvement of these anatomical malformations with increasing age, are not being addressed. Also, abnormal vascular development and ventilation- perfusion abnomalities as described in CDH patients [76], may influence diffusion capacity but studies relating diffusion capacity to vascular anatomy are lacking . We consider this a limitation of the previously mentioned studies. Additional information on anatomy would contribute to our knowledge on congenital pulmonary anomalies and the future perspective of today's survivors. Therefore, imaging could enable and substantiate interpretation of these lung function results.

*Reference values for exercise capacity*

A limitation of the study on exercise capacity is the lack of recent reference values for exercise capacity in young adults indicated as $V0_2$ peak. It could be argued that the reference values for $VO_2$ peak may not be appropriate for our population, because they were collected several years ago and in a different population [77]. We recalculated our results with different sets of reference values and chose the reference data by Wasserman et al. These reference data enabled us to compare our results with other studies and these calculations also took weight and height into account to correct for differences in gender distribution [78].

## Recommendations for clinical practice

From the results of our studies we concluded that $FRC_p$ does not accurately reflect lung volume but that it is rather a measure for hyperinflation. $V'max_{FRC}$ remained stable in the first year of life in our studied populations and is only indicative, but not conclusive for airway malacia. $FRC_p$ and $V'max_{FRC}$ measurement were considered of limited value for daily practice our studied population of infants with CDH, EA and CLL.

Lung function can be assessed accurately but we do not foresee ILFT as a routine in infants with congenital pulmonary anomalies. These are at risk for multiple problems that may interact with each other: residual lung hypoplasia, chronic lung disease resulting from prolonged ventilation, recurrent RTI, growth impairment, GERD, delayed motor function development, and impaired exercise tolerance. For these children, especially those with CDH and EA who suffered from a complicated course, we recommend standardized multidisciplinary follow-up until adulthood including assessment of respiratory symptoms, longitudinal lung function measurements and lung imaging. In

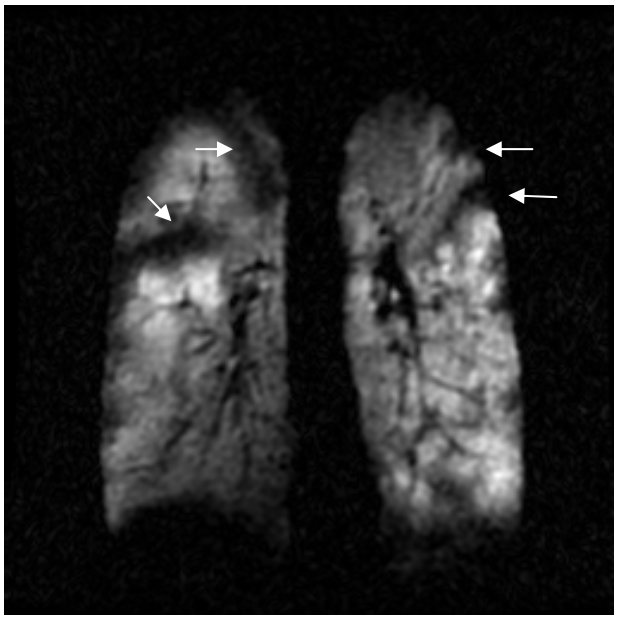
case of respiratory problems and/or lung function abnormalities, we recommend referral to a pediatric pulmonologist for monitoring. Early, adequate treatment of infections and asthma may prevent deterioration of lung function. Active treatment of GERD, improving nutritional status and the low-threshold use of antibiotics, prophylactic antibiotics and vaccination for respiratory syncytial and influenza virus is recommended in case of recurrent respiratory tract infections.

With the increased survival of CDH patients with more severe pulmonary hypertension in the first weeks of life we recommend cardiac evaluation in the first years of life with a focus on persistent pulmonary hypertension as well as prolonged follow-up on respiratory morbidity and exercise capacity.

We saw two adult CDH patients with gastrointestinal symptoms caused by recurrent diaphragmatic hernia within 3 years after participation (Chapter 7). Therefore, thorough examination, including appropriate imaging techniques, should be considered in CDH patients in case of suspect gastrointestinal symptoms.

**Recommendations for future research**

Studies on the morphological substrate of functional lung changes in CDH are scarce. Today's survivors of CDH may develop into COPD patients in the future. Furthermore, it is unknown to what extent compensatory lung growth occurs after birth. Volumetric imaging techniques like CT and MRI scans enable to identify the degree of air trapping [79-80] and can be used to monitor progression of the morphological changes. Alveolar dimensions can be measured non-invasively with a recently developed Magnetic Resonance Imaging (MRI) technique using hyperpolarized $^{3}$-Helium ($^{3}$He-MRI) as a contrast agent. With this technique we can also determine other unique structural and functional parameters, such as homogeneity of ventilation and flow velocities in isolated airways 81-83. A recent study in patients with chronic obstructive pulmonary disease produced time-series of images showing ventilation defects with delayed filling of peripheral airspaces, probably due to collateral ventilation 84. Delayed filling of the 3He can be expected in case of collateral ventilation but also in partial obstruction, narrowing of the peripheral airways, and lung hyperinflation. This technique, however, requires specific equipment and availability of 3He, which is not widespread. Recently we had the opportunity to apply this technique in a small subgroup of our young adult CDH patients; results will follow soon. Valuable information on lung development in younger CDH survivors, especially those with more severe forms of lung hypoplasia and/or pulmonary hypertension, could be obtained with this specific, or other imaging techniques in the near future.



$^{3}$He-MRI image from an 18-year old CDH patient. The left-sided diaphragmatic defect was closed primarely in the neonatal period. Image was acquired after inhalation of $^{3}$He over the period of a single breath-hold. Hypoventilated areas with filling defects of varying size are present in both lungs. (Image courtesy of J. M. Wild, Department of Academic Radiology, University of Sheffield, UK).

Early intervention programs with exercise training and lifestyle-coaching might contribute to better exercise capacity in CDH and ECMO-treated patients. Encouraging these children to be physically active may prevent deterioration of exercise capacity during childhood and/or adulthood. It would be interesting to see if exercise capacity improved in all patients with long term respiratory morbidity. Physical activity might be less effective for those with severely compromised pulmonary function.

Lung clearance index (LCI) is a rather simple, sensitive and reproducible marker of deranged ventilation and can identify early lung disease in children [85]. It measures inert gas washout and identifies ventilation heterogeneity due to regional differences in airway calibre. LCI measurements are currently being performed in our population of patients with congenital pulmonary malformations and results are expected soon.

In EA, planned international prospective randomized clinical trials with allocation to either thoracotomic, or thoracoscopic type of repair followed by longitudinal assessment of lung function and respiratory morbidity could further elucidate which of the two is most beneficial on the long term. As the thoracoscopic type of EA repair is $CO_2$ inflation-assisted, long-term neuro-cognitive developmental assessment in a standardized and validated manner should be incorporated in the follow-up program as well.

For children with CLL we recommend to evaluate postnatal natural history and, in case of resection, compensatory lung growth in the first year of life. Standardized pre- and

postnatal imaging contribute to the current, limited knowledge on this subject. For the future we recommend prolonged pulmonary follow-up to identify any long term effects of CLL and to shed a light on the question whether surgical or observational management should be preferred as the best ‘therapeutic’ modality.

## Major findings and recommendations

The studies presented in this thesis show that children with congenital pulmonary malformations such as congenital diaphragmatic hernia, esophageal atresia and congenital lung lesions are at risk for respiratory morbidity and long-term lung function abnormalities. Intensive follow-up with evaluation of respiratory morbidity and lung function to improve long-term care, opens the possibility for tailormade early interventions.

## References


1. Gischler SJ, van der Cammen-van Zijp MH, Mazer P, Madern GC, Bax NM, de Jongste JC, van Dijk M, Tibboel D, IJsselstijn H. A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. J Pediatr Surg 2009;44(9):1683-1690.

2. D. Veenma A, Tibboel dKaD. Developmental and Genetic aspects of Congenital Diaphragmatic Hernia Pediatr Pulmonol accepted Feb 2012.

3. Kinsella JP, Ivy DD, Abman SH. Pulmonary vasodilator therapy in congenital diaphragmatic hernia: acute, late, and chronic pulmonary hypertension. Semin Perinatol 2005;29(2):123-128.

4. Thebaud B, Tibboel D. Pulmonary hypertension associated with congenital diaphragmatic hernia. Cardiol Young 2009;19 Suppl 1:49-53.

5. Sluiter I. Congenital Diaphragmatic Hernia: a vascular disease. Functional and structural studies of the pulmonary vasculature in Congenital Diaphragmatic Hernia. Thesis 2012.

6. Mohseni-Bod H, Bohn D. Pulmonary hypertension in congenital diaphragmatic hernia. Semin Pediatr Surg 2007;16(2):126-133.

7. Deakins KM. Bronchopulmonary dysplasia. Respir Care 2009;54(9):1252-1262.

8. Merritt TA, Deming DD, Boynton BR. The 'new' bronchopulmonary dysplasia: challenges and commentary. Semin Fetal Neonatal Med 2009;14(6):345-357.

9. Speer CP. Inflammation and bronchopulmonary dysplasia: a continuing story. Semin Fetal Neonatal Med 2006;11(5):354-362.

10. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. J Pediatr Surg 2002;37(3):357-366.

11. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. Pediatrics 1985;76(4):488-494.

12. Wung JT, Sahni R, Moffitt ST, Lipsitz E, Stolar CJ. Congenital diaphragmatic hernia: survival treated with very delayed surgery, spontaneous respiration, and no chest tube. J Pediatr Surg 1995;30(3):406-409.

13. Moyer V, Moya F, Tibboel R, Losty P, Nagaya M, Lally KP. Late versus early surgical correction for congenital diaphragmatic hernia in newborn infants. Cochrane Database Syst Rev 2002(3):CD001695.

14. van den Hout L, Schaible T, Cohen-Overbeek TE, Hop W, Siemer J, van de Ven K, Wessel L, Tibboel D, Reiss I. Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. Fetal Diagn Ther 2011;29(1):55-63.

15. Reiss I, Schaible T, van den Hout L, Capolupo I, Allegaert K, van Heijst A, Gorett Silva M, Greenough A, Tibboel D, Consortium CE. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. Neonatology 2010;98(4):354-364.

16. Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. Prenat Diagn 2008;28(7):592-603.

17. van den Hout L, Tibboel D, Vijfhuize S, te Beest H, Hop W, Reiss I, Consortium C-E. The VICI-trial: high frequency oscillation versus conventional mechanical ventilation in newborns with congenital diaphragmatic hernia: an international multicentre randomized controlled trial. BMC Pediatr 2011;11:98.

18. Khan AM, Lally KP. The role of extracorporeal membrane oxygenation in the management of infants with congenital diaphragmatic hernia. Semin Perinatol 2005;29(2):118-122.

19. Morini F, Goldman A, Pierro A. Extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia: a systematic review of the evidence. Eur J Pediatr Surg 2006;16(6):385-391.

20. Koumbourlis AC, Wung JT, Stolar CJ. Lung function in infants after repair of congenital diaphragmatic hernia. J Pediatr Surg 2006;41(10):1716-1721.

21. Basek P, Bajrami S, Straub D, Moeller A, Baenziger O, Wildhaber J, Bernet V. The pulmonary outcome of long-term survivors after congenital diaphragmatic hernia repair. Swiss Med Wkly 2008;138(11-12):173-179.

22. IJsselstijn H, Tibboel D, Hop WJ, Molenaar JC, de Jongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. Am J Respir Crit Care Med 1997;155(1):174-180.

23. Peetsold MG, Heij HA, Nagelkerke AF, IJsselstijn H, Tibboel D, Quanjer PH, Gemke RJ. Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia. Eur Respir J 2009;34(5):1140-1147.

24. Arena F, Baldari S, Centorrino A, Calabro MP, Pajno G, Arena S, Ando F, Zuccarello B, Romeo G. Mid- and long-term effects on pulmonary perfusion, anatomy and diaphragmatic motility in survivors of congenital diaphragmatic hernia. Pediatr Surg Int 2005;21(12):954-959.

25. Peetsold MG, Vonk-Noordegraaf A, Heij HH, Gemke RJ. Pulmonary function and exercise testing in adult survivors of congenital diaphragmatic hernia. Pediatr Pulmonol 2007;42(4):325-331.

26. Beals DA, Schloo BL, Vacanti JP, Reid LM, Wilson JM. Pulmonary growth and remodeling in infants with high-risk congenital diaphragmatic hernia. J Pediatr Surg 1992;27(8):997-1001; discussion 1001-1002.

27. Falconer AR, Brown RA, Helms P, Gordon I, Baron JA. Pulmonary sequelae in survivors of congenital diaphragmatic hernia. Thorax 1990;45(2):126-129.

28. Hofhuis W, Hanekamp MN, IJsselstijn H, Nieuwhof EM, Hop WC, Tibboel D, de Jongste JC, Merkus PJ. Prospective longitudinal evaluation of lung function during the first year of life after extracorporeal membrane oxygenation. Pediatr Crit Care Med 2011;12(2):159-164.

29. Eber E ZM. Pediatric pulmonary function testing. Prog Respir Res, Basel, Karger 2005;33:94-102.

30. van den Hout L, Reiss I, Felix JF, Hop WC, Lally PA, Lally KP, Tibboel D, Congenital Diaphragmatic Hernia Study G. Risk factors for chronic lung disease and mortality in newborns with congenital diaphragmatic hernia. Neonatology 2010;98(4):370-380.

31. Greenough A. Long term respiratory outcomes of very premature birth (<32 weeks). Semin Fetal Neonatal Med 2012;17(2):73-76.

32. Greenough A, Dixon AK, Roberton NR. Pulmonary interstitial emphysema. Arch Dis Child 1984;59(11):1046-1051.

33. Altenburg WA, de Greef MH, Ten Hacken NH, Wempe JB. A better response in exercise capacity after pulmonary rehabilitation in more severe COPD patients. Respir Med 2011.

34. Narang I, Bush A, Rosenthal M. Gas transfer and pulmonary blood flow at rest and during exercise in adults 21 years after preterm birth. Am J Respir Crit Care Med 2009;180(4):339-345.

35. van der Cammen-van Zijp MH, Gischler SJ, Hop WC, de Jongste JC, Tibboel D, IJsselstijn H. Deterioration of exercise capacity after neonatal extracorporeal membrane oxygenation. Eur Respir J 2011;38(5):1098-1104.

36. Beardsmore CS, Westaway J, Killer H, Firmin RK, Pandya H. How does the changing profile of infants who are referred for extracorporeal membrane oxygenation affect their overall respiratory outcome? Pediatrics 2007;120(4):e762-768.

37. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723-1729.

38. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr 2011;23(2):167-172.

39. Pfister RH, Goldsmith JP. Quality improvement in respiratory care: decreasing bronchopulmonary dysplasia. Clin Perinatol 2010;37(1):273-293.

40. Agrawal L, Beardsmore CS, MacFadyen UM. Respiratory function in childhood following repair of oesophageal atresia and tracheoesophageal fistula. Arch Dis Child 1999;81(5):404-408.

41. Delacourt C, de Blic J. Pulmonary outcome of esophageal atresia. J Pediatr Gastroenterol Nutr 2011;52 Suppl 1:S31-32.

42. Beardsmore CS, MacFadyen UM, Johnstone MS, Williams A, Simpson H. Clinical findings and respiratory function in infants following repair of oesophageal atresia and tracheo-oesophageal fistula. Eur Respir J 1994;7(6):1039-1047.

43. Chetcuti P, Phelan PD, Greenwood R. Lung function abnormalities in repaired oesophageal atresia and tracheo-oesophageal fistula. Thorax 1992;47(12):1030-1034.

44. Malmstrom K, Lohi J, Lindahl H, Pelkonen A, Kajosaari M, Sarna S, Malmberg LP, Makela MJ. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. J Pediatr 2008;153(3):396-401.

45. Sistonen S, Malmberg P, Malmstrom K, Haahtela T, Sarna S, Rintala RJ, Pakarinen MP. Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. Eur Respir J 2010;36(5):1106-1112.

46. Sistonen SJ, Pakarinen MP, Rintala RJ. Long-term results of esophageal atresia: Helsinki experience and review of literature. Pediatr Surg Int 2011;27(11):1141-1149.

47. van der Zee DC, Bax KN. Thoracoscopic treatment of esophageal atresia with distal fistula and of tracheomalacia. Semin Pediatr Surg 2007;16(4):224-230.

48. Sistonen SJ, Helenius I, Peltonen J, Sarna S, Rintala RJ, Pakarinen MP. Natural history of spinal anomalies and scoliosis associated with esophageal atresia. Pediatrics 2009;124(6):e1198-1204.

49. Burge D, Wheeler R. Increasing incidence of detection of congenital lung lesions. Pediatr Pulmonol 2010;45(1):103; author reply 104.

50. Laberge JM, Puligandla P, Flageole H. Asymptomatic congenital lung malformations. Semin Pediatr Surg 2005;14(1):16-33.

51. Davenport M, Warne SA, Cacciaguerra S, Patel S, Greenough A, Nicolaides K. Current outcome of antenally diagnosed cystic lung disease. J Pediatr Surg 2004;39(4):549-556.

52. Sauvat F, Michel JL, Benachi A, Emond S, Revillon Y. Management of asymptomatic neonatal cystic adenomatoid malformations. J Pediatr Surg 2003;38(4):548-552.

53. Frey U. Clinical applications of infant lung function testing: does it contribute to clinical decision making? Paediatr Respir Rev 2001;2(2):126-130.

54. Hulskamp G, Hoo AF, Ljungberg H, Lum S, Pillow JJ, Stocks J. Progressive decline in plethysmographic lung volumes in infants: physiology or technology? Am J Respir Crit Care Med 2003;168(8):1003-1009.

55. Hulskamp G, Pillow JJ, Dinger J, Stocks J. Lung function tests in neonates and infants with chronic lung disease of infancy: functional residual capacity. Pediatr Pulmonol 2006;41(1):1-22.

56. Gustafsson PM, Kallman S, Ljungberg H, Lindblad A. Method for assessment of volume of trapped gas in infants during multiple-breath inert gas washout. Pediatr Pulmonol 2003;35(1):42-49.

57. Morris MG, Gustafsson P, Tepper R, Gappa M, Stocks J, Testing EATFoSfIRF. The bias flow nitrogen washout technique for measuring the functional residual capacity in infants. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. Eur Respir J 2001;17(3):529-536.

58. Thurlbeck WM, Kida K, Langston C, Cowan MJ, Kitterman JA, Tooley W, Bryan H. Postnatal lung growth after repair of diaphragmatic hernia. Thorax 1979;34(3):338-343.

59. Hayward MJ, Kharasch V, Sheils C, Friedman S, Dunleavy MJ, Utter S, Zurakowski D, Jennings R, Wilson JM. Predicting inadequate long-term lung development in children with congenital diaphragmatic hernia: an analysis of longitudinal changes in ventilation and perfusion. J Pediatr Surg 2007;42(1):112-116.

60. Dotta A, Palamides S, Braguglia A, Crescenzi F, Ronchetti MP, Calzolari F, Iacobelli BD, Bagolan P, Corchia C, Orzalesi M. Lung volumes and distribution of ventilation in survivors to congenital diaphragmatic hernia (CDH) during infancy. Pediatr Pulmonol 2007;42(7):600-604.

61. Hofhuis W, Huysman MW, van der Wiel EC, Holland WP, Hop WC, Brinkhorst G, de Jongste JC, Merkus PJ. Worsening of V'maxFRC in infants with chronic lung disease in the first year of life: a more favorable outcome after high-frequency oscillation ventilation. Am J Respir Crit Care Med 2002;166(12 Pt 1):1539-1543.

62. Chan EY, Bridge PD, Dundas I, Pao CS, Healy MJ, McKenzie SA. Repeatability of airway resistance measurements made using the interrupter technique. Thorax 2003;58(4):344-347.

63. McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. Eur Respir J 2000;15(5):833-838.

64. Merkus PJ, Mijnsbergen JY, Hop WC, de Jongste JC. Interrupter resistance in preschool children: measurement characteristics and reference values. Am J Respir Crit Care Med 2001;163(6):1350-1355.

65. Oostveen E, MacLeod D, Lorino H, Farre R, Hantos Z, Desager K, Marchal F, Measurements ERSTFoRI. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 2003;22(6):1026-1041.

66. Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, Hall GL, Welsh L, Kirkby J, Nystad W, Badier M, Davis S, Turner S, Piccioni P, Vilozni D, Eigen H, Vlachos-Mayer H, Zheng J, Tomalak W, Jones M, Hankinson JL, Stocks J, Asthma UKSCG. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. Am J Respir Crit Care Med 2009;180(6):547-552.

67. Quanjer PH, Stocks J, Cole TJ, Hall GL, Stanojevic S, Global Lungs I. Influence of secular trends and sample size on reference equations for lung function tests. Eur Respir J 2011;37(3):658-664.

68. Quanjer PH, Borsboom GJ, Kivastik J, Merkus PJ, Hankinson JL, Houthuijs D, Brunekreef B, Ihorst G, Kuhr J. Cross-sectional and longitudinal spirometry in children and adolescents: interpretative strategies. Am J Respir Crit Care Med 2008;178(12):1262-1270.

69. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008;177(3):253-260.

70. Koopman M, Zanen P, Kruitwagen CL, van der Ent CK, Arets HG. Reference values for paediatric pulmonary function testing: The Utrecht dataset. Respir Med 2011;105(1):15-23.

71. Stam H, Hrachovina V, Stijnen T, Versprille A. Diffusing capacity dependent on lung volume and age in normal subjects. J Appl Physiol 1994;76(6):2356-2363.

72. Stam H, van den Beek A, Grunberg K, Stijnen T, Tiddens HA, Versprille A. Pulmonary diffusing capacity at reduced alveolar volumes in children. Pediatr Pulmonol 1996;21(2):84-89.

73. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.

74. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. Eur Respir J 2001;17(2):302-312.

75. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson D, Macintyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26(3):511-522.

76. Bjorkman KC, Kjellberg M, Bergstrom SE, Jonsson B, Lindahl S, Radell P, Rohdin M, Sanchez-Crespo A. Postoperative regional distribution of pulmonary ventilation and perfusion in infants with congenital diaphragmatic hernia. J Pediatr Surg 2011;46(11):2047-2053.

77. Wasserman K HJ, Sue DY, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation. Fourth ed Philadelphia: Lippincott Williams& Wilkins 2005.

78. van der Cammen-van Zijp M. Pulmonary morbidity in children with congenital anomalies; long-term effect on exercise capacity and motor function. Thesis 2010.

79. Khan S, Kurland G, Newman B. Controlled-ventilation volumetric CT scan in the evaluation of acquired pulmonary lobar emphysema: a case report. Pediatr Pulmonol 2007;42(12):1222-1228.

80. Wilson AC. What does imaging the chest tell us about bronchopulmonary dysplasia? Paediatr Respir Rev 2010;11(3):158-161.

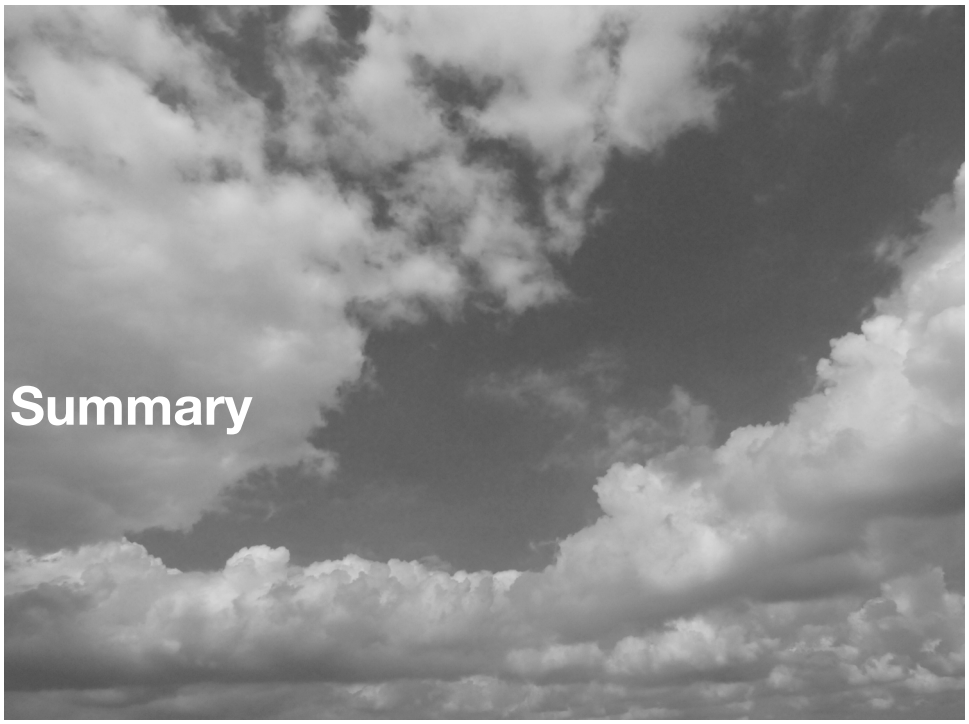
81. Deppe MH, Parra-Robles J, Ajraoui S, Wild JM. Combined measurement of pulmonary inert gas washout and regional ventilation heterogeneity by MR of a single dose of hyperpolarized 3He. Magn Reson Med 2011;65(4):1075-1083.

82. Gierada DS, Woods JC, Jacob RE, Bierhals AJ, Choong CK, Bartel ST, Chang YV, Das NA, Hong C, Lutey BA, Ritter JH, Pilgram TK, Cooper JD, Patterson GA, Battafarano RJ, Meyers BF, Yablonskiy DA, Conradi MS. Emphysema quantification in inflation-fixed lungs using low-dose computed tomography and 3He magnetic resonance imaging. J Comput Assist Tomogr 2010;34(5):773-779.

83. Wild JM, Ajraoui S, Deppe MH, Parnell SR, Marshall H, Parra-Robles J, Ireland RH. Synchronous acquisition of hyperpolarised 3He and 1H MR images of the lungs - maximising mutual anatomical and functional information. NMR Biomed 2011;24(2):130-134.

84. Marshall H, Deppe MH, Parra-Robles J, Hillis S, Billings CG, Rajaram S, Swift A, Miller SR, Watson JH, Wolber J, Lipson DA, Lawson R, Wild JM. Direct visualisation of collateral ventilation in COPD with hyperpolarised gas MRI. Thorax 2012.

85. Horsley AR, Gustafsson PM, Macleod KA, Saunders C, Greening AP, Porteous DJ, Davies JC, Cunningham S, Alton EW, Innes JA. Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. Thorax 2008;63(2):135-140.


Summary

## Summary

In **Chapter 1** we describe a prospective longitudinal cohort study on lung function and respiratory morbidity of infants with congenital diaphragmatic hernia (CDH) during their first year of life. The cohort consisted of 43 infants, 12 (28%) of whom were treated with extracorporeal membrane oxygenation (ECMO). Sixteen of all infants (41%) developed chronic lung disease (CLD), defined as oxygen dependency at day 28. Respiratory morbidity and lung function were assessed at 6 and 12 months of age. The following lung function parameters were measured: functional residual capacity ($FRC_p$) and maximal expiratory flow at functional residual capacity ($V'max_{FRC}$). While the $FRC_p$ was generally above the expected range, the $V'max_{FRC}$ was below normal. Both outcome measures did not significantly change from 6 to 12 months. Presence of CLD, ECMO-treatment, higher maximum mean airway pressure, and longer duration of ventilation were associated with significantly higher $FRC_p$ values. $V'max_{FRC}$ was not associated with any of these characteristics. The $FRC_p$ values reported in our study may reflect hyperinflation. However, since $FRC_p$ values did not increase over time, there does not seem to be progressive hyperinflation of the alveoli in the first year of life. Decreased maximal expiratory flows in our study may reflect abnormal airway size or flawed alveolar architecture, perhaps due to airway damage from mechanical ventilation. Thus, CDH survivors are at risk for respiratory morbidity with lung function abnormalities, especially those who were treated with ECMO and/or were ventilated for a long time. These patients' lung function should be closely monitored.

In **Chapter 2** describes a study similar to the one in chapter 1 in 37 infants who had undergone repair of esophageal atresia. In addition we assessed whether type of repair– thoracotomic or thoracoscopic – had any influence on lung function. $FRC_p$ values were in the upper normal range and increased from 6 to 12 months. $V'max_{FRC}$ was below the normal range without a significant change from 6 to 12 months. Lung function parameters did not differ between the groups of infants with a thoracotomic or thoracoscopic type of repair. Flow limitation, which may reflect severe airway malacia, was observed in 7 (19%) patients. Persistent higher airway obstruction caused by tracheomalacia and recurrent respiratory tract infections (RTI) might have caused a mild form if hyperinflation, reflected by $FRC_p$ in the upper normal range. First-year test results were of limited predictive value for respiratory morbidity at 2 and 5 years of age. Evaluation of lung volume within the context of planned international trials could further elucidate which type of surgery – thoracotomic or thoracoscopic type – is most beneficial on the long term. Frequent monitoring focussed on RTI prevention and nutritional status is recommended.

In **Chapter 3** we focussed on clinical course and lung function in 30 infants with congenital lung lesions. Most of them suffered from congenital cystic adenomatoid malformation (n=17), followed by bronchopulmonary sequestration (n=9), bronchogenic cyst (n=1) and congenital lobar emphysema (n=3). Respiratory symptoms and lung function were evaluated at 6 and 12 months of age. In addition we assessed whether respiratory morbidity and lung function would differ between infants with asymptomatic lesions (n=17) who received observational management and infants whose affected lung parts were resected, the intervention group (n=13). Respiratory morbidity was not different between both groups. Mean $FRC_p$ values were in the upper normal range; $V'max_{FRC}$ was significantly below normal. Both parameters did not significantly change over time and did not differ between infants in the observation or intervention group. No significant associations were found between $FRC_p$ and $V'max_{FRC}$ and clinical characteristics at both time points. We assume $FRC_p$ does not accurately reflect lung volume in the case of congenital lung lesions. Standardized pre- and postnatal imaging could contribute to the current, limited knowledge on compensatory lung growth after resection of lung parts. More understanding is important because improved antenatal detection has led to a higher prevalence of congenital lung lesions. For the future we recommend prolonged pulmonary follow-up of lung structure and function.

In **Chapter 4** we assessed lung function at 5, 8 and 12 years of age in 121 children treated with neonatal extracorporeal membrane oxygenation (ECMO) and identified any effects of diagnosis and perinatal characteristics. Seventy children had suffered from meconium aspiration syndrome (MAS), 20 from CDH and 31 from other conditions. Dynamic and static lung volumes, reversibility of airway obstruction and diffusion capacity were measured. Mean SDS $FEV_1$ before and after bronchodilation was significantly higher at 5 years than at 8 and 12 years. Mean SDS for all spirometric values were significantly lower in the CDH group compared with the other diagnostic groups. Airway patency in patients with MAS and other diagnoses was within the normal range and remained stable over time. A significant volume of trapped air was observed in 86% of the patients with CDH, 50% with MAS and 58% with other diagnoses. After bronchodilation mean SDS $FEV_1$ and SDS FVC were negatively influenced by duration of ventilation and duration of ECMO. We concluded that lung function is compromised after neonatal ECMO treatment and that it tends to deteriorate over time in CDH patients only. Therefore we assume that the underlying condition and not the ECMO-treatment itself is responsible for the compromised lung function after neonatal ECMO. Prolonged follow-up, especially of patients with CDH, is recommended.

In **Chapter 5** we examined a previously studied cohort of 27 young adults with CDH and 30 age matched controls without CDH and lung hypoplasia who had undergone similar neonatal intensive care treatment. The mean age of the former CDH patients was now

26.8 years. The non-CDH patients had been matched as best as possible for present age, gestational age, birth weight, duration of mechanical ventilation, duration of supplemental oxygen and gender. Dynamic and static lung volumes and diffusion capacity were measured and the prevalence of respiratory symptoms was assessed. Present data were compared with those measured 15 years earlier in childhood. Airflow obstruction and diffusion capacity had slightly deteriorated since childhood. Lung volumes were normal in CDH and non-CDH patients. In both groups, the prevalence of asthma was higher compared with the normal population. We concluded that CDH and non-CDH patients, who underwent similar neonatal intensive care treatment, had mild airflow obstruction and reduced diffusion capacity at adult age, both of which had slightly deteriorated since childhood in CDH patients only. Differences between groups were only minor, indicating that not only residual sequelae of CDH but mainly intensive care treatment contributed to outcome. Although improved ventilation techniques and ECMO can reduce lung injury, long-term follow-up of CDH patients is still recommended seeing that more patients with severe forms of lung hypoplasia and pulmonary hypertension survive nowadays.

In **Chapter 6** we determined long-term outcome of exercise capacity, severity of fatigue, and level of physical activity in this same cohort as described in Chapter 5. Maximal cardiopulmonary exercise testing was performed on an electrically braked cycle ergometer. Cardio respiratory fitness was defined as the mean oxygen uptake (VO2 peak: in ml/min/kg) during the final 30 seconds of exercise. Mean VO2 peak did not significantly differ between the groups: in former CDH patients it was 96.4%; in controls 98.0% predicted. Neither did exercise capacity, severity of fatigue, and level of physical activity significantly differ between the groups. More CDH patients than controls reported difficulties in their daily activities as estimated with the Life-H questionnaire. We concluded that residual lung hypoplasia did not play an important role in this cohort of young adults. Future studies need to elucidate whether exercise capacity is impaired in patients with more severe lung hypoplasia.

In 2 of the 27 former CDH patients (7%) a large diaphragmatic defect was accidentally discovered within the 3 years following this study. In **Chapter 7** we reported on their lung function before and after repair of this recurrent defect. They both had a history of mild and aspecific abdominal complaints. Lung function was not substantially compromised within 2 years before and after repair. No striking differences in airflow or lung volumes were observed in the second test. We speculate that at the first evaluation, abdominal organs were not present at all in the thoracic cavity or were present but did not considerably compromise lung function. Although recurrence of CDH in adulthood is reported to be rare, thorough examination, including chest X-ray, should be considered in former patients in case of unexplained gastrointestinal symptoms.

In the concluding **General Discussion** we discuss our findings and make recommendations for future studies.

These are the major recommendations:

- The use of imaging techniques such as the recently developed Magnetic Resonance Imaging (MRI) technique using hyperpolarized 3-Helium (3He-MRI) as a contrast agent could yield valuable information on lung development in younger CDH survivors, especially those with more severe forms of lung hypoplasia and/or pulmonary hypertension.
- Early intervention programs aimed at physical activity (of aimed at exercise training and lifestyle-coaching) could contribute to better exercise capacity in former CDH patients.
- International trials evaluating lung volume could elucidate which type of surgery – thoracoscopic or thoracotomic type – in patients with pulmonary congenital anomalies requiring intrathoracic surgery is most beneficial on the long term.
- Standardized pre- and postnatal imaging and prolonged pulmonary follow-up of infants with congenital lung lesions could help evaluate the postnatal natural history and, in case of resection of lung part(s), compensatory lung growth in the first year of life.


Samenvatting

# Samenvatting

**Hoofdstuk 1** betreft een prospectief, longitudinaal onderzoek naar de longfunctie en luchtwegklachten in het eerste levensjaar van 43 kinderen met een congenitale hernia diafragmatica (CHD). Extracorporele membraan oxygenatie (ECMO) werd toegepast bij 12 van de kinderen, en 16 hadden nog zuurstof nodig op dag 28 na de geboorte hetgeen wijst op een chronisch longbeeld. Bij routinecontrole op de leeftijd van 6 en 12 maanden werd gestandaardiseerd vastgelegd of er luchtwegklachten waren en werd de longfunctie gemeten. In het bijzonder werd gekeken naar de functioneel residuale capaciteit ($FRC_p$), een maat voor de longinhoud, en maximale expiratoire flow bij functioneel residuale capaciteit ($V'max_{FRC}$), een maat voor de doorgankelijkheid van de luchtwegen. $FRC_p$ waarden lagen aan de bovengrens van de normale spreiding van gezonde kinderen; $V'max_{FRC}$ was lager dan waardes bij gezonde controles. Beide uitkomstmaten veranderden niet significant tussen 6 en 12 maanden. Zuurstofbehoefte op dag 28, ECMO-behandeling, hogere gemiddelde beademingsdruk en langere beademingsduur waren geassocieerd met significant hogere $FRC_p$ waarden. Dit gold niet voor $V'max_{FRC}$. De hogere $FRC_p$ waarden zouden kunnen wijzen op hyperinflatie (toegenomen luchthoudendheid van de longen), echter zonder progressie van 6 naar 12 maanden. De lagere $V'max_{FRC}$ zou er op kunnen wijzen dat de dimensies of de structuur van de longen en/of luchtwegen afwijken van normaal – wellicht als gevolg van kunstmatige beademing. De conclusie is dat CHD-patiënten een verhoogd risico hebben op het ontwikkelen van luchtwegklachten of abnormale longfunctie, vooral als ze ECMO-behandeling hebben gekregen en/of lang zijn beademd. Alle reden om deze patiënten tot de leeftijd van 18 jaar regelmatig te controleren.

Bij oudere patiënten met een slokdarmafsluiting (oesofagusatresie) is in de literatuur een beperkte longfunctie beschreven. In **hoofdstuk 2** wordt eenzelfde onderzoek beschreven als bij CHD-patiënten, maar nu bij 37 kinderen met een slokdarmafsluiting. De $FRC_p$ waarden lagen aan de bovengrens van de normale spreiding van gezonde kinderen en namen toe van 6 naar 12 maanden. $V'max_{FRC}$ was beneden gemiddeld ten opzichte van gezonde kinderen en veranderde niet in de tijd. We keken of er verschil was in longfunctie bij kinderen die met thoracotomie of met thoracoscopie (kijkoperatie) waren geopereerd. Er bleek geen significant verschil te zijn. Flow limitatie, hetgeen een ernstige verslapping van de luchtwegen kan representeren, werd bij 7 patiënten vastgesteld. Dit kan wijzen op ernstige verslapping van de bovenste luchtwegen. De verslapping van de luchtwegen met daardoor vernauwing hiervan, samen met herhaalde luchtweginfecties kunnen hyperinflatie met een $FRC_p$ aan de bovengrens van de normale spreiding veroorzaken. De resultaten van onderzoek op de leeftijd van 6 en 12 maanden bleken van weinig voorspellende waarde voor het optreden van luchtwegklachten op de leeftijd van 2 en 5 jaar. Grote internationale studies zijn nodig

om op te helderen welk type operatie – thoracotomisch of thoracoscopisch - op de lange termijn het meeste voordeel biedt. Regelmatige controle zou gericht moeten zijn op de preventie van recidiverende luchtweginfecties en verbetering van de voedingstoestand van deze kinderen.

Door verbetering van prenatale echografische technieken en de invoering van de standaard 20-weken echo in januari 2007 worden vaker congenitale longafwijkingen (CLA) gediagnostiseerd. **Hoofdstuk 3** beschrijft een onderzoek naar het klinische beloop en de longfunctie bij 30 kinderen met een congenitale longafwijking te weten; congenitale cysteuze adenomateuze malformatie (n=17), bronchopulmonaal sekwester (n=9), bronchogene cyste (n=1) en congenitaal lobair emfyseem (n=3). Het longfunctie onderzoek werd op dezelfde manier verricht als bij de kinderen met CHD of een slokdarmafsluiting, met metingen op de leeftijd van 6 en 12 maanden. Verschillen in luchtwegklachten en longfunctie werden vergeleken tussen kinderen met een CLA die na de geboorte asymptomatisch bleek en waarvoor een afwachtend beleid werd afgesproken (n=17) en kinderen die een resectie van het aangedane longdeel(-delen) ondergingen (n=13). Er bleken geen significante verschillen te zijn. Er werden geen significante associaties gevonden tussen $FRC_p$ en $V'max_{FRC}$ en klinische karakteristieken op beide tijdstippen. Wij nemen aan dat $FRC_p$ geen goede maat is voor het longvolume bij kinderen met een congenitale longafwijking. We bevelen het gebruik van geavanceerde beeldvormende technieken aan om inzicht te krijgen in de eventuele compensatoire longgroei na resectie van een longdeel(-delen). Ook deze kinderen zouden regelmatig gedurende langere tijd moeten worden gecontroleerd.

In **hoofdstuk 4** worden de resultaten beschreven van longfunctiemetingen op de leeftijd van 5, 8 en 12 jaar bij kinderen die als pasgeborenen ECMO-behandeling hadden gekregen. Het ging om 70 kinderen met een meconium aspiratie syndroom (MAS), 20 met een CHD, en 31 kinderen die met ECMO werden behandeld vanwege een andere aandoening. Dynamische en statische longvolumes, reversibiliteit van luchtwegobstructie, en diffusiecapaciteit werden gemeten. De gemiddelde standaard deviatie score (SDS) van $FEV_1$ voor en na bronchodilatatie op 5-jarige leeftijd was significant hoger dan op 8- en 12-jarige leeftijd. Gemiddelden van SDS van alle spirometrische waarden waren significant lager voor kinderen met CHD vergeleken met de andere groepen. De luchtwegdoorgankelijkheid was bij de patiënten met MAS en andere afwijkingen normaal en bleef stabiel over de tijd. Een hoog volume aan “trapped air” werd gevonden bij 86% van de patiënten met een CHD, bij 50% met MAS en bij 58% met andere diagnoses. SDS $FEV_1$ en SDS FVC na bronchodilatatie werden negatief beïnvloed door de duur van de beademing en de duur van ECMO. Wij concludeerden dat de longfunctie bij CHD-patiënten na neonatale ECMO slechter is dan die bij kinderen die vanwege een andere aandoening met neonatale ECMO zijn behandeld en dat deze

alleen bij CHD-patiënten neigt tot verslechtering in de tijd. Wij nemen daarom aan dat het onderliggend lijden en niet de ECMO behandeling zelf verantwoordelijk is voor deze slechtere longfunctie na neonatale ECMO behandeling. We bevelen langdurige follow-up aan, zeker van de CHD-patiënten.

In een eerdere studie, in de jaren 90, hebben we een cohort van kinderen met CHD (leeftijd 7-18 jaar) onderzocht. Deze werden vergeleken met 30 leeftijdgematchte controles zonder CHD en longhypoplasie, die als pasgeborenen ook intensive care behandeling hadden ondergaan. We hebben nu dit cohort onderzocht op de gemiddelde leeftijd van 26,8 jaar. De resultaten zijn beschreven in **hoofdstuk 5.** Dynamische en statische longvolumina en diffusiecapaciteit werden gemeten en eventuele respiratoire symptomen werd vastgesteld. Luchtwegobstructie en diffusiecapaciteit waren in beide groepen weinig verslechterd sinds de kindertijd. De longvolumes waren normaal in beide groepen. De prevalentie van astma was in beide groepen hoger dan die in de normale populatie. Wij concludeerden dat zowel bij CHD-patiënten en niet-CHD-patiënten, die ook intensive care behandeling hebben ondergaan als pasgeborenen, milde luchtwegobstructie en verminderde diffusiecapaciteit voorkomt op de volwassen leeftijd met geringe verslechtering sinds de kinderleeftijd. De verschillen tussen de groepen waren slechts gering, wat er op wijst dat niet zo zeer de afwijking, maar vooral de intensive care behandeling bijdragen aan de uitkomsten. Omdat door verbeterde behandelingsmogelijkheden de overleving van patiënten met een ernstiger vorm van longhypoplasie en pulmonale hypertensie is toegenomen, bevelen wij lange termijn follow-up van CHD patiënten aan.

In **hoofdstuk 6** rapporteren we de resultaten van een maximale inspanningstest op een fietsergometer, waarbij ook de zuurstofopname werd gemeten, in hetzelfde cohort zoals beschreven in hoofdstuk 5. Beide groepen scoorden binnen de norm zonder significant verschil tussen de groepen: CHD 96,4% en controles 98,0% van de voorspelde waarde. Er werden geen significante verschillen gevonden in het duuruithoudingsvermogen, mate van vermoeidheid en niveau van dagelijkse activiteit. Meer CHD-patiënten rapporteerden in de Life-H vragenlijst problemen bij hun dagelijkse activiteiten. Wij concludeerden dat residuale longhypoplasie geen belangrijke rol speelde in dit cohort van jong volwassenen. Toekomstig onderzoek moet uitwijzen of bij patiënten met een ernstiger vorm van longhypoplasie het duuruithoudingsvermogen is verminderd.

Bij twee van die jong volwassen patiënten met een CHD (7%) werd bij toeval binnen 3 jaar na het bovenstaand beschreven onderzoek weer een gat in het middenrif ontdekt. Beiden hadden een voorgeschiedenis met milde en aspecifieke buikklachten. In

**hoofdstuk 7** beschrijven wij hun longfunctie voor en na operatieve correctie. Bij beiden waren er geen noemenswaardige verschillen gevonden in luchtwegdoorgankelijkheid en longvolume voor en na de operatie. Wij veronderstellen dat er bij de eerste meting of geen buikorganen in de borstholte waren doorgedrongen, of wel, maar dan zonder nadelige invloed op de longfunctie. Alhoewel een recidief hernia diafragmatica bij volwassenen zeldzaam wordt geacht, is nader radiologisch onderzoek het overwegen waard bij onverklaarbare gastro-intestinale klachten.

In de **algemene discussie** bespreken we onze bevindingen en doen we aanbevelingen voor toekomstige studies.

De belangrijkste aanbevelingen zijn:

- Toepassing van beeldvormende technieken zoals de recent ontwikkelde Magnetic Resonance Imaging (MRI) met gehyperpolariseerd 3-Helium als contrast. Vooral bij CHD patiënten met ernstiger vormen van longhypoplasie en/of pulmonale hypertensie en persisterende longfunctie afwijkingen kan de longontwikkeling geëvalueerd worden..
- Uitvoering van grote internationale trials om te bepalen welke vorm van chirurgie bij kinderen met een slokdarmafsluiting op de lange termijn het gunstigst is – thoracoscopisch of thoracotomisch.
- Voor kinderen met een CLA is evaluatie van het postnatale, natuurlijke beloop van belang. Gestandaardiseerde pre- en postnatale beeldvorming en langdurige follow-up kunnen bijdragen aan de huidige, beperkte kennis over dit onderwerp. In geval van resectie van een long deel(-delen), kan de compensatoire longgroei in het eerste levensjaar van kinderen met een CLA geëvalueerd worden.
- Kinderen met congenitale longafwijkingen zoals congenitale hernia diafragmatica, oesofagusatresie en congenitale cysteuze longafwijkingen lopen risico op het ontwikkelen van luchtwegklachten en lange termijn longfunctie afwijkingen. Intensieve follow-up met evaluatie van luchtwegklachten,de longfunctie, en het uithoudingsvermogen (of: conditie) biedt de mogelijkheid tot goede lange termijn zorg en gerichte interventies.

## List of abbreviations

| | |
|---|---|
| AB | Antibiotics |
| AM | Activity Monitor |
| ANOVA | Analysis of Variance |
| ATS | American Thoracic Society |
| BC | Bronchogenic Cyst |
| BD | Bronchodilation |
| BMI | Body Mass Index |
| BPD | Bronchopulonary Dysplasia |
| BPS | Bronchopulmonary Sequestration |
| CCAM | Congenital Cystic Adenomatoid Malformation |
| CDH | Congenital Diaphragmatic Hernia |
| CI | Confidence Interval |
| CLD | Chronic Lung Disease |
| CLE | Congenital Lobar Emphysema |
| CLL | Congenital Lung Lesion |
| CPET | Cardiopulmonary Exercise Testing |
| CT | Computer Tomography |
| $DL_{CO}$ | Carbon Monoxide Diffusion Capacity |
| $DL_{CO}/V_A$ | $DL_{CO}$ corrected for alveolar volume |
| EA | Esophageal Atresia |
| ECMO | Extracorporeal Membrane Oxygenation |
| ECRHS | European Community Respiratory Health Survey |
| ERS | European Respiratory Society |
| $FEF_{25-75}$ | Forced Midexpiratory Flow |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FRC | Functional Residual Capacity |
| FVC | Forced Vital Capacity |
| GERD | Gastro-Esophageal Reflux Disease |
| HFO | High Frequency Oscillation |
| HR | Heart Rate |
| IPPV | Intermittent Positive Pressure Ventilation |
| $K_{CO}$ | $DL_{CO}$ corrected for alveolar volume |
| LIFE-H | Life Habits Questionnaire |
| MAP | Mean Airway Pressure |
| MAS | Meconium Aspiration Syndrome |
| MCA | Multiple Congenital Anomalies |
| MMEF | Maximal Mid Expiratory Flow |
| MRI | Magnetic Resonance Imaging |
| iNO | inhaled Nitric Oxide |
| OI | Oxygenation Index |

| | |
|---|---|
| PPHN | Persistent Pulmonary Hypertension of the Newborn |
| RDS | Respiratory Distress Syndrome |
| RER | Respiratory Exchange Ratio |
| RR | Respiratory Rate |
| RTI | Respiratory Tract Infection |
| RV | Residual Volume |
| SD | Standard Deviation |
| SDS | Standard Deviation Score |
| SE | Standard Error |
| SF-36 | Short Form-36 |
| SIMV | Synchronized Intermittent Mandatory Ventilation |
| SNAP | Score for Acute Neonatal Physiology |
| TEF | Tracheo-Esophageal Fistula |
| TLC | Total Lung Capacity |
| VA | Veno-arterial |
| VAT | Ventilatory Anaerobic Treshold |
| $VE/VCO_2$ | Ventilatory Equivalents for Carbon Dioxide Output |
| $V'max_{FRC}$ | Maximal Flow at Functional Residual Capacity |
| VTA | Volume Trapped Air |

## Dankwoord

Ik heb dit proefschrift met plezier en voldoening geschreven en dit dankwoord maakt het voor mij helemaal af. Een heleboel mensen hebben bijgedragen aan het tot stand komen hiervan en hoe vaak krijg je in je leven de kans om degenen die belangrijk voor je zijn zo expliciet te bedanken? Niet vaak genoeg dus ik pak met veel genoegen deze gelegenheid met beide handen aan!

Mijn promotoren, Prof.dr. D. Tibboel en Prof.dr. J.C. de Jongste dank ik enorm voor hun waardevolle begeleiding.

Beste Dick, onze historie beslaat inmiddels 20 jaar. Tijdens de vele en soms heftige diensten samen, congressen en talloze gesprekken ben ik jou als mens, arts en wetenschapper enorm gaan waarderen. Jouw tomeloze energie, inzicht en liefde voor het vak hebben de afdeling kinderchirurgie met de intensive care en de lange termijn follow-up gemaakt tot wat hij nu is. Vele mensen heb jij geinspireerd en gemotiveerd om boven zichzelf uit te stijgen. Ook mij. Dit proefschrift kent een lange aanloop en je hebt mijn keuzes en beslissingen hierin altijd gerespecteerd. Met immense bewondering, en dankbaarheid en trots voor de ruimte en kansen die je mij gegund hebt.

Beste Johan, vanaf het begin ben jij betrokken bij mijn onderzoeken op het, aanvankelijk wat ontoegankelijke, gebied van de longfunctie. Bij het vinden van mijn weg hierin waren jouw heldere commentaren en suggesties naar aanleiding van mijn manuscripten zeer waardevol. Dank voor je humoristische mails als het even tegenzat met de acceptatie van een, naar mijn mening, toch echt briljant manuscript. Dat zette de mondhoeken weer de goede kant op. Hartelijk dank voor al jouw inbreng en begeleiding!

Mijn co-promotor, Dr. H. Meijers-IJsselstijn. Beste Hanneke, een betere co-promotor had ik mij niet kunnen wensen! Altijd bereid om mee te denken en mijn wetenschappelijke brouwsels, ook op oneigenlijke tijdstippen om te werken, per ommegaande te beoordelen en te verbeteren. Als mijn ‘innerlijke peptalk’ het even liet afweten, had jij onmiddellijk een extern peptalkje paraat. We lagen op ramkoers in de laatste fase van het afronden van het proefschrift. Superbedankt voor je fantastische begeleiding!

De overige leden van de promotiecommissie, Prof.dr. R. Wijnen, Prof.dr. H. Tiddens en Prof.dr. I. Reiss wil ik bedanken voor hun bereidheid om plaats te nemen in de kleine commissie en voor hun beoordeling van het manuscript. De overige leden dank ik allen van harte voor hun bereidheid zitting te nemen in de grote commissie.

Saskia Gischler en Petra Mazer. Jullie hebben de chirurgische lange termijn follow-up opgezet en de zinvolheid hiervan met de eerste studies aangetoond. Dankzij jullie pionierswerk kan ik sinds 2005 met veel genoegen op dit bootje meevaren. Dank voor jullie inzicht, humor en relativerend vermogen.

Annemarie Illsley, Anne Zirar, Annabel van Gils, Marlous Madderom en Kim Gevers. Lieve collega's. Mijn innige dank voor jullie belangstelling, steun en gezelligheid voor, tijdens en hopelijk ook nog lang na dit promotietraject.

Monique van der Cammen. Lieve Monique, nog niet zo lang geleden zat jij zelf in het roerige promotieschuitje en ik ben heel blij met jouw begripvolle hulp en steun in de fase van de afronding van het proefschrift. Daarnaast heb ik geleerd van jouw kennis maar bovenal van je vermogen om op een zo positief mogelijke manier om te gaan met tegenslag. Veel dank en alle goeds voor jou en Ton in de toekomst!

Sandra Lever, Eveline Nieuwhof en Els van der Wiel. Superbedankt voor al jullie inspanningen om onze patienten tot ongekende hoogten (L/sec !) aan te sporen om een perfecte longfunctie te blazen. Sandra, bedankt voor jouw nimmer aflatende bereidheid te helpen bij het completeren van mijn databestanden en de gezellige bijkletsmomentjes.

Dr. W.C.J. Hop. Beste Wim, ben ik statistiek nog leuk gaan vinden ook. Van de gepaarde t-toets naar de rue Mouffetard en via Haute Marne weer terug naar de Mixed Models. Heel wat productieve en ook gezellige uurtjes in jouw werkkamer op de 21$^{e}$ doorgebracht. Ik hoop dat je snel je droomstulpje vindt in La douce France en daar lekker kunt gaan genieten van je pensioen. Bedankt voor je significante hulp ($p<0.001$) bij het ontwarren van mijn bestanden en onderzoeksvragen.

Ko Hagoort. Beste Ko, enorm bedankt voor jouw altijd supersnelle correcties en suggesties om mijn breedsprakerige 'tante Bep' Engels tot begrijpelijk en keurig strak, decent English te restylen! En wat een eindsprint. Ik ben heel blij met het resultaat.

Lieke van den Hout. Lieve Lieke, heel gezellig en leerzaam om met jou samen het artikel over longfunctie bij baby's met CDH te schrijven. Je lag straatlengten op mij voor met je kennis over statistiek en SPSS en je hebt mij daarin een heel eind op weg geholpen. Dank voor je geduld en bereidheid om de kennis met mij te delen.

Roxanne Laas. Lieve Roxanne. Dank voor jouw hulp bij het onderzoek met de jong volwassen patienten met een CDH en natuurlijk voor het opzetten van het uitgebreide ECMO bestand. Daar hebben we inmiddels de vruchten van kunnen plukken. Mooi toch! Het was heel gezellig samenwerken met jou. Veel succes in de kindergeneeskunde.

Zonder de nodige administratieve en praktische ondersteuning van Adriana Pieter en Petra Schenk was het met het plannen van de poli en schrijven van dit proefschrift een stuk minder soepel gelopen. Lieve Adriana en Petra, bedankt voor jullie onmisbare hulp.

Mijn speciale dank gaat uit naar alle kinderen en hun ouders die deel uitmaken van onze follow-up en de jong volwassenen met een congenitale hernia diafragmatica die deel hebben genomen aan ons onderzoek. Zonder jullie was dit proefschrift er niet geweest. Ik heb grote bewondering voor jullie veerkracht en doorzettingsvermogen.

Lieve familie en vrienden, jullie hebben allemaal op je eigen manier met mij meegeleefd en het is maar de vraag of ik het zonder de support, interesse en begrip van de harde kern zo goed had doorstaan. Heel veel dank hiervoor.

Veel dank aan mijn lieve en zorgzame grootouders voor hun onvoorwaardelijke liefde. In mijn hart zijn jullie er gewoon bij op 15 juni.

Daan en Jet. Lief zusje en lief vriendinnetje. Wat heerlijk dat jullie naast mij staan, tijdens de verdediging van mijn proefschrift maar ook in het leven. Dat maakt mij blij!

Lieve pap en mam, dit proefschrift draag ik op aan jullie. De basis hiervan is alle liefde, het vertrouwen en de ruimte die ik van jullie heb gekregen om mijn eigen pad te volgen. Jullie onvoorwaardelijke steun en de liefdevolle zorg voor Max en Elise hebben dit mogelijk gemaakt. Jullie willen graag dat ik het wat rustiger aan ga doen. Ga het echt proberen maar het blijft lastig met de genen die ik van jullie heb gekregen. Where would I be without you…! Kus

Max en Elise. Mijn lieve vrolijke schatten, dank voor jullie begrip dat ik de afgelopen maanden zo druk ben geweest. Tijd om weer leuke dingen te gaan doen! xxx

Henk, mijn lief. De laatste woorden van dit dankwoord zijn voor jou. Het leven met jou is mooi. Na alle bergen die wij hebben overwonnen was het promotietraject niet meer dan een glooiend heuveltje. Dankzij jouw niet aflatende interesse, vertrouwen en liefde was het goed te doen. Dank voor…, tja wat niet allemaal. We vieren het leven en daar gaan we lekker mee door. Ik hou van je.

# Curriculum Vitae

Marjolein Spoel was born on 16 January 1965 in Rotterdam. She obtained the athenaeum certificate at *Scholengemeenschap Van Oldenbarnevelt* in Rotterdam and started her medical study at Erasmus University Medical School in Rotterdam. After having received her medical degree, cum laude, in November 1992, she was employed as a resident in the department of Paediatric Surgery and Intensive Care Medicine (Prof.dr. Tibboel) at the Erasmus MC-Sophia Children's Hospital in Rotterdam until 2002. In that year she took up a position as a physician in the department of Youth Health Care at *Rivas Zorggroep*, Gorinchem. She still is employed there part-time. In 2002-2004 she was trained as an acupuncturist at the NAAV Institute, Breukelen, The Netherlands. In 2005 she resumed working at Erasmus MC, having joined the surgical long-term follow-up team for children with congenital anomalies, instituted by the department of Paediatric Surgery and the Intensive Care Unit in the Sophia Children's Hospital. In 2006 she started working on the research reported in this thesis.

# Publications
# &
# PhD Portfolio

# Publications

Heineman E, Dejong CH, Piena-Spoel M, Liefaard G, Molenaar JC, Tibboel D. Prospective evaluation of faecal fatty acid excretion in short bowel syndrome in newborns. J Pediatr Surg 1996;31(4):520-525.

Piena M, Albers MJ, Van Haard PM, Gischler S, Tibboel D. Introduction of enteral feeding in neonates on extracorporeal membrane oxygenation after evaluation of intestinal permeability changes. J Pediatr Surg 1998;33(1):30-34.

Piena-Spoel M, Sharman-Koendjbiharie M, Yamanouchi T, Tibboel D. "Gut-feeling" or evidence-based approaches in the evaluation and treatment of human short-bowel syndrome. Pediatr Surg Int 2000;16(3):155-164.

Piena-Spoel M, Albers MJ, ten Kate J, Tibboel D. Intestinal permeability in newborns with necrotizing enterocolitis and controls: Does the sugar absorption test provide guidelines for the time to (re-) introduce enteral nutrition? J Pediatr Surg 2001;36(4):587-592.

Wertheim HF, Albers MJ, Piena-Spoel M, Tibboel D. The incidence of septic complications in newborns on extracorporeal membrane oxygenation is not affected by feeding route. J Pediatr Surg 2001;36(10):1485-1489.

Ksiazyk J, Piena M, Kierkus J, Lyszkowska M. Hydrolyzed versus nonhydrolyzed protein diet in short bowel syndrome in children. J Pediatr Gastroenterol Nutr 2002;35(5):615-618.

Sharman-Koendjbiharie M, Hopman WP, Piena-Spoel M, Albers MJ, Jansen JB, Tibboel D. Gut hormones in preterm infants with necrotizing enterocolitis during starvation and reintroduction of enteral nutrition. J Pediatr Gastroenterol Nutr 2002;35(5):674-679.

Sharman-Koendjbiharie M, Piena-Spoel M, Hopman WP, Albers MJ, Jansen JB, Tibboel D. Gastrointestinal hormone secretion after surgery in neonates with congenital intestinal anomalies during starvation and introduction of enteral nutrition. J Pediatr Surg 2003;38(11):1602-1606.

Hanekamp MN, Spoel M, Sharman-Koendjbiharie I, Peters JW, Albers MJ, Tibboel D. Routine enteral nutrition in neonates on extracorporeal membrane oxygenation. Pediatr Crit Care Med 2005;6(3):275-279.

Hanekamp MN, Spoel M, Sharman-Koendjbiharie M, Hop WC, Hopman WP, Jansen JB, Tibboel D. Gut hormone profiles in critically ill neonates on extracorporeal membrane oxygenation. J Pediatr Gastroenterol Nutr 2005;40(2):175-179.

Olieman JF, Penning C, Spoel M, IJsselstijn H, van den Hoonaard TL, Escher JC, Bax NM, Tibboel D. Long-term impact of infantile short bowel syndrome on nutritional status and growth. Br J Nutr 2011:1-9.

Spoel M, van den Hout L, Gischler SJ, Hop WC, Reiss I, Tibboel D, de Jongste JC, IJsselstijn H. Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia. Pediatr Crit Care Med 2011.

Spoel M, vd Cammen-v Zijp M, Hop WCJ, Tibboel D, de Jongste JC, IJsselstijn H. Lung function in young adults with congenital diaphragmatic hernia; a longitudinal evaluation. Pediatr Pulmonol 2012; Accepted.

Spoel M, Laas R, Gischler SJ, Hop WJC, Tibboel D, de Jongste JC, IJsselstijn H. Diagnosis-related deterioration of lung function after extracorporeal membrane oxygenation. Eur Respir J. 2012 Apr 10 [Epub ahead of print]

**PhD Portfolio,**

| | |
|---|---|
| Summary of PhD training and teaching activities | 373 hours and 19 ECTS |
| Name PhD student | Marjolein Spoel |
| Erasmus MC Department | Intensive Care and Pediatric Surgery |
| PhD period | 2006-2012 |
| Promotores | Prof.dr. D. Tibboel, Prof.dr. J.C de Jongste |
| Co-promotor | Dr. H. Meijers-IJsselstijn |

| | Year | Workload |
|---|---|---|
| **General academic skills** | | |
| - Paediatric Clinical Epidemiology | 2006 | 30 hours |
| - Biomedical English Writing and Communication | 2008 | 4 ECTS |
| - Research Integrity (BROK) | 2010 | 2 ECTS |
| **Reseach skills** | | |
| - Introduction course on Statistics & survival analysis | 2012 | 10 hours |
| **International conferences** | | |
| - 17th European Respiratory Society Conference, Stockholm (poster contribution) | 2007 | 1 ECTS |
| - American Thoracic Society International Conference, Toronto (poster contribution, 2x) | 2008 | 2 ECTS |
| - Congress European Society of Peadiatric and Neonatal Intensive Care (ESPNIC), Verona (poster presentation) | 2009 | 1 ECTS |
| - British Association of Pediatric Surgeons (BAPS), Graz (oral presentation) | 2009 | 2 ECTS |
| - First International Workshop on Esophageal Atresia, Lille (poster contribution) | 2010 | 1 ECTS |
| - Congenital Diaphragmatic Hernia Congress, Rome (poster contribution, 2 Oral presentations) | 2011 | 3 ECTS |
| **National Conferences** | | |
| 29e congres Nederlandse Vereniging Kindergeneeskunde (poster contribution) | 2007 | 1 ECTS |
| 32$^{e}$ congres Nederlandse Vereniging Kindergeneeskunde (oral presentation) | 2010 | 2 ECTS |
| **Other** | | |
| Begeleiding afstudeerproject medisch student | 2009 | 90 hours |
| Multidisciplinair follow-up overleg (tweemaal per maand) | 2006-2012 | 1 hr each (140) |
| Maandelijkse researchbespreking kinderchirurgie | 2008-2012 | 1 hr each (45) |
| Presentatie tijdens researchbespreking kinderchirurgie (3 maal) | 2008-2012 | 8 hr each (24) |
| Maandelijks klinisch promovendi overleg | 2010-2012 | 1 hr each (18) |
| Presentatie tijdens klinisch promovendi overleg (1 maal) | 2011 | 8 hours |
| Presentatie tijdens kinderchirugen overleg | 2010 | 8 hours |