A new Light on Lung Disease in Congenital Diaphragmatic Hernia

Een nieuw licht op longziekte bij een aangeboren gat in het middenrif

Lieke de Jongste-van den Hout

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Voor opa

Jij leerde mij dat alles mogelijk is

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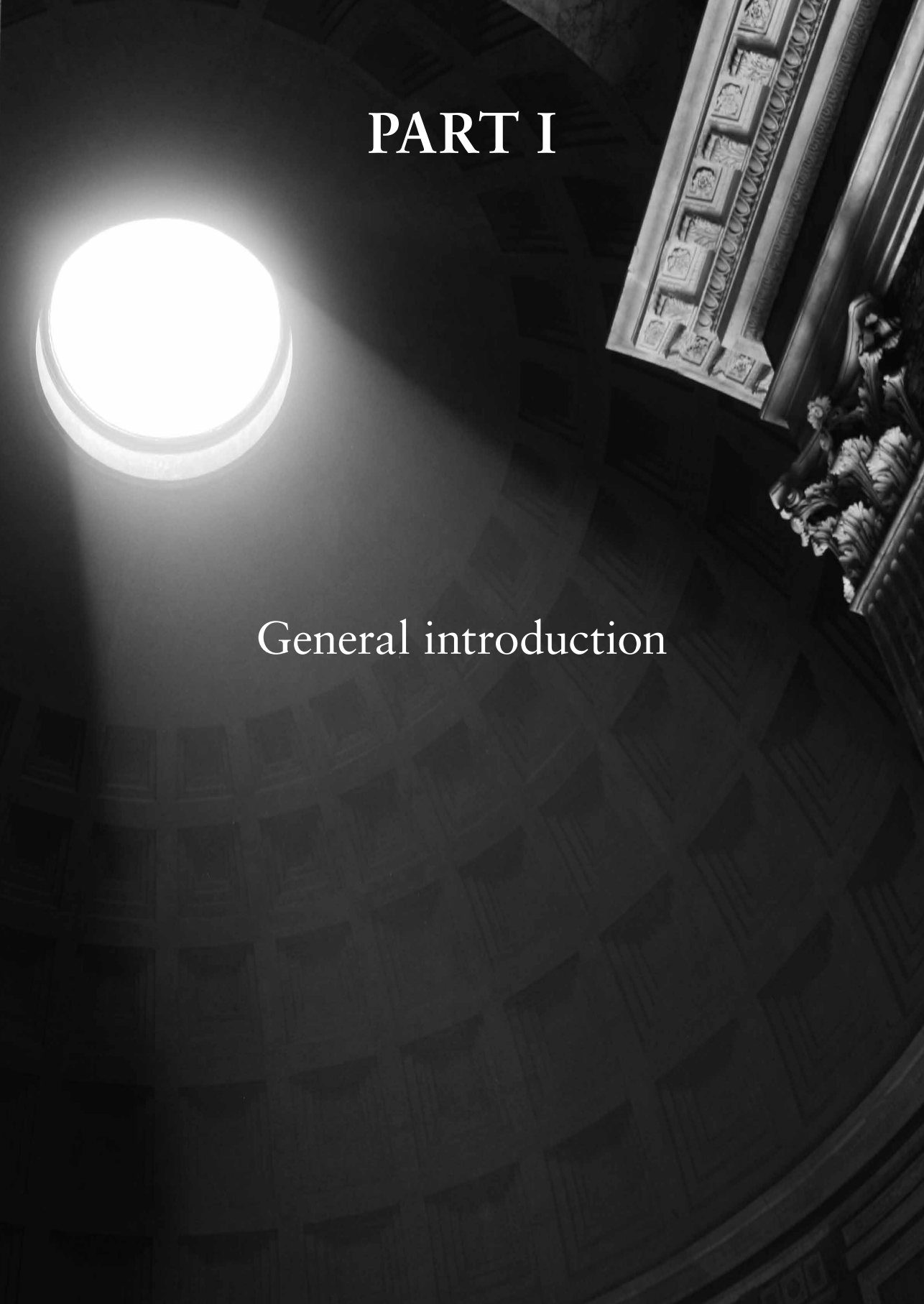
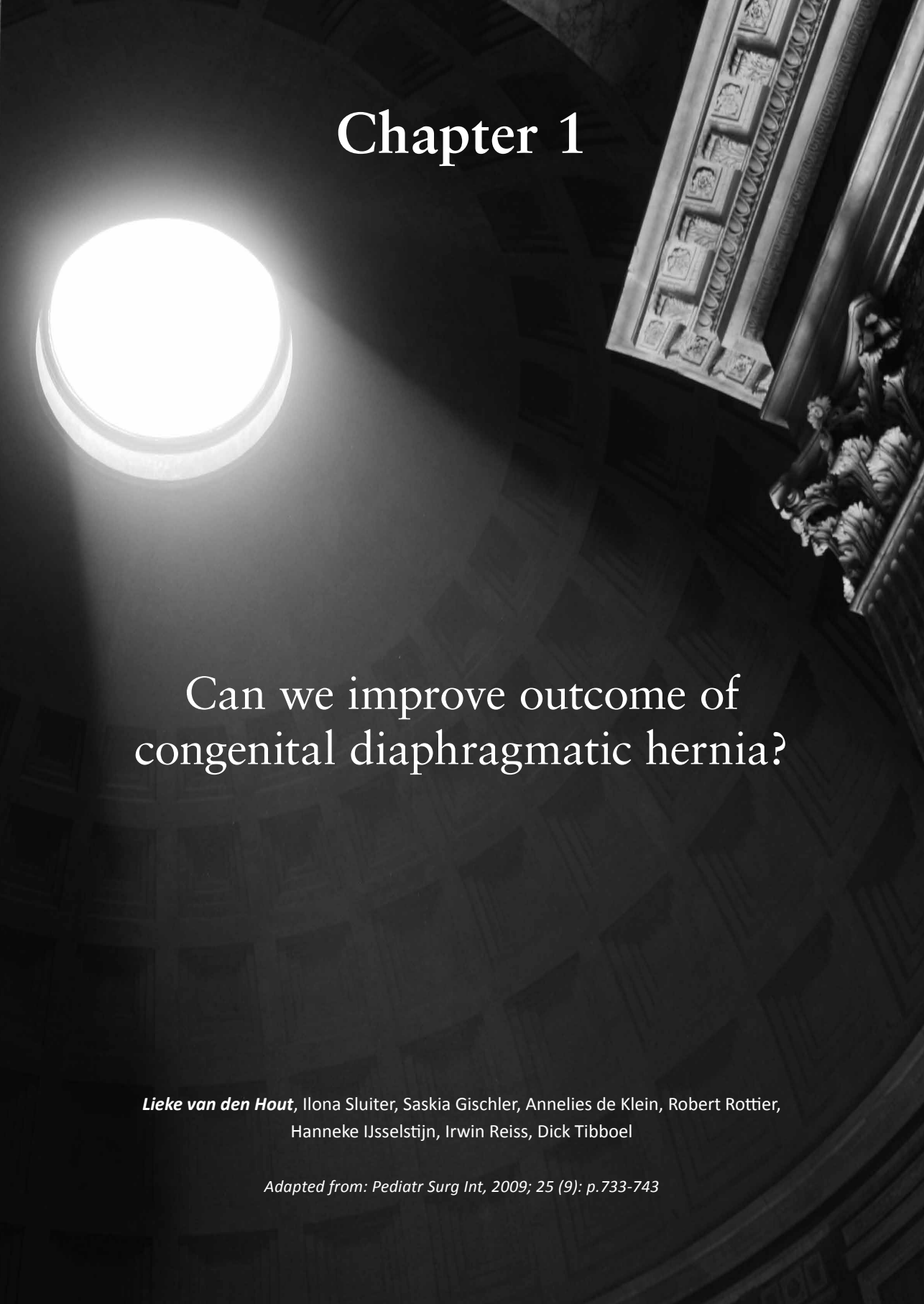


PART I

General introduction



Chapter 1

Can we improve outcome of congenital diaphragmatic hernia?

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Background

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[1]. The defect is usually – reportedly in 84% of the cases – located on the left side of the diaphragm. Right-sided CDH and bilateral CDH, which occur in 14% and 2% of cases, are associated with a worse prognosis[2]. CDH can present as an isolated defect or in combination with other congenital anomalies, such as congenital heart disease or chromosomal anomalies[2].

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[1]. 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[3]. Although survival rates have improved over the years, mortality rates in live-born patients still range from 10-35%[4-7], depending on case selection. Moreover, surviving neonates carry a substantial risk of developing secondary morbidity, such as cardiopulmonary, gastro-intestinal and neurological problems[8].

Etiology

Between the fourth and twelfth week of gestation, the diaphragm arises from the septum transversum, the pleuroperitoneal folds, the esophageal mesentery, and partly from the thoracic body wall. The neuromuscular component of the diaphragm may be formed by myogenic cells and axons which coalesce with the pleuroperitoneal folds[9-10].

Several hypotheses have been suggested in search for an explanation of the embryologic events that lead to defective development of the diaphragm. A strong candidate is mesenchymal malformation of the pleuroperitoneal folds[9]. Moreover, the 'dual hit' hypothesis has suggested an early insult in lung development before diaphragm development, followed by further lung growth restriction later in gestation[11]. It is still not clear, however, whether the pulmonary hypoplasia is induced by or results from the diaphragmatic defect.

It is also believed that several genetic and environmental factors may play a role in the development of CDH. One such environmental factor, as evidenced from animal models of CDH, is retinoic acid (RA), a derivative from vitamin A. It has a key role in embryonic development, including the diaphragm and the lungs[12]. Disturbances in the RA pathway by gene knock-outs, teratogens or maternal vitamin A deficiency may lead to the development of CDH[9,13-14]. Furthermore, retinol plasma concentrations in CDH patients may be lower than those in healthy newborns[15]. At least, administration of retinoic acid at the end of pregnancy was found to stimulate alveolar development in rats with CDH[13].

Aneuploidies, genetic syndromes and structural abnormalities of chromosomes, such as deletions, duplications, inversions and translocations, may indicate the involvement of genetic factors. The most reported aneuploidies in CDH patients are trisomy 13, 18, 21 and 45X; the most reported genetic syndrome is Fryns syndrome[16-17]. The transcription factor COUP-TF2, situated on chromosome 15q26, is one of the most likely candidate loci for CDH[18]. Essential for normal limb- and skeletal muscle development, COUP-TF2 is instrumental in the RA signaling pathway and interacts with other CDH candidate genes such as FOG2[14,19]. Mutations in FOG2 cause abnormal diaphragmatic development and pulmonary hypoplasia[20]. Thus, both genetic anomalies and disturbances in RA metabolism may be involved in the development of CDH.

Antenatal management

More detailed ultrasound techniques allow for prenatal detection of CDH in almost 60 % of the cases[21]. Several prenatal predictors have been proposed to determine postnatal chances of survival. These predictors may also be used to determine the need for fetal surgery.

The lung-to-head ratio (LHR), first described by Metkus et al. in 1996, is the most used prenatal predictor of survival in fetuses who have CDH[22-25]. It is obtained by dividing the contralateral lung area to the fetal head circumference[22]. Good predictive value has been reported for isolated cases of left-sided CDH, especially when the liver is in intrathoracic position[24,26-28]. Others, however, others doubt whether the LHR could predict postnatal outcome[29-30]. A debatable point is the inter-observer variety that may occur. Moreover, suitability of the LHR as a predictor of survival in right-sided CDH has not yet been documented[31]. Furthermore, LHR may also depend on the gestational age at measurement and may be less reliable in mid-gestation[25,32].The observed-expected LHR, which is independent of the timing of assessment, may therefore be regarded as a better prenatal predictor[33]. Recently, the O/E LHR is being more and more used as a prenatal predictor of outcome, rather than the LHR. An O/E LHR below 25% is reported to be associated with a less than 20% chance of survival[34].

Recently, the fetal lung volume (FLV) has been proposed as a prenatal predictor of survival in fetuses with CDH. The lower the FLV, the lower the chance of survival and the higher the need for ECMO[35-36]. It is mostly measured by magnetic resonance imaging (MRI), a reliable method with good interobserver agreement for measurement of the FLV[37]. Being dependent on the gestational age at measurement, it is best described as a ratio of the measured volume to the expected volume[38]. A recent study reported the observed-expected FLV to be a better predictor of survival than the observed-expected LHR[39].

However, in most centres the LHR is usually considered in combination with the liver's position to predict postnatal survival. In isolated cases of CDH, a LHR < 1.0 in combination with an intrathoracic position of the liver is considered unfavorable and warranting a fetal surgical intervention[22-23]. The intervention is a fetal tracheal occlusion (FETO) procedure, based on the principle that plugging of the trachea – by means of a balloon – will enhance lung growth. Outcomes of

FETO-procedures in CDH pregnancies vary. Some studies reported higher survival rates after a FETO-procedure, but others mentioned complications such as premature rupture of membranes or premature birth[23].

Prenatal prediction of survival confronts parents and doctors with difficult decisions on treatment strategies and possible prenatal interventions. So far it is not yet clear which is the most reliable prenatal predictor of survival. Measurement of the FLV by MRI has shown promising results. However, the high costs and restricted availability of MRI systems may limit its clinical application.

Postnatal management

Critical care during the first hours of life

Prenatal diagnosis of CDH calls for delivery in a high-volume center with expertise in the care for newborns with CDH. A planned delivery, either an induced vaginal delivery or a caesarean section, is a good option because most babies with CDH immediately present with cardiorespiratory stress. Physical examination may reveal a barrel-shaped chest, a scaphoid abdomen, absence of breathing sounds at the ipsilateral side, shifted cardiac sounds, and bowel sounds in the chest. A chest X-ray may show subnormal lung expansion and herniated bowels, filled with air or fluid, at the side of the defect. A small abdominal cavity may be seen, as well as displacement of the heart and other mediastinal structures to the contralateral side. Liver herniation may appear as a large soft tissue mass in the thoracic cavity, in which case there is no intra-abdominal liver shadow.

Immediate intubation is almost always indicated. To further help lung expansion and decompression of the abdominal contents, a nasogastric tube with continuous or intermittent suction and an enema are indicated. Bag masking may lead to gastro-abdominal distension and therefore has to be avoided. Ventilation management in the delivery room consists of conventional mechanical ventilation or bag ventilation. Peak pressures should be as low as possible, preferably below 25 cm H_2O, with a FiO_2 of 1.0.

Blood pressure support should be given to maintain arterial blood pressure levels at a normal level for gestational age. In case of severe right-to-left shunting, higher blood pressures (meaning above ≥ 50 mmHg) have to be pursued. In case of hypotension and/or poor perfusion, isotonic fluid therapy (10-20 ml/kg) may be given, preferentially based on cardiac ultrasounds evaluating function and contractility of the heart. Further blood pressure support consists of administration of inotropic agents, with dopamine, epinephrine, norepinephrine, and dobutamine as primary drugs of choice.

Newborns with CDH will be sedated and anaesthetized. Depth of sedation has to be evaluated by validated analgesia and sedation scoring systems, such as the COMFORT Scale [40]. Paralysis should be avoided, as it may have negative adverse effects on ventilation.

Ventilatory support

Pulmonary maldevelopment and asymmetry of the chest cavity seen in CDH makes ventilation a major challenge. Prolonged mechanical ventilation and oxygen toxicity may cause lung damage, which is predisposing to the development of chronic lung disease. In children, this is defined as pulmonary morbidity as a consequence of an acute neonatal respiratory disorder, and characterized by abnormal alveolarization and pulmonary vascular development[41-44]. Overdistension of the lungs and oxygen toxicity may be responsible for capillary leakage in the endothelium and epithelium, rupture of the basement membrane, leakage of fluid in the alveolar spaces, a general inflammatory response, and impaired surfactant secretion[2].

Moreover, genetic polymorphisms coding for vascular endothelial growth factor may be risk factors for chronic lung disease in newborns[45]. The best-known type of chronic lung disease in infants is bronchopulmonary dysplasia (BPD), which occurs mostly in premature and low birth weight infants. Despite the fact that they are usually born at term, one third of newborns with CDH will develop BPD, versus 20% of preterm infants[42,46-47].

Researchers have sought to reduce the risk of ventilator-induced lung injury and subsequent pulmonary morbidity by means of optimizing ventilation strategies. Since Wung et al. reported improved survival rates by using a 'gentle' ventilation strategy, this has become the cornerstone for ventilation management in newborns with CDH[7,48-49]. 'Gentle' ventilation is based on low peak inspiratory pressures, oxygen saturations of > 80 %, and toleration of a rise in CO_2 level. This strategy is also called permissive hypercapnia[2,49]. Aggressive ventilation strategies with high peak inspiratory pressures cannot always be avoided, however, especially in centers without ECMO facilities.

A new method, high frequency oscillatory ventilation (HFO), was proposed to increase survival and reduce BPD in newborns with CDH[49-53]. It effectively achieves adequate gas exchange by means of an oscillatory pump which combines very high respiratory rates with low tidal volumes. HFO is claimed to reduce the severity of lung injury induced by mechanical ventilation, by promoting uniform lung inflation, reducing barotrauma, and decreasing the activity of inflammatory mediators[49,54-57]. It is mostly indicated when hypercarbia persists, refractory to conventional ventilation. Nevertheless, some centers also use HFO as an initial ventilation strategy. Observational and retrospective studies have suggested that HFO is a safe ventilation strategy in both preterm and term neonates[49-52,57]. However, a Cochrane review found only a borderline significant reduction in the rate of chronic lung disease in preterm infants with the elective use of HFO as compared with conventional ventilation[55]. A second Cochrane review described the use of HFO as a rescue therapy when conventional ventilation failed in term and near-term infants with severe pulmonary dysfunction. Only one trial compared these two ventilation strategies prospectively, resulting in no significant differences in outcome, need for ECMO, or complications[57-58]. On the negative side, HFO may cause lung hyperinflation, which may give rise to higher alveolar and mean airway pressures in some patients. The adverse effects on venous return and pulmonary vascular resistance may then increase the risk of pulmonary barotrauma and hemodynamic instability[49].

So far, there are only retrospective studies comparing the use of HFO and conventional ventilation in newborns with CDH. In one such study the use of HFO prevented hyperventilation as well as the need for ECMO[51]. Other studies showed effective CO_2 reduction and increased survival in neonates with CDH and a lower incidence of chronic lung disease with elective use of HFO. A limitation of these studies is that they compared different eras and that therapy protocol was not standardized. Therefore, the results might have been positively influenced by other improvements in neonatal medicine during the last decades[49,51-53].

Although suggested in many papers, newborns with CDH have no surfactant deficiency[46]. Surfactant inactivation may result either from underdevelopment of the lungs or from mechanical ventilation and oxygen toxicity[59-62]. A large retrospective study reported no benefit of surfactant therapy in newborns with CDH. In fact, survival rates in surfactant treated patients were lower, and both the need of ECMO and the incidence of chronic lung disease were higher[63]. Moreover, surfactant therapy may have adverse side effects such as severe hypotension. Therefore, the use of surfactant is not recommended.

Treatment of pulmonary hypertension

As stated before, pulmonary hypertension is a major cause of mortality in infants with CDH. Severe pulmonary hypertension usually presents several hours after birth, after an initial period of relative stability[64]. In healthy neonates, pulmonary vascular resistance decreases after birth as a result of oxygenation, shear stress and ventilation. This does not occur in all newborns with CDH, and the pulmonary vascular walls may remain thickened as a consequence. Pulmonary hypertension is essentially a reversible process, but may become chronic if treatment should fail. Chronic pulmonary hypertension is usually unresponsive to therapy and may lead to right ventricular failure and death. Apart from the initial morphological changes, the vascular changes that occur immediately after the neonatal period are due to hypoxia and hyperoxic exposure of the individual cells in addition to injury and inflammatory mediators. As such, we consider pulmonary hypertension to be a part of the disease spectrum in CDH patients and which we propose to name “pulmonary vascular disease”.

Treatment of pulmonary hypertension in infants with CDH is based on several underlying signaling pathways involved in the regulation of the vascular tone and the pathogenesis of pulmonary hypertension[65]. Nitric Oxide (NO) is perhaps the best-known endothelial derived vasodilator. Inhalation of NO (iNO) interferes with the cGMP pathway and results in vasodilatation by reducing intracellular calcium levels[66]. In 1992, iNO was introduced as a treatment for pulmonary hypertension. It may decrease the pulmonary vascular resistance and right ventricle afterload, without a decrease in arterial pressure[67]. Several randomized trials with iNO showed improved oxygenation and a lesser need of ECMO. However, iNO did not reduce mortality in infants with persistent pulmonary hypertension[68]. Also, a large RCT demonstrated no reduction in mortality and need of ECMO in infants with CDH[69]. As a negative effect, rebound pulmonary hypertension

may occur if iNO is weaned. Although iNO is used as the golden standard for treating newborns with pulmonary hypertension, still some 30% of newborns with CDH do not respond to iNO treatment[70-71]. However, although no data are available to show a constant effect in patients with CDH, so far all trials on iNO are severely underpowered for CDH. At present the use of iNO as drug of choice for the treatment of persistent pulmonary hypertension is being questioned. Taking into account the concept of right ventricular workload, more attention is paid to the ductus of Botalli and potential restriction of closure. In a number of studies, PGE1 is advised as first choice. However, no randomized controlled trails are available to prove its superiority.

Another therapeutic strategy that interferes with the cGMP pathway is Sildenafil, which is a PDE-5 inhibitor. Sildenafil may decrease the pulmonary artery pressure more effectively than does iNO. However, both are equally effective in decreasing the pulmonary vascular resistance[72]. Moreover, Sildenafil may increase the efficacy of iNO and may prevent rebound pulmonary hypertension during weaning of iNO[73]. In infants with CDH, Sildenafil improved cardiovascular function and oxygenation in pulmonary hypertension[74-75].

Inhibition of PDE-3, which metabolizes cAMP, is another option for the treatment of pulmonary hypertension. Milrinone, a PDE-3 inhibitor, was found to decrease the pulmonary artery pressure and pulmonary resistance in animals. Milrinone improved oxygenation in neonates with severe persistent pulmonary hypertension of the newborn and poor iNO responsiveness[76]. So far, the use of Milrinone has not yet been evaluated in infants with CDH.

Prostacyclin (PGI_2) is an endothelial-derived vasodilator that decreases intracellular calcium levels and thus leads to vasodilatation[77]. Case reports described the successful use of prostaglandin treatment in neonates with pulmonary hypertension[78-80]. De Luca et al. published case reports on the use of epoprostenol and iloprost, respectively, in the treatment of pulmonary hypertension in infants with CDH. For both agents the child's clinical condition improved for several hours[74,80].

Inhibitors of endothelin (ET), which is a potent vasoconstrictor produced in the vascular endothelium, may also improve pulmonary hypertension. In randomized controlled trials, bosentan, a non-selective ET receptor antagonist, was reported to improve exercise capacity and hemodynamics in adults with pulmonary hypertension[81-82]. A case report described the safe and effective use of bosentan in two neonates with pulmonary hypertension due to transposition of the great arteries[83]. Still, liver toxicity was reported as an important adverse effect of bosentan[82]. Sitaxsentan and ambrisentan are specific ET-A receptor antagonists which may be more effective and less hepatotoxic than bosentan[84-85]. No randomized controlled trials have been carried out yet to test the effect of endothelin receptor antagonists in neonates. However, a recent study by Keller et al. evaluated the use of this treatment in CDH patients[86].

Platelet derived growth factors (PDGFs) are upregulated in pulmonary hypertension[87-88]. Imatinib, a PDGF inhibitor, was reported to have a dose-dependent positive effect on right ventricle hypertrophy and reverse pulmonary vascular remodeling in patients with pulmonary hypertension[87,89]. A recent case report described the use of a tyrosine kinase inhibitor in a newborn with CDH. It gradually decreased the pulmonary artery pressure and improved the child's clinical condition[90].

Finally, the RhoA and Rho-kinase pathways are involved in maintaining the pulmonary vascular tone and their downstream effectors form a key pathway for the regulation of the vascular tone. In animal models, Fasudil, a Rho-kinase inhibitor, showed promising results in the treatment of pulmonary hypertension. Fasudil improved pulmonary hypertension, right ventricle hypertrophy and also reversed endothelial dysfunction in rats with pulmonary hypertension[91]. In another study, Fasudil generated a vasodilatory effect in rats who were unresponsive to iNO[92].

Long-term morbidity and multidisciplinary follow-up

Approximately 87% of CDH survivors have longer lasting associated morbidity, such as pulmonary, gastro-intestinal and neurological problems. Moreover, they are at risk of developing surgical problems in later life, such as CDH recurrence or bowel obstructions because of adhesions. Associated cardiac or chromosomal anomalies in children with CDH may involve a wide range of problems, which may need thorough multidisciplinary follow-up.

Pulmonary morbidity

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[8,46-47,93-95]. Pulmonary hypoplasia and lung damage due to mechanical ventilation predispose newborns with CDH to develop chronic pulmonary symptoms. Patients who received ECMO and/or a patch repair are more likely to develop pulmonary complications[96]. Long-term pulmonary sequelae may range from full clinical recovery to impaired lung function, respiratory tract infections, cor pulmonale, and even death. Up to 33% of CDH patients are oxygen-dependent for a longer time, compared to 20% of premature and low birth weight infants[41,47,96].

Forty-three percent of CDH patients are discharged home with diuretics, and 17% with bronchodilators[96]. Furthermore, during the first year of life approximately 35% required bronchodilator and/or steroid therapy[96]. Half of the CDH survivors show asthma-like symptoms, such as wheezing and bronchospasm, at one point during childhood[95]. However, asthma-like symptoms seem to decline over the years; a study in adolescent survivors showed that only 22% had asthmatic symptoms[95].

CDH survivors are also at risk of developing recurrent pulmonary infections. Pneumonia occurs in 7% of infants during the first year of life[97]. RSV infection, which is the most common cause of respiratory distress in infants, may put CDH survivors at a higher risk. RSV vaccination may therefore be recommended[8]. However, studies indicated no significant differences in respiratory symptoms between CDH survivors and controls[46,95].

Many studies report obstructive lung function abnormalities in CDH survivors; restrictive and combined obstructive/restrictive abnormalities are reported to a lesser extent[46, 95-100]. Lung function abnormalities occur in 28-52%[96-97]. Longer duration of ventilation is associated with worse

pulmonary function[46]. Furthermore, chest wall deformities, which occur in 46% of the patients, may be responsible for lung function anomalies[46,95]. CDH survivors showed higher rates of bronchial hyperreactivity after provocation tests than controls[46,95]. It is hypothesized that this is due to ventilation-induced lung damage rather than to pulmonary hypoplasia[46]. Apart from lung function anomalies, abnormalities on chest X-rays are reported in 33-80% of the patients[47,96]. These include hyperlucency, hyperinflation, persistent lung hypoplasia, decreased pulmonary vascularity, persistent lung opacities, mediastinal shift, and abnormal diaphragmatic profile[2,47,93]. Lung function abnormalities in CDH survivors are relatively mild and usually improve over time, especially after the first six months[99]. 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[46].CDH patients usually have a good exercise tolerance and 83% of adult survivors of CDH consider themselves healthy[97,100]. 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 and good monitoring of medication use and pulmonary problems. New techniques allow us to perform lung function measurements at a very early age, from six months on. Lung function tests early in life are necessary to start timely treatment that may prevent further damage from chronic lung disease.

Gastro-intestinal morbidity

Gastroesophageal reflux (GER) is a common problem in CDH survivors. It may be a source of feeding problems, failure to thrive, esophagitis, and respiratory problems if not treated adequately. Possible explanations of GER in CDH survivors are esophageal dysmotility, esophageal ectasia, maldevelopment or weakness of the crura, shortening of the esophagus, disruption of the angle of His, and a higher intra-abdominal pressure as a result of the return of the herniated viscera into the abdomen after surgical repair[101-102].

The incidence of GER is 20-84% during the first year of life[103]. An incidence of 63% was reported in adult survivors of CDH, co-existing with a Barrett's esophagus in 54%[104]. Up to 23% of affected infants need such a surgical correction, such as fundoplication[101-102]. Risk factors for a fundoplication in CDH survivors are a patch repair and an intrathoracic position of the liver[101].

Intestinal obstruction occurs in 4.2 –20% of CDH survivors, compared to 2.2% in other infants who had a laparotomy. This increased susceptibility may be due to postoperative transient paralysis of the bowels and intestinal kinking caused by the malrotation[103-104]. Two third of patients who had an intestinal obstruction needed surgical correction[104].The high incidence of GER and intestinal obstruction calls for long-term follow-up of gastro-intestinal problems in CDH survivors. Moreover, growth impairment is often reported in CDH survivors, especially in children

who underwent an ECMO-procedure. Adequate treatment of GER and feeding problems may improve growth impairment[100,105].

Neurological morbidity

Neurodevelopmental problems are often reported in CDH survivors[100]. These may be related to hypoxic brain injury and ECMO treatment. ECMO may be a risk factor for brain injury as it requires anticoagulant treatment and ligation of the carotid artery. Furthermore, there is a risk for hypoxic brain injury before and during ECMO[93]. In general, neurological sequelae occur in 10-30 % of the children who underwent an ECMO procedure[106-107]. Nineteen percent of CDH survivors treated with ECMO had severe long-term neurodevelopmental problems, including speech problems and seizure disorders[108]. However, other studies reported that ECMO was not a risk factor for poor long-term neurological outcome[109-110].

Sensoneurinal hearing loss is also reported in CDH survivors. Ototoxic medication for persistent pulmonary hypertension has been described as a risk factor for hearing loss. A recent study reported a 10% incidence of hearing problems in CDH survivors at the age of three years[111].

Motor problems are reported in 60% of CDH survivors during the first year of life and in 73% at the age of three years[100,111]. Duration of ventilation was a predictor of motor problems at the age of one year. Language problems were detected in 60% of the children at the age of three years[111]. Social and behavioral problems were recorded in approximately 10% of cases[111]. A study by Bouman et al. reported a mean IQ of 85 in CDH survivors, which is one standard deviation below the norm of 100. Also, only half of these children were at the expected school level[112].

Long-term neurodevelopmental follow-up is important in CDH survivors. Regular neurological, developmental and (neuro) psychological assessment by a specialized paediatrician and a child's psychologist is recommended. In case of motor, cognitive, speech and behavorial problems, further treatment by a physiotherapist, a speech therapist or a child's psychologist needs to be considered. Therefore, neurodevelopmental follow-up is preferably in the hands of a multidisciplinary team.

Mortality in CDH

In the earlier days, CDH was regarded as a surgical emergency and postnatal care was mainly directed towards early repair of the defect[113]. Also, CDH patients were treated with aggressive ventilator treatment using hyperalkalosis and high oxygen concentrations - thereby triggering pathways leading to irreversible pulmonary damage. In the 1980s, treatment strategies changed. First, the concept of 'gentle ventilation and permissive hypercapnea' was gradually introduced. In 1985, a landmark paper by Wung et al. first described the concept of 'gentle ventilation' and permissive hypercapnea for infants with severe respiratory failure[114]. This ventilation strategy, which stands for providing lower peak pressures and tolerating higher CO_2 levels in order to avoid barotrauma and oxygen toxicity, improved survival rates[114]. Secondly, delayed surgical repair, i.e.

repair after an initial period of stabilisation, was offered to infants with CDH. Also, some centers started to use HFO and/or ECMO as a rescue therapy in the most severely ill CDH patients.
Several studies evaluated outcome of CDH patients treated with these new strategies. For one, Wilson et al. reported outcome for CDH patients after the introduction of delayed surgery, permissive hypercapnea and ECMO treatment as a rescue therapy[115]. After the introduction of permissive hypercapnea, however, overall survival rates significantly improved from 44% to 69%[115]. To evaluate a possible beneficial effect of ECMO as a rescue therapy, Azarow et al. compared the results of Wilson et al. with their findings in patients treated with hyperalkalosis, high oxygen concentrations and rescue HFO (the so-called tale of two cities paper)[116]. The authors reported that neither use of HFO nor ECMO as a rescue therapy in severely ill CDH patients improved survival.
Another paper by Wung et al. reported an improved survival rate – from 75% to 94% –in CDH patients treated with permissive hypercapnea, delayed repair and no routine placement of a chest tube[7]. Moreover, use of this treatment protocol reduced the need for ECMO therapy from 35% to 6%[7]. Other studies also reported an increase in survival after the introduction of 'gentle ventilation', permissive hypercapnea and delayed repair was also reported by[4,6,117-118]. Moreover, some studies reported high survival rates with the use of HFO as initial ventilation strategy[5,52]. A study by Ng et al. reported an increase in survival from 38% to 73% after the introduction of initial ventilatory support with HFO[51].
Although studies have reported improved survival rates over the years, it must not be left unmentioned that studying survival in CDH patients may be complicated. In CDH, true mortality rates may be higher when taking into account antenatal death, termination of pregnancy, or death before reaching a specialized treatment center. This is called 'hidden mortality' and was first described by Harrison et al.[119]. Population-based survival rates in CDH are substantially lower than institution-based survival rates[120]. Recent studies reported an institutional survival rate of 68-80% population-based survival rate of 36-52%[121-122].The 'hidden mortality' was estimated to be 20-35% by previous studies[121-124]. A paper by Stege et al. showed that case selection may occur, due to terminations of pregnancy and associated anomalies, in reporting survival rates in CDH[125]. Single-center studies on mortality in CDH may thus be influenced by selection and referral bias, since they represent aspecific cohort which may not be representative for the total population[120]. Furthermore, variability in CDH management between institutions and lack of standardized treatment makes it difficult to compare patient outcomes[120,126].
Although many improvements in CDH treatment have been made over the years, CDH remains a life-threatening condition. However, survival rates improved significantly over the years in patient with CDH. For the major part, 'gentle' ventilation strategies, permissive hypercapnea and delayed repair accounted for better survival. The roles of ECMO treatment and HFO remain still unclear. Also, single-center studies on mortality in CDH may be complicated by selection and referral bias.

Research in CDH

Recently, a number of reviews were published either dealing with specific center experience or reviewing the different treatment modalities[2,127]. However, progress in CDH research is hampered by the relative low numbers of patients (less than 10 cases a year in over 80 % of centers); the absence of international therapy guidelines; and the lack of evidence of many therapeutic modalities.

Taking this into account, the problem of CDH can be classified as five-fold:

* nearly absent knowledge of the etiology
* variability of phenotype and absence of accepted parameters of pre- and postnatal prediction of outcome and targeted intervention
* absence of properly designed clinical trials with enough power to determine optimal therapy for respiratory insufficiency and pulmonary hypertension
* lack of interdisciplinary structured follow up and a database to evaluate morbidity throughout childhood
* translation of data of animal models of CDH for clinical practice

The CDH-EURO Consortium

In 2007, the international CDH-EURO Consortium was set up to enhance collaboration in the above-mentioned areas of interest. This is a European cooperative network of centres that all have an expertise in treating infants with CDH. This network aims at enhancing research, exchanging knowledge and developing standardized treatment protocols. Recently, a standardized treatment protocol based on levels of evidence was published by this group[128]. However, this protocol was based on retrospective studies and case reports, since randomized controlled trials are lacking in the field of CDH. In 2008, therefore, the first randomized clinical trial in CDH was started as an initiative of the CDH-EURO Consortium. This trial, the VICI-trial, compares HFO versus conventional ventilation as an initial ventilation mode in infants with CDH with pulmonary morbidity and mortality as outcome measures.

The CDH Study Group

CDH is a severe congenital anomaly that may put a considerable disease burden on both parents and child. Early recognition of problems and improvement of treatment strategies may increase survival and prevent secondary morbidity. Therefore, excellent pre- and postnatal healthcare, standardized treatment protocols, and a well-organized multidisciplinary follow-up program are of high importance in this vulnerable group of patients. This calls for extensive collaboration between hospitals, also because of the relative small number of CDH patients in single centers.
The CDH Study Group, founded in 1995, is the largest worldwide voluntary network of centers specialized in treatment of patients with CDH. The network was established to ask and identify specific clinical questions, to recommend specific therapy and to monitor outcome in CDH. To

this aim, the participating centres record CDH patients' data anonymously in a large patient database, the CDH Registry. In 2008, this database was reported to provide over 4000 data on patients[129] and nowadays about 5000 patient data are included. Over 50 institutions actively participate in the CDH Study Group. Any individual participating centre has access to all data. These data may be used to report on therapy, to establish risk stratification, to predict outcome or as concurrent comparative data for randomized clinical trials[129].

The CDH Study Group has produced over 20 reports using data from the CDH Registry. The first dates from 1998 and reported on outcome, ECMO treatment and surgical repair[130]. A more recent study evaluated outcome in high-risk CDH patients with diaphragmatic agenesis and found that mortality had declined in these patients[131]. Furthermore, recent studies described outcome in preterm CDH patients[132] and assessed risk factors for worse outcome in ECMO patients[133]. Last, a study described in this thesis reported on prevalence and risk factors for pulmonary morbidity in CDH patients[134].

In 2001, the CDH Study Group created a risk assessment tool using birth weight and Apgar scores at five minutes of life to estimate severity of disease[135]. In 2007, a study by Schultz et al. proposed a simplified predictive score for patients with CDH that uses PaO_2 and PCO_2 values[136].

With regard to associated anomalies in CDH, the CDH Study Group reported on Fryns Syndrome[137] and cardiac anomalies[138]. Furthermore, worse outcome and associations with other anomalies were reported in patients with bilateral diaphragmatic defects[139]. Evaluation of CDH patients diagnosed after 30 days of life revealed that left-sided patients more often presented with gastro-intestinal symptoms and right-sided patients more often with respiratory symptoms[140].

With regard to treatment strategies, the CDH Study Group reported no benefit from surfactant therapy[63,141-142] and prenatal steroid therapy[143]. The mode of delivery was not associated with survival, although caesarean delivery was associated with a slightly better outcome in non-ECMO patients[144]. With regard to timing of delivery, early term delivery was associated with better outcome[145]. With regard to surgical repair, a study revealed that the size of the defect, indicated by a patch repair, was strongly associated with mortality[146]. Furthermore, a study which evaluated surgical repair in ECMO patients reported that CDH repair after ECMO therapy is associated with better survival than repair during ECMO therapy[147]. However, other authors concluded that early repair of CDH in neonates on ECMO can be accomplished with acceptable rates of morbidity and mortality[148].

Aim and outline of this thesis

This thesis aims to improve the knowledge on pulmonary morbidity in infants with CDH. Furthermore, strategies to improve pulmonary morbidity and mortality are described. The content is divided into three parts.

In part I, an overview of the several problems in CDH is given in *chapter 1*. Furthermore, the prevalences of pulmonary morbidity, defined as bronchopulmonary dysplasia, and lung function anomalies in a cohort of children born at the Erasmus Medical center are evaluated in *chapter 2*.

In part II, risk factors for chronic lung disease and mortality in infants with CDH using the large patient database of the CDH Registry are described in *chapter 3*. The prevalence and risk factors of severe pulmonary morbidity are studied in *chapter 4*.

In part III, strategies to reduce mortality and pulmonary morbidity are described. In *chapters 5 and 6*, a standardized treatment protocol and its possible role in improvement of outcome in CDH patients are described. In *chapter 7*, the use of prenatal predictors of outcome is evaluated. In *chapter 8*, a randomized clinical trial protocol regarding ventilation strategies is described. *Chapter 9* provides a general discussion and overview of future perspectives; and c*hapter 10* summarizes the results.

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Chapter 2

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

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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'maxFRC) and functional residual capacity (FRCp) were measured with Masterscreen Babybody (Viasys). Z-scores were calculated for V'maxFRC.
Main results: Mean V'maxFRC values at 6 and 12 months were significantly below the expected values (mean Z-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. FRCp values were generally high, 47% were above the suggested normal range, and did not change significantly over time. Mean FRCp values were significantly higher in ECMO patients compared with 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 FRCp. None of the perinatal characteristics was associated with V'maxFRC. Mean weight Z-scores were significantly below zero at both time points ($p<0.001$). Mean weight Z-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 treatment is believed to reduce the harmful effects of mechanical ventilation in the most severe cases. However, decreased mortality may lead to more respiratory morbidity and concomitant growth impairment in ECMO-treated CDH patients. 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]. CDH is often associated with lung hypoplasia and pulmonary hypertension, in which case ventilatory support of variable duration is required. 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 cardiorespiratory condition has been optimized[2]. These strategies have raised survival rates of CDH patients to almost 80%[3-4]. This improvement goes hand in hand, however, with 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

Patients

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 infants were treated according to a standardized treatment protocol[13]. 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)[13]. Patients who were treated with ECMO all underwent

veno-arterial ECMO support , which was applied in case of reversible severe respiratory failure as described by Reiss et al[13].

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 program 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 following ECMO and for all CDH patients treated in our institution. The Medical Ethical Review Board ErasmusMC 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 FRCp (V'maxFRC), 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'maxFRC (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'maxFRC, we used the reference values provided by Hoo and colleagues[19]. Z-scores were calculated as the difference between observed and predicted value divided by the residual standard deviation from the reference values for V'maxFRC. Functional residual capacity (FRCp) was measured by whole body plethysmography (Masterscreen Babybody, Viasys, Hochberg, Germany). The mean FRCp (ml/kg) of 3 to 5 technically acceptable measurements was calculated. FRCp was expressed in ml/kg with as suggested by Hülskamp et al[20]. The normal range suggested by this study was in the order of 13 to 26 ml/kg. VmaxFRC Z-scores and FRCp (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]. Z-scores for weight and height were calculated using Growth Analyser version 3.5 (Dutch Growth Foundation). Z-scores < -1.96 (2.5th percentile of the reference population) were considered abnormally low; Z-scores > 1.96 (97.5th percentile of the reference population) were considered abnormally high. Z-scores for patients treated with ECMO were calculated separately.

The above-mentioned factors were the secondary outcome measures.

Data Analysis

Clinical 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 (SE). FRCp, VmaxFRC Z-scores and Z-scores for weight and length were evaluated longitudinally using repeated measurements ANOVA, a method which allows for missing data at one time point[22].

Possible associations between clinical characteristics and lung function parameters were also analyzed using ANOVA to correct for missing values. For this purpose, highest MAP and the duration of ventilation were transformed logarithmically to reduce the effect of outlying observations. In this regard, we specifically performed ANOVA analyses corrected for ECMO treatment, to evaluate a possible influence of ECMO treatment on FRCp , VmaxFRC Z-scores and Z-scores for weight and length. Possible associations between clinical characteristics and ECMO treatment were evaluated in an ANOVA model corrected for time. 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 were admitted with an overall survival of 48 patients (77%). Forty-three infants with CDH were included (Figure 1). Three infants were not measured because of clinical instability and need for supplemental oxygen at the time of lung function assessment and two infants were lost to follow-up. 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 respiratory tract infection (n=1) and first measurement performed with different equipment (n=4). Baseline characteristics of the 43 infants are shown in Table 1.

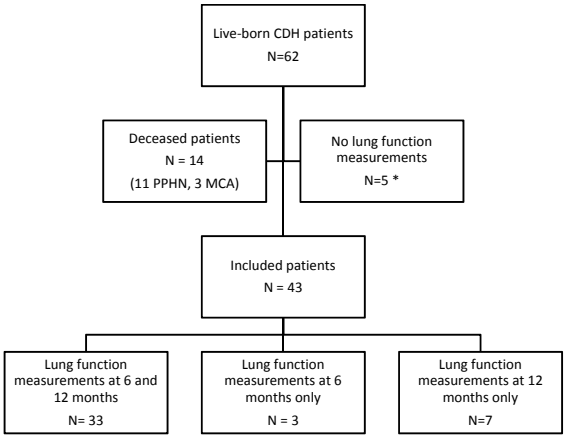

Figure 1. Flowchart
*2 patients were lost to follow up, 3 patients still had oxygen therapy at the time of lung function assessment and therefore measurements could not be performed. CDH: congenital diaphragmatic hernia. PPHN: therapy resistant persistent pulmonary hypertension of the neonate. MCA: multiple congenital anomalies.

Table 1. Baseline characteristics for 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).*

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)	36.5 (12-52)	16 (0-41)	0.095
Initial treatment with HFO	17 (40%)	4 (33%)	13 (42%)	0.735
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 (14-30)	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%)	0.15
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 (3-141.3)	37.0 (9.6-141.3)	18.5 (3.0-104.5)	0.171

*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 measurements for V'maxFRC were obtained in 29 patients at 6 months and in 38 patients at 12 months. For FRCp, reliable 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 which 17 (52%) ≥ 40 breaths/min. At 12 months 18 infants (47%) had a RR of ≥ 35 breaths/min of which 7 (18%) ≥ 40 breaths/min. Forty-seven percent of FRCp measurements were > 26 ml/kg (39% at 6 months and 55% at 12 months). The mean FRCp and mean Z-score of V'maxFRC did not change significantly over time. The results of the ANOVA analysis are presented in Table 2.

Table 2. Mean values of lung function parameters at 6 and 12 months

	6 months	12 months	P-value comparing the two time points
FRC_p (ml/kg)	28.1 (1.1)	28.7 (0.8)	0.518
$V'max_{FRC}$ (Z-score)†	-1.4 (0.1)†	-1.5 (0.1)†	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

Mean (SE) values from ANOVA are shown. FRCp: functional residual capacity. RR: respiratory rate. V'maxFRC (Z-score) †: p<0.001 below the reference value (Z=0).

Association between lung function parameters and clinical characteristics

In all included patients, a longer duration of ventilation was associated with higher FRCp values at both 6 and 12 months (p=0.001). Doubling of the ventilation time resulted in a 1.9 ml/kg mean increase in FRCp. Higher MAP was also significantly associated with higher FRCp values at both time points (p=0.002).

FRCp values were significantly higher (p=0.049) and V'maxFRC Z-scores were significantly lower (p=0.048) in patients who received treatment with inhaled nitric oxide.

No other significant associations between clinical characteristics and FRCp values or V'maxFRC Z-scores were found.

Lung function in ECMO patients

A total of twelve patients received ECMO therapy (see table 1) for a median of 7.1 days (range 3-12.1). The median day on which ECMO therapy was started was the second day of life (range 1-4). In table 1, clinical characteristics for both ECMO and non-ECMO patients are described. Patients who received ECMO therapy 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) and were ventilated for a longer time (p=0.002) than non-ECMO patients (see table 1). One ECMO patients had a ventricular septum defect which was surgically corrected at the age of 2 months; no other patients were diagnosed with congenital heart anomalies or any other congenital anomalies.

Mean FRCp values differed significantly between ECMO- and non-ECMO-treated patients at the age of six and twelve months (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'maxFRC Z-scores at 6 and 12 months were -1.52 (0.31) and -1.54 (0.25) respectively. Mean (SE) V'maxFRC Z-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 a possible effect of clinical characteristics and need for ECMO therapy on FRCp values, these characteristics were introduced in an ANOVA model to correct for possible effects of time. When corrected for duration of ventilation and highest mean airway pressure, the difference in FRCp values between ECMO and non-ECMO patients was not significant anymore (p=0.108 and p=0.369). No other associations between patient characteristics and FRCp values were found when corrected for ECMO.

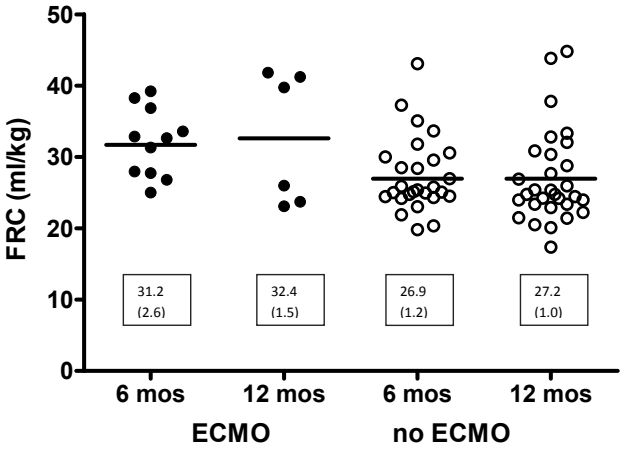

Figure 2. FRCp at 6 and 12 months in ECMO and non-ECMO treated CDH patients. FRCp (ml/kg) measurements in CDH patients who were treated with ECMO (2 panels left side; ECMO) and in those who were not treated with ECMO (2 panels right side; no ECMO) at the age of 6 and 12 months. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with SE between parentheses.

BPD and ECMO

A total of 16 patients developed BPD (41%, missing=4, see table 1). At both time points, BPD patients' mean FRCp was significantly higher than that of the non-BPD patients (p<0.001, Figure 3). This difference (6.2 ml/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'maxFRC Z-scores (p=0.159).

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

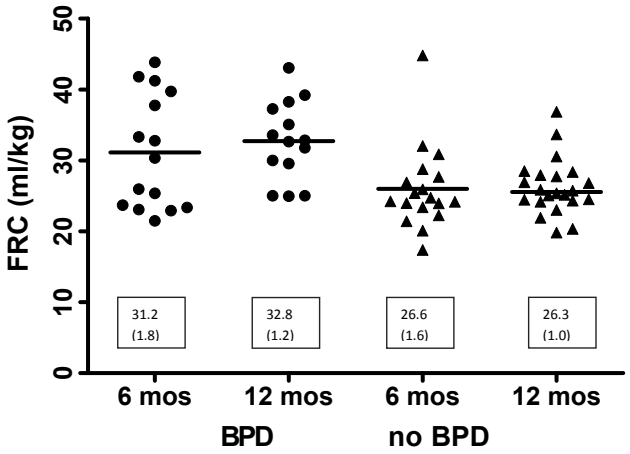

Figure 3. FRCp at 6 and 12 months in CDH patients with and without BPD. FRCp (ml/kg) measurements in CDH patients who developed BPD (2 panels left side; BPD) and those who did not develop BPD (2 panels right side; no BPD) at the age of 6 and 12 months. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with SE between parentheses.

Since FRCp did not change significantly over time we clustered data on FRCp obtained at 6 and 12 months. Thus, we obtained measurements of patients treated with ECMO who developed BPD (ECMO-BPD), of those treated with ECMO without BPD (ECMO-no BPD), of patients who did not undergo ECMO treatment but developed BPD (no ECMO-BPD) or did not develop BPD (no ECMO-no BPD). The individual measurements for these categories are shown in Figure 4.

Respiratory morbidity and physical growth

At 6 months, 4 patients (12%) had received at least one therapeutic course of antibiotics in the preceding 6 months; 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 the ages of 6 and 12 months, 12 (28%) and 6 patients (14%) respectively had an abnormally low weight. Mean weight Z-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 Z-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 Z-scores were 0.02 (0.18) and 0.07 (0.16) at 6 and 12 months, respectively. Height Z-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 Z-scores did not differ significantly between patients with and without ECMO.

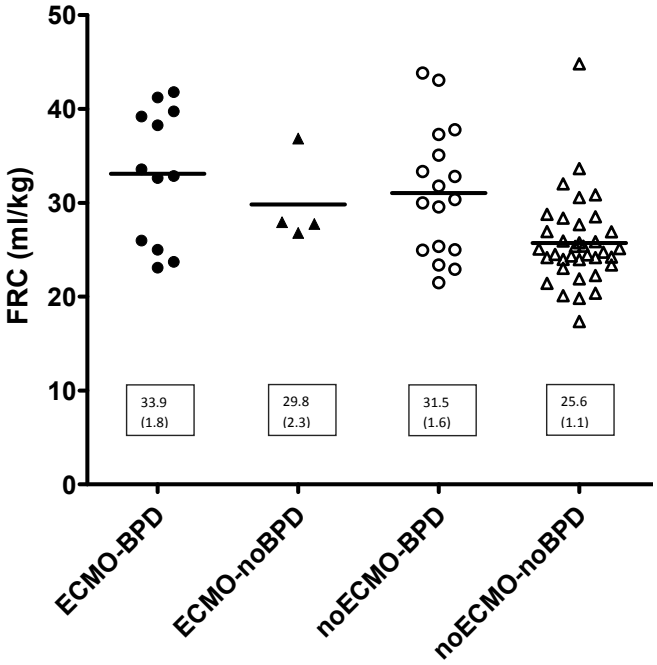

Figure 4. FRCp (ml/kg) measurements in four different groups of CDH patients at 6 and 12 months. Closed symbols represent ECMO-treated newborns; open symbols represent non-ECMO treated patients. BPD is indicated as circles; no-BPD as triangles. Thus, 4 different groups are shown. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with SE between parentheses.

Discussion

This prospective longitudinal study revealed that functional residual capacity 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 did not change significantly during the first year of life. ECMO-treatment was associated with significantly higher lung volumes. Presence of BPD, higher MAP and longer duration of ventilation were associated with higher FRCp at follow-up. None of the perinatal characteristics was associated with V'maxFRC.
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 FRCp Z-scores, measured with the nitrogen washout technique, were initially below average but increased after the first 6 months of life; V'maxFRC was below average within the first year of life[8]. A study using the sulphur hexafluoride wash-in/wash-out technique found similar FRCp levels in 13 CDH patients and in age-matched healthy controls[23]. Earlier, our group found higher FRCp in ECMO-treated

CDH patients than in infants who needed ECMO-support for meconium aspiration syndrome[9]. These findings on FRCp are in line with the present findings.

In the present study, FRCp values were generally above the expected range. This is likely to be due to 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 FRCp 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 from their ventilation–perfusion data that most of the lung growth in their CDH population was caused by the expansion of already existing alveoli and not by an increase in the number of alveoli[32]. Thus, the normal, near-normal or elevated FRCp values in our study are more likely to reflect hyperinflation than true lung tissue growth. FRCp values do not increase from 6 to 12 months which indicates there is no progressive hyperinflation of existing alveoli in the first year of life. Indeed, studies in older children after repair of CDH showed mildly increased residual volume and mild airway obstruction[10-12]. Hence, follow-up of lung function is important to clarify the role of increased lung volume. In the present study, functional residual capacity in ECMO-treated patients was higher than in the other patients. We 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, we found significantly higher use of HFO ventilation, which is used in case conventional ventilation provides insufficient oxygenation, in the ECMO treated group. Also, total ventilation time was significantly higher in the ECMO treated group. Although ECMO patients did not develop BPD significantly more often and were not ventilated with a significantly higher MAP, these signs of more severe respiratory problems were associated wither higher FRCp.

The decreased maximal expiratory flows in our study are in agreement with findings from similar studies in CDH patients[6-8,33]. Abnormal development of airway size or altered alveolar architecture may play a role here together with airway damage from mechanical ventilation. We found no 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 FRCp cannot be explained by differences in airway obstruction only.

Although 37% 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 increase in the measured airflow obstruction is indicative of abnormal airway structure and fibrosis due to lung injury rather than caused by increased airway responsiveness. CDH patients showed impaired growth during the first year of life, especially the ECMO-treated patients with weight Z-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 FRCp values in ml/kg. The earlier reference equations to compute FRCp into Z-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 FRCp on weight is relatively linear and passes close to the origin[34]. 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'maxFRC, 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[35].

In summary, CDH survivors are at risk for respiratory morbidity with hyperinflation and growth impairment. ECMO treatment is believed to reduce the harmful effects of mechanical ventilation in the most severe cases. However, decreased mortality may lead to more respiratory morbidity and concomitant growth impairment in ECMO-treated CDH patients. Close follow-up of these patients is needed to establish long-term evolution of lung function.

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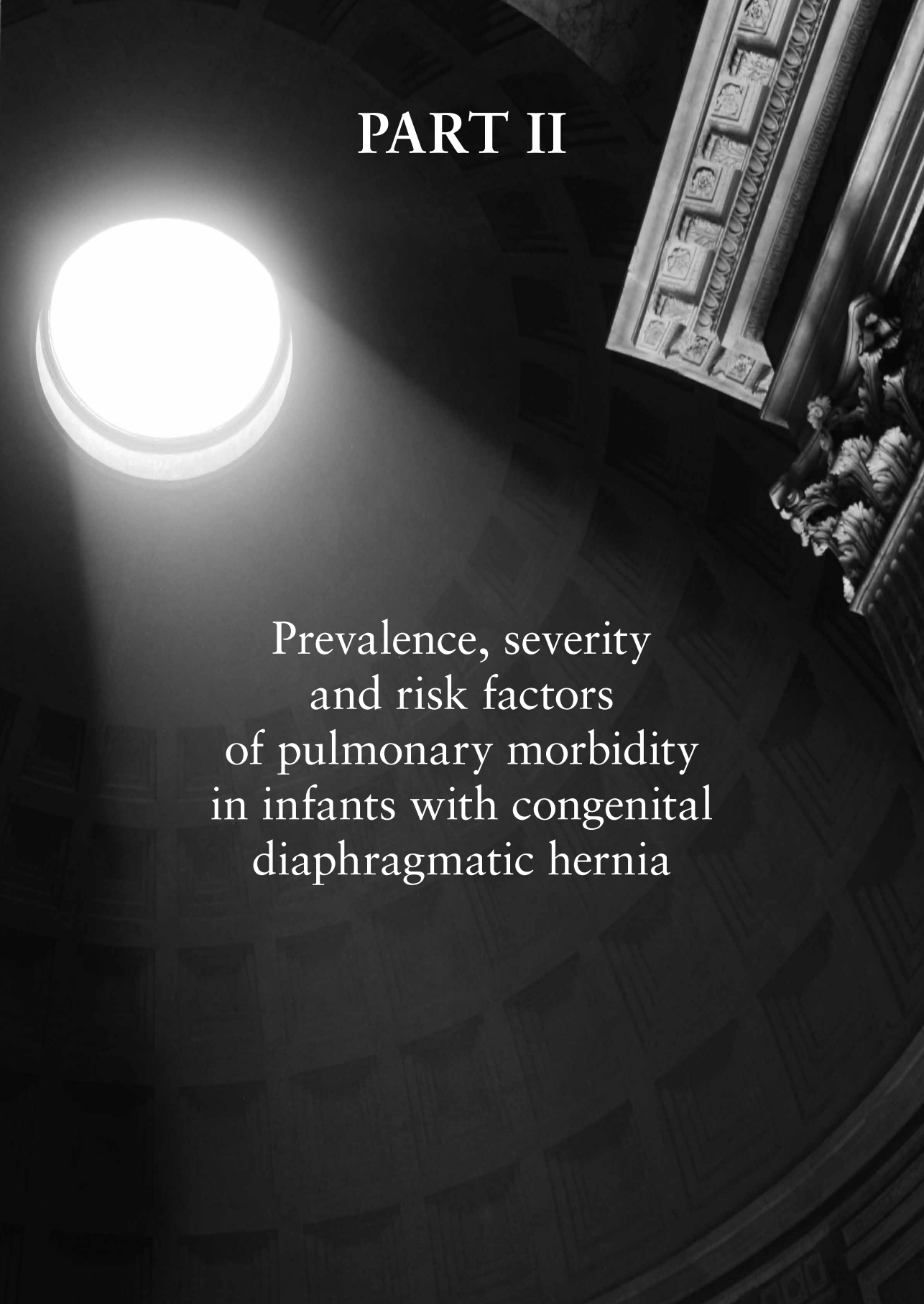

PART II

Prevalence, severity and risk factors of pulmonary morbidity in infants with congenital diaphragmatic hernia

Chapter 3

Risk factors for chronic lung disease and mortality in newborns with congenital diaphragmatic hernia

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Abstract

Background: Congenital diaphragmatic hernia (CDH) is associated with a mortality of 10-35% in live-born infants. Moreover, CDH survivors are at a substantial risk of developing long-term pulmonary sequelae, such as bronchopulmonary dysplasia (BPD).

Objective: This article aims to evaluate risk factors associated with BPD and mortality in neonates with congenital diaphragmatic hernia, with a special focus on the initial ventilation mode.

Patients and methods: Eligible for inclusion were live born infants with CDH born from 2001 through 2006 at the centers participating in the CDH Study Group. BPD, defined as oxygen dependency at day 30, and/or mortality by day 30 served as primary endpoint.

Results: A total of 2,078 neonates were included in the analysis. At day 30, 56% of the patients had either died or met the criteria for BPD. In infants who survived until day 30, the prevalence of BPD was 41%. The overall mortality rate was 31%. HFO as initial ventilation mode, a right-sided defect, a prenatal diagnosis, a lower Apgar score at five minutes, a cardiac anomaly, a chromosomal anomaly and a lower gestational age were associated with BPD and/or mortality by day 30.

Conclusion: Despite improvements in neonatal care, BPD and early mortality in newborns with congenital diaphragmatic hernia are still considerable. Several important risk factors for worse outcome are reported in this nonrandomized prospective observational study.

Introduction

Congenital diaphragmatic hernia (CDH) is a rare congenital anomaly which occurs in approximately 1 in every 2,500 live births[1]. It is associated with severe pulmonary hypoplasia and pulmonary hypertension. Mortality rates ranging from 10 to 35% have been reported, depending on case selection[1-5]. Survival rates have increased with improvements in neonatal care, including 'gentle' ventilation strategies, delayed surgery and extra corporeal membrane oxygenation (ECMO) in selected cases[4-8]. Survivors of CDH remain at a high risk, however, of developing secondary morbidity. Long-term pulmonary sequelae, such as chronic lung disease, persistent pulmonary hypertension, asthmatic symptoms, and recurrent respiratory tract infections have been reported in 30 to 50% of cases[9-14]. Alarmed by this information, the American Academy of Pediatrics developed official guidelines for structural and interdisciplinary follow-up[15].

Bronchopulmonary dysplasia (BPD) is a chronic respiratory disorder presenting early after birth. It mostly occurs in premature infants or term infants who have acute pulmonary disease. Ventilator-induced lung injury and high concentrations of oxygen predispose newborns to develop BPD[16-17]. In newborns with CDH the severity of lung hypoplasia may also be predictive for the development of BPD[13-14,18].

Research efforts have been directed at optimizing ventilation strategies for newborns with CDH. The 'permissive hypercapnia' approach, for example, led to higher survival rates and less pulmonary morbidity[5,19]. Around the world newborns with CDH typically receive conventional ventilation, with high frequency oscillatory ventilation (HFO) as rescue therapy. In certain cases, however, HFO will serve as the initial ventilation mode[20]. Observational and retrospective studies have reported that HFO as an initial ventilation mode may be an effective method to reduce mortality and chronic lung disease in children with CDH[7,21-24]. So far, no prospective trials have been carried out to determine if initial ventilation treatment with HFO may reduce long-term pulmonary sequelae. Moreover, most studies so far have focused on mortality and need for ECMO rather than on chronic lung disease as outcome measures[9,18,25].

The aim of this study is to describe possible risk factors for BPD and early mortality in infants with CDH. More specifically, this paper aimed to determine if the initial ventilation mode, either conventional ventilation or HFO, has some bearing on outcome.

Methods

Patients

We retrieved data from the large multi-institutional database of the CDH study group. This cooperative network of over 50 centers was established in 1995 to compile data on live born children with CDH. Data on prenatal evaluation, mode of delivery, neonatal care, surgery and clinical outcome until hospital discharge or death are prospectively recorded on standardized registry forms and entered into a central database[26].

In the CDH registry database, data on mode and duration of ventilation were available from the year 2001 until the year 2006. Therefore, we only included children born between January 2001 and December 2006. The large majority had been treated with conventional ventilation or HFO as initial ventilation mode. The few newborns treated with high frequency jet ventilation were excluded from the analysis. Newborns with central or bilateral CDH were excluded as well because their clinical course differs from that of those with a more common left- or right-sided CDH[27].

For the purpose of this article, data from 64 centres were collected. Centers are arbitrarily coded in the CDH registry database as a 'high-volume' or a 'low-volume' center. High-volume centers are those that admit more than 10 newborns with CDH per year. Furthermore, centres were coded as ECMO-centers or non-ECMO-centres.

The primary outcome measure in this study was BPD and/or mortality by day 30. Secondly, separate analyses were performed for mortality by day 30 and BPD. Bancalari et al. have defined BPD as oxygen dependency at day 28 or at 36 weeks postmenstrual age, depending on gestational age at birth[28]. The CDH registry database, however, holds data on oxygen dependency at day 30 instead of day 28. This is why we used oxygen dependency at day 30 as the criterion for BPD. The severity of BPD is determined at day 56 or at discharge, whichever comes first[28]. This, however, could not be determined since data on oxygen dependency at day 56 were not recorded in the CDH registry. Data on oxygen dependency at discharge or transfer are presented in a descriptive way.

Statistical analysis

To test associations between individual putative risk factors and outcome measures, univariate analyses were performed, using Chi-squared and Mann-Whitney U tests where appropriate. Baseline variables that showed a significant effect in univariate analysis were entered into multiple logistic regression analyses for BPD and/or mortality by day 30 and BPD and mortality by day 30 alone using a stepwise backward elimination method. P values for trend over the study years for all 3 outcome measures were also calculated using logistic regression. As many data on medication for pulmonary hypertension and position of the liver were missing, we did not use these variables in the statistical analysis. Results of the regression analyses are given as odds-ratios (OR) with 95% CI. Data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, Illinois). A two-sided p value less than 0.05 was considered statistically significant.

Results

The CDH database held data on 4,466 patients born from 1995 onwards. Eligible subjects were those born between 2001 and 2006, a total of 2,134 children. Of these, 56 were excluded based on our exclusion criteria or incorrect data, leaving 2,078 subjects (Figure 1). Analysis revealed no significant differences in baseline patient characteristics, the prevalence of BPD (p=0.762) and

the survival rate (p=0.122) between the included patients and patients who were born before 2001 (n=2120). BPD and/or mortality by day 30 was present in 56% (n=1116/2003, missing data=75) of the included patients and 58% (n=1162/2012, missing data=8) of the nonincluded patients who were born before 2001 (p=0.144). Patient characteristics are shown in table 1.

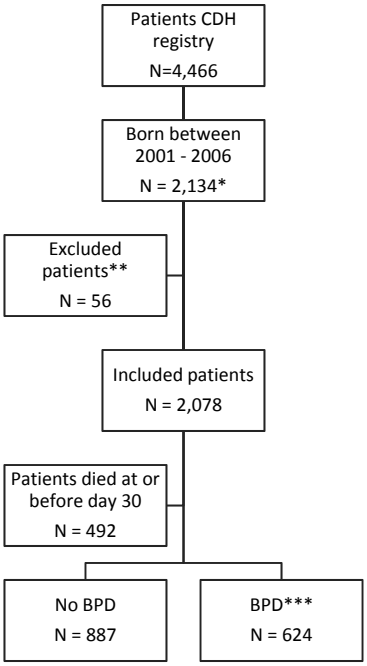

Figure 1. Flowchart of patient inclusion and exclusion in the present study.
* 2,120 patients were born before 2001; 212 patients were born after 2006
**Due to bilateral CDH (n=13), central CDH (n=4), High frequency jet ventilation (N=13) or incorrect data on survival (N=26)
*** Data on BPD were missing for 75 patients

Bronchopulmonary dysplasia and mortality by day 30

By day 30, 56% of all infants (n=1,116/2,003, missing data=75) had either died or met the criteria for BPD. Mortality by day 30 was 24% (n=492/2,078). Overall mortality until hospital discharge for all 2078 newborns was 31% (n=634/2,078). Of the newborns that survived until day 30, 41% met the criteria for BPD (n=624/1,511, missing data=75). Of these infants, 56% (n=344/612, missing data=12) had mechanical ventilation, 9% had CPAP (n=57/612) and 34% (n=211/612) had a nasal cannula at day 30. Of the infants that survived, 21% was oxygen dependent (n=304/1,423, missing data=21) at discharge or transfer. Of these, seventeen percent were mechanically ventilated at discharge or transfer (n=51/295, missing data=11), 2% received CPAP (n=6/295) and 81% (n=238/295) had a nasal cannula.

Table 1. Baseline characteristics for all live-born patients with CDH (n=2,078) born between 2001 and 2006*

Variable	Number of patients	%
Males	1,235/2,076	59
Birth in high-volume center	1,132/2,078	54
Birth in ECMO center	1,910/2,078	92
Inborn	837/2,076	40
Vaginal delivery	1,021/1,855	55
Prenatal diagnosis	1,246/2,073	60
Cardiac Abnormality	322/2,077	16
Chromosomal Abnormality	89/2,077	4
Other abnormality**	176/2,078	8
Left-sided defect	1735/2,060	84
Continuous variables	**Median**	**Range**
Gestational age at birth, weeks	38	23-42
Birth weight, kg	3.03	0.57-4.90
Apgar score at 5 min	7	0-10

*numbers do not always add up to 2078 because of missing data

** Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality

The prevalence of BPD and/or death by day 30 did not change over the study years (p for trend=0.251). The prevalences of mortality by day 30 and BPD alone did also not change significantly over the study years (p for trend=0.625 and 0.317, respectively).

Extra Corporeal Membrane Oxygenation (ECMO)

A total of 1,910 infants were born in an ECMO-center. Overall, an ECMO procedure was performed in 29% of the patients (n=595/2,078). The median day on which ECMO was started was on the second day of life (range 0-129). The median duration of the ECMO treatment was 10 days (range 0-42). A total of 283 patients (48%) had surgical correction of the diaphragmatic defect during the ECMO treatment.

A total of 93% infants (n=523/564, missing data=31) who underwent an ECMO procedure had either died by day 30 or met the criteria for BPD compared with 41% of the infants (n=591/1,439, missing data=44) who did not underwent an ECMO procedure (p<0.001). By day 30, 38% of the patients who underwent an ECMO procedure had died (n=212/564, missing data=31), compared to 19% (n=280/1,483) of the patients who did not undergo an ECMO procedure (p<0.001). Overall mortality after an ECMO procedure was 51% (n=285/564, missing data=31). BPD was present in 88% of the patients who underwent an ECMO procedure and survived until day 30 (n=311/352) compared to 27% of the patients who did not undergo an ECMO procedure and survived until day 30 (n=313/1,159, p<0.001).

Surgical repair

A surgical repair was done in 83% of all patients (n=1,729/2,078). Median day of surgical repair was the fourth day of life (range 0-112). A patch repair, as opposed to primary repair, was performed in 49% (n=837/1,725, missing data =4) of the cases.

Seventy-five percent of the infants (n=599/801, missing data=36) who underwent a patch repair had either died by day 30 or met the criteria for BPD compared with 20% of the infants (n=171/854, missing data=34) who did not underwent a patch repair (p<0.001). Of patients who underwent a patch repair, 16% (n=132/837) had died by day 30 compared to 2% (n=18/888) of patients who underwent a primary repair (p<0.001). BPD was present in 70% of the patients who underwent a patch repair and survived until day 30 (n=467/669, missing data=36) compared to 18% of the patients who underwent a primary repair and survived until day 30 (n=153/852, missing data=34, p<0.001).

Initial ventilation mode

Of all patients, 35% received HFO (n=674/1,936) and 65% received conventional ventilation (n=1,262/1,936, missing data=142) as initial ventilation mode. The median duration of ventilation in children initially treated with HFO was 17 days (range 1-199) compared to 11 days (range 0-741) in children treated with conventional ventilation (p<0.001).

Differences in baseline patient characteristics between patients who received initially HFO or conventional ventilation are presented in table 2. Patients who received HFO as initial ventilation mode were significantly more often prenatally diagnosed (p<0.001), inborn (p<0.001) and born in an ECMO-center (p<0.001), had significantly more other abnormalities (p=0.031) and had a significantly lower median birth weight (p<0.001) and Apgar score at 5 min (p<0.001). Patients

Table 2. Baseline patient characteristics for patients with CDH who received initial ventilatory treatment with HFO (n=674) or with CMV (n=1,261) *

Variable	HFO	%	CMV	%	p value
Males	391/674	58	753/1,260	60	0.485
Birth in high-volume center	398/674	59	708/1,262	56	0.230
Birth in ECMO center	651/674	96	1144/1,262	91	<0.001
Inborn	360/674	53	422/1,260	33	<0.001
Vaginal delivery	312/588	53	665/1,161	57	0.104
Prenatal diagnosis	480/674	71	673/1,261	53	<0.001
Cardiac Abnormality	93/674	14	203/1,261	16	0.203
Chromosomal Abnormality	33/673	5	46/1,262	4	0.226
Other abnormality**	69/674	10	92/1,262	7	0.031
Left-sided defect	562/673	84	1057/1,258	84	0.819
Continuous variables	**Median**	**Range**	**Median**	**Range**	**p-value**
Gestational age at birth (wks)	38	26-42	38	26-42	0.126
Birth weight (kg)	3.0	0.6-4.9	3.1	0.7-4.8	<0.001
Apgar score at 5 minutes	7	1-9	7	0-10	<0.001

* numbers do not always add up 1,935 to because of missing data

** Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality

who received initial treatment with HFO had significantly more often BPD and/or died by day 30 compared to patients who received initial treatment with conventional ventilation (p<0.001, data shown in table 3 and table 4).

Table 3. Univariate analyses of baseline variables for patients who had BPD at day 30 and/or died by day 30 (n=1,116, missing data=75) born between 2001 and 2006*

Variable	BPD and/or death by day 30	%	p value
Gender			0.160
Male	649/1,192	54	
Female	467/809	58	
Volume center			0.085
High	521/900	58	
Low	595/1,103	54	
Birth in ECMO center			0.006
Yes	1,040/1,836	57	
No	76/167	46	
Birth location			<0.001
Inborn	534/812	66	
Outborn	582/1,189	49	
Method of delivery			<0.001
Caesarean section	496/807	61	
Vaginal delivery	499/985	51	
Prenatal diagnosis			<0.001
Yes	802/1,204	67	
No	310/794	39	
Cardiac abnormality			<0.001
Yes	242/312	78	
No	874/1,690	52	
Chromosomal abnormality			<0.001
Yes	78/87	90	
No	1,037/1,915	54	
Other abnormality**			1.000
Yes	94/169	56	
No	1,022/1,834	56	
Side defect			<0.001
Left	879/1,667	53	
Right	229/328	70	
Initial ventilation mode			<0.001
HFO	460/632	73	
CMV	564/1,233	46	
Continuous variables			
Gestational age, weeks	6 (0-10)		<0.001
Birth weight, kg	2.93 (0.57-4.80)		<0.001
Apgar score at 5 min	38 (23-42)		<0.001

*numbers do not always add up to 1,116 because of missing data

**Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality

Table 4. Univariate analyses of baseline variables for patients who had BPD day 30 (n=624) or who had died by day 30 (n=492) born between 2001 and 2006*

Variable	BPD	%	p value	Death by day 30	%	p value
Gender			0.420			0.150
Male	370/913	41		279/1,235	23	
Female	254/596	43		213/841	25	
Volume center			0.071			0.398
High	303/690	44		276/1,132	24	
Low	321/821	39		236/946	25	
Birth in ECMO center			<0.001			0.016
Yes	601/1,397	43		439/1,910	23	
No	23/114	20		53/168	32	
Birth location			<0.001			<0.001
Inborn	260/538	48		274/837	33	
Outborn	364/971	37		218/1,239	18	
Method of delivery			0.007			<0.001
Caesarean section	255/566	45		241/834	29	
Vaginal delivery	294/780	38		205/1,021	20	
Prenatal diagnosis			<0.001			<0.001
Yes	434/836	52		368/1,246	30	
No	188/672	28		122/827	15	
Cardiac abnormality			<0.001			<0.001
Yes	127/197	64		115/322	36	
No	497/1,313	38		377/1,755	21	
Chromosomal abnormality			<0.001			<0.001
Yes	23/32	72		55/89	62	
No	601/1,479	41		436/1,988	22	
Other abnormality**			0.445			0.241
Yes	46/121	38		48/176	27	
No	578/1,390	42		444/1,902	23	
Side defect			<0.001			0.001
Left	497/1,285	39		382/1,735	22	
Right	127/226	56		102/335	30	
Initial ventilation mode			<0.001			<0.001
HFO	229/401	57		231/674	34	
CMV	346/1,015	34		218/1,262	17	
Continuous variables	**Median(range)**			**Median(range)**		
Gestational age,weeks)	38 (23-42)		<0.001	38 (26-42)		<0.001
Birth weight,kg	3.00 (0.64-4.8)		<0.001	2.79 (0.57-4.48)		<0.001
Apgar score	7 (0-10)		<0.001	6 (0-9)		<0.001

*numbers do not always add up to 624 and 492 because of missing data

** Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality

Of the infants who received initially HFO, 39% (n=260/674) underwent an ECMO procedure compared with 23% (n=296/1,262) of the infants who received initially conventional ventilation (p<0.001). In total, 526 patients who initially received HFO and 1,100 patients who initially received conventional ventilation underwent a surgical repair. Of those patients, 64% of the patients who were initially treated with HFO (n=336/524, missing data=2) underwent a patch

repair, as opposed to primary closure, compared with 40% (n=441/1,098, missing data=2) of patients treated with conventional ventilation as an initial ventilation mode (p<0.001).

Multivariate analysis

The univariate analysis of baseline variables for BPD and/or mortality by day 30 is presented in table 3. Separate univariate analyses for BPD and mortality by day 30 are presented in table 4. Baseline variables that were significant were entered into multiple logistic regression analyses for all 3 outcome measures. Variables regarding surgical repair and ECMO therapy were not entered into the multivariate analyses, because we only included those variables that were known at baseline.

As 223 patient data on method of delivery were missing, we excluded this variable from the multivariate analyses. Birth weight and gestational age were both significant in the univariate analyses, but due to their high correlation with each other, only gestational age was added to the multivariate analysis.

The baseline variables location of birth (in or outborn), birth in ECMO-center (yes or no), prenatal diagnosis, cardiac abnormality, chromosomal abnormality, side of the defect (left or right side), Apgar score at 5 min, the initial mode of ventilation and gestational age were all entered in the multivariate analyses for early mortality and chronic lung disease.

The results of the final multivariate analyses are shown in table 5, 6 and 7. A lower gestational age, a cardiac anomaly, a chromosomal anomaly, a prenatal diagnosis, a right-sided defect, a lower Apgar score at 5 min and HFO as initial ventilation mode were associated with a higher risk for BPD and/or death by day 30. Having a chromosomal anomaly was also associated with early mortality, but not with BPD. Additionally, being inborn was associated with a higher risk for mortality by day 30 and with a reduced risk for BPD.

Table 5. Multivariate logistic regression analysis of BPD and/or death by day 30 (n=1,686)*

Variable	Odds ratio	95% CI	p value
Gestational age in weeks	0.84	0.81-0.90	<0.001
Cardiac abnormality	2.62	1.85-3.72	<0.001
Chromosomal abnormality	3.04	1.42-6.51	0.004
Prenatal diagnosis	3.90	3.00-5.00	<0.001
Right-sided defect	2.76	1.96-3.89	<0.001
Apgar score	0.61	0.57-0.65	<0.001
HFO as initial ventilation mode	2.53	1.95-3.27	<0.001

*Nonsignificant variables in the multivariate analysis for BPD and/or death by day 30: birth in ECMO-center (OR 1.39, 95% CI 0.80-2.44, p=0.244) and location of birth (OR 1.1, 95% CI 0.83-1.46, p=0.487). OR=Odds ratio CI=Confidence interval

Table 6. Multivariate logistic regression analysis for BPD (n=1,293)*

Variable	Odds ratio	95% CI	p value
Gestational age in weeks	0.87	0.82-0.92	<0.001
Cardiac abnormality	2.42	1.85-3.67	<0.001
Inborn	0.70	0.52-0.95	0.023
Prenatal diagnosis	4.27	3.05-5.80	<0.001
Right-sided defect	2.51	1.73-3.64	<0.001
Apgar score	0.66	0.61-0.71	<0.001
HFO as initial ventilation mode	2.29	1.73-3.04	<0.001

*Nonsignificant variables in the multivariate analysis for: birth in ECMO-center (OR 1.81, 95% CI 0.94-3.48, p=0.074) and having a chromosomal abnormality (OR 1.37, 95% CI 0.57-3.26, p=0.480). OR=Odds ratio CI=Confidence interval

Table 7. Multivariate logistic regression analysis for mortality by day 30 (n=1,749)*

Variable	Odds ratio	95% CI	P-value
Gestational age in weeks	0.87	0.83-0.92	<0.001
Cardiac abnormality	1.54	1.11-2.14	0.010
Chromosomal abnormality	4.49	2.63-7.67	<0.001
Inborn	1.76	1.30-2.38	<0.001
Prenatal diagnosis	1.80	1.28-2.02	<0.001
Right-sided defect	1.88	1.35-2.63	<0.001
Apgar score	0.68	0.64-0.73	<0.001
HFO as initial ventilation mode	1.85	1.42-2.41	<0.001

*Nonsignificant variable in the multivariate analysis for: birth in ECMO-center (OR 0.71, 95% CI 0.37-1.34, p=0.286). OR=Odds ratio CI=Confidence interval

Although we did not include variables that were not known at baseline, we did test for various interactions between these variables and the baseline variables. In this regard, we found an interaction between the need for ECMO treatment and the initial mode of ventilation in the multivariate analyses for BPD and/or death by day 30 and BPD alone. This revealed that in patients who underwent an ECMO procedure, the initial ventilation mode of ventilation was not associated with these outcome measures anymore.

Also, we found an interaction between the location of birth and HFO as initial ventilation mode. In patients who were born outside a tertiary clinic, HFO was still associated with a higher risk of BPD and/or death by day 30 and BPD alone. In patients who were born inside a tertiary clinic, HFO gave a slightly higher risk of BPD and/or death by day 30 and BPD alone. This was, however, not significant because confidence intervals overlapped.

We did not find any interactions between birth in an ECMO center, the volume of the center and the initial ventilation mode. Also, we did not find any variables that modified the effect of HFO in the analysis for early mortality.

Discussion

In this study, 56% of all the infants included had either died or met the criteria for bronchopulmonary dysplasia at day 30. In survivors of CDH, BPD, with a prevalence of 41%, remains an important clinical issue. Moreover, the prevalence of BPD and/or early mortality remained constant over the years of the study period, despite promising advances in neonatal care and urgent reports of centers around the world. Unexpectedly, this study showed that initial ventilatory treatment with HFO was associated with worse postnatal outcome.

We can propose several causes for the high prevalence of BPD. Firstly, these children's hypoplastic lungs may be more susceptible to oxygen toxicity than the lungs of other newborns with respiratory distress[12]. Moreover, maldevelopment of the pulmonary vasculature may contribute to pulmonary hypertension, which in itself increases morbidity and mortality in BPD[29]. Thirdly, the asymmetry of the lungs may result in areas of differential compliance and the subsequent risk of overexpansion of the alveoli[12-13]. Fourthly, although centers mostly use gentle ventilation strategies nowadays, aggressive ventilation strategies with high peak inspiratory pressures cannot always be avoided. Subsequent volutrauma, barotrauma, and atelectrauma may contribute to significant pulmonary injury, including diffuse alveolar damage, hyaline membrane formation, and intra-alveolar hemorrhage[23,30].

This study suggests that HFO as the initial ventilation mode is a risk factor for BPD and/or mortality by day 30 and for BPD and mortality separately. This was a somewhat surprising finding because previous retrospective and observational studies indicated that HFO as the initial ventilation mode might be an effective method to increase survival and reduce BPD in newborns with CDH[21-22,24]. It was thought to ameliorate ventilation-induced lung injury by promoting uniform lung inflation, reducing barotrauma, and suppressing inflammatory mediators[23,30-33]. On the other hand, HFO might well cause lung hyperinflation. The resultant higher alveolar and mean airway pressures would then raise the risk of pulmonary barotrauma and hemodynamic instability, due to adverse effects on venous return and pulmonary vascular resistance[23].

A possible explanation for the association of HFO as the initial ventilation mode and BPD as well as early mortality might be that infants who initially received HFO were more severely ill from the start. Compared with those patients who received conventional ventilation initially, patients who received HFO as initial treatment had a significant lower Apgar score at 5 min and a lower birth weight. Patients who received HFO were more often inborn and prenatally diagnosed compared with infants who received conventional ventilation. HFO was also associated with a significantly longer duration of ventilation compared with conventional ventilation. Furthermore, patients who received initial treatment with HFO underwent an ECMO procedure more often. Moreover, they more often had a patch repair, which might be associated with a larger defect size and more severe pulmonary hypoplasia. Therefore, we may speculate that these infants' condition was worse than that of infants on conventional ventilation from the start.

In this regard, it is unfortunate that some variables that might have given an indication of the severity of disease could not be included in the multivariate analyses because they were not

known at baseline. However, we did test for various interactions between variables. In this regard, we found that in patients who underwent an ECMO procedure, the initial mode of ventilation was no longer associated with BPD and/or death by day 30 and BPD alone. Also, HFO gave only a slightly higher risk of BPD and/or death by day 30 and BPD alone in patients who were born inside a tertiary clinic. Moreover, we did not find any variables that modified the effect of HFO in the analysis for early mortality. Baseline data on prenatal predictors of outcome, such as the lung-to-head ratio, were not available. It may, for example, be speculated that fetuses with a lower lung-to-head ratio and a possible worse outcome may have been treated initially with HFO. A right-sided defect was associated with a higher risk for BPD and/or early mortality and BPD and early mortality separately. This is in line with previous studies, which reported a higher risk for mortality and worse outcome in patients with right-sided defects[34-35].

Furthermore, a prenatal diagnosis was another important risk factor BPD and/or early mortality and BPD and early mortality separately. Infants who are diagnosed prenatally are more likely to have more obvious anomalies and a more severe herniation visible on ultrasound, which may explain this higher risk of a worse outcome. However, prenatal detection of the diaphragmatic defect in infants with CDH may be dependent on the quality of obstretric care and prenatal screening.

A low Apgar score at 5 min of life was also associated with a higher risk of worse outcome. This is in line with a previous study by the CDH study group, which reported that the Apgar score at 5 min predicted mortality in newborns with CDH[36]. Furthermore, a cardiac abnormality, a chromosomal anomaly and a lower gestational age were also associated with worse outcome.

Being inborn, i.e. in a tertiary clinic, was a risk factor for early mortality in this study. This may be explained by the fact that mortality is not always reported in pregnancy terminations, stillbirths and outborn children who die shortly after birth[37]. As a consequence, the mortality rate for inborn children with CDH may be relatively higher. However, it must be taken into account that the study centers in the CDH Registry use different referral policies.

This study did not show a relation between the volume of the centre and postnatal outcome. However, a previous study reported higher survival rates in high-volume centres, defined as more than 6 patients with CDH admitted per year[38]. This difference may be explained because we used a different cutoff to define the volume of the centre. Also, no association was found between postnatal outcome and birth in an ECMO center. In the multivariate analysis, no associations were found in the multivariate analysis between birth in an ECMO center, birth in a high-volume center and the initial ventilation mode. More specific data on the type of center and the treatment protocols they used are lacking, since all centres are anonymously coded in the CDH registry. Differences between the various centres may therefore still play a role in outcome in infants with CDH, although we were not able to find such an association in this study.

This study showed that gender was not a risk factor for worse outcome in newborns with CDH. Studies in preterm infants reported boys to be at higher risk for BPD and mortality in general[39-40]. As newborns with CDH are usually born at term, the above-mentioned mechanisms reported for premature infants may not be fully applicable to them.

Although ECMO could not be included in the multivariate analysis, because it is not a baseline characteristic, ECMO was associated with a higher risk for BPD and early mortality in univariate analyses. Patients with CDH who need ECMO therapy are likely to have severe pulmonary hypoplasia and pulmonary hypertension, resulting in a higher risk of worse outcome. Mortality after an ECMO procedure was 51%, which is comparable to previous studies and data of the Extracorporeal Life Support Organization registry[41-42]. The role of ECMO in the treatment of infants with CDH is still unclear[43]. In nonrandomized trials, ECMO has been reported, however, to improve survival in infants with CDH[44-45].

This is the first study to describe chronic lung disease and its risk factors in a large number of patients with CDH. However, its possible limitations should not go unmentioned. For one, some important data could not be determined, such as disease severity, pulmonary hypertension, the position of the liver, the severity of BPD and prenatal predictors of outcome. Therefore, additional research should be performed taking into account the full spectrum of the disease. Moreover, patients who received HFO underwent an ECMO procedure more often and the association between BPD and/or death by day 30 and BPD alone and the initial ventilation mode was not shown in infants who received ECMO therapy. Therefore, confounding by indication may have biased our results. Furthermore, selection bias could have occurred because only data from hospitals participating in the CDH Study Group were retrieved. In addition, these hospitals used different treatment protocols and referral policies, which may have influenced outcomes. In this regard, oxygen dependency was not defined according to standard practice in our study centres. A previous study by Walsh et al. reported a lower incidence of BPD if oxygen dependency was confirmed by a room-air challenge test[46]. Since data on room-air challenge tests were not available in our study, our results may have been biased.

Conclusion

Bronchopulmonary dysplasia and mortality in newborns with CDH remain important problems, despite improvements in neonatal care. Moreover, BPD may lead to long-term pulmonary morbidity. HFO has been heralded as a promising ventilation treatment to reduce mortality and pulmonary morbidity in CDH newborns. However, in the present study, initial ventilation treatment with HFO was associated with a higher risk of a worse outcome. Nonetheless, the results of this study must be interpreted with caution, because selection bias and confounding by indication may have occurred. Therefore, further prospective studies are needed to study risk factors and optimal ventilation strategies in children with CDH. In addition, standardized treatment protocols and follow-up guidelines, such as developed by the American Academy of Pediatrics in 2008, should be implemented as crucial ways to improve healthcare in children with CDH[15]. This calls for extensive collaboration between centers with an expertise in the treatment of newborns with CDH, such as the CDH-EURO Consortium, which recently initiated the VICI trial, a randomized controlled trial on ventilation strategies in infants with CDH (www.vicitrial.com).

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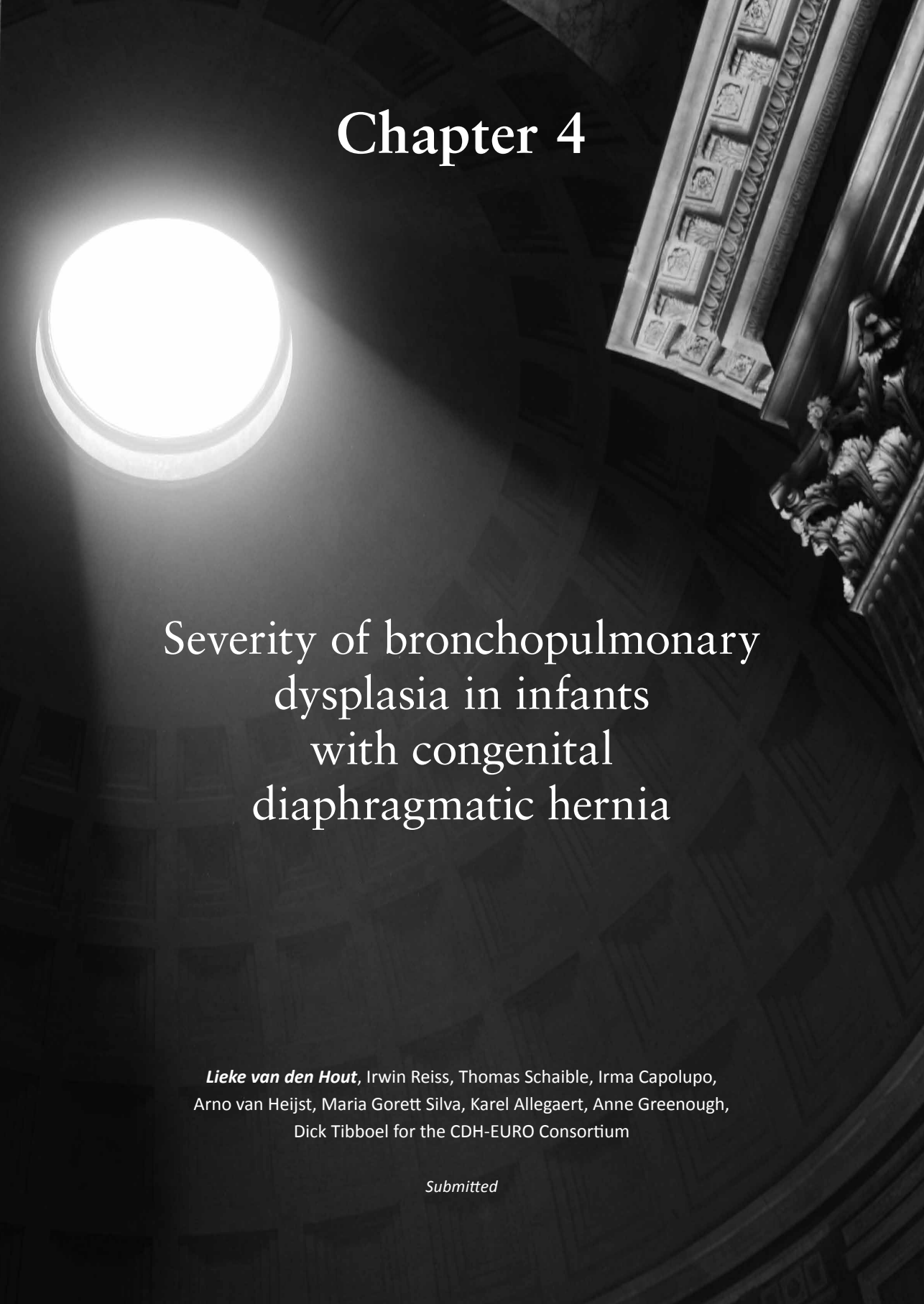

Chapter 4

Severity of bronchopulmonary dysplasia in infants with congenital diaphragmatic hernia

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Submitted

Abstract

Background: Long-term pulmonary sequelae, such as bronchopulmonary dysplasia (BPD), occur in infants with congenital diaphragmatic hernia (CDH).
Objective: To determine the prevalence and severity of BPD in infants with CDH and to identify risk factors.
Methods: Data were collected on CDH patients born between 2005 and 2008 at eight high-volume centres (that is, more than 10 admissions of CDH infants per year) in Europe. The primary endpoint was the severity of BPD. Secondary endpoints were BPD, defined as oxygen dependency at day 28, and mortality by day 28. The severity of BPD was determined at day 56 or at discharge, whichever came first, as mild (no supplementary oxygen), moderate (supplementary oxygen < 30%) or severe (supplementary oxygen > 30%). Risk factors associated with the severity of BPD were assessed by comparing infants with severe to moderate BPD to those with mild BPD.
Results: The outcomes of 364 CDH infants were analysed. By day 28, 32% of the infants had died. In the patients who survived after day 28, 45% had BPD, of those, 27% had severe BPD, 20% moderate BPD and 53% had mild BPD at day 56. Moderate or severe BPD was commoner in infants who had required ECMO ($p=0.002$), been treated with inhaled nitric oxide ($p=0.001$) and who had required a longer duration of ventilation ($p<0.001$).
Conclusion: Moderate or severe BPD is common in CDH patients, particularly if they required treatment for pulmonary hypertension. Future studies are needed to decrease long-term pulmonary sequelae.

Introduction

Survival rates of infants with congenital diaphragmatic hernia (CDH) are between 32-80%, depending on case selection[1]. Survivors of congenital diaphragmatic hernia (CDH), often suffer chronic morbidity including pulmonary problems[2]. Recurrent respiratory infections and asthmatic symptoms can occur in later infancy, childhood and throughout adolescence[2-3]. Recent data from the CDH Registry report that 41% of survivors of CDH developed bronchopulmonary dysplasia (BPD)[4].

The NIH consensus recommended that infants who are diagnosed as having BPD, should be re-examined at 36 weeks PMA if born prematurely or 56 days/discharge if born at term to determine if they have mild, moderate or severe BPD[5] (Table 1). It has subsequently been shown that using such a classification more accurately predicts chronic respiratory morbidity[6]. The severity of BPD in CDH patients has not been reported by many studies. Neonatal centres often use different treatment protocols for infants with CDH, which makes it difficult to evaluate and compare outcome in these infants. The CDH-EURO consortium is a cooperative network of high volume centres (at least 10 infants with CDH per year) in Europe. The consortium was established with the aim of using standardised evidence based, postnatal care[7]. The aim of this study was to determine the severity of BPD in CDH infants cared for by the CDH-EURO consortium centres and to identify risk factors for moderate or severe BPD.

Table 1. Definition of BPD according to Jobe and Bancalari[5]

Gestational age	< 32 weeks	> 32 weeks
Time point assessment	36 wks PMA or discharge to home, whichever comes first	> 28 days but < 56 days of life or discharge to home, whichever comes first
	Treatment with oxygen > 21% for at least 28 days PLUS	
Mild BPD	On room air at 36 wks PMA or at DC, whichever comes first	On room air at day 56 postnatal age or DC, whichever comes first
Moderate BPD	< 30% O_2 at 36 wks PMA or DC, whichever comes first	< 30% O_2 at 56 d of life or DC whichever comes first
Severe BPD	≥ 30% O_2 and/or pos. pressure at 36 wks PMA or DC whichever comes first	≥ 30% O_2 and/or pos. pressure at 56 d of life or DC whichever comes first

DC = discharge

Methods

Patients

Data were analyzed from infants with CDH born between January 2005 and September 2008 in eight centres participating in the CDH-EURO Consortium. CDH patients were included if they were intubated within the first six hours after birth (high-risk CDH), since patients developing respiratory distress at a later time may have a different course of disease. Infants with central or bilateral CDH were excluded, because their clinical course differs from that of those with a more common left- or right-sided CDH[8]. In four centres ECMO was performed and in two centres fetal

tracheal occlusion was performed. Data on prenatal evaluation, mode of delivery, respiratory support, surgical repair and medication were collected. Lung-to-head ratios (LHR) were measured in prenatally diagnosed infants by ultrasound. The LHR was determined by Metkus and Lipschutz et al.[9-10]. A transverse section of the fetal lung area contralaterally to the diaphragmatic defect was taken at the level of the four chamber-view. Thereafter, the lung area was determined by multiplying the longest axis by the longest measurement perpendicular to it.
The primary outcome was the severity of BPD. Secondary outcomes were BPD and mortality.

Analysis

Differences were assessed for statistical significance using the Chi-squared and Mann-Whitney U as appropriate. Subgroup analyses for all baseline variables were performed for all ECMO patients versus non-ECMO patients. The patients for whom this subgroup analyses were performed were all born in a center that provided ECMO therapy. The breslow day test for stratified analysis was used as appropriate. Risk factors associated with the severity of BPD were assessed by comparing infants with severe or moderate BPD to those with mild BPD.
Baseline variables that were significant at p=0.1 in the univariate analysis were entered into multiple logistic regression analysis, using a stepwise backward elimination method. P-values for the trend over the study years for BPD, severe BPD and death by day 28 were also calculated using logistic regression. Results of the regression analyses are given as odds-ratios (OR) with 95% confidence limits (CI). Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, Illinois). A two-sided p-value less than 0.05 was considered statistically significant.

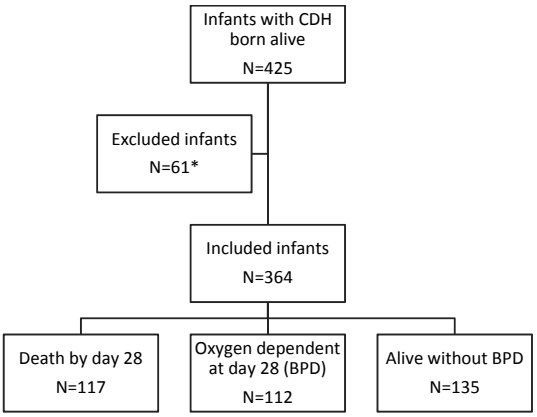

Figure 1. Consort diagram
*bilateral CDH (n=5), central CDH (n=2), intubated later than the first six hours of life (n=48), no ventilation started (n=2), no data on oxygen dependency at day 28 (n=4)

Results

Four hundred and twenty five eligible subjects were born between 2005 and 2008. Sixty one met the exclusion criteria, thus, 364 children were included in the analysis (Figure 2).

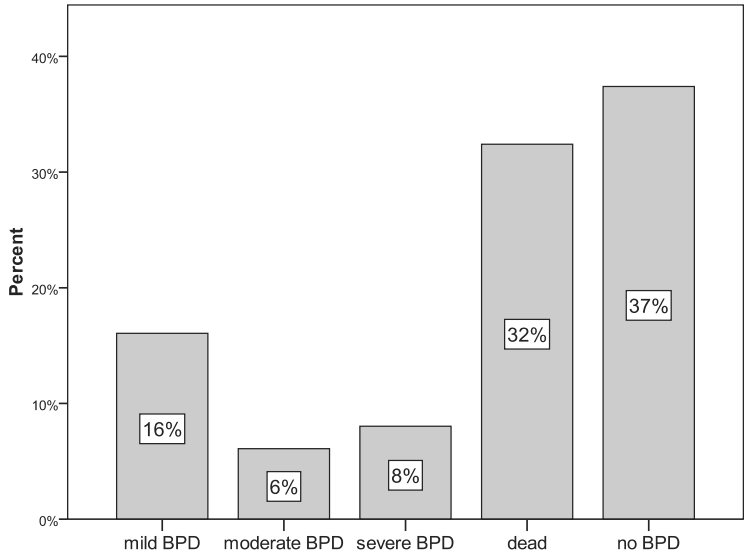

Figure 2. Outcome at day 56 or discharge for all included patients (n=364).

The infants included in the analysis had a higher lung to head ratio, were more likely to be inborn, but less likely to have a vaginal delivery or be born prematurely with a birth weight less than 2000 grams (Table 2).

Table 2. Comparison of the demographics of infants who were included or excluded. Data are demonstrated as n (%) or median (range).

	Included (n=364)	Excluded (n=61)	p-value
Male gender	226 (62)	41 (67)	0.343
Prenatal diagnosis	316 (87)	24 (39)	<0.001
Lung-to-head ratio*	1.3 (0.1-5.0)	2.0 (0.7-3.8)	0.068
Inborn	314 (86)	9 (15)	<0.001
Treatment in ECMO centre	264 (73)	35 (57)	0.025
Vaginal delivery	160 (44)	37 (61)	0.005
Cardiac anomaly	71 (20)	11 (18)	0.894
Chromosomal anomaly	6 (2)	3 (5)	0.113
Other anomaly**	55 (15)	6 (10)	0.370
Left-Sided defect	303 (83)	42 (69)	0.401
Intra-thoracal position of the liver	186 (51)	22 (36)	0.100
HFO as initial ventilation mode	79 (22)	8 (13)	0.214
Gestational age at birth < 37 wks	125 (34)	14 (23)	0.178
Birth weight < 2000 gr	33 (9)	3 (5)	0.450
Apgar score at 5 minutes***	8 (0-10)	8 (2-10)	<0.001

* Not measured in 149 patients (103 included patients)

** Other abnormality was classified as congenital anomaly other than a congenital heart disease or a chromosomal abnormality (urogenital=19, orthopaedic=6, abdominal=19, neurological=5 and multiple=12).

*** missing in 92 patients (79 included patients)

Thirty two percent of the infants had died by day 28. The median age at death was 6 (range 0-300) days; 42% of the patients died in the first week after birth. The survival rate at discharge was 65% for included patients and 78% for excluded patients (p=0.052). The prevalence of mortality did not change significantly over the study years (p=0.931).
Forty five percent of survivors developed BPD (n=112/247). Excluded patients had a significant lower prevalence of BPD (27%, p=0.039). Fifty-three percent of those with BPD had mild (n=58/109), 20% (n=22/109) had moderate and 27% (n=29/109) had severe BPD (see also figure 2). Three patients with BPD died before day 56 and were therefore not categorized. No significant differences in severity of BPD were found between included and excluded patients. The overall prevalence of BPD (p=0.482) and the prevalence of moderate or severe BPD did not change significantly over the study years (p=0.390).

Prenatal characteristics

Prenatal diagnosis and lung-to-head ratio
Three hundred and eighteen infants were diagnosed antenatally at a median gestational age of 29 (range 15-39) weeks. In 265 of the prenatally diagnosed infants the lung-to-head ratio was measured (median 1.3, range 0.1-5.0). Median lung-to-head ratio was not significantly different in patients with mild BPD compared to patients with moderate or severe BPD (p=0.284, see table 3).

Fetal tracheal occlusion
Fifty six patients underwent a fetal tracheal occlusion (FTO). Eighty percent of these patients had an intrathoracic position of the liver. Median lung-to-head ratio in these patients was 0.78 (range 0.1-1.4). By day 28, 57% (n=32/56) of the patients who had a FTO died compared to 27% in patients who had not (p<0.001). The overall mortality after an FTO was 61%. Of the "FTO" patients who survived until day 28, 38% (n=9/24) were diagnosed with BPD compared with 46% (n=103/223) in patients who had not undergone FTO (p=0.551). Moderate or severe BPD was present in five and mild BPD was present in three of the eight patients who survived until day 56 (see table 3, p=0.289).

Mode of delivery
One hundred and ninety patients were born by caesarean section (56%) and 160 by vaginal delivery (44%). By day 28, 41% of the patients who were born by a vaginal delivery developed BPD compared to 48% of the patients who were born by a caesarean section (p=0.373). Moderate or severe BPD was present in 59% of the infants born by vaginal delivery compared with 38% of the infants born by caesarean section (p=0.063, see table 3). Compared to patients born by caesarean section, patients born by vaginal delivery were significantly more often outborn and not prenatally diagnosed (3% vs. 26%, p<0.001) and born before a gestational age of 37 weeks (29% vs. 41%, p=0.023).

Table 3. Demographics according to BPD severity (n=109). The numbers do not always add up to 109 because of missing values.

	Mild BPD	%	Moderate or severe BPD	%	p-value
Gender					0.214
Male	32/67	48	35/67	52	
Female	26/42	62	16/42	38	
Prenatal diagnosis					1.000
Yes	50/94	53	44/94	47	
No	8/15	53	7/15	47	
Birth location					0.238
Inborn	51/91	56	40/91	44	
Outborn	7/18	39	11/18	61	
Treatment in ECMO centre					0.494
Yes	50/97	52	47/97	48	
No	8/12	67	4/12	33	
Fetal tracheal occlusion					0.289
Yes	3/8	38	5/8	62	
No	55/101	54	46/101	46	
Method of delivery					0.063
Caesarean section	34/55	62	21/55	38	
Vaginal delivery	19/46	41	27/46	59	
Cardiac Abnormality					0.402
Yes	13/29	45	16/29	55	
No	45/80	56	35/80	44	
Chromosomal Abnormality					0.217
Yes	0/2	0	2/2	100	
No	58/107	54	49/107	46	
Other abnormality					0.567
Yes	10/16	63	6/16	37	
No	47/92	51	45/92	49	
Side defect					0.900
Left	46/85	54	39/85	46	
Right	12/24	50	12/24	50	
Position of the liver					0.067
Intrathoracic	40/76	53	36/76	47	
Intraabdominal	17/24	71	7/24	29	
Initial ventilation mode					0.239
HFO	10/14	71	4/14	29	
CMV	48/95	51	47/95	49	
Surfactant					0.632
Yes	17/36	47	19/36	53	
No	29/53	55	24/53	45	
ECMO treatment					0.002
Yes	16/47	34	31/47	66	
No	34/50	68	16/50	32	
Gestational age at birth < 37 wks					0.676
Yes	21/42	50	21/42	50	
No	37/66	56	29/66	44	
Birth weight < 2000 gr					0.280
Yes	2/6	33	4/6	67	
No	56/103	54	47/103	46	
Median Apgar at 5 minutes, range	8 (1-10)		7 (3-10)		0.031
Median Lung-to-head ratio, range	1.2 (0.7-2.7)		1.1 (0.8-2.7)		0.284

Postnatal therapy

Ventilatory treatment

Seventy eight percent of the infants were supported initially with conventional ventilation (n=283/362, missing data=2) and 22% with HFO (n=79/362) (see table 1). Compared to patients initially supported with conventional ventilation, patients who were supported initially with HFO were significantly more often prenatally diagnosed and born at a tertiary centre (p<0.001), more often underwent a fetal tracheal occlusion (p=0.003), more often had an intrathoracic position of the liver (p<0.001) and had lower Apgar scores at 5 minutes (p<0.006).

Thirty five infants who initially received HFO (44%) and 232 who initially received conventional ventilation (64%) underwent a surgical repair (p<0.001). Of those patients, 91% of the patients who were initially supported with HFO (n=32/35) underwent a patch repair, as opposed to primary closure, compared with 61% (n=139/228, missing=4) of patients supported with conventional ventilation (p=0.001).

Forty five of the infants that initially received HFO and 217 of the infants that initially received conventional ventilation were born in an ECMO-centre. Twenty seven percent (n=12/45) of the patients who received HFO were treated with ECMO and 33% (n=72/217) of the patients who received conventional ventilation (p=0.499).

No significant differences in mild and moderate or severe BPD prevalence were seen between patients who were supported initially with HFO and patients supported initially with conventional ventilation (p=0.239, see table 3).

The median duration of ventilation was 15 (range 1-251) days and was significantly longer in the infants who developed moderate or severe BPD (p<0.0001).

Surfactant

Ninety four of 323 infants were treated with surfactant (29%, missing=41). Of these patients, 56% (53/94) were born before a gestational age of 37 weeks compared with 26% (n=61/231) of the patients who did not receive surfactant (p<0.001). Moderate or severe BPD was present in 53% (n=19/36) of the survivors with BPD who received surfactant compared to 45% (n=24/53) of the survivors with BPD that did not receive surfactant (p=0.632).

Inhaled nitric oxide

Inhaled nitric oxide (iNO) was administered in 62% (n=225/364) of the patients. The median duration of treatment with iNO was 5 (range 1-121) days. Moderate or severe BPD was present in 55% (n=48/87) of the survivors with BPD who received iNO and 14% (n=3/22) of the survivors with BPD who did not receive iNO (p=0.001).

Extra corporeal membrane oxygenation (ECMO)

Two hundred and sixty four infants were admitted to an ECMO centre and 32% underwent ECMO (n=84/264). ECMO was performed at a median age of one (range 0-19) day after birth.

The median duration of ECMO treatment was 9 (range 2-19) days. ECMO patients more often had an intrathoracic liver (80%) than non-ECMO patients (48%) (p<0.001). Seventy-three ECMO-patients underwent a surgical repair of the diaphragmatic defect (87%). Overall survival after ECMO was 60% (n=50/84).
Of the ECMO patients that survived until day 28, 87% (n=47/54) developed BPD, compared with 34% (n=50/146) of the non-ECMO patients (p<0.001). Subgroup analysis in patients born in an ECMO center revealed that moderate or severe BPD was present in 73% of the patients who were prenatally diagnosed and underwent an ECMO procedure compared with 30% of the patients who were prenatally diagnosed and did not have ECMO therapy (p=0.020). No other significant differences were found in this subgroup analysis between ECMO and non-ECMO patients.

Surgical repair
A surgical repair was performed in 74% (n= 268/364) of the cases. The median age at time of surgical repair was three (range 0-42) days. In patients who underwent a surgical repair, a patch repair, as opposed to primary repair, was used in 66% (n=170/258, missing=6) of the patients. An intrathoracic liver was seen in 69% of the patients who underwent a patch repair and in 24% of the patients who underwent a primary repair (p<0.001). Moderate or severe BPD was present in 48% (n=44/92) of the patients who developed BPD and underwent a patch repair and 46% (n=6/13) of the patients who developed BPD and underwent a primary repair (p=1.000).

Duration of hospital admission
The median stay on the intensive care unit was 32 (range 5-251) days. The median stay on the NICU was 44 (range 10-86) days for infants with mild BPD and 94 (range 24-251) days for infants with moderate or severe BPD (p<0.001).

Multivariate analysis
Multivariate analysis revealed that ECMO therapy (OR 4.92, 95% CI 1.95-12.39, p=0.001), corrected for birth at ECMO center, and a vaginal delivery (OR 2.62, 95% CI 1.09-6.29, p=0.031) were the only independent risk factors for moderate or severe BPD. When a subgroup of patients who were only born in an ECMO center was analysed, ECMO therapy remained the only significant risk factor moderate or severe BPD (OR 4.12, 95% CI 1.77-9.60, p=0.001).

Discussion

We have demonstrated 45% survivors of CDH develop BPD, with almost half developing moderate or severe BPD. This is one of the first studies to describe the severity and possible risk factors of moderate or severe BPD in infants with CDH. Another recent study by our group reported comparable prevalences of mild, moderate and severe BPD in infants with CDH in two high-volume centers[11]. However, this paper reported these figures in a descriptive way and thus did

not describe any risk factors for moderate or severe BPD. High peak pressures during mechanical ventilation and high levels of oxygen may cause severe lung injury and mortality in infants with CDH[12-13]. Longer duration of supplementary oxygen was more present in infants with moderate or severe BPD than in patients with mild BPD.

ECMO provides short-term support for respiratory failure[14-15]. The benefits of ECMO in infants with CDH, however, are unclear, since large prospective studies on ECMO treatment in infants with CDH are lacking[16]. In this study, an ECMO procedure was performed on about one third of the patients who were treated in an ECMO-centre. The median duration of ECMO was 9 days, which is comparable to a previous study[17]. Multivariate analysis revealed that moderate or severe BPD was significantly more common in "ECMO" patients compared to non-ECMO patients. Subgroup analysis revealed that especially ECMO patients who were prenatally diagnosed had a high rate of moderate or severe BPD. The overall prevalence of BPD after an ECMO procedure in this study was eighty seven percent, which is comparable to a previous study[4].

Pulmonary hypertension due to maldevelopment of the pulmonary vessels may also contribute to pulmonary morbidity in patients with CDH[17-19]. Inhaled nitric oxide is often given to CDH patients with pulmonary hypertension, although a large trial demonstrated no reduction in mortality or need of ECMO[20]. However, this study was seriously underreported for CDH as a subset. Our study showed that infants treated with inhaled nitric oxide and thus likely to have signs of pulmonary hypertension more often developed severe or moderate BPD, suggesting that pulmonary vessel maladaptation may contribute to the chronic respiratory morbidity of CDH infants.

In our study, a vaginal delivery was also an independent risk factor for moderate or severe BPD. Further analysis revealed that infants born by vaginal delivery were significantly more outborn and not prenatally diagnosed, i.e. at home or outside a tertiary center, than patients born by caesarean section. We speculate that initial ventilation strategies, especially use of high inspiratory pressures, might have been sub-optimal in newborns that were born by vaginal delivery outside a tertiary clinic. Also, patients born by vaginal delivery had a significantly lower gestational age, which has been reported as a risk factor for BPD by a previous study of the CDH Study Group[4]. That study, however, did not find an independent association between the mode of delivery and BPD or mortality[4], but they did not analyze the severity of BPD. However, when a subgroup of patients who were only born in an ECMO center was analysed, the mode of delivery was no longer a significant risk factor for moderate or severe BPD.

Previous studies reported an intrathoracic position of the liver to be associated with mortality, BPD and need for ECMO[11,21-22]. An intrathoracal position of the liver may be associated with a larger defect size and thus a larger degree of pulmonary hypoplasia. Furthermore, the lung-to-head ratio has been reported to be associated with mortality, BPD and need for ECMO[10-11,21,23-24]. In our study, however, those prenatal predictors of outcome were not associated with an increase in moderate or severe BPD. This may be due to our small sample size of patients who were diagnosed with BPD. Other previously reported predictors of BPD and/or mortality in CDH, such as the type of repair[25], the side of the defect[4], and the gestational age at birth[4], were also

not associated with the severity of BPD. The Apgar score, also previously reported as a predictor of outcome[26], was not independently associated with the severity of BPD.

We included infants who underwent a fetal tracheal occlusion, which has been reported to improve survival in high-risk patients with CDH[27]. It might be hypothesized that fetal tracheal occlusion could reduce long-term pulmonary morbidity, because of the effect on lung growth[28]. Our study, however, showed no significant differences between severity in BPD in patients who underwent a fetal tracheal occlusion and patients who did not. Moreover, moderate or severe BPD tended to occur more often in patients who underwent a fetal tracheal occlusion; probably because patients who are treated with antenatal surgery are considered to be at high risk of adverse outcome.

This study has several limitations. Firstly, this was a retrospective study. Secondly, selection bias may have influenced our results, since excluded patients had a lower mortality rate and a significantly lower prevalence of BPD than included patients. There were, however, no significant differences in severity of BPD between included and excluded patients. Based on the higher mortality and BPD prevalence, we speculate that the included patients were more severely ill. The results of this study may therefore not be applicable to all CDH patients, but rather to a specific subgroup who were intubated shortly after birth. Lastly, the need for supplementary oxygen at days 28 or 56 was not routinely determined by a room air challenge test at all participating centres, which may have influenced our results.

Conclusion

In conclusion, BPD is common in survivors of CDH and almost half suffer from moderate or severe BPD. Patients with signs of pulmonary hypertension are most at risk. Long term studies are required to determine whether CDH infants with moderate or severe BPD form a vulnerable group of patients at greater risk of long-term respiratory morbidity. Multicentre, randomized trials aiming to optimize management and long term outcome are required in this high risk group of infants.

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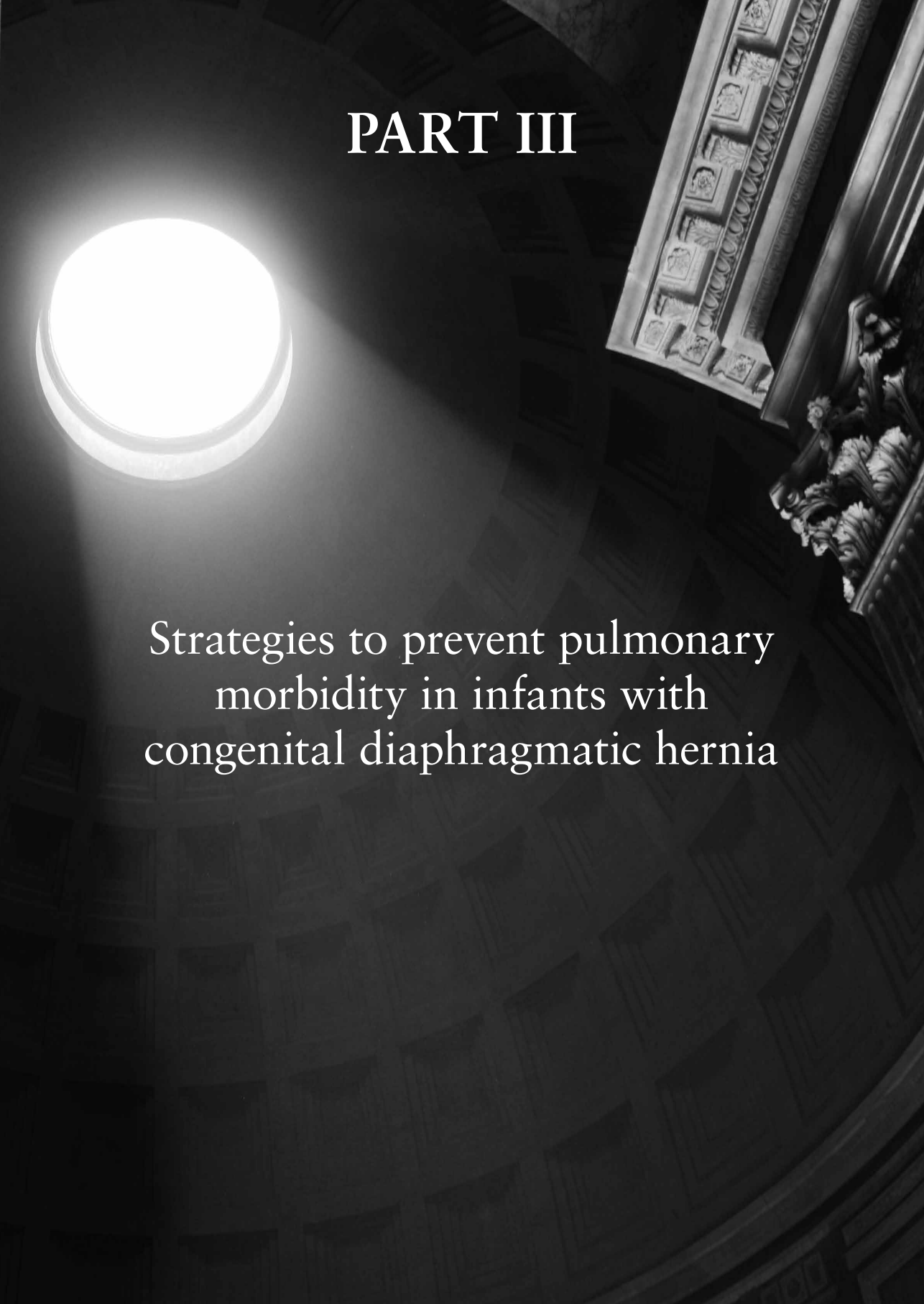
PART III



Strategies to prevent pulmonary morbidity in infants with congenital diaphragmatic hernia

Chapter 5

Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH-EURO Consortium Consensus

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Abstract

Congenital diaphragmatic hernia (CDH) is associated with high mortality and morbidity. To date, there are no standardized protocols for the treatment of infants with this anomaly. However, protocols based on the literature and on expert opinion, might improve outcome. This paper is a consensus statement from the CDH-EURO Consortium prepared with the aim of achieving standardized postnatal treatment in European countries. During a consensus meeting between high-volume centers with an expertise in the treatment of congenital diaphragmatic hernia in Europe (CDH-EURO Consortium) the most recent literature on Congenital Diaphragmatic Hernia was discussed. Thereafter, five experts graded the studies according to the Scottish Intercollegiate Guidelines Network (SIGN) Criteria. Differences in opinion were solved by discussion until full consensus was reached. The final consensus statement, therefore, represents the opinion of all consortium members. Multicenter randomized controlled trials on congenital diaphragmatic hernia are lacking. Use of a standardized protocol, however, may contribute to more valid comparison of patient data in multicenter studies and identification of areas for further research.

Introduction

Congenital diaphragmatic hernia (CDH) is a congenital anomaly which affects 1 in 3000 live births[1]. Despite advances in neonatal care, CDH is associated with a high risk of mortality and morbidity[2]. The combination of pulmonary hypoplasia and abnormal morphology of the pulmonary vasculature leads to severe respiratory insufficiency in over 90% of cases in the first hours after birth. Infants with CDH are at increased risk of developing persistent pulmonary hypertension of the newborn (PPHN) due to a pathological development of the pulmonary vasculature. Several triggers such as hypoxemia, acidosis and pulmonary vascular damage caused by mechanical ventilation sustain the PPHN through reactive vasoconstriction and vascular remodeling. Therefore, it would seem best to achieve optimal management of elevated pulmonary arterial pressure and prevent further damage to the lung before undertaking surgical repair of the diaphragmatic defect.

Single centre experience may not be representative as they often include a small number of patients[3]. A literature review by Logan et al.[4] revealed a limited number of clinical trials examining interventions to improve survival of infants with CDH. Recently, Deprest et al. published a manuscript, together with some experts of the CDH-EURO Consortium, on the perinatal management of isolated CDH[5]. However, there are no extensive standardized protocols for the postnatal management of CDH. As a consequence, members of the CDH-EURO consortium, a collaboration of specialized CDH centers in Western Europe, have developed a consensus statement for the postnatal treatment of patients with CDH based on the recent literature and expert opinion.

The members of the CDH-EURO Consortium from centres in which more than ten infants with CDH are treated per year, held a consensus meeting. It covered all aspects of the treatment of infants with CDH and was based on a summary of recent relevant literature. The studies were graded according to the Scottish Intercollegiate Guidelines Network (SIGN) Criteria[6]. This grading system is based on study design and methodological quality of individual studies. Five experts individually determined the levels of evidence of the literature on the guidance of a SIGN-checklist. Four of these have clinical experience with CDH and all five have scientific schooling and experience. Differences in opinion were solved by discussion until full consensus was reached. The final consensus statement, therefore, represents the opinion of all consortium members. The levels of evidence and grades of recommendation according to the SIGN criteria are presented in table 1 and 2, respectively.

Prenatal diagnosis and delivery

With the increased use of prenatal ultrasound, many cases of CDH are now detected before birth. After diagnosis, a more detailed evaluation should be performed to determine the location of the defect, the absolute and observed/expected lung-to-head ratio (O/E LHR), the position of the liver and the presence or absence of other associated congenital anomalies or syndromes[7-8].

Table 1. levels of evidence

level	Description of evidence
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies *or* high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Table 2. grades of recommendation

Grade	Description of Grade
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population *or* a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 *or* extrapolated evidence from studies rated as 2+

In infants with CDH, other associated congenital anomalies are present in 10-40 % of the cases[9-10]. Cardiac anomalies are present in about 25% of the infants with CDH[9,11].

If CDH is diagnosed prenatally, an experienced tertiary center with a high case volume may be the optimal environment for the delivery and further treatment of an infant with CDH. A recent study by Grushka et al. has shown that survival was higher in infants born in centers that have more than six cases a year admitted to their ward[12]. There were, however, no differences in the need for ECMO treatment or duration of ventilation between centers that admitted more than six and centers that admitted less than six cases per year[4,12].

There is still some doubt about the preferred mode of delivery and the timing of delivery in case of a CDH pregnancy. Recent studies from the CDH study group reported no significant differences in overall survival between patients with CDH born by spontaneous vaginal delivery, induced vaginal delivery and elective caesarean section[13-14]. Survival without the use of ECMO, however, was higher for patients born by elective caesarean section according to one study[13]. With regards to the timing of delivery, a recent paper by Stevens et al. reported that infants with CDH born at a gestational age of 37-38 weeks with a birth weight above 3.1 kilogram had a higher survival rate, less need for ECMO and a greater rate of survival if ECMO was used than infants with CDH born at a gestational age of 39-41 weeks[14]. The reason for this difference in outcome is not clear, but case selection, differences among centers and an increase in pulmonary vascular abnormalities

in later gestational ages have been proposed as possible explanations[14]. Earlier data of the ELSO Registry reported higher survival rates and a shorter duration of ECMO treatment in infants born at a gestational age of 40-42 weeks compared to infants with CDH born at a gestational age of 38-39 weeks who were treated with ECMO[15]. The best mode and timing of delivery in infants with CDH is still unclear and therefore deserves further study.

If there is premature labor or a risk of preterm delivery between 24 and 34 weeks gestational age, antenatal steroid therapy should be given according to the guidelines of the NIH[16]. Although there are no studies specifically focusing on this issue in premature infants with CDH, the consortium sees no reason to defer from this policy as prenatal steroid therapy has been shown to be of benefit in babies born prematurely without CDH. Prenatal steroid therapy given after a gestational age of 34 weeks has shown no benefit with regard to survival and respiratory outcome in infants with CDH[17].

Recommendations:

- Following prenatal diagnosis, the absolute and O/E LHR and the position of the liver should be evaluated. (Grade of recommendation=D)
- Planned vaginal delivery or cesarean section after a gestational age of 37 weeks in a designated tertiary center should be pursued. (Grade of recommendation=D)
- In case of preterm labour prior to 34 weeks of gestation, antenatal steroids should be given. (Grade of recommendation=D)

Initial treatment and procedures in the delivery room

Initial treatment and procedures in the delivery room are based on the guidelines of the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with treatment recommendations (CoSTR)[18].

Monitoring and goal of treatment

Measurements of heart rate, pre- and postductal saturations and if necessary invasive or noninvasive blood pressure are recommended. The key principles of successful delivery room resuscitation and stabilization are the avoidance of high airway pressures and the establishment of an adequate preductal arterial saturation. Previous studies advised to keep preductal arterial saturations between 85% and 95%, because higher levels may lead to administration of a high oxygen concentration, more aggressive ventilation and a subsequent risk of oxygen toxicity and ventilator-induced lung injury[19-21]. However, some members of the consortium agreed on preductal saturation boundaries in the delivery room of 80% to 95% in infants with CDH based on expert opinion.

Intubation and ventilation

Although there is no specific evidence, the consortium recommends intubating infants with CDH immediately after birth. This is done to reduce a possible risk of pulmonary hypertension due to prolonged acidosis and hypoxia which might be caused by delayed intubation. Ventilation by bag and mask may cause distension of the stomach and must be avoided as it may limit expansion of the hypoplastic lung. Low peak pressures, preferably below 25 cm H_20, are given to avoid lung damage to the hypoplastic and contralateral lung[22]. FiO_2 should be started at 1.0 and adjusted downwards to achieve preductal saturations between 80 and 95%.

Nasogastric tube

Immediate placement of an oro- or nasogastric tube with continuous or intermittent suction will help to prevent bowel distension and any further lung compression. Until surgical repair, continuous suctioning is the recommended procedure to decompress the abdomen.

Vascular access

A central or peripheral venous line should be inserted to allow the administration of fluids and, if necessary, inotropic vasopressor drugs. An arterial line should be inserted for blood sampling and monitoring the arterial blood pressure, preferably this should be done in the labour ward. As preductal PaO_2 measurements reflect the cerebral oxygenation, the arterial line should be inserted into the right radial artery if possible. An umbilical arterial line may be placed, but as this reflects the postductal situation it is less desirable than a right radial artery line.

Blood pressure support

In infants with CDH, pulmonary vascular resistance remains elevated after birth, resulting in right-to-left shunting of blood through the ductus arteriosus and/or foramen ovale. This can lead to hypoxemia and acidosis, which in turn can perpetuate pulmonary hypertension. Measures to increase systemic blood pressure may minimize right-to-left shunting. However, there is no need to increase blood pressure levels to supranormal values if preductal saturations are between 80 and 95%. Thus, the consortium advises to maintain arterial blood pressures at normal levels for gestational age[23]. Only if preductal saturations fall below the target values higher blood pressures should be pursued. If there is hypotension and/or poor perfusion, 10-20 ml/kg NaCl 0.9% should be administered once or twice. If perfusion and blood pressure do not improve, inotropic and vasopressor agents should be considered according to the local practice of the hospital.

Sedation and analgesia

There is no specific evidence on sedation and analgesia in infants with CDH. However, several investigators have studied physiological responses of neonates to awake intubation and reported significant rises in systemic arterial blood pressure and intracranial pressure, as well as significant decreases in heart rate and transcutaneous oxygen saturations[24]. As soon as venous access is established, sedation and analgesia should be started without delay. Careful monitoring of

the blood pressure is warranted in these situations. There is debate whether infants with CDH should receive a neuromuscular blocking agent. Indeed, many of the consortium members do not routinely paralyse CDH infants.

Enema

Some centers give enemas to infants with CDH with the goal to decompress the bowel by inducing defecation. There is no evidence that this procedure improves outcome.

Surfactant

Preliminary data indicated that surfactant therapy may be associated with a higher mortality rate, greater use of ECMO therapy, and more chronic lung disease in infants with CDH[25]. In preterm infants with CDH, surfactant administration was also associated for lower survival rate[26]. Therefore, the routine use of surfactant replacement in infants with CDH should be avoided.

Recommendations:

* After delivery the infant should be intubated immediately without bag and mask ventilation. (Grade of recommendation=D)
* The goal of treatment in the delivery room is achieving acceptable preductal saturation levels between 80-95%. (Grade of recommendation=D)
* Ventilation in the delivery room may be done by conventional ventilator or ventilation bag with a peak pressure as low as possible, preferably below 25 cm H_2O. (Grade of recommendation=D)
* An oro-or nasogastric tube with continuous or intermittent suction should be placed. (Grade of recommendation=D)
* Arterial blood pressure has to be maintained at a normal level for gestational age. In case of hypotension and/or poor perfusion, 10-20 ml/kg NaCl 0.9% should be administered 1 to 2 times and inotropic agents should be considered. (Grade of recommendation=D)
* Sedatives and analgesics should be given. (Grade of recommendation=D)
* No routine use of surfactant in either term or preterm infants with CDH. (Grade of recommendation=D)

Ventilation management in the intensive care unit

A ventilation strategy aiming for preductal saturations between 85 and 95%, postductal saturation levels above 70% and arterial CO_2 levels between 45-60 mm Hg (permissive hypercapnia) is well accepted. In the first two hours, preductal saturations levels as low as 70% may be accepted, if they are slowly improving without ventilator changes and organ perfusion is acceptable, indicated by a pH greater than 7.2 and the $paCO_2$ < 65 mm Hg[27-28]. Thereafter, preductal saturation levels are preferably kept between 85 and 95%. In individual cases, however, levels down

to 80% may be accepted, providing organs are well perfused, as indicated by a pH above 7.2, lactate levels < 5 mmol/L and urinary output above 1 ml/kg/hr. Oxygen toxicity can be avoided by decreasing FiO_2 guided by the saturation levels described above[29].

The optimal initial ventilation mode for newborns with CDH is not clear. Nevertheless, there is accumulating evidence that ventilator induced lung injury may have a significant negative impact on outcome in newborns with CDH[30-33]. Permissive hypercapnia and 'gentle ventilation' in neonates with CDH has been reported to increase survival[29,34-36].

Conventional ventilation

Until now, the most experience exists with pressure-controlled ventilation as conventional ventilation mode in infants with CDH. Based on retrospective studies[27-29,35-37] and clinical experience, the consortium recommends limitation of peak pressures to 25 cm H_2O or less, a positive end-expiratory pressure (PEEP) of 2 to 5 cm H_2O and adjustment of the ventilator rate to obtain $PaCO_2$ levels between 45 and 60 mm Hg. If a PIP of over 28 cm H_2O is necessary to achieve pCO_2 and saturation levels within the target range, other treatment modalities should be considered. Weaning from ventilation should preferentially be by means of decreasing PIP; frequency and/or the PIP-PEEP should be modified to achieve $PaCO_2$ levels above 45 mm Hg.

High-frequency oscillatory ventilation (HFOV)

The physiological rationale for use of HFOV derives from its ability to preserve end-expiratory lung volume while avoiding overdistension, and therefore lung injury, at end-inspiration. Retrospective studies have demonstrated effective CO_2 reduction and increased survival in neonates with CDH[38-39]. However, a prospective randomised controlled trial on the use of HFOV as an initial ventilation mode in infants with CDH is still lacking.

The indications for HFOV are not clearly defined. Mostly it is used as rescue therapy in severe and persisting hypoxemia and hypercapnia on conventional ventilation. In some centers it is the standard initial ventilation mode. There is no evidence for the initial settings of HFOV in infants with CDH. The mean airway pressure, however, should be adjusted to have an adequate expansion of the lungs. A chest radiograph should be performed to confirm that the lungs are not overinflated, as defined by a contralateral lung expansion such over eight ribs are visible above the diaphragm[40].

Chest Radiograph

In all patients, a chest radiograph should be made as soon as possible to assess the initial condition. Chest radiographs should be repeated guided by the patient's clinical condition and mode of ventilation.

Recommendations:

* Adapt treatment to reach a preductal saturation between 85-95% and a postductal saturation above 70%. (Grade of recommendation=D)

- In individual cases, preductal saturation above 80% might be acceptable, as long as organs are well perfused. (Grade of recommendation=D)
- The target $PaCO_2$ range should be between 45-60 mm Hg. (Grade of recommendation=D)
- Pressure-controlled ventilation: initial settings are positive inspiratory pressure (PIP) 20-25 cm H_2O and positive end expiratory pressure of 2-5 cm H_2O; ventilator rate of 40-60/min. (Grade of recommendation=D)
- High frequency oscillation (HFOV): initial setting mean airway pressure (MAP) 13-17 cm H_2O, frequency 10 Hz, Δp 30-50 cm H_2O depending on chest wall vibration. (Grade of recommendation=D)
- After stabilization, the fraction of the oxygen concentration (FiO_2) should be decreased if preductal saturation is above 95%. (Grade of recommendation=D)

Further management in the intensive care unit

Monitoring

Heart rate, invasive blood pressure and pre- and postductal saturation should be monitored routinely.

Hemodynamic management

Hemodynamic management should be aimed at achieving appropriate end-organ perfusion determined by heart rate, capillary refill, urine output and lactate levels. If the heart rate is within the normal range, capillary refill is below 3 seconds, urine output is over 1.0 ml/kg/hr, lactate concentration is below 3 mmol/L and there are no symptoms of poor perfusion, no inotropic support is required.

If there are signs of poor perfusion or the blood pressure is below the normal level for gestational age with a preductal saturation of below 80%, echocardiography should be performed to determine whether the poor perfusion is due to hypovolemic or cardiogenic shock. If there is hypovolemia, saline fluid therapy should be started (10 to 20 ml/kg of NaCl 0.9% up to three times during the first one to two hours). If necessary, this should be followed by inotropic therapy. Hydrocortisone may be used for treatment of hypotension after conventional treatment has failed[41]. In case of poor perfusion, vasopressor therapy should be started. In case of cardiogenic shock, as demonstrated by dysfunction of the left and/or right ventricle, inotropic agents should be considered[42].

Recommendations:

- If symptoms of poor perfusion and/or blood pressure below the normal level for gestational age occur associated with preductal saturation below 80%, Echogardiographic assessment should be performed. (Grade of recommendation=D)

* In case of hypovolemia, isotonic fluid therapy 10-20 ml/kg NaCl 0.9% up to three times during the first two hours may be given and inotropics should be considered. (Grade of recommendation=D)

Pulmonary hypertension management

The physiological basis of pulmonary hypertension in infants with CDH is a decreased number of pulmonary arterial structures associated with significant adventitial and medial wall thickening due to an increased amount of smooth muscles cells in pulmonary arteries of all sizes, with abnormal intra-acinar arterioles. As a result, elevated pulmonary vascular resistance may lead to right-to-left shunting after birth. This may result in hypoxemia and a difference in pre-and post-ductal oxygen saturation. However, absence of a pre- and postductal gradient in oxygenation does not exclude the diagnosis of pulmonary hypertension in the newborn, since the right-to-left shunting may occur predominantly through the foramen ovale rather than through the ductus arteriosus. Therefore, two-dimensional echocardiography performed within the first 24 hours after birth remains one of the best modalities for the real-time assessment of pulmonary arterial diameter and right heart function[43-45]. Especially in severe cases of pulmonary hypertension, a cardiac ultrasound may help to evaluate right ventricular dysfunction and/or right ventricular overload, which can also lead to left ventricular dysfunction. In patients with CDH, left ventricular dysfunction, either caused by right ventricular overload or a relative underdevelopment of the left ventricle, is associated with a poor prognosis[46].

If preductal saturations fall below 85% and there are signs of poor organ perfusion, treatment of pulmonary hypertension should be initiated by optimizing blood pressure. An adequate intravascular volume should be maintained with intravenous fluids as described above. Transfusion of packed red blood cells may be required to optimize tissue oxygen delivery. No studies show evidence of increasing systemic vascular resistance to treat right-to-left shunting, but a number of centers advise to use inotropics such as dopamine, dobutamine and epinephrine to maintain blood pressure at the normal levels for gestational age. Most recent publications advise to keep the systemic blood pressure over 40 mm Hg[47]. A study by Storme et al successfully used norepinephrine to increase systemic blood pressure in neonates with PPHN[48].

If pulmonary hypertension persists, pulmonary vasodilator therapy should be given, with inhaled nitric oxide (iNO) as the first therapeutic choice. Endogenous nitric oxide regulates vascular tone by relaxation of vascular smooth muscle cells. In several studies inhaled nitric oxide (iNO) produces potent and selective pulmonary vasodilation. In neonates with PPHN, iNO improves oxygenation and decreases the need for extracorporeal membrane oxygenation. The largest randomized controlled trial of early iNO therapy in infants with PPHN due to CDH did not demonstrate a beneficial effect for iNO[49]. The immediate short-term improvements in oxygenation seen in some treated infants may be of benefit, however, for transport or the bridging period to ECMO. At an oxygenation index of 20 or higher and/or a pre- and postductal saturation

difference of 10% or more, iNO may be given for at least one hour[50]. Studies to date have not reported a consistent effect according to iNO dose[51-52]. Therefore, this needs further prospective study.

If there is no or an insufficient response to iNO, intravenous prostacyclin or prostaglandin E1 should be considered. In recent case reports, these agents have been used successfully in treating pulmonary hypertension in neonates with and without CDH[53-57]. The effects of treatment for pulmonary hypertension may be best addressed by repeated cardiac evaluation[46]. A 10 to 20% reduction in the pre-postductal saturation difference or a 10 to 20% increase in PaO_2, however, may be used as guidance in evaluating the course of pulmonary hypertension[58].

In the presence of systemic or suprasystemic pulmonary artery pressure, the right ventricle might be overloaded, as demonstrated by enlargement of the right ventricle and a leftward shift of the interventricular septum. This can lead to insufficient filling of the left ventricle and poor systemic perfusion. To protect the right ventricle from excessive overload due to increased afterload, re-opening of the ductus arteriosus might be performed[46].

Sildenafil, a phosphosdiesterase 5 inhibitor, has been used in the treatment of pulmonary hypertension in adults and in the management of postoperative pulmonary hypertension in children with CDH[59-60]. Case reports in newborns with CDH suggest some improvement in oxygenation and cardiac output from Sildenafil alone or in combination with inhaled nitric oxide[60]. Currently, there are no randomized controlled trials studying the use of phosphodiesterase inhibition in infants with CDH, although a recent open label study reported on pharmacokinetics in neonates treated with sildenafil[61]. Other pulmonary vasodilators that have been used in pulmonary hypertension in infants include endothelin antagonists and tyrosine kinase inhibitors[62-67]. The consortium recommends that Sildenafil and other pulmonary vasodilators should only be used in the chronic phase of pulmonary hypertension in CDH, because there is no evidence that this helps in the acute phase in infants with CDH.

Recommendations:

- Perform echocardiography within the first 24 hours after birth. (Grade of recommendation=D)
- Blood pressure support should be given to maintain arterial blood pressure levels at normal level for gestational age. (Grade of recommendation=D)
- Inhaled nitric oxide should be considered if there is evidence of extrapulmonary right-to-left shunting and the oxygenation index is above 20 and/or the saturation difference is more than 10%. (Grade of recommendation=D)
- In case of suprasystemic pulmonary artery pressure and right-to-left shunting through the foramen ovale, iv prostaglandin E1 has to be considered. (Grade of recommendation=D)

Extracorporeal membrane oxygenation

The role of extracorporeal membrane oxygenation (ECMO) in the treatment of infants with CDH is still unclear[68]. In non randomized trials, ECMO has been reported, however, to improve survival in infants with CDH[69-70]. In some reports, oxygenation index, alveolar-arterial O_2 difference or a combination of both is used as a selection criterion for ECMO. In other reports, ECMO is considered if there is poor systemic perfusion, with sustained hypoxemia with inadequate oxygen delivery and persistent metabolic acidosis. Some centers only consider ECMO in infants with CDH if they show an adequate amount of lung parenchyma suggested by a period of adequate preductal oxygenation and/or ventilation[71]. The use of ECMO has decreased[22], ECMO is now more often used in preoperative stabilization[72]. Reports of stabilization and subsequent repair on ECMO have highlighted the benefit of delaying surgery and do it after ECMO rather than on ECMO, particularly among high-risk infants[73]. A meta-analysis of retrospective studies suggests that the introduction of ECMO has improved survival in infants with CDH[74]. A meta-analysis of RCTs with small sample sizes indicated a reduction in early mortality with ECMO, but no long-term benefit[74].

Criteria for ECMO are (grade of recommendation=D):

- Inability to maintain preductal saturations > 85% or postductal saturations >70%
- Increased $paCO_2$ and respiratory acidosis with pH < 7.15 despite optimalization of ventilatory management
- Peak inspiratory pressure > 28 cm H_2O or mean airway pressure > 17 cm H_2O is required to achieve saturation > 85%
- Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥ 5 mmol/l and pH < 7.15
- Systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output < 0.5 ml/kg/hour for at least 12-24 hours
- Oxygenation index (MAP x FiO_2 x 100/paO_2) ≥ 40 consistently present

Timing of surgical repair and post-operative management

Survival rates in infants with CDH undergoing surgical repair after pre-operative stabilization range from 79 to 92%[4,34-35,75]. There are controversies about timing of the surgical repair in patients who require ECMO therapy. Early studies reported a high rate of hemorrhagic complications and high mortality when bleeding developed[73,76]. A retrospective study from the CDH registry showed increased survival among patients who undergo repair of CDH after ECMO therapy relative to those who undergo repair while on ECMO[77]. The routine use of a chest tube postoperatively has been abandoned, an effusion usually quickly fills the pleural cavity after repair. Moreover, this promotes infectious contamination of the pleural space without any

benefits such as acceleration of ipsilateral lung expansion postoperatively. In individual cases, a pleural effusion after repair may compromise pulmonary function and ventilation, necessitating chest tube insertion[78].

Recommendations:

- Surgical repair of the defect in the diaphragm should be performed after physiological stabilization, defined as follows (Grade of recommendation=D):
  - Mean arterial blood pressure normal for gestational age
  - Preductal saturation levels of 85 to 95% SaO_2 on fractional inspired oxygen below 50%
  - Lactate below 3 mmol/l
    - Urine output more than 2 ml/kg/hour
- No routine chest tube placement. (Grade of recommendation=D)
- Repair on ECMO may also be considered. (Grade of recommendation=D)

Sedation and analgesia

A wide range of sedation and analgesia practices has been described. Most centres use opioid analgesics such as morphine sulfate or fentanyl. Neuromuscular blocking is sometimes used in cases of asynchronous breathing. Although there is no specific evidence in infants with CDH, neuromuscular blocking is, associated with several major side-effects and should be avoided[79]. The infant's condition using validated analgesia and sedation scoring systems, such as the COMFORT behaviour score[80], should be regularly assessed.

Recommendations:

- Infants should remain sedated and monitored using validated analgesia and sedation scoring systems. (Grade of recommendation=D)
- Neuromuscular blocking agents should be avoided if possible. (Grade of recommendation=D)

Fluid management and parenteral feeding

Restrictive fluid management in the first 24 hours consists of 40 ml/kg/day of fluids, including medication, with additional saline fluid therapy for intravascular filling. Thereafter, fluid and caloric intakes should be increased based on clinical condition. Glucose, lipids and proteins should be given according the ESPGHAN/ESPEN guidelines[81]. Diuretics should be given in case of a positive fluid balance, aiming for diuresis of 1-2 ml/kg/hr.

Recommendations:

* 40 ml/kg/day including medication for the first 24 hours, intake increases thereafter. (Grade of recommendation=D)
* Diuretics should be considered in case of a positive fluid balance, aim for diuresis of 1-2 ml/kg/hr. (Grade of recommendation=D)

Enteral feeding and gastro esophageal reflux

Nutritional morbidity remains a problem in survivors of CDH during infancy and early childhood, particularly gastro esophageal reflux (GER) ranging from 20 to 84% during the first year of life[82]. In survivors of CDH, GER may be treated both by antireflux medication and by surgical intervention. No prospective studies are available on the specific type of antireflux mediation. Other common sequelae are oral aversion and need for tube enteral feeding. No prospective studies are available on the type of antireflux mediation.

Recommendations:

* Enteral feeding should be started postoperatively combined with antireflux medication. (Grade of recommendation=D)

Conclusion

The European task force for CDH (CDH-EURO Consortium) has agreed on a protocol of standardized postnatal treatment guidelines. This protocol was a prerequisite for a multicenter randomised trial of ventilation modes in infants with CDH (VICI-trial, www.vicitrial.com). At present this protocol cannot be more than a consensus document because data from multicenter randomized controlled trials are lacking. The consortium prepared these consensus guidelines with the aim of providing neonatologists and pediatric intensive care physicians with a protocolized European treatment strategy. Use of this protocol will also contribute to more valid comparison of patient data in multicenter studies and to identification of areas for further research. It was beyond the scope of these consensus guidelines to describe long-term follow-up in infants with CDH. However, long-term follow-up in children with CDH is highly important because approximately 87% of survivors of CDH have longer lasting associated morbidities, such as pulmonary, gastro-intestinal and neurological problems[83]. The American Academy of Pediatrics section on Surgery and the Committee on Fetus and Newborn published a comprehensive plan for the detection and management of these associated morbidities[84].

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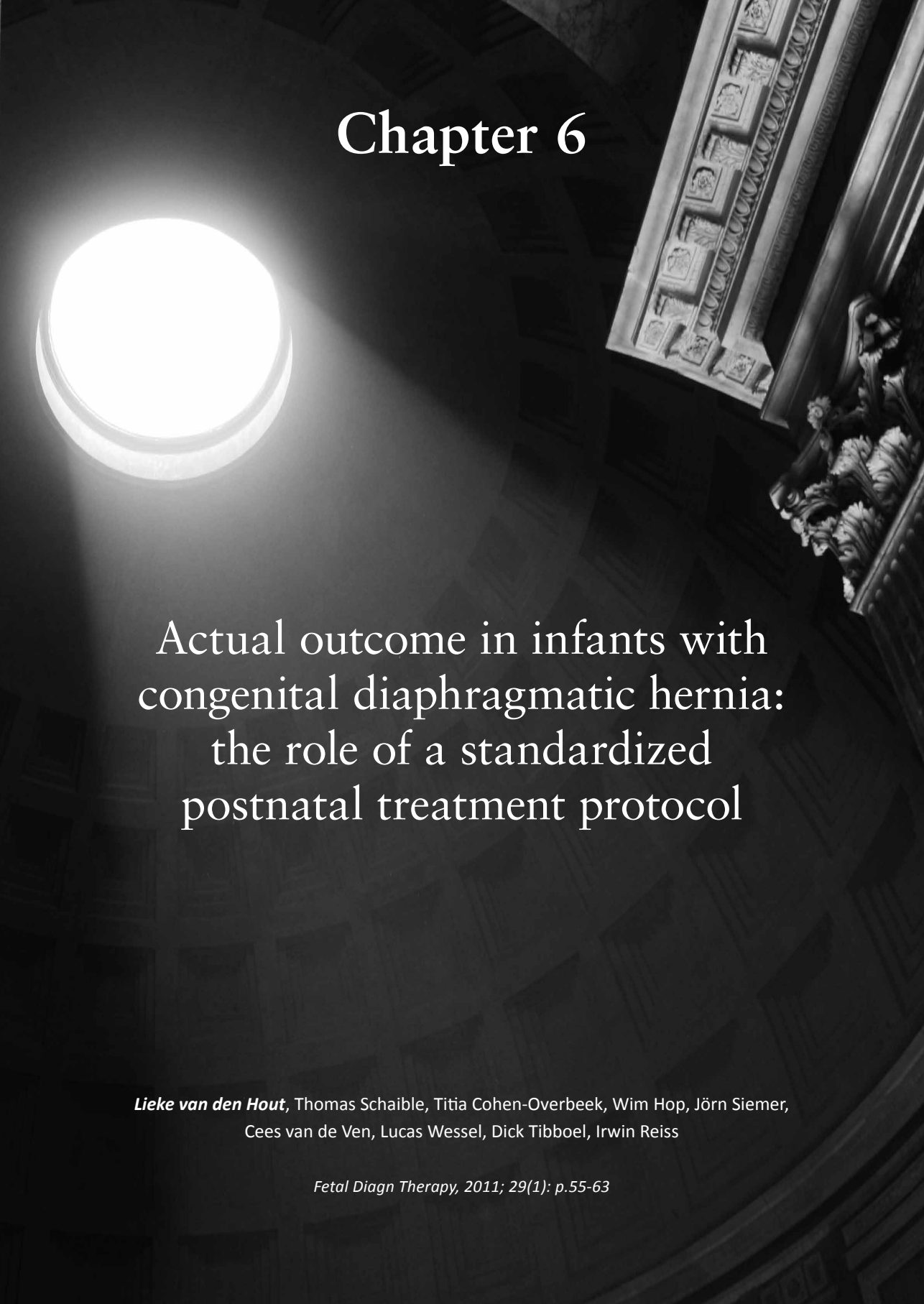
Chapter 6



Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol

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Abstract

Background: Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly with a high rate of mortality and morbidity.

Objective: Our aim was to determine a possible effect of standardized treatment on outcome in infants with CDH.

Methods: All prenatally diagnosed patients with unilateral CDH born alive between January 2006 and December 2009 at the Erasmus MC or the University Hospital Mannheim were eligible for inclusion. Patients who underwent a fetal tracheal occlusion were excluded. From November 1, 2007, all CDH patients were treated according to a standardized treatment protocol. Patients were divided into two chronological groups according to their date of birth: without standardized treatment (group 1, Jan 2006-Oct 2007) and with standardized treatment (group 2, Nov 2007-Dec 2009). Outcome measures were mortality by day 28, bronchopulmonary dysplasia (BPD), defined as oxygen dependency at day 28, and need for extra corporeal membrane oxygenation (ECMO) therapy. Univariate and multivariate analyses were performed.

Results: 167 patients were included. By day 28, 18% of the infants had died. Of the patients who were alive at day 28, 49% had BPD. An ECMO procedure was performed in 31% of the patients. Overall mortality for all included patients was 22%. In group 1, overall mortality was 33% and in group 2 overall mortality was 12% (p=0.004). A standardized treatment protocol was independently associated with a reduced risk for mortality by day 28 (OR 0.28, 95% CI 0.11-0.68). Higher observed-to-expected lung-to-head ratios were independently associated with a lower risk for mortality by day 28 (OR 0.97, 95% CI 0.95-0.99), BPD (OR 0.97, 95% CI 0.94-0.98) and need for ECMO (OR 0.98, 95% CI, 0.96-0.99). An intrathoracic position of the liver was independently associated with an increased risk for BPD (OR 3.12, 95% CI 1.41-6.90) and need for ECMO therapy (OR 3.25, 95% CI 1.54-6.88).

Conclusion: Survival rates in patients with CDH increased significantly after the implementation of a standardized treatment protocol.

Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly, which occurs in 1 in 3,000-4,000 live-born infants[1]. Overall mortality of all live-born patients with CDH is about 20-35%[2-3]. The main causes of mortality are pulmonary hypoplasia and therapy resistant pulmonary hypertension[4]. Over the past decades, survival rates may have improved because of advances in neonatal care, such as 'gentle ventilation' with permissive hypercapnia and delayed surgical repair[4-6]. On the other hand, assumed benefits of treatment with inhaled nitric oxide or extra corporeal membrane oxygenation (ECMO) remain controversial in infants with CDH[7-8]. Moreover, many survivors of CDH suffer from secondary morbidity, such as pulmonary complaints, gastroesophageal reflux disease and neurodevelopmental problems[9]. Pulmonary morbidity, such as bronchopulmonary dysplasia (BPD), asthmatic symptoms and recurrent respiratory tract infections, is present in 30-50% of all survivors of CDH[3,9-14].

Several prenatal predictors have been proposed to predict outcome in infants with CDH. The most well known is the lung-to-head ratio (LHR), which is obtained by dividing the lung area contralateral to the defect by the biparietal head circumference[15-16]. The position of the liver is also reported to be a good predictor of outcome in infants with isolated CDH[16-17]. Since the measurement of the LHR is dependent on the gestational age at time of measurement, it may be best described as the observed-to-expected lung-to-head ratio (O/E LHR)[18]. Prenatal measurements in fetuses with CDH are also important in deciding whether a fetal tracheal occlusion may be indicated.

Although many research efforts have been made in the field of CDH, therapeutic strategies for infants with CDH are not standardized and centers often use different treatment protocols that are not evidence-based[4,19]. A recent study by Tracy et al. reported that standardized therapy guidelines may help to prevent mortality in infants with CDH[19]. However, this study was performed over a 12-year period of time and other factors may have influenced outcome. Moreover, it is not known whether a standardized treatment protocol may reduce the risk of secondary morbidity, such as BPD. Therefore, we aimed to describe if the use of a standardized treatment protocol improved survival rates, secondary pulmonary morbidity, defined as BPD, and need for ECMO therapy.

Materials and Methods

Patients

Prenatally diagnosed patients with CDH born between January 1, 2006 and December 31, 2009 at the Erasmus MC-Sophia (the Netherlands) or the University Medical Center Mannheim (Germany) were eligible for inclusion. Since November 1, 2007, all CDH patients born in these centers are treated according to a standardized treatment protocol that was developed at a consensus meeting between the two centers. Patients are divided into two chronological groups

to determine the effect of the standardized treatment protocol. Patients born between January 1, 2006 and October 31, 2007, before the standardized treatment protocol was developed, are described as group 1. Patients born between November 1, 2007 and December 31, 2009, after the treatment protocol was developed, are described as group 2.

Patients who underwent a fetal tracheal occlusion were excluded from the analysis, because this procedure may have relevant impact on the fetal lung volume and the postnatal clinical course[20-21]. Patients with bilateral CDH were also excluded from the analysis, since these patients may have a different course of the disease than patients with unilateral CDH[22]. Furthermore, patients who received no treatment after birth, because of the presence of other congenital anomalies or a syndrome, were excluded from the analysis. In total, there were 3 patients who received no treatment (1=esophageal atresia, 1=Cornelia de Lange syndrome, 1=giant omphalocele). Patients who died in utero or in whom the pregnancy was terminated were also excluded. Three patients died in utero or during birth and in 6 patients the pregnancy was terminated (see fig. 1, patient flow chart).

We retrospectively collected data on prenatal evaluation, LHR, position of the liver (intrathoracic or intra-abdominal), mode of delivery, birth, ventilatory treatment, surgical repair and type of surgical repair.

This study was approved by the medical ethics committees of both study centers. Of the included patients, 19 were previously described in a study of Büsing et al.[23].

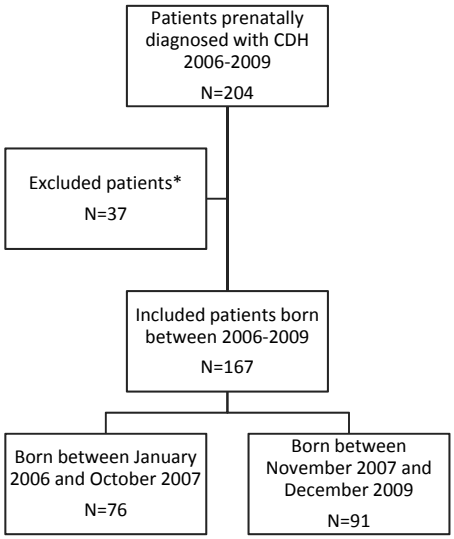

Figure 1. patient flow chart

* fetal tracheal occlusion (n=21), bilateral (n=4), termination of pregnancy (n=6), died in utero (n=1), died during birth (n=2), No treatment (n=3)

Measurement of the lung-to-head ratio and the position of the liver

An experienced gynecologist performed ultrasonography using a 3.5-MHz convex transducer (EUB, 5500E, Hitachi, Wiesbaden, Germany). LHR was calculated as described by Metkus et al.[15] and Lipschutz et al.[24]. A transverse section of the fetal lung area contralaterally to the diaphragmatic defect was taken at the level of the four-chamber view. Thereafter, the longest diameter of the contralateral lung was multiplied by the longest diameter perpendicular to it. LHR was determined by dividing the lung area expressed in square milliliters by the head circumference expressed in millimeters. The position of the liver was also determined by ultrasound and described as intrathoracic or intra-abdominal. The expected LHR for all patients with isolated left-sided CDH was calculated using the formula described by Peralta et al.[25]: left LHR= -1.4815 + 0.1824 * gestation in weeks – 0.0023 * (gestation in weeks)^2 ; right LHR= -2.2418 + 0.2712 * gestation in weeks – 0.0033 * (gestation in weeks)^2.

Standardized treatment protocol

Before 2006, both the Erasmus MC-Sophia (the Netherlands) and the University Medical Center Mannheim (Germany) treated patients with CDH using the concept of 'gentle ventilation'[5], delayed repair and ECMO therapy if necessary[26]. Both centers aimed to develop a standardized treatment protocol that gave a clear definition of treatment and ventilation goals based upon recent literature. No major changes in overall treatment strategies took place in the centers during the study period.

The protocol was developed at a consensus meeting between the two centers in October 2007. For the development of the protocol, relevant literature was reviewed and expert opinion was discussed. Although there are some recent reviews of the most important literature[4,27], most studies in the field of CDH are single-center retrospective studies. Until now, no randomized controlled trials have been done. Therefore, our protocol has to be viewed as a guideline for treatment in CDH. Nevertheless, by use of this protocol we are able to make a more valid comparison of patient data in our centers and to identify areas for further research. Reiss et al. recently published this standardized treatment protocol, which is described in short below[28].

Postnatal management

After birth, infants were immediately intubated. Low peak pressures, preferably < 25 cm H_20, were given. Our goals were to achieve preductal saturations between 85 and 95%, postductal saturation levels above 70% and arterial CO_2 levels between 45-60 mm Hg (permissive hypercapnia). Infants were either initially ventilated by conventional ventilation or high-frequency oscillation (HFOV). In case of conventional ventilation the following settings were used: a peak inspiratory pressure (PIP) of 20-25 cm H_2O, a positive end-expiratory pressure (PEEP) of 2-5 cm H_2O and a frequency of 40-60 per minute. If a PIP > 28 cm H_2O was necessary to achieve pCO_2 and saturation levels within the target range, other treatment modalities, such as rescue HFOV and ECMO, were considered. The initial settings in case of HFOV were: a mean airway pressure (MAP) of 13-17 cm H_2O, a frequency of 10 Hz, an amplitude (Δp, cm H_2O) of 30-50 obtaining

chest vibrations, and an inspiration/expiration rate (I:E) of 1:1. In case of HFOV, a chest radiograph was made to confirm that the lungs were not overinflated, as defined by a contralateral lung expansion of over 8 ribs.

Weaning from conventional ventilation was done by means of decreasing PIP. Frequency and/or the PIP-PEEP were modified to achieve $PaCO_2$ levels > 45 mmHg. In case of HFOV, Δp was decreased if the $paCO_2$ was < 45 mmHg and FiO_2 was decreased if preductal saturation levels were > 95%.

In case of hypovolemia and /or cardiogenic shock, saline fluid therapy was started (10-20 ml/kg of NaCl 0.9% up to three times during the first 1-2 h), which was followed by inotropic therapy if necessary. In case of persisting signs of pulmonary hypertension inhaled nitric oxide (iNO) was given. At an oxygenation index of 20 or higher and/or a pre- and postductal saturation difference of 10% or more, 10-20 ppm iNO was given for at least 1 hour. Intravenous prostacyclin or prostaglandin E1 was considered in case of no response to iNO. Sildenafil was only considered in the chronic phase of pulmonary hypertension.

The following criteria were used to consider extracorporeal membrane oxygenation (ECMO): the inability to maintain preductal saturations > 85% or postductal saturations > 70%, an increased $paCO_2$ and respiratory acidosis with pH < 7.15 despite optimalization of ventilatory management, PIP > 28 cm H_2O or MAP > 17 cm H_2O necessary to achieve saturation > 85%, inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥ 5 mmol/l and pH < 7.15, systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output < 0.5 ml/kg/hour for at least 12-24 h, oxygenation index (MAP x FiO_2 x 100/paO_2) ≥ 40 consistently present.

Surgical repair of the defect in the diaphragm should be performed after physiological stabilization. At surgery, no chest tubes were routinely placed. Postoperatively, enteral feeding was started in combination with antireflux medication.

The infant's condition using validated analgesia and sedation scoring systems was regularly assessed. No routine paralysis was used.

Outcome measures and statistical analysis

Primary outcome measures in this study were mortality by day 28, bronchopulmonary dysplasia (BPD) and need for ECMO therapy. BPD was defined according to the definition of Jobe and Bancalari[29] as oxygen dependency at day 28 or at 36 weeks postmenstrual age, depending on gestational age at birth. The severity of BPD was determined on day 56 or at discharge, whichever came first, according to the amount of oxygen use and type of ventilation.

Univariate analyses were performed for all three outcome measures, using Chi-squared and Mann-Whitney U tests where appropriate. Baseline variables that showed a significant effect in univariate analysis were entered into multiple logistic regression analyses for mortality by day 28, BPD and need for ECMO using a stepwise backward elimination method. Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, Ill.,USA). A two-sided p-value less than 0.05 was considered statistically significant.

Results

A total of 167 patients were included (see fig. 1, patient flow chart). In total, 76 patients were born between January 1, 2006 and the October 31, 2007 (Group 1) and 91 patients were born between November 1, 2007 and December 31, 2009 (Group 2). Baseline patient characteristics of all patients are described in table 1.

Table 1. Baseline patient characteristics of all patients included (n=167). Numbers do not always add up due to missing values.

Variable	Patients included (n, %)
Male gender	100/167 (60)
Left-sided	148/167 (89)
Cardiac anomaly*	28/167 (17)
Chromosomal anomaly**	2/167 (1)
Other anomaly***	22/167 (13)
Vaginal delivery	49/165 (30)
Intrathoracic position of the liver	74/164 (45)
HFO as initial ventilation mode	28/167 (17)
Born in Erasmus Medical Center	39/167 (23)
Continuous variables	**Median (Range)**
LHR	1.4 (0.2-3.5)
O/E LHR, %	55 (8-135)
Birth weight, g	3,000 (1,250-4,050)
Gestational age, weeks	38 (31-41)

* A severe cardiac anomaly, characterized as either lethal or needed surgery within the first months of life, was present in 21% (n=6/28). Forty-three percent of the patients with a cardiac abnormality had also another congenital anomaly (n=12/28).

** Wolf Hirschhorn syndrome (n=1), deletion 8p (n=1)

*** Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality.

Survival, BPD and severity of BPD

By day 28, 18% (n=30/167) of the infants had died. Of the patients who were alive at day 28, 49% (n=66/136, missing=1) were oxygen dependent and thus diagnosed with BPD.

Of the patients with BPD, 53% (n=31/58, missing =8) had mild, 28% had moderate (n=16/58) and 19% (n=11/58) had severe BPD at day 56. Four patients died at day 56 and in 4 other patients the severity of BPD was unknown, because data on oxygen dependency were missing.

Overall mortality for all included patients was 22% (n=37/167).

The univariate analyses of mortality by day 28 and BPD are presented in table 2 and 3, respectively.

Table 2. Univariate analysis of baseline variables for patients who died by day 28 (n=30) and who were alive (n=137). Numbers do not always add up to 167.

Variable	Died by day 28	%	Alive at day 28	%	p value
Gender					0.547
Male	16/100	16	84/100	84	
Female	14/67	21	53/67	79	
Method of delivery					0.857
Cesarean section	22/116	19	94/116	81	
Vaginal delivery	8/49	16	41/49	84	
Cardiac Abnormality					0.061
Yes	9/28	32	19/28	68	
No	21/139	15	118/139	85	
Chromosomal Abnormality					1.000
Yes	0/2	0	2/2	100	
No	30/165	18	135/165	82	
Other abnormality*					0.079
Yes	7/22	32	15/22	68	
No	23/145	16	122/145	84	
Side defect					0.185
Left	24/148	16	124/148	84	
Right	6/19	32	13/19	68	
Position of the liver					0.115
Intrathoracic	18/74	24	56/74	76	
Intra-abdominal	12/89	13	77/89	87	
Initial ventilation mode					0.775
HFOV	4/28	14	24/28	86	
CMV	26/139	19	113/139	81	
Center of Birth					0.095
Erasmus Medical Center	3/39	8	36/39	92	
Mannheim University Hospital	27/128	21	101/128	79	
Continuous variables	**Median**	**Range**	**Median**	**Range**	**p value**
LHR	1.1	0.3-3.0	1.5	0.2-3.5	<0.001
O/E LHR, %	45	10-135	56	8-124	0.002
Gestational age at birth, weeks	37	32-39	38	31-41	0.089
Birth weight, g	2750	1215-3670	3000	1645-4050	0.002

* Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality

Need for ECMO

An ECMO procedure was performed in 31% of the cases (n=51/167). In all patients, a venoarterial ECMO procedure was performed. Median duration of ECMO treatment was 10 days (range 3-19). Overall mortality after an ECMO procedure was 49% (n=25/51). By day 28, 35% patients who underwent an ECMO procedure had died (n=18/51) compared with 10% (n=12/116) of the patients who did not undergo an ECMO procedure (p<0.001). BPD was present in 94% (n=31/33) of the patients who were alive after ECMO treatment at day 28 compared with 34% (n=35/103, missing=1) of the patients who were alive at day 28 and did not undergo ECMO treatment (p<0.001). The univariate analysis for need for ECMO is presented in table 4.

Table 3. Univariate analysis of baseline variables for patients who had BPD (n=66) and who did not have BPD (n=70). Numbers do not always add up to 136 due to missing values.

Variable	BPD	%	No BPD	%	p value
Gender					0.257
Male	44/83	53	39/83	47	
Female	22/53	42	31/53	58	
Method of delivery					0.166
Cesarean section	50/93	54	43/93	46	
Vaginal delivery	16/41	39	25/41	61	
Cardiac Abnormality					0.890
Yes	10/19	53	9/19	47	
No	56/117	48	61/117	52	
Chromosomal Abnormality					0.497
Yes	0/2	0	2/2	100	
No	66/134	49	68/134	51	
Other abnormality*					0.904
Yes	8/15	53	7/15	47	
No	58/121	48	63/121	52	
Side defect					1.000
Left	60/123	49	63/123	51	
Right	6/13	46	7/13	54	
Position of the liver					<0.001
Intrathoracic	38/55	69	17/55	31	
Intra-abdominal	28/77	36	49/77	64	
Initial ventilation mode					0.701
HFOV	13/24	54	11/24	46	
CMV	53/112	47	59/112	53	
Center of Birth					0.706
Erasmus Medical Center	16/36	44	20/36	56	
Mannheim University Hospital	50/100	50	50/100	50	
Continuous variables	**Median**	**Range**	**Median**	**Range**	**p value**
LHR	1.4	0.2-3	1.7	0.8-3.5	<0.001
O/E LHR, %	51	8-97	61	41-124	0.001
Gestational age at birth, weeks	37	33-40	38	31-41	0.004
Birth weight, g	2940	1650-3900	3030	1645-4050	0.014

* Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality

Effect standardized treatment protocol

By day 28, 29% of the patients in group 1 (n=22/76) had died compared to 9% of the patients in group 2 (n=8/91, p=0.001). In group 1, overall mortality was 33% (n=25/76) and in group 2 overall mortality was 12% (n=12/99, p=0.004).

Of the patients who were alive at day 28, 47% (n=25/53, missing=1) had BPD in group 1 compared with 49% (n=41/83) in group 2 (p=0.938).

Table 4. Univariate analysis of baseline variables for patients who underwent an ECMO procedure (n=51) and who did not (n=116). Numbers do not always add up to 167 due to missing data.

Variable	ECMO	%	No ECMO	%	p value
Gender					0.742
Male	32/100	32	68/100	68	
Female	19/67	28	48/67	72	
Method of delivery					0.329
Cesarean section	39/116	34	77/116	66	
Vaginal delivery	12/49	24	37/49	76	
Cardiac Abnormality					0.356
Yes	6/28	21	22/28	79	
No	45/139	32	94/139	68	
Chromosomal Abnormality					1.000
Yes	0/2	0	2/2	100	
No	51/165	31	114/165	69	
Other abnormality*					1.000
Yes	7/22	32	15/22	68	
No	44/145	30	101/145	70	
Side defect					0.153
Left	42/148	28	106/148	72	
Right	9/19	47	10/19	53	
Position of the liver					<0.001
Intrathoracic	34/74	46	40/74	54	
Intra-abdominal	16/89	18	73/89	82	
Initial ventilation mode					0.185
HFOV	12/28	43	16/28	57	
CMV	39/139	28	100/139	72	
Center of Birth					0.575
Erasmus Medical Center	10/39	26	29/39	74	
Mannheim University Hospital	41/128	32	87/128	68	
Continuous variables	**Median**	**Range**	**Median**	**Range**	**p value**
LHR	1.1	0.3-2.6	1.6	0.2-3.5	<0.001
O/E LHR, %	48	10-135	56	8-124	0.001
Gestational age at birth, weeks	37	33-40	38	31-41	0.123
Birth weight, g	2870	2000-3900	3000	1215-4050	0.094

* Other abnormality is classified as having another congenital anomaly than congenital heart disease or a chromosomal abnormality

In group 1, an ECMO procedure was necessary in 37% (n=28/76) of the patients compared with 25% (n=23/91) of the patients in group 2 (p=0.148). In group 1, mortality after ECMO was significantly higher than in group 2 (64%, n=18/28, vs. 30%, n=7/23, p=0.034). Of the patients who were alive after ECMO treatment, 100% (n=10/10) was diagnosed with BPD in group 1 compared with 88% in group 2 (n=14/16, p=0.684).

Prenatal measurements of the lung-to head ratio

All included patients were prenatally diagnosed with CDH. LHR was measured in 155 patients, for whom the median age at ultrasound measurement was 30 weeks (range 18-41). The median LHR

was 1.4 (0.2-3.5, see table 1) and the median O/E LHR was 55% (range 8-135%). The median LHR and O/E LHR were significantly lower in patients who died (p<0.001 and p=0.002), in patients with BPD (p<0.001 and p=0.001) and in patients who underwent an ECMO procedure (p<0.001 and p=0.001) compared with patients who were alive, had no BPD or did not undergo an ECMO procedure (see tables 2-4).
In the excluded patients who underwent a FTO, the median O/E LHR was 42% (range 27-84%), which was significantly lower than in the included patients who did not underwent a FTO (55%, p=0.003). In fetuses in whom the pregnancy was terminated the median O/E LHR was 29% (range 22-60%) which was lower, although not significantly, than in the included patients who were born alive (55%, p=0.118).

Surgical repair

A total of 151 patients (90%) underwent a surgical repair. Median day of life at surgical repair was the fourth day of life (range 0-68). A patch repair, as opposed to primary repair, was performed in 82% of the patients (n=122/149, missing=2).
Of all patients who underwent a surgical repair, 10% (n=15/151) had died by day 28. Of the patients who underwent a patch repair, 11% (n=13/122) had died by day 28 compared with 7% of patients who underwent a primary repair (n=2/27, p=0.771). In patients alive at day 28, BPD was significantly more present in patients who underwent a patch repair (54%, n=59/109) than in patients who underwent a primary repair (24%, n=6/25, p=0.013).

Multivariate analysis

A multivariate analysis was performed for all baseline variables which were significant in the univariate analyses for mortality, BPD and need for ECMO (see tables 2-4). Only baseline variables were included in the multivariate analyses, since other variables, which were not known at baseline may have been influenced by postnatal management.
The following variables were regarded as baseline variables: period of treatment (group 1 or group 2), center of birth (Erasmus Medical Center or University Hospital Mannheim), gender, method of delivery (vaginal or cesarean section), cardiac abnormality (yes or no), chromosomal abnormality (yes or no), congenital abnormalities other than cardiac or chromosomal abnormalities (yes or no), side of the defect (left or right), the position of the liver (intrathoracic or intra-abdominal), initial ventilation mode (HFOV or conventional ventilation), LHR, O/E LHR, gestational age at birth and birth weight. With regard to the prenatal measurements, we only included the O/E LHR in the multivariate analysis since the LHR is not corrected for gestational age at the time of measurement.
Although we did not include variables that were not known at baseline, we did test for various interactions between these variables and the baseline variables. For all three outcome measures, no such interactions were found. Especially, no interactions were found with regard to side of the defect and the center in which the patient was born.
The results of the multivariate analyses for all outcome measures are presented in table 5-7.

Table 5. Multivariate analysis for mortality by day 28 (n=155)

Variable	Odds ratio	95% CI	p-value
Standardized treatment	0.28	0.11-0.68	0.005
Higher O/E lung-to-head ratio	0.97	0.95-0.99	0.042

Birth weight was not significant in multivariate analysis (OR 1.00, 95% CI 0.94-1.04, p=0.07).

Table 6. Multivariate analysis for BPD (n=121)*

Variable	Odds ratio	95% CI	p-value
Intrathoracic position liver	3.12	1.41-6.90	0.005
Higher O/E lung-to-head ratio	0.97	0.94-0.98	0.003

Birth weight (OR 1.01, 95% CI 0.98-1.04, p=0.595) and gestational age at birth (OR 0.82, 95% CI 0.63-1.08) were not significant in multivariate analysis.

Table 7. Multivariate analysis for ECMO (n=151)

Variable	Odds ratio	95% CI	p-value
Intrathoracic position liver	3.25	1.54-6.88	0.002
Higher O/E lung-to-head ratio	0.98	0.96-0.99	0.020

Discussion

This article showed that use of a standardized treatment protocol was independently associated with an increase in survival in infants with CDH. Survival rates increased significantly from 67% to 88% after implementation of the protocol (p=0.004).

Previously, it has been reported that standardized treatment protocols may have a positive effect on patient outcome[30]. Protocols may help to induce more consistent care and may reduce variability in decision-making. They may also give a more clearly definition of treatment goals. Protocols may not only be helpful for the treating physician, but for also for other people involved in the care for the patient[30]. Especially in severely ill patients, in whom decision-making may be complex and more disciplines may be involved, protocolized care may be of great value[31].

Standardized protocols are still lacking in the field of CDH, also because randomized clinical trials have not been carried out in these patients[4]. However, some centers described their treatment protocols and possible beneficial effects of these protocols[2,19,32-33]. In these studies the outcome in patients who received standardized treatment, including 'gentle' ventilation strategies and delayed repair, were compared to patients born in an earlier period who received very different treatment. Recently, a study by Tracy et al. reported that a standardized treatment protocol improved survival in infants with CDH[19]. In this study, all infants were treated with 'gentle' ventilation, permissive hypercapnia, delayed repair and ECMO if necessary[19]. However, a relatively small sample of patients (n=69) was evaluated and no multivariate analysis was performed to correct for possible confounders.

Furthermore, we reported that the prevalence of BPD is 49% in survivors of CDH. Use of a standardized treatment protocol had no effect on the rate of BPD in our patients. However, because survival rates improved after standardized care was implemented, relatively more infants in the second group were expected to suffer from secondary morbidity. Because the prevalence of BPD

remained the same, we may speculate a possible beneficial effect of standardized treatment on the presence of BPD.

One third of the patients underwent an ECMO procedure. Overall mortality after an ECMO procedure was similar to the most recent data of the CDH Registry that reported an overall mortality of 51% after an ECMO procedure[3]. Standardized treatment had no significant effect on the use of ECMO therapy. Nonetheless, after implementation of the study protocol, we observed a trend towards a decreased use of ECMO. We may speculate that decisions to start ECMO therapy may have been based on more firm criteria after implementation of the treatment protocol.

We also reported that a lower O/E LHR was independently associated with mortality, BPD and need for ECMO therapy. Lower O/E LHRs were also associated with mortality in previous studies[18,34]. A recent study by Jani et al. reported the O/E LHR to be associated with BPD, defined as oxygen dependency at day 28, and the duration of ventilation[35]. In contrast to our findings, need for ECMO therapy was not associated with the O/E LHR in a recent study[36]. However, in this study the authors pointed out that the indications for ECMO therapy varied widely in their study centers[36]. In our centers, ECMO criteria were well defined and did not change over time.

In addition, an intrathoracic liver position was independently associated with an increased risk for BPD and need for ECMO therapy. It may be hypothesized that in case of an intrathoracic liver position, the defect size may be larger which may result in a higher degree of pulmonary hypoplasia. Postnatal outcome in infants with an intrathoracic liver position may therefore be worse. In contrast to previous research[16-17], an intrathoracic position of the liver was not associated with an increased risk for mortality in our study.

Although our study was one of the first studies that reported postnatal outcome in infants with CDH treated according to a standardized treatment protocol in two high-volume centers, it has some important limitations. First, this is a retrospective study. Furthermore, excluded patients who underwent a fetal tracheal occlusion (median O/E LHR 42%), and fetuses in whom the pregnancy was terminated (median O/E LHR 29%) had lower measurements of the O/E LHR than included patients. Selection bias may therefore have influenced our study and results should be interpreted with caution. Although treatment strategies in general, treating physicians, nursing staff and training at our centers remained constant during the study period, we cannot rule out the possibility that these factors may also have influenced our results. Also, it was difficult to correct for factors which may indicate the severity of illness in the patients, such as the degree of pulmonary hypertension.

In conclusion, this is one of the first studies that evaluated the effect of a standardized treatment protocol in infants with CDH. Although implementation of a standardized treatment protocol improved survival rates, no significant changes in the prevalence of BPD or the use of ECMO therapy were observed. Furthermore, we reported the O/E LHR to be associated with mortality, BPD and need for ECMO therapy. Also, an intrathoracic position of the liver was associated with need for ECMO therapy and BPD. This reveals that not only survival may be predicted antenatally, but also need for ECMO therapy and pulmonary morbidity. Last, cooperation between different centers is highly important to develop protocols and to enhance further research in the field of CDH, such as randomized clinical trials.

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Chapter 7

Prediction of chronic lung disease, survival and need for ECMO therapy in infants with congenital diaphragmatic hernia: additional value of fetal MRI measurements?

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Abstract

Introduction: The lung-to-head ratio (LHR), measured by ultrasound, and the fetal lung volume (FLV), measured by MRI, are both used to predict survival and need for extracorporeal membrane oxygenation (ECMO) in infants with congenital diaphragmatic hernia (CDH). The aim of this study is to determine whether MRI measurements of the FLV, in addition to standard ultrasound measurements of the LHR, give better prediction of chronic lung disease, mortality by day 28 and need for ECMO.

Materials and Methods: Patients with unilateral isolated CDH born between January 2002 and December 2008 were eligible for inclusion. LHR and FLV were expressed as observed-to-expected values (O/E LHR and O/E FLV). Univariate and multivariate analyses were performed. Receiver operating characteristic curves were constructed and areas under the curve (AUC) were calculated to determine predictive values.

Results: 90 patients were included in the analysis. Combined measurement of the O/E LHR and O/E FLV gave a slightly better prediction of chronic lung disease (AUC=0.83 and AUC=0.87) and need for ECMO therapy (AUC=0.77 and AUC= 0.81) than standard ultrasound measurements of the O/E LHR alone. Combined measurement of the O/E LHR and O/E FLV did not improve prediction of early mortality (AUC=0.90) compared to measurement of the O/E LHR alone (AUC=0.89). An intrathoracal position of the liver was independently associated with a higher risk of early mortality ($p<0.001$), chronic lung disease ($p=0.007$) and need for ECMO therapy ($p=0.001$).

Discussion: Chronic lung disease and need for ECMO therapy are slightly better predicted by combined measurement of the O/E LHR and the O/E FLV. Early mortality is very well predicted by measurement of the O/E LHR alone.

Conclusion: Clinical relevance of additional MRI measurements may be debated.

Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly, which occurs in 1 in 3000 to 4000 live born infants[1]. CDH has a mortality rate of about 30%[2]. Importantly, surviving neonates are at a substantial risk of developing secondary morbidity. Long-term pulmonary sequelae, such as bronchopulmonary dysplasia, occur in approximately 40% of CDH survivors[2].
Detailed ultrasound techniques allow for prenatal detection of CDH in almost 60% of the cases[3]
Prenatal radio-diagnostic imaging has led to the development of several prenatal predictors for neonatal outcome in fetuses with CDH. The lung-to-head ratio (LHR), which is usually measured by ultrasound, is the most widely used prenatal predictor of survival in fetuses that have CDH. It is obtained by dividing the area of the lung contralateral to the diaphragmatic defect by the fetal head circumference[4-5]. Good predictive value has been reported in isolated cases of left-sided CDH, especially if the liver is situated in the thorax[6]. In cases of isolated CDH, an LHR <1.0 in combination with an intrathoracal position of the liver is considered a bad prognostic sign[3] However, there are authors who doubt whether the LHR can predict postnatal outcome[7]. Recently, fetal lung volume (FLV), which is measured by magnetic resonance imaging (MRI), was proposed as a prenatal predictor of survival and the need for extracorporeal membrane oxygenation (ECMO) in fetuses with CDH[8]. Both the LHR and FLV are best described as the ratio of the measured over the expected value, the observed-to-expected LHR and FLV (O/E LHR and O/E FLV)[9].
Although previous studies suggested prenatal predictors, including LHR and FLV, for mortality and need for Extra Corporeal Membrane Oxygenation (ECMO), reliable prenatal predictors for chronic lung disease are lacking. Also, hospitals often use different prenatal and postnatal treatment protocols in patients with CDH. Measurements of the O/E LHR throughout pregnancy by ultrasound are usually standard practice. Some specialists, however, perform additional measurements of the O/E FLV by MRI. The aim of this study is to determine if additional measurement of the O/E FLV by MRI gives a better prediction of chronic lung disease, early mortality and need for ECMO therapy than measurement of the O/E LHR by ultrasound only, within the context of a standardized postnatal treatment protocol.

Materials and Methods

Patients

This was a retrospective single-center study. Eligible for inclusion were live-born infants with isolated unilateral CDH, born between January 2002 and December 2008 in the University Medical Centre Mannheim (Germany), which is a national referral center for CDH. All patients were treated according to a standardized treatment algorithm as determined by the CDH Euro Consortium and described by Reiss et al.[10]. As described in this paper, an ECMO procedure was started in case of severe persisting pulmonary hypertension.

Patients with congenital anomalies or with bilateral CDH were excluded from the analysis, because these patients have a different course than the more common unilateral isolated defects. Patients who underwent a fetal tracheal occlusion were also excluded from the analysis, since this therapy has a relevant impact on the fetal lung volume and the postnatal clinical course. Furthermore, we only included patients if prenatal measurements of both O/E LHR and O/E FLV were performed within a maximum time range of one week.
The research ethics committee of the study center approved this study. Informed consent for both the MRI and ECMO therapy was received from all parents.

Radio-diagnostic imaging

Measurement of the observed-to-expected lung-to-head ratio
One of two experienced gynecologists performed ultrasonography using a 3.5-MHz convex transducer (EUB, 5500E, Hitachi, Wiesbaden, Germany). The lung area was calculated as described by Metkus et al.[5] and Lipschutz et al.[4]. A transverse section of the fetal lung area contralaterally to the diaphragmatic defect was taken at the level of the four chamber-view. Thereafter, the lung area was determined by multiplying the longest axis by the longest measurement perpendicular to it.
The LHR was determined by dividing the lung area expressed in square milliliters by the head circumference expressed in millimeters. The expected LHR was calculated using the formula described by Peralta et al.: left LHR= -1.4815 + 0.1824 * gestation in weeks – 0.0023 * (gestation in weeks)^2 ; right LHR= -2.2418 + 0.2712 * gestation in weeks – 0.0033 * (gestation in weeks)^2.

Measurement of the observed-to-expected fetal lung volume
Multiplanar T2-weighted HASTE-images (TR/TE 1.000/85; section thickness 4 mm; flip angle 150^o, matrix size, 512 x 512) were obtained with a 1.5-T superconducting MRI system (Magnetom Vision, Sonata or Avanto, Siemens Medical Solutions, Erlangen, Germany). One of two experienced radiologists performed planimetry with volume analysis software (Argus Leonardo workstation, Siemens Medical Solutions, Erlangen, Germany). Segmentation was determined by semi-automatic hand tracing. The regions of interest followed the lung boundaries and did not include the main vessels of the pulmonary hila. Volumes of these delineated regions were automatically calculated and thereafter summed to determine the total lung volume. Images of good quality from at least two section planes were used for delineation of the lung area. The mean values of the lung volumes determined in this manner were used. The expected lung volume was calculated by the formula furnished by Rypens et al.[11]: 0.0033 * (gestation in weeks)$^{2.86}$.

Determination of the position of the liver and intestine
Position of the liver was determined by MRI, as in fetuses with CDH the position of the liver is determined most accurately by MRI[12]. The position of the stomach and bowels were determined by MRI and were described as intra-thoracic or intra-abdominal.

Outcome measures

The outcome measures were chronic lung disease, mortality by day 28 and need for ECMO therapy. Chronic lung disease (CLD) was defined as oxygen-dependency on day 28, as described by Bancalari et al. The severity of CLD was determined on day 56 or at discharge, whichever came first, from the oxygen use and type of ventilation[13].

Statistical analysis

Univariate analysis was done by Chi-Squared or Mann-Whitney tests for categorical and continuous outcomes, respectively.

Both O/E LHR and O/E FLV had skewed distributions and were therefore transformed logarithmically (base 10) in order to achieve approximate normal distributions. Because O/E LHR and O/E FLV were found to decrease with advancing gestational age at the time of measurement (figure 1), these two variables were further expressed as Z-scores in the logistic regression modeling. These Z-scores were based on regression analysis and resulted in the following equations:

Z-score O/E LHR= (Log (O/E LHR) - 1.866 - (-0.006*gestational age at time of measurement in weeks))/ 0.155

Z-score O/E FLV= (Log (O/E FLV) - 1.727 - (-0.009*gestational age at time of measurement in weeks))/ 0.182

Three multiple logistic regression analyses were performed to evaluate putative factors predicting CLD, mortality by day 28 and need for ECMO therapy. Baseline predictive models for all three outcome measures were constructed considering baseline factors which were significant in the univariate analyses. Thereafter, the Z-scores of the O/E LHR and O/E FLV were added to these models. Receiver-operating characteristic curves (ROC-curves) were constructed to determine the predictive value of O/E LHR and O/E FLV. An area under the curve (AUC) of > 0.8 was considered to indicate good predictive value. A p-value (two-sided) of <0.05 was considered significant. All analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, Illinois) or LOGXACT for Windows version 4.0.2 (Cytel Software Corporation, Cambridge, Massachusetts).

Results

Study population

Between 2002 and 2008, 189 live-born patients with unilateral isolated CDH were admitted to our hospital. Of those, 90 patients were included in the analysis (figure 2). Table 1 shows differences between included and non-included patients with unilateral isolated CDH.

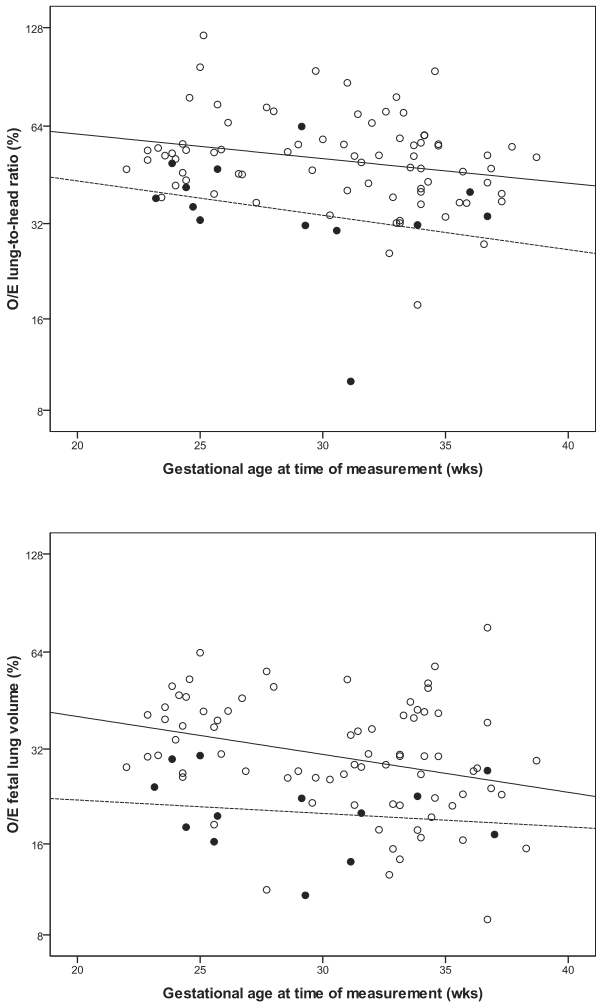

Figure 1A and 1B. The scatterplot of the O/E LHR and O/E FLV versus the gestational age at the time of measurement. The open dots represent the patients alive at day 28 and the closed dots represent the patients who died by day 28. The solid and dotted lines represent the least squares regression lines for the patients alive at day 28 and the patients who died by day 28, respectively. Note the logarithmically scaled vertical axes.

Ultrasound and MRI measurements

Median gestational age at time of ultrasound and MRI measurements was 31.0 weeks (range 22.0-38.7) and 31.1 weeks (range 22.0-38.7), respectively. For all patients, the median O/E LHR was 48.4% (range 10.0%-121.2%) and the median O/E FLV was 28.3% (range 9.0%-76.1%). An intrathoracal position of the liver was observed in 59% of the patients (n=53/90).

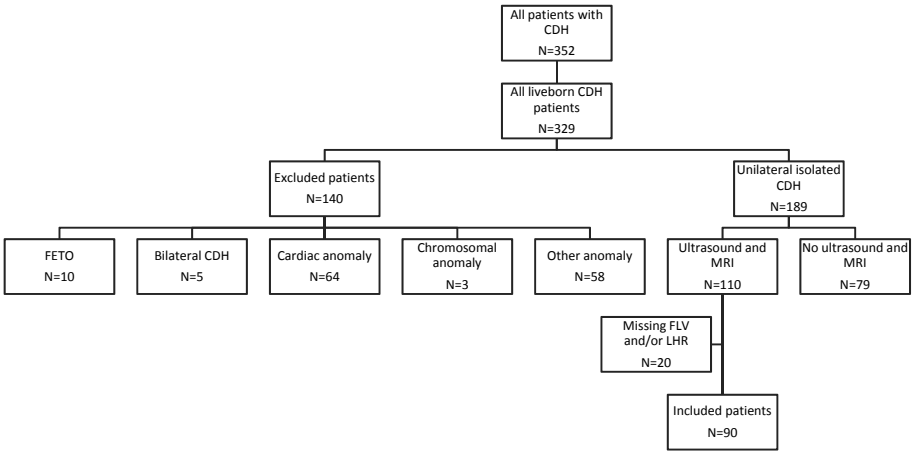

Figure 2. Patient selection

Table 1. Patient characteristics of included (n=90) and non-included patients (n=99) with unilateral isolated CDH

	Included patients (n=90)	Non-included patients (n=99)	p-value
Male gender	64% (58/90)	59% (58/99)	0.961
Left-sided CDH	92% (83/90)	73% (72/99)	0.001
Birth at our centre	99% (89/90)	44% (44/99)	<0.001
Caesarean section	89% (79/89)	59% (58/99)	<0.001
Patch repair *	69% (55/80)	62% (51/82)	0.477
Need for ECMO	34% (30/89)	51% (50/98)	0.025
Chronic lung disease**	43% (38/89)	44% (43/98)	0.474
Overall Mortality	21% (19/90)	25% (25/99)	0.832
	Median (range)	**Median (range)**	
Gestational age at birth (wks)	37.0 (32.0-41.43)	38.0 (27.0-42.0)	<0.001
Birth weight (kg)	3.0 (1.7-4.1)	3.1 (1-4.9)	0.068
Apgar at 5 minutes	7 (1-10)	8 (3-10)	<0.001
Duration of ventilation (days)	17.8 (0-108.8)	19.7 (0-80.4)	0.90
Length of ICU stay (days)	31.6 (5.9-170.6)	34.6 (7.4-201.0)	0.99

Numbers do not always add up to 189, because of missing data

* as opposed to primary repair, data only available for those patients that survived until surgery

** defined as oxygen dependency at day 28

Outcome measures

Chronic lung disease

Of the patients who survived until day 28, 50% of patients met the criteria for CLD (n=38/76, missing=1). At day 56, 19 of these patients were classified as having mild CLD (51%), 10 as having moderate CLD (27%) and 8 as having severe CLD (22%). One patient with CLD died before day 56 and could therefore not be classified. Median O/E LHR for patients with CLD was 45.8% (range 25.8%-94.4%) versus 53.2% (range 17.7%-121.2%) for patients without CLD (p=0.002). Median

O/E FLV was 26.7% for patients with CLD (range 9.0%-52.8%) versus 39.6% (range 15.4%-76.1%) for patients without CLD (p<0.001).

Mortality
Thirteen patients died by day 28 (14%). The median O/E LHR for these patients was 36.1% (range 10.0%-63.8%) versus 51.7% (range 17.7%-121.2%) for survivors past day 28 (p=0.001). The median O/E FLV was 20.1% (range 10.9%-30.5%) versus 30.4% (range 9.0%-76.1%) for survivors (p=0.001).

ECMO
Thirty percent of the patients (n=30/99, missing=1) needed ECMO. Of these, 50% (n=15/30) survived until discharge. Median O/E LHR for ECMO patients was 40.3% (range 10.0%-70.9%) versus 51.9% (range 17.7%-121.2%) for non-ECMO patients (p=0.002). Median O/E FLV was 22.6% for ECMO patients (range 3.8%-70.4%) versus 30.8% (range 10.9%-76.1%) for non-ECMO patients (p<0.001).

Prediction of outcome
Univariate analyses for all three outcomes was performed for the following variables: gender, side of the defect (left or right), position of the liver, stomach or bowels (intra-thoracic or intra-abdominal), gestational age at the time of birth and birth weight. The results of these univariate analyses are presented in tables 2A, 2B and 2C, respectively.
Variables that were significant in these univariate analyses were entered into the multivariate regression analyses. As birth weight and gestational age are strongly correlated, only gestational age at birth was included in the multivariate analysis, together with the position of the liver, gender and the side of the defect. Although not significant in univariate analyses, the side of the defect and gender were entered into all three logistic regression models because they are well-known prenatal risk factors for bad outcome. Z-scores of the O/E LHR and O/E FLV were added successively to the regression models. No model was constructed for the O/E FLV alone, because measurement of the O/E FLV by MRI is normally only done in addition to previous ultrasound measurements in the clinical setting. Receiver Operating Characteristic curves (ROC-curves) for all three outcome measures were constructed and Areas Under the Curve (AUCs) were calculated.

Chronic lung disease
Among the infants who survived until day 28, an intrathoracal position of the liver (p=0.007) and a lower gestational age (p=0.006) were significant in multivariate analysis for CLD. A baseline predictive model with these two variables resulted in an AUC of 0.79.
The O/E LHR was added to the model successively. This resulted in an AUC of 0.83, taking into account the position of the liver and the gestational age at birth. Further addition of the O/E FLV to the model resulted in an AUC of 0.87. The ROC-curve for CLD is presented in figure 3.

Table 2A. Univariate analysis for patients with chronic lung disease (n=38) and patients without chronic lung disease (n=38, missing=1).

Variable	CLD	%	No CLD	%	p
Gender					0.818
Male	22/42	53	20/42	47	
Female	16/34	47	18/34	53	
Side defect					1.000
Left	35/70	50	35/70	50	
Right	3/6	50	3/6	50	
Liver position					0.011
intra-thoracal	27/42	64	15/42	36	
intra-abdominal	11/34	32	23/34	68	
Stomach position					0.375
intra-thoracal	33/62	53	29/62	47	
intra-abdominal	5/14	36	9/14	64	
Bowel position					0.500
intra-thoracal	37/73	51	36/73	49	
intra-abdominal	1/3	33	2/3	67	
Continuous variables	**Median (range)**		**Median (range)**		
Gestational age (wks)	36.9 (32.0-40.0)		37.7 (35.1-39.7)		0.001
Birth weight (kg)	2.8 (1.7-3.8)		3.1 (1.9-4.1)		0.001

Table 2B. Univariate analysis for patients who died by day 28 (n=13) and patients who were alive by day 28 (n=77).

Variable	Died by day 28	%	Alive at day 28	%	p
Gender					0.098
Male	11/54	20	43/54	80	
Female	2/36	10	34/36	90	
Side defect					1.000
Left	12/83	14	71/83	86	
Right	1/7	14	6/7	86	
Liver position					0.003
intra-thoracal	13/53	25	40/53	75	
intra-abdominal	0/37	0	37/37	100	
Stomach position					0.208
intra-thoracal	13/76	17	63/76	83	
intra-abdominal	0/14	0	14/14	100	
Bowel position					1.000
intra-thoracal	13/87	15	74/87	85	
intra-abdominal	0/3	0	3/3	100	
Continuous variables	**Median (range)**		**Median (range)**		
Gestational age (wks)	37.1 (34.7-39.1)		37.4(32.0-41.4)		0.441
Birth weight (kg)	2.8 (2.3-3.7)		3.0 (1.7-4.1)		0.726

Table 2C. Univariate analysis for patients who underwent an ECMO procedure (n=30) and patients who did not underwent an ECMO procedure (n=59, missing=1).

Variable	ECMO	%	Non-ECMO	%	p
Gender					0.455
Male	20/53	38	33/53	52	
Female	10/36	28	26/36	72	
Side defect					0.907
Left	27/82	33	55/82	67	
Right	3/7	43	4/7	57	
Liver position					0.001
intra-thoracal	26/55	47	29/55	53	
intra-abdominal	4/34	12	30/34	88	
Stomach position					0.127
intra-thoracal	28/75	37	47/75	67	
intra-abdominal	2/14	14	12/14	86	
Bowel position					0.286
intra-thoracal	30/86	35	56/86	65	
intra-abdominal	0/3	0	3/3	100	
Continuous variables	**Median (range)**		**Median (range)**		
Gestational age (wks)	37.0 (34.6-40.0)		37.6(32.0-39.7)		0.029
Birth weight (kg)	2.9 (2.2-3.7)		3.0 (1.7-4.1)		0.224

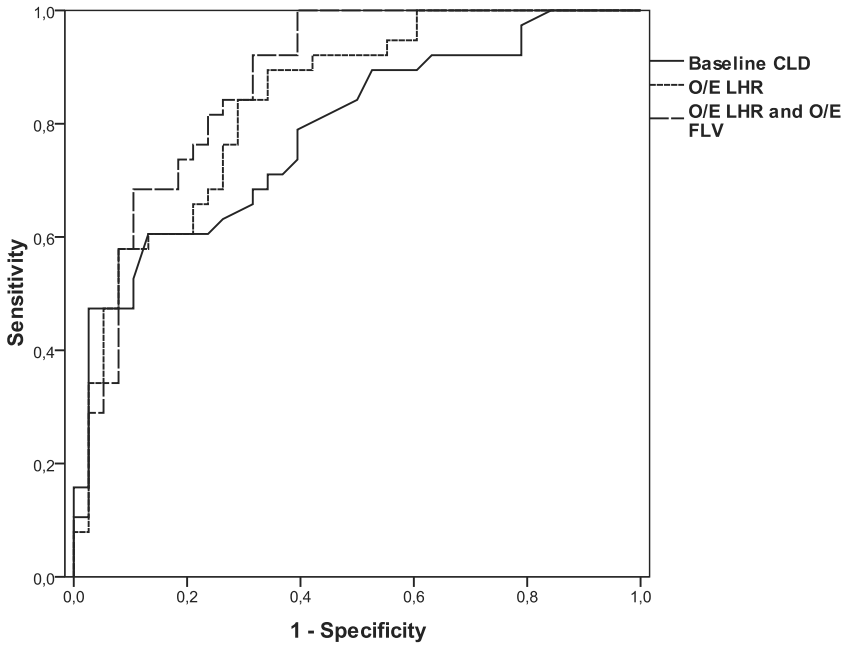

Figure 3. ROC-curve for the prediction of chronic lung disease in 76 infants with CDH

Mortality by day 28

Multivariate analysis showed that an intrathoracal position of the liver ($p<0.001$) was the major factor associated with mortality by day 28. The sensitivity of an intrathoracal liver position to predict mortality by day 28 was 100% (n=13/13) and the specificity was 48% (n=37/77).
Thereafter, the O/E LHR was added to the logistic model. Taking into account the position of the liver, the AUC of the O/E LHR was 0.89. Further adding of the O/E FLV to the model resulted in an AUC of 0.90 for the combined measurement of the O/E LHR and O/E FLV.

Need for ECMO

An intrathoracal position of the liver was the only variable that was significant in the multivariate analysis for the need for ECMO therapy ($p=0.001$). The sensitivity of an intrathoracal liver position to predict need for ECMO therapy was 87% (n=26/30) and the specificity was 51% (n=30/59).
The O/E LHR was added to this model, which resulted in an AUC of 0.77. Further addition of the O/E FLV to the model resulted in an AUC of 0.81 for the combined measurement of the O/E LHR and O/E FLV.

Discussion

Combined measurement of the O/E LHR and O/E FLV provides a slightly better prediction of chronic lung disease and need for ECMO in fetuses with isolated unilateral CDH than measurement of the O/E LHR alone. However, early mortality is very well predicted by ultrasound measurement alone.
So far, only a few studies described the role of prenatal factors in the prediction of chronic lung disease in fetuses with CDH. A study by Heling et al. did not demonstrate any correlation between LHR and postnatal ventilation parameters[14]. A recent study by Jani et al. reported the O/E LHR to be a good predictor for both chronic lung disease and duration of ventilation[15]. There are no reports on prediction of chronic lung disease by prenatal MRI measurement of the O/E FLV. Previous studies reported O/E LHR to be a good and the O/E FLV to be a slightly better predictor for survival and ECMO treatment[16-17]. With regard to the need for ECMO therapy, we also found that the O/E FLV was a slightly better predictor. However, mortality was predicted very well by ultrasound measurements alone in our study. It must be taken into account that previous studies did not evaluate the predictive value of combined ultrasound and MRI measurements.
Although O/E FLV measurements by MRI had only slight additional value in predicting chronic lung disease and need for ECMO and no additive value in predicting mortality, it is important to investigate if fetal MRI may be of value in specific high-risk cases. We may speculate that in certain fetal conditions, such as a very large defect, shifted intrathoracal bowel and liver position and fluid around the heart, this may be the case. Furthermore, in cases of maternal obesity, MRI measurements may very well be of additional value. In our study, we only included infants with isolated CDH. Therefore, we could not evaluate if MRI measurements might give additional

information on other congenital anomalies, which may be possible. On the other hand, MRI measurements may not be the preferred way to visualize congenital heart anomalies, which occur in 20% of the CDH patients, since dynamic ultrasound measurements may give a better visualization of the fetal heart.

Furthermore, an intrathoracal position of the liver was independently associated with a higher risk of early mortality, chronic lung disease and need for ECMO therapy. Previous studies also reported an intrathoracal position of the liver to be associated with worse outcome[6,18]. An intrathoracal position of the stomach was also reported to be possibly associated with worse outcome by previous studies[18], whereas in our study the position of the stomach was not an independent predictor of postnatal outcome. Also, the side of the defect was not independently associated with outcome in our study. A right-sided defect was also reported to be a possible prenatal predictor of mortality[18] whereas others found no influence at all[16].

We found that both O/E LHR and O/E FLV were influenced by the gestational age at the time of radio-diagnostic imaging. This is a somewhat surprising finding because observed-to-expected ratios are meant to take away the effect of gestational age. In contrast to our findings, no influence of gestational age at the time of O/E LHR measurement was reported by previous studies[19]. It is unlikely that this would have affected our results, because we calculated Z-scores to correct for this.

This study has some limitations. First, this is a retrospective study and selection bias could have occurred because only data of patients who underwent both prenatal MRI and ultrasound were used. Compared to non-included patients, more left-sided defects, which may be associated with a different outcome than right-sided defects, were seen in included patients. Gestational age at birth was significantly lower in our study population compared to non-included patients. This may be explained because patients who underwent both prenatal measurements were known to our clinic and were more often born by a planned caesarean section. Non-included patients had been more often transferred to our clinic after birth, mostly because their condition was worsening and an ECMO procedure was necessary. This may also explain the fact that non-included patients had a significantly higher need for ECMO therapy than included patients. Although these differences make it difficult to extrapolate our results to all infants with unilateral isolated CDH, they should have no impact on the essential results of our study as we compared the prognostic accuracy of two imaging parameters but not outcome measures of different therapeutic regimes. Also, only data on live-born infants were used. Although these data are not shown in the article, prenatal measurements of the O/E LHR and O/E FLV were lower in patients with unilateral isolated CDH who died in utero than in patients who were born alive. As a consequence, this may have influenced our results.

Another limitation is that the prenatal measurements were performed and evaluated by two specialists. However, both were experienced radiologists and O/E FLV is reported to be associated with a low interobserver difference[20].

Conclusions

We reported that prenatal measurements by MRI are of possible additional value for the prediction of chronic lung disease and the need for an ECMO procedure. However, early mortality is also very well predicted by ultrasound measurements of the O/E LHR alone. Given that an MRI is a far more expensive procedure than an ultrasound, the cost-effectiveness of performing an MRI in addition to ultrasound may also be debated. Moreover, many other prenatal and postnatal factors may influence outcome in infants with CDH. Furthermore, we reported that an intrathoracal position of the liver was independently associated with a higher risk of early mortality, chronic lung disease and need for ECMO therapy, which is in line with previous studies. Future research must be directed towards development of predictive scoring models, which may allow for prenatal determination of prognosis in fetuses with CDH, and determination of specific cases in which a fetal MRI may be of additional value. Cooperation between centers and centralization of care are important prior conditions for further clinical research into prenatal radio-diagnostic imaging. In this regard, it is very important to refer pregnant women to a prenatal clinic where there is experience in prenatal measurement of CDH fetuses. Meanwhile, measurement of the O/E LHR by ultrasound is a good method for prenatal prediction of outcome in fetuses with CDH.

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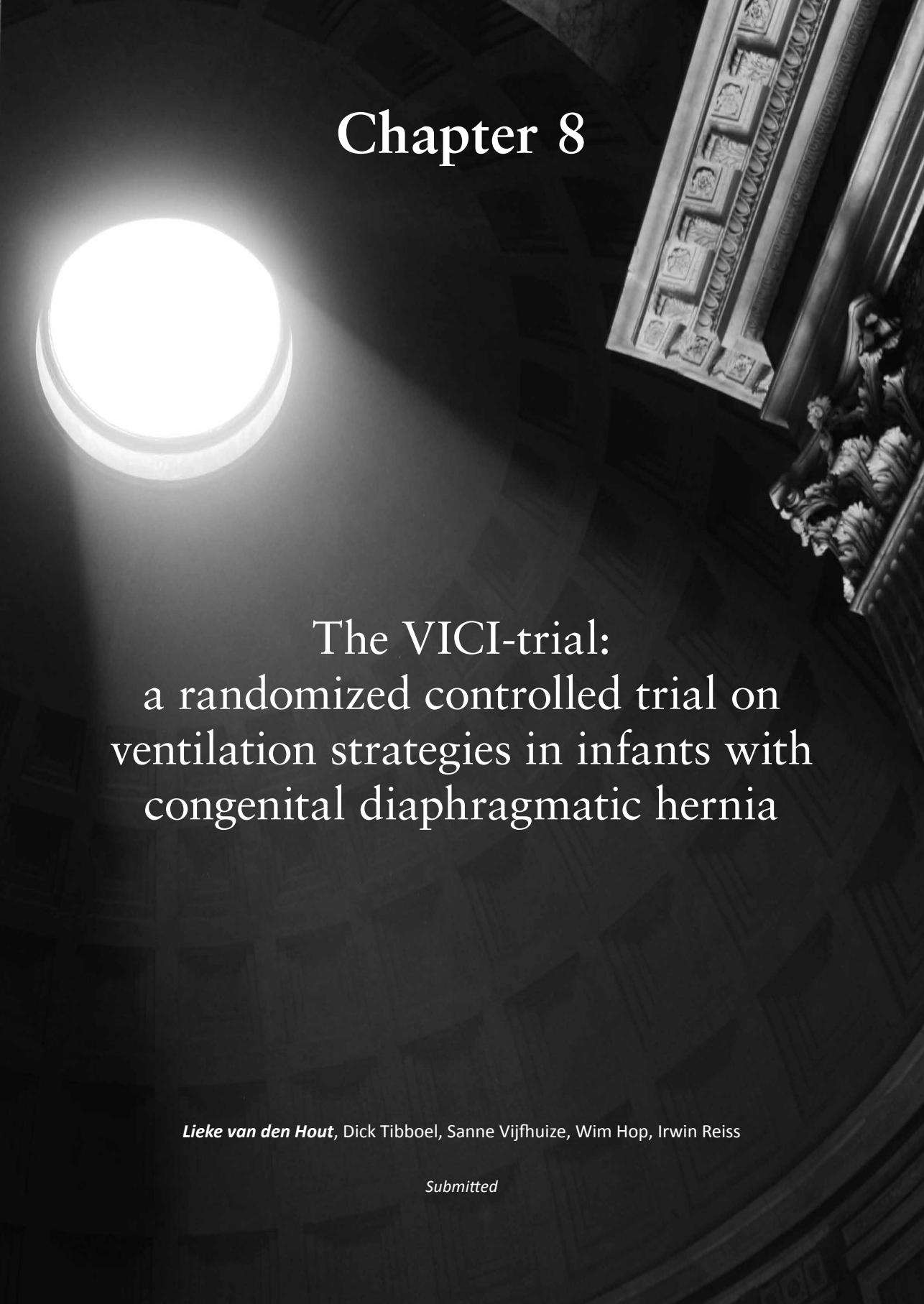


Chapter 8

The VICI-trial: a randomized controlled trial on ventilation strategies in infants with congenital diaphragmatic hernia

Lieke van den Hout, Dick Tibboel, Sanne Vijfhuize, Wim Hop, Irwin Reiss

Submitted

Abstract

Background: Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm resulting in pulmonary hypoplasia and pulmonary hypertension. It is associated with a high risk of mortality and pulmonary morbidity. Previous retrospective studies have reported high frequency oscillatory ventilation (HFO) to reduce pulmonary morbidity in infants with CDH, while others indicated HFO to be associated with worse outcome. We therefore aimed to develop a randomized controlled trial to compare initial ventilatory treatment with high-frequency oscillation and conventional ventilation in infants with CDH.

Methods/design: This trial is designed as a multicentre trial in which 400 infants (200 in each arm) will be included. Primary outcome measures are BPD, described as oxygen dependency by day 28 according to the definition of Jobe and Bancalari, and/or mortality by day 28. All liveborn infants with CDH born at a gestational age of over 34 weeks and no other severe congenital anomalies are eligible for inclusion. Parental informed consent is asked antenatally and the allocated ventilation mode starts within two hours after birth. Laboratory samples of blood, urine and tracheal aspirate are taken at the first day of life, day 3, day 7, day 14 and day 28 to evaluate laboratory markers for ventilator-induced lung injury and pulmonary hypertension.

Discussion: To date, randomized clinical trials are lacking in the field of CDH. The VICI-trial, as the first randomized clinical trial in the field of CDH, may provide further insight in ventilation strategies in CDH patient. This may hopefully prevent mortality and morbidity.

Trial registration: this trial is registered in the Dutch trial register (number NTR 1310)

Background

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm, which occurs in approximately one in 3000 live births[1]. In CDH, the diaphragmatic defect allows abdominal organs to herniate into the chest cavity. As a consequence, underdevelopment of the lungs and abnormal pulmonary vasculature growth may occur, resulting in pulmonary hypoplasia and pulmonary hypertension[2-3].

Children with CDH mostly present with immediate cardiorespiratory distress during the first hours of life. The initial therapy for these children is mechanical ventilation and cardiorespiratory stabilization in support of optimal management of the pulmonary hypoplasia and pulmonary hypertension[4]. Thereafter, surgical repair of the diaphragmatic defect is indicated[4]. Although many advances in treatment for CDH patients have been made throughout the years, CDH remains a life-threatening condition with a reported mortality of 20-70%, depending on case selection[5].

Survivors of CDH are at risk of developing secondary morbidity, such as gastro-intestinal, neurodevelopmental and pulmonary sequelae. Throughout infancy and childhood, a broad spectrum of pulmonary morbidity may occur, such as bronchopulmonary dysplasia (BPD), persistent pulmonary hypertension, recurrent respiratory tract infections and asthmatic symptoms[6]. BPD is characterized by disturbances of the normal alveolarization. Ventilator-induced lung injury, oxygen toxicity, pulmonary inflammatory responses, and severe pulmonary hypertension predispose infants with CDH to develop BPD[7-8]. A recent report of the CDH Registry reported the prevalence of BPD to be 41% in infants with CDH[9]. About half of the CDH survivors with BPD are reported to have moderate or severe BPD[10]. Moreover, lung function anomalies are often present in these patients[11-14].

Optimizing ventilation strategies in patients with CDH may help to prevent chronic respiratory disease. However, evidence-based standardized treatment protocols based are lacking in the field of CDH. Consequently, ventilation strategies may differ between centres and ventilatory support is often based upon expert opinion[7]. To date, conventional ventilation is the most widely used initial ventilation mode in newborns with CDH, while in many institutions high frequency oscillatory ventilation (HFO) is used as rescue therapy. In some centres, however, HFO is used as the initial ventilation mode.

HFO achieves adequate gas exchange by an oscillatory pump, which combines very high respiratory rates and low tidal volumes. HFO may improve gas exchange, promote uniform lung inflation, reduce barotrauma, and decrease the presence of inflammatory mediators[7, 15-18]. HFO has been used in preterm infants with respiratory distress syndrome, either as an elective ventilation strategy or as a rescue therapy[16]. A Cochrane review, on the use of elective HFO compared to conventional ventilation in preterm infants, found a borderline significant reduction in the rate of chronic lung disease with the use of HFO[16]. A second Cochrane review described the use of HFO as a rescue therapy in term and near term infants with severe pulmonary dysfunction. Only one trial compared these two ventilation strategies prospectively, resulting in no significant

difference in outcome, need for extracorporeal membrane oxygenation (ECMO), or complications[15,19].

In infants with CDH, retrospective and observational studies reported improved survival and a lower incidence of chronic lung disease with elective use of HFO[20-25]. HFO was reported to provide better oxygenation and higher MAP without increasing the incidence of barotraumas[20-21]. In one study, the use of HFO avoided hyperventilation as well as the need for ECMO[17]. Moreover, inhaled nitric oxide was documented to result in better gas exchange following recruitment of the lungs by HFO[26]. On the contrary, HFO may cause lung hyperinflation in some patients, which may induce higher alveolar and mean airway pressures[21]. This may result in an increased risk of pulmonary barotrauma and hemodynamic instability[21]. A recent study by the CDH Registry reported HFO as initial ventilation mode to be associated with an increased rate of mortality and BPD[9]. In this study, it is speculated that infants who received initially HFO were more severely ill from the start[9].

Conclusively, chronic pulmonary morbidity and high mortality rates are major problems in infants with CDH. Several retrospective and observational studies have reported that mechanical ventilation strategies may have an impact on outcome and pulmonary morbidity in CDH patients. Therefore, we aimed to develop a randomized controlled trial to compare initial ventilatory treatment with HFO and conventional ventilation in infants with CDH.

The primary objective of this trial is to determine if there is a difference in the incidence of BPD and/or death within the first 28 days of life between newborns with congenital diaphragmatic hernia treated with high frequency oscillatory ventilation (HFO) and those treated with conventional mechanical ventilation (CMV) as initial ventilation mode. Secondarily, we also aim to compare the severity of BPD, ventilator-induced lung injury and pulmonary hypertension by using clinical and laboratory parameters.

Methods and Design

This study is designed as a prospective, randomized controlled multicentre trial. All participating centres are member of the CDH-EURO Consortium. This is a collaboration between European tertiary centres, who have an expertise in the field of CDH. The CDH-EURO Consortium was started in 2006 and aims at cooperation between centres, enhancement of research in the field of CDH and development of standardized evidence-based treatment protocols.

Outcome measures

The primary outcome measure is BPD and/or death within the first 28 days of life. Secondary outcome parameters are overall mortality, severity of BPD, number of days on the ventilator, number of treatment failures, ventilation-induced lung injury and pulmonary hypertension according to clinical and laboratory parameters and need for ECMO (only for ECMO centres). BPD

is defined as oxygen dependency at day 28, according to the definition of Jobe and Bancalari[27] (see table 1).

Table 1. definition of BPD according to Jobe and Bancalari

Gestational age	< 32 weeks	> 32 weeks
Time point assessment	36 wks PMA or discharge to home, whichever comes first	> 28 days but < 56 days of life or discharge to home, whichever comes first
Treatment with oxygen > 21% for at least 28 days PLUS		
Mild BPD	On room air at 36 wks PMA or at DC, whichever comes first	On room air at day 56 postnatal age or DC, whichever comes first
Moderate BPD	< 30% O2 at 36 wks PMA or DC, whichever comes first	< 30% O2 at 56 d of life or DC whichever comes first
Severe BPD	≥ 30% O2 and/or pos. pressure at 36 wks PMA or DC whichever comes first	≥ 30% O2 and/or pos. pressure at 56 d of life or DC whichever comes first

Inclusion and exclusion criteria

The study population consists of all infants antenatally diagnosed with CDH born at one of the participating centres. Exclusion criteria are:

* Birth before a gestational age of 34 weeks
* Severe chromosomal anomalies, like trisomy 18 or trisomy 13, which may imply a decision to stop or not to start life-saving medical treatment
* Severe cardiac anomalies, expected to need corrective surgery in the first 60 days of life (such as transposition of the great arteries, truncus arteriosus or double outlet right ventricle)
* Renal anomalies associated with oligohydramnios
* Severe orthopaedic and skeletal deformities, which are likely to influence thoracic, and/or lung development (such as chest wall deformities and spine anomalies)
* Severe anomalies of the central nervous system

Statistical analysis

We estimated that a total of 400 newborns can be included within a period of three years. In a previous study of the CDH study group, the incidence of BPD and/or death within the first 28 days of life is reported to be about 50%[9]. Assuming a difference of 15% in BPD and/or death within the first 28 days between both treatment groups, 186 patients are required per arm for a power of 80% at two-sided alpha is 0.05. To allow for some non-evaluable patients and dropouts, 200 patients per group will be included. To achieve equal distribution of the two ventilation modes among the participants, block randomization stratified per centre will be carried out. The data-analysis will be carried out at the Erasmus MC, Rotterdam. An intention-to-treat analysis will be performed. A p-value (two-sided) < 0.05 will be considered significant in all analyses.

The primary endpoint will be evaluated using multiple logistic regression analysis taking account of: centre, lung-to-head ratio, position of the liver (intra-abdominal or intra-thoracic) and the side of the defect (left, right or central). A subgroup analysis will be carried out in operated

infants to evaluate the defect size, according to the CDH study group defect size scale (www.cdhsg.net).

The secondary endpoints will be evaluated by using the following statistical tests. Overall mortality in the first year of life will be analysed by Kaplan-Meier curves and Log rank tests. The chi-square test will be used to analyse number of treatment failures, presence of pulmonary hypertension according to echocardiographic parameters, requirement of medication at discharge and during the first year of life, and need for ECMO therapy (in ECMO centres). The Mann-Whitney test is used to evaluate the severity of chronic lung disease, number of days on the ventilator and the fraction of days with required medical treatment for pulmonary hypertension during the hospital admission. In the evaluation of the severity of chronic lung disease and the number of days on the ventilator, deaths are counted as worst outcome according to the intention-to-treat principle. Repeated measures ANOVA is used to evaluate levels of laboratory markers for ventilator-induced lung injury or pulmonary hypertension and pulmonary function at the age of six and twelve months.

All the above-mentioned analyses will allow for centre by stratification.

Study procedures

Parental informed consent will be obtained antenatally to enhance quick randomization. Following antenatal diagnosis, the parents are to be counseled and will receive information about the study, including a patient information letter and an informed consent form. If both parents decide to participate in the study, as soon as possible after birth central randomization will take place by the treating physician using a website. This way concealed allocation is guaranteed. Within two hours after delivery, the allocated ventilatory treatment has to be started.

All infants participating in the VICI-trial are treated according to the same standardized treatment protocol which has been published recently[4]. This protocol of standard practice was decided upon available evidence and consensus between the participating centres. According to this protocol, a chest radiograph is made as soon as possible after birth to assess the initial condition and is repeated guided on the patient's condition. Also, echocardiography is performed within the first 24 hours after birth to assess pulmonary arterial diameter and right heart function. In all patients, a chest radiograph and echocardiography are repeated at day 28.

The patient receives the allocated ventilation treatment during the entire admission period on the intensive care unit. During surgery, the child preferably remains on the allocated ventilation type, provided the treating surgeon agrees. Should the surgeon opt for the other ventilation mode, the patient is switched to the allocated ventilation treatment again after surgery. If the patient has to be re-intubated within the first 60 days after the start of the allocated treatment, the patient receives the allocated treatment again. Patients are observed up to day 60 after birth or until discharge whichever comes first.

Treatment failure

In case of one or more failure criteria, the allocated ventilatory treatment may be switched. Also, an ECMO procedure may be started in centres where ECMO is available. After the ECMO-procedure has ended, the patient preferably receives the initial allocated ventilation mode. Because an intention-to-treat analysis will be performed, data from these patients are stored and analysed the same way as data from patients in whom no switching of ventilation mode or ECMO procedure took place.

The following failure criteria are applicable to the study patients:

* Inability to maintain preductal saturations above 85% (± 7 kPa or 52 mmHg) or postductal saturations above 70 % (±5.3 kPa or 40 mmHg)
* Increase in CO_2 > 65 torr or mmHg (8.5 kPa) despite optimalization of ventilatory management
* PIP > 28 cm H_2O or MAP > 17 cm H_2O
* Inadequate oxygen delivery with metabolic acidosis defined as lactate ≥ 5 mmol/l and pH < 7.20
* Hypotension resistant to fluid therapy and adequate inotropic support, resulting in a urine output < 0.5 ml/kg/hour
* Oxygenation index consistently ≥ 40

Laboratory analyses

During the study, blood, urine and tracheal samples are collected. Separate parental informed consent is asked for taking, analysing and storing these samples.

Blood, urine and tracheal samples are taken within the first 2 hours of life and on days 3, 7, 14 and 28. Blood sampling is only done if a central or peripheral line is present and in combination with routine laboratory measurements. Urine sampling is only done if the patient has a urine catheter. Sampling of tracheal aspirates is only done during routine suctioning. In that way, sampling of laboratory markers are of minimal burden for the patient.

Blood samples

Blood markers are determined by immuno-assay analysis and are necessary support evidence of chronic lung disease and to further evaluate its severity[28-32].

The following laboratory markers are measured:

* Markers for inflammation and pulmonary vascular endothelial dysfunction and pulmonary hypertension (intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), sP- and sE-selectine, pro-brain natriuretic peptide (Pro-BNP), vascular endothelial growth factor (VEGF), von Willebrand factor, thrombomodulin, factor VIII and Asymmetric Dimethylarginine (ADMA)
* Markers for the nitroxide pathway (nitrate and nitrite)

Urine samples

Two urine samples from an 8-hour urine collection are taken to measure desmosine, an elastolytic degradation product of elastin. It gives an indication of the degradation of lung elastic fibres in ventilated neonates. One sample of 20 ml containing 0.2 % boric acid and one sample of 10 ml will be stored at –20 degrees Celsius. Desmosine will be measured by mass-spectrometry, a highly sensitive way of measuring this laboratory marker[33-34].

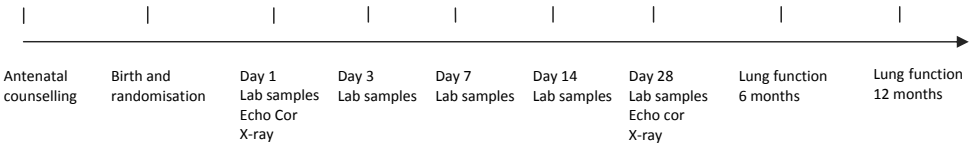
Tracheal aspirate

Protein profiling by proteomics are used for identifying specific groups of proteins, which are involved in the pathogenesis of chronic lung disease. During routine tracheal suctioning, flushing with 0.5-1.0 ml saline is performed according to standard practice. The tracheal aspirates are centrifuged for 10 minutes at 3000 rpm and are stored at –80 degrees Celsius[35-36].

Follow-up

At all participating centres, routine follow-up takes place at the age of 6 months, 12 months, 24 months, 5 years, 8 years, 12 years and 18 years in all patients with CDH, including participants of the VICI-trial. During follow-up visits, routine physical examination and additional testing (e.g. lung function tests or developmental tests) take place. Lung function tests are done at the age of six and twelve months, if this is part of the centre's routine follow-up. FRC (functional residual capacity) and LCI (lung clearance index) are measured by using helium gas dilution. The LCI is the cumulative expired volume required to clear an inert gas from the lungs, divided by the FRC. In some centres FRC and LCI are measured by SF6 and plethysmographic measurements. Lung function tests are performed before and after bronchodilation. Therefore, a bronchodilator is administered by a face mask and a spacer.

For the purpose of this study, parents complete a patient diary card on a daily basis for one month at the age of six and twelve months. By using this diary card information about whether their child coughed, wheezed and/or needed medication is collected. This gives a quantitative assessment of morbidity.



Overview study procedures

Safety reporting

An adverse event or complication is defined as any undesirable occurrence in a patient. Mortality is regarded a serious adverse event. Adverse events or complications are reported to the study coordinator within 24 hours. Thereafter, the study coordinator informs the data safety

monitoring board, who monitors the incidence of mortality on a continuous base. If at some point a large difference in mortality between the two treatment groups is noticed, the data safety monitoring board may recommend ending the study.

Data collection

Demographic and neonatal characteristics as well as data on the clinical course and treatment of all patients will be collected in a central database in Rotterdam. Corporeal material collected during the study is stored at the local centres.

Since it should be impossible to identify a specific patient, data are sealed by a code and a patient number replaces personal data. All centres keep a logbook of the number of eligible non-participants, including the reasons for not participating.

Patient data are stored during the study and for fifteen years after the study has ended. If the parents consent, corporeal material is also stored for fifteen years after the study has ended. This material may be used in future for a study with the same research aims.

Ethical approval

In October 2008, this study has been given approval by the medical ethics committee of the ErasmusMC Rotterdam. Thereafter, the local medical ethics committees of the other participating centres gave their approval. Once a year, a summary of the trial's progress is send to the medical ethics committee of the ErasmusMC, Rotterdam, the Netherlands. Information is provided on the numbers of subjects included, (serious) adverse events, other problems and amendments.

Discussion

Congenital diaphragmatic hernia (CDH) is associated with a high risk pulmonary morbidity[6]. Several previous studies have reported a wide range of pulmonary problems throughout childhood in these patients[6]. A recent study of our group in collaboration with the CDH Registry reported a 41% prevalence of bronchopulmonary dysplasia (BPD) in survivors of CDH[9]. This study reported the initial ventilation mode to be possibly associated with BPD in these patients. This formed the rationale for our study, which aims at comparing HFO and conventional ventilation as initial ventilation modes in infants with CDH.

Our study is the first randomized clinical trial in the field of CDH. Previous studies were retrospective or observational reports, mostly from single centres. Moreover, progress in CDH research is hampered due to small numbers of patients and lack of evidence-based treatment strategies. Cooperation between centres is therefore highly important to enhance research, exchange knowledge and compare data in larger groups of patients. The CDH Study Group is an example of a worldwide network which has established a large database on CDH patients. To date, the CDH Study Group has published numerous reports in the field of CDH, which contain valuable information on survival, treatment strategies and morbidity in infants with CDH. Another example is

the CDH-EURO consortium, a European collaboration between tertiary centres with an expertise in treatment of CDH, which also initiated the VICI-trial. The consortium also developed a recently published standardized treatment protocol[4]. This treatment protocol makes valuable comparison of patient data possible, since all CDH patients, including the VICI-trial patients, born in these centres are treated according to this protocol.

HFO and conventional ventilation are both safe, effective and widely used strategies to ventilate infants with respiratory distress. Although observational and retrospective studies have suggested that HFO may improve survival and pulmonary outcome in infants with CDH, no prospective randomized controlled trials have been carried out to compare initial ventilation strategies in these patients. Therefore, no specific conclusions about certain benefits or disadvantages of either HFO or CMV can be made.

As the first randomized clinical trial in CDH infants, the VICI-trial will provide a clearer view on ventilatory treatment strategies and possible prevention of mortality and morbidity. Still, there are many questions left in the field of CDH and clinical trials are highly needed to improve care and establish standardized treatment. Cooperative networks between centres, such as the CDH-EURO Consortium, play a major role in this.

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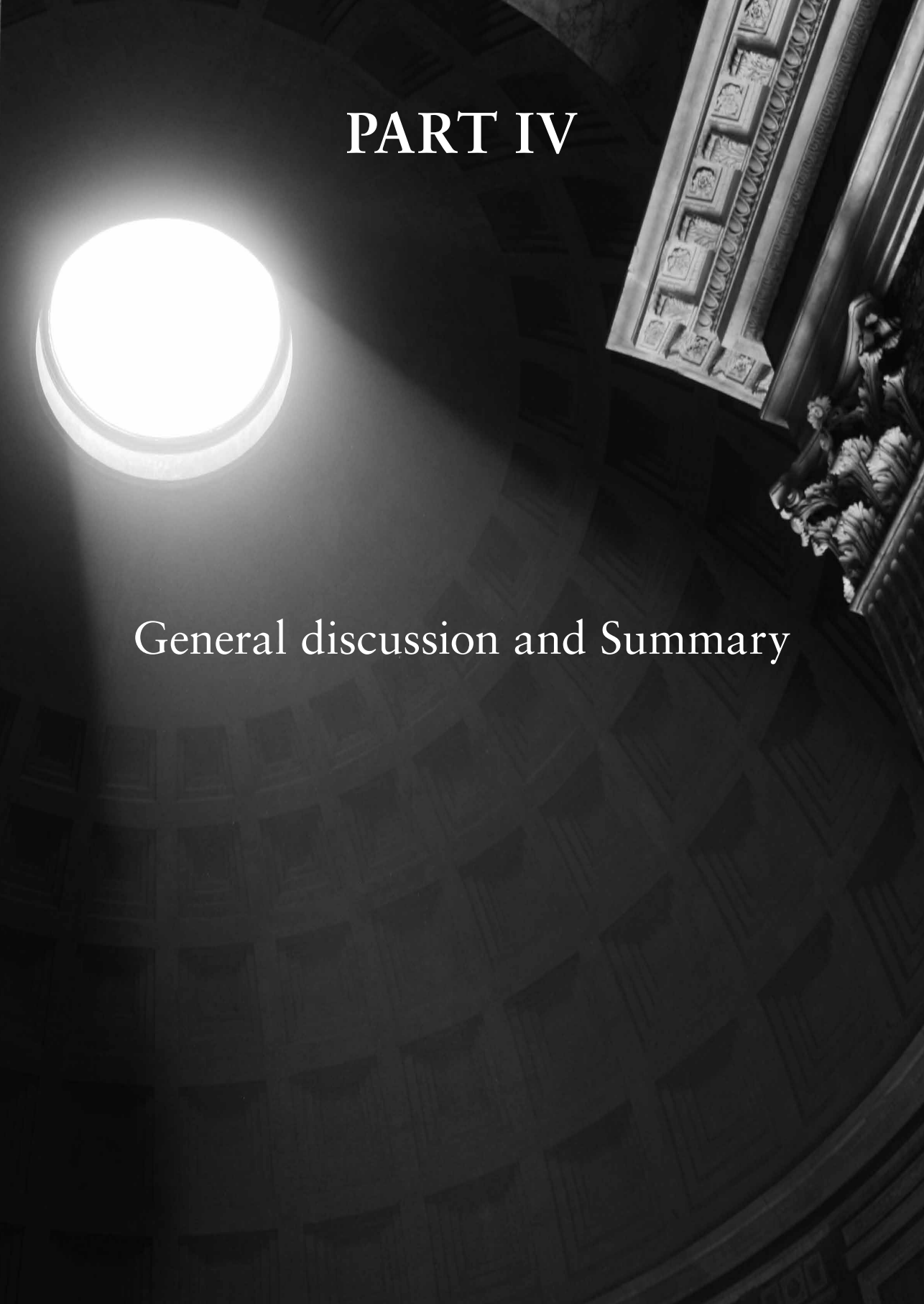
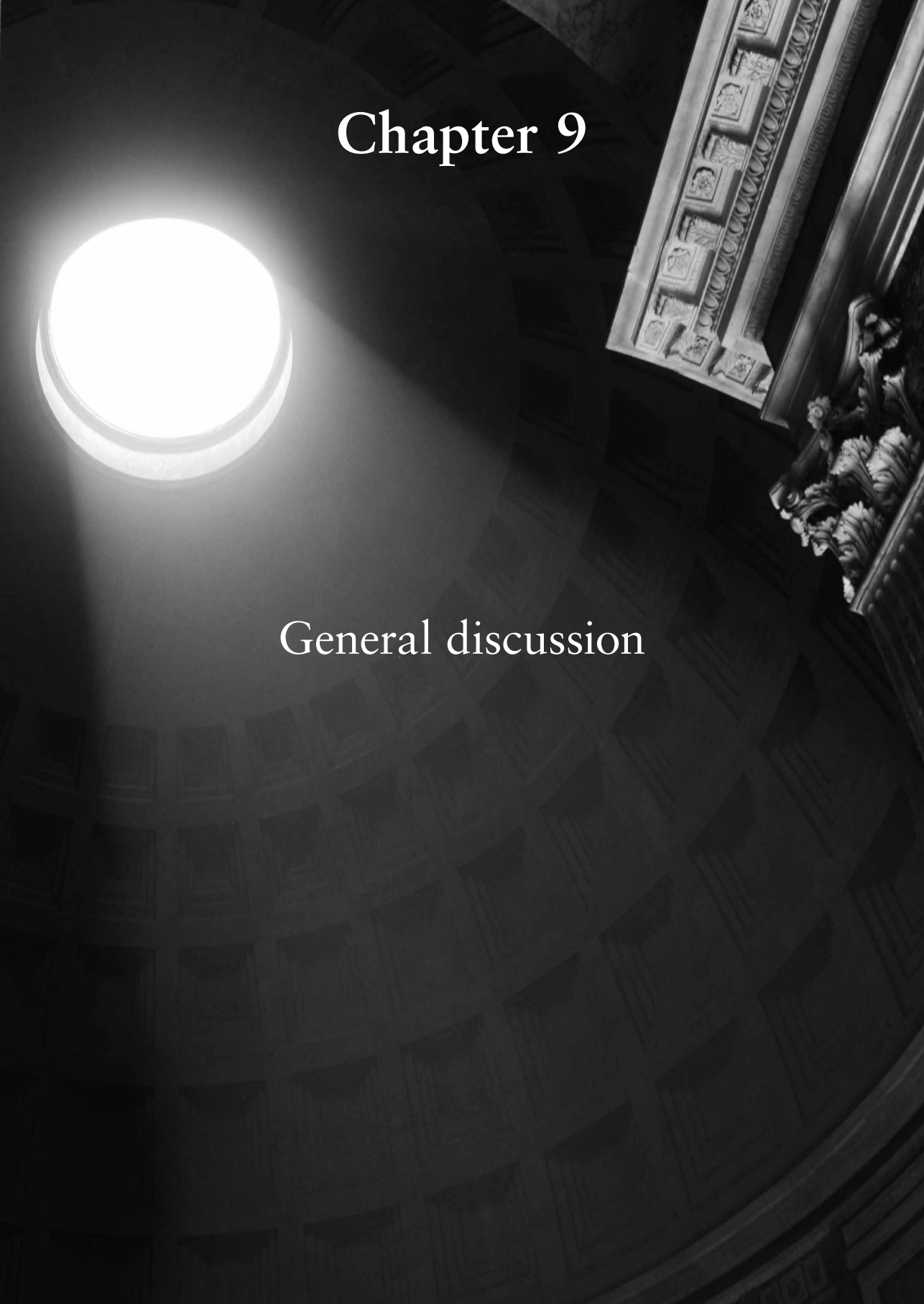


PART IV

General discussion and Summary

Chapter 9



General discussion

Background

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm which may cause pulmonary hypoplasia and pulmonary hypertension. The mortality rate ranges from 10-70%, depending on case selection. Many of the survivors, however, are at significant risk of pulmonary morbidity.

The pre- and postnatal care of patients with CDH presents many challenges (chapter 1). In chapter 2, we evaluated pulmonary function in the first year of life in a cohort of 43 infants born at the Erasmus MC-Sophia Children's Hospital. It appeared that 41% had bronchopulmonary dysplasia (BPD). Moreover, lung function anomalies reflecting air trapping were seen, especially in those who underwent ECMO therapy or were ventilated for a long time. Possible risk factors for BPD were identified in chapter 3. Among other things, HFO as initial mode of ventilation proved to be an important risk factor for pulmonary morbidity. In chapter 4, an evaluation of CDH-EURO Consortium data revealed that about half of the CDH survivors have moderate or severe BPD, especially those with pulmonary hypertension.

Having established high prevalences of pulmonary morbidity and identified important risk factors, we described several strategies to improve outcome. One, implementation of a standardized treatment protocol, significantly improved survival rates (chapters 5 and 6). Furthermore, of the antenatal measurements, MRI measurements of the fetal lung volume slightly better predicted chronic lung disease in CDH than ultrasound measures (chapter 7). However, survival was very well predicted by ultrasound measurements alone. Finally, we described a protocol for a randomized clinical trial regarding initial ventilation mode, the results of which will hopefully help to prevent pulmonary morbidity in future CDH patients (chapter 8).

Long-term pulmonary morbidity has been widely studied in preterm ventilated infants, but less so in survivors of CDH. This may be due to the rarity of the anomaly and the lack of evidence-based therapeutic approaches so far. Therefore, little is known on the causes of pulmonary morbidity in CDH. Based on the findings of our studies and the literature so far, we will elaborate on the possible pathophysiology of pulmonary morbidity in CDH, the role of risk factors such as postnatal ventilation and pulmonary hypertension, and on preventive strategies to reduce pulmonary morbidity. Moreover, we give recommendations for future research.

The etiology of congenital diaphragmatic hernia

The diaphragm develops in the fourth to tenth week of gestation – probably from the septum transversum, pleuroperitoneal membrane, oesophageal mesenchyme and paraxial mesoderm of the body wall. Others, however, hypothesized that the diaphragm originates from the pleuroperitoneal fold[1]. Overall, the exact developmental mechanism is largely unknown and research is still ongoing.

In case of interruption of normal diaphragmatic development, a diaphragmatic defect will occur. This may lead to herniation of the abdominal organs into the thoracic cavity. According to the dual hit hypothesis, it has been proposed that two insults, one affecting the lungs before diaphragm

development and one affecting both lungs after the diaphragmatic defect has occurred, may be responsible for CDH[2].

The etiology of CDH is multifactorial and many genes, growth factors and pathways have been reported to be involved in lung and diaphragm development[3]. In the nitrofen-based model, it is shown that the retinoic acid pathway as one example for cellular metabolism may affect lung development but many other developmental processes as well[4-6]. In this regard, the maternal intake of retinol may be associated with CDH[7]. Occasionally, CDH patients showed mutations in the transcription factors COUP-TFII, situated on chromosome 15, GATA4 and FOG2, situated on chromosome 8 – factors which are involved in retinoic acid metabolism and regulation[5,8-9]. We speculate that interplay of environmental and genetic factors, possibly involving the retinoic acid pathway, is responsible for the development of CDH[3], although extensive genetic analysis failed to proof a single gene defect as a causative agent. These factors, however, may all differently affect the development of the diaphragm, the pulmonary parenchyma, and the vasculature. Nowadays, however, no single genetic mutation or environmental factor has been pinpointed as the only cause for the diaphragmatic defect and pulmonary maldevelopment in isolated CDH[5].

Future Perspectives

The roles of (epi) genetic deletions and duplications in the etiology of CDH and in pathways involved in pulmonary and diaphragm development should be detailed.

Mechanisms of pulmonary injury in congenital diaphragmatic hernia

Injury to the pulmonary parenchyma and to the pulmonary vasculature may be responsible for the development of chronic lung disease in patients with CDH. These types of injury may interact in a complex way and lead to impaired alveolarisation and pulmonary hypertension. In the following part, we discuss both mechanisms of pulmonary injury paying attention to postnatal ventilation, treatment strategies for pulmonary hypertension, and ECMO treatment in patients.

Injury to the pulmonary parenchyma

Neonates who present with cardiorespiratory distress which requires intubation and ventilation are at risk for developing injury to the pulmonary parenchyma. The majority of these infants are prematurely born, having immature lungs and a surfactant deficiency, and therefore most of the studies describing possible mechanisms of pulmonary injury are performed in preterm infants. From these studies, several causes for pulmonary injury have been identified.

First, pulmonary injury may be due to alterations and imbalances in the levels of pro-inflammatory and anti-inflammatory cytokines[10-13]. Beside this, oxidative stress due to high oxygen concentrations may induce apoptosis and necrosis in the lungs. The subsequent release of cytokines may then result in abnormal alveolarisation[11,13-14]. Studies in preterm mechanically ventilated infants, have reported extravasation of neutrophils and macrophages to specific areas of lung injury

soon after birth[12]. These cells produce cytokines that induce an inflammatory response, resulting in alveolar damage[11-12,15]. Mechanical ventilation in itself is associated with increased levels of cytokines. Baro- and volutrauma due to mechanical ventilation may cause ventilator-induced lung injury (VILI), which comprises alveolar septal damage, inflammation, fibrosis and pulmonary edema[11,15]. Moreover, postnatal infections, such as sepsis and airway colonization, may also predispose for pulmonary injury, because they are associated with release of inflammatory and vasoactive cytokines in the lungs[12]. Last, environmental factors such as maternal smoking and alcohol intake, as well as mutations in lung development pathways may play a role in pulmonary injury and repair[12-13,16].

Pulmonary injury

Infants with CDH, who are mostly born at term, form a different population than preterms. In infants with CDH, a structural defect in early fetal development causes pulmonary hypoplasia and maldevelopment of the lungs. Typically, one side of the lungs may be more affected than the other side, since the diaphragmatic defect is mostly unilateral. However, bilateral hypoplasia may also occur in very large defects and bilateral CDH. Importantly, the hypoplastic lungs in CDH infants are not reported to be immature and surfactant and maturation factors are not decreased in infants with CDH[17-18]. Disturbances in surfactant metabolism are reported in CDH patients who required ECMO and are mainly based on surfactant inactivation[19]. This might be due to severe pulmonary injury following mechanical ventilation or the severity of the disease itself. Exogeneous surfactant therapy has not been reported to be beneficial in CDH patients[18,20-21].

In the earlier days , infants with CDH were ventilated with high peak pressures, high oxygen concentrations and high tidal volumes to prevent hypoxia as a trigger for persistent pulmonary hypertension. As in preterm infants, ventilation with high peak pressures and high oxygen concentrations may cause an inflammatory and toxic cascade resulting in pulmonary damage. A paper by Wung et al. revealed that 'gentle' ventilation and tolerance of higher CO_2 values (permissive hypercapnea) resulted in better outcome and less pulmonary morbidity in infants with severe respiratory failure, including infants with CDH[22-24]. Moreover, peak pressures below 25 cm were reported to minimize lung injury[24-25]. This demonstrates that ventilator-induced lung injury plays an important role in the course of the disease.

Although ventilation in CDH is based on low peak pressures and permissive hypercapnea, the optimal initial 'gentle' ventilation mode and target tidal volumes are not clearly defined[26]. To date, either conventional ventilation, with HFO as a rescue strategy in case of CO_2 retention, or high frequency oscillation (HFO) is applied initially. In HFO, the very high respiratory rates and low tidal volumes is reported improve gas exchange, promote uniform lung inflation, reduce barotrauma, and counteract inflammatory mediators in preterm infants and animal studies[26]. HFO as initial ventilation strategy in preterm infants proved to be associated with a slight reduction in chronic lung disease[27]. On the other hand, the only two prospective trials comparing conventional ventilation and HFO in term infants with respiratory distress reported no differences in outcome[28]. Recent observational and retrospective studies in infants with CDH have reported

better survival rates and less pulmonary morbidity after initial treatment with HFO[29-33]. HFO was reported to provide better oxygenation without increasing the incidence of barotraumas[30,32]. HFO was also reported to avoid hyperventilation and need for ECMO treatment[34]. Furthermore, inhaled nitric oxide might result in better gas exchange used in combination with HFO for maximal recruitment[35]. However, to date there are no prospective randomized clinical trials with enough power to demonstrate a possible beneficial effect of either conventional or HFO on pulmonary morbidity in CDH patients.

As a negative effect, HFO may cause lung hyperinflation in some patients, which may induce higher alveolar and mean airway pressures. This may have adverse effects on venous return and pulmonary vascular resistance, thereby inducing hemodynamic instability[32]. Furthermore, low mean airway pressures may not allow the alveoli to open, resulting in atelectasis and an alveolar inflammatory reaction. The effect of HFO might also be influenced by the physiology of the hypoplastic lungs. In case of CDH, the airways of the ipsi-and contralateral lung are different which might theoretically cause an unequal airflow distribution resulting in pulmonary injury.

In a retrospective study, we found that HFO as initial ventilation mode was associated with a higher mortality rate and with as higher incidence of BPD (chapter 3). We speculate that initial ventilatory support with HFO, which is believed to reduce barotraumas, was given to those infants who were more severely ill from the start. Hypothetically, these may also had unfavorable prenatal characteristics, such as an intrathoracic position of the liver or a low lung-to-head ratio. Regrettably, prenatal measurements were not recorded for the patients described in chapter 3. Moreover, we speculate that adverse reactions due to HFO, such as hemodynamic instability and an inflammatory response in the alveoli could have contributed to worse outcome[32].

In eight European high-volume centres, however, we did not find any association between the severity of BPD and the initial mode of ventilation (chapter 4). In these studies, we used retrospective data from centres using different treatment protocols. Also, patient selection might have influenced those results. On the other hand, in a small single-center study, the initial ventilation mode was not associated with reduced pulmonary function in the first year of life (chapter 2). In this study, it was shown that ECMO treatment and longer duration of ventilation were independently associated with signs of air trapping. All studies taken together, there is a discrepancy about the influence of different initial ventilation modes on pulmonary outcome and mortality in patients with CDH. In chapter 8, therefore, we propose a study protocol for a randomized clinical trial comparing initial treatment with HFO and conventional ventilation in newborns with CDH. The primary outcome measure in this study is BPD and/or death within the first 28 days of life.

To date, the underlying pathomechanisms which may predispose CDH patients to develop pulmonary injury are not fully understood. Since most studies on pulmonary injury are performed in preterm infants, it is difficult to extrapolate these results to infants with CDH.

Future perspectives

Biomarkers, such as cytokines, are a potential good research target because they can be used to determine the degree of VILI, lung repair, remodeling and possible compensatory lung growth. Even more, insight in possible disturbances of lung structure which is responsible for the susceptibility of VILI in CDH patients should be the focus of further research in a translational matter. The best initial ventilation mode in newborns with CDH to prevent VILI and thus to decrease mortality and pulmonary morbidity has to be determined, even in long-term follow-up programs[36-37]. Recent studies have reported possible involvement of stem cells in chronic lung disease of the newborn. For example, hyperoxia decreased bone-marrow derived lung endothelial progenitor cells[13]. Also, intratracheal or intravenous bone-marrow derived stem cells (BMSCs) reduced alveolar and pulmonary vascular abnormalities and improved survival in animal models. Stem cell studies may perhaps open the way to new therapeutic strategies to prevent BPD. It is more important to understand a possible role of progenitor cells and stem cells in infants with CDH[38]. Finally, in view of the possible lung function anomalies, it is essential to follow survivors of CDH throughout childhood and adulthood, especially those who have been ventilated for a long time. Different protocols and methods are used to determine lung function in infants and reference data for currently used equipment are lacking. Therefore, more efforts have to be made to standardize lung function measurements in infants.

Pulmonary vascular injury

Chronic lung disease in infanthood is not only associated with damage to the pulmonary parenchyma but also with possibly altered angiogenic homeostasis due to inflammatory responses and ventilator-induced lung injury[14,39-40]. Moreover, high oxygen concentrations due to mechanical ventilation may cause down regulation or imbalance of angiogenic growth factors[14,40-41]. Under normal circumstances intra-uterine lung development takes place under hypoxic conditions. In this scenario, the regulation of hypoxic inducible factors and their downstream genetic factors plays a central role in lung development. In CDH patients, these pathways might be disturbed[42]. In children with CDH, mechanical ventilation with high concentration of oxygen can result in a hyperoxic environment in which oxidative stress might occur. This immediate change in oxygen gradient from hypoxic to hyperoxic may lead to disbalances of hypoxia inducible factors which play a pivotal role in appropriate vascular development[42-43]. This may lead pulmonary vascular abnormalities, which may contribute to progressive pulmonary hypertension. Also, mitochondrial oxygen stress due to high concentration of oxygen might negatively influence pulmonary vascular resistance[44-45]. Chronic lung disease, associated with VILI and high oxygen concentrations, is increasingly viewed as a cause of pulmonary hypertension[39].

Studies in adult patients with emphysema have reported a blockade of the vascular endothelial growth factor (VEGF) receptor[14]. VEGF plays a central role in pulmonary angiogenesis and is regulated by other angiogenic growth factors, such as NO and angiopoietin[14]. In animal models and humans who died of BPD the number of pulmonary vessels was reduced, perhaps due

to a decrease in angiogenic growth factors[46]. Finally, also polymorphisms of genes encoding angiogenic growth factors have been reported to be associated with BPD[11].

Pulmonary hypertension

Pulmonary hypertension in infants with CDH may be caused by either structural or functional abnormalities of pulmonary vasculature[47-48]. The pulmonary artery density is decreased and the media and adventitia of the small pulmonary arteries are thickened[40]. Furthermore, there may be imbalances in the angiogenic homeostasis[14]. Persistent pulmonary hypertension may reduce the pulmonary blood flow on the affected side and thus lead to failure to thrive and respiratory problems[40]. Pulmonary hypertension in preterm infants who suffered from BPD was also associated with a higher risk of mortality[49].

The gold standard to assess pulmonary hypertension is a cardiac ultrasound, which allows evaluating the direction and amount of shunting (right-to-left, bidirectional or left-to-right) and tricuspid regurgitation[48,50]. In this regard, a plea has been made to routinely perform repeated ultrasound measurements in infants with CDH to evaluate the course of pulmonary hypertension over time or to guide the effect of treatment[40,48]. Recently, measurements of biomarkers, such as NT-proBNP, proved to be useful to assess pulmonary hypertension and cardiac function in infants with CDH[51].

Also, deregulation of endothelin receptors, abnormalities in the NO-cGMP-pathway[52-53], down regulation of VEGF and fibroblast growth factor deficiency may be related to pulmonary hypertension in CDH[40,54]. In the early phase, inhaled nitric oxide (iNO) is an option in severe cases[48], as it was found to improve pulmonary hypertension and reduce the need for ECMO[55-56]. However, others reported no improvement of survival or need for ECMO after administration of iNO in a relatively small sample of infants with CDH[57-58]. Short-term effects of iNO may nevertheless be beneficial for transport or until ECMO treatment can be started[40,48]. Milrinone may be of use in CDH patients with decreased left ventricular function, because it reduces the left ventricular afterload. Prostaglandin can be used to maintain ductal patency and enhances the right ventricular contribution to systemic blood flow[40,47-48,59].

Infants with CDH often develop refractory pulmonary hypertension resistant to iNO, or even develop persistent pulmonary hypertension[48]. Sildenafil, a lung-selective phosphodiesterase-5 inhibitor, proved to be effective in infants with persistent pulmonary hypertension[48,60]. Also prostacyclin, epoprostenol, and bosentan, an endothelin antagonist, at least improved pulmonary hypertension in adults and children[40,47,61]. Lastly, promising results have been reported on the use of iNO, either alone or in combination with other medications, administered through a nasal cannula in infants with CDH who suffer from persistent pulmonary hypertension and are not mechanically ventilated[47]. However, apart from the above findings, there is limited experience regarding treatment strategies for pulmonary hypertension in infants with CDH. Treatment is mostly based on observational studies and case reports as randomized controlled trials evaluating the effects of these pharmacological therapies in infants with CDH have not yet been performed. Moreover, little is known on the toxicity, side effects and dose regimens in infants with CDH.

The role of ECMO treatment

Extra corporeal membrane oxygenation (ECMO) is a form of cardiopulmonary bypass which may be used in infants with severe but reversible cardiopulmonary failure in whom conventional treatment strategies fail. ECMO improved survival rates in infants with respiratory failure due to meconium aspiration, respiratory distress syndrome or sepsis[62]. Its benefits for infants with CDH are still unclear[63]. However, unpublished data from our group revealed higher survival rates in ECMO centres without differences in BPD prevalence. Pulmonary hypertension in infants with CDH may only be partially reversible because of pre-existing structural pulmonary vascular anomalies exist and persist, resulting in chronic pulmonary hypertension[41].

Recent data of the ELSO Registry are consistent with a survival rate of 52% in infants with CDH after ECMO treatment – much lower than that after ECMO treatment in infants with other respiratory failure[62]. In this thesis, we report survival rates from 49% to 60% in the different studies.

Previous studies of the UK Collaborative ECMO trial and the CDH Registry failed to show improvement of survival in ECMO-treated CDH patients[64-65]. Also, survival rates in a study of the Boston group, which used ECMO treatment in half of the CDH patients, did not differ from those in a study of the Toronto group, which did not use standardized ECMO treatment[66-67]. However, some other studies did report improved survival rates following the implementation of ECMO in their treatment algorithm[68-69].

Although the role of ECMO has not been clearly defined and ECMO criteria may vary widely among different centres, an ECMO procedure is carried out in about one third of the CDH patients born in an ECMO center (Chapters 3 and 4). Also, a great deal of these procedures are performed before surgical repair, probably to achieve pre-operative stabilization and to avoid pulmonary injury due to 'aggressive' mechanical ventilation[62].

In chapter 5, we propose ECMO criteria based upon preductal saturations, signs of respiratory acidosis, need for high peak inspiratory pressures or mean airway pressures, signs of severe systemic hypotension, or a consistently present oxygenation index above 40. After implementation of these criteria, mortality after ECMO dropped from 64% to 34% and the overall rate of ECMO procedures from 37% to 25%.

Besides a high mortality rate, ECMO is also associated with a high rate of pulmonary morbidity. In chapters 3 and 4, we report an 88% and 87% incidence of BPD, respectively. Moreover, patients who underwent an ECMO procedure had more often moderate or severe BPD and lung function abnormalities (chapter 2). This high rate of pulmonary morbidity may be due to disease severity and/or a long duration of mechanical ventilation. On the other, ECMO was also believed to prevent pulmonary morbidity by avoiding ventilation with high peak pressures for a prolonged period of time. In this thesis, we failed to find any preventive effect of ECMO treatment on pulmonary morbidity. However, this may be due to case selection and the retrospective design of our studies. In chapter 2, only a small sample of patients was used. Also, different treatment protocols were used and prenatal characteristics were not well recorded in the patients described in chapter 3 and 4.

Future perspectives

First, the physiology and regulation of the pulmonary vascular smooth muscle cells in CDH patients have to be investigated, including mechanisms of pulmonary angiogenesis that might explain the postnatal "maladaption" of the pulmonary circulation. Also, finding biomarkers for pulmonary vascular disease severity would be worthwhile. And then, new strategies and targets for therapy, including dose regimens and side-effects, have to be studied. Importantly, possible roles of echocardiographic markers should be evaluated. Cardiac catheterization, for example, since some pulmonary vascular abnormalities may not be detected on ultrasound. Moreover, evaluation of lung function throughout childhood and adulthood may be important for ECMO-treated patients because they are at high risk for developing lung function abnormalities. Also, evaluating pulmonary perfusion by lung scintigraphy in specific high-risk CDH patients may be recommended[70]. Lastly, endothelial progenitor cells may also be promising in ECMO-treated patients[38].

Surgical management

Surgical management

In earlier days, CDH used to be regarded as a surgical emergency and surgical repair usually took place soon after birth when the newborn's condition was still unstable. In the past two decades we have seen a shift towards surgical treatment of the diaphragmatic defect after a period of clinical stabilization, a strategy that improved survival rates[22,24,33,71]. However, criteria for stabilization and timing of surgical repair may vary widely among centres[72]. A Cochrane review, for that matter, reported no differences in outcome for repair within or after the first 24 hours of life. It was noted, however, that randomized clinical trials on this subject are sparse[73]. In chapter 5, we propose criteria for 'physiological' stabilization based on saturation levels, lactate, urine output, and mean arterial blood pressure. These criteria have to be regarded as a guideline, since evidence on this point is still lacking.

Timing of surgical repair in CDH patients treated with ECMO also remains controversial. If surgery had not taken place before ECMO treatment, it was performed during ECMO treatment in about half of cases[74-76]. The latter strategy has the advantage of direct cardiopulmonary support during repair. On the other hand, it carries the risk of bleedings, even if aminocaproic acid is used[74-75,77-78]. Furthermore, the CDH Study Group found that repair during ECMO treatment is associated with lower survival rates than is repair after ECMO[74-75]. On the contrary, Dassinger et al. reported higher survival rates associated with repaired during ECMO treatment[79].

Subcostal laparotomy (open repair) is the common approach for surgical repair of the defect in CDH. However, some centres have reported better cosmetic results, less or no differences in postoperative pain and possibly improved respiratory compliance after minimal invasive surgery[80-83]. This strategy, however, was associated with a higher recurrence rate. Nevertheless,

there are still too few studies on long-term outcomes, especially pulmonary morbidity, after minimal invasive surgery[84].

A patch is used when the defect is too large for primary closure and is reported to be associated with the severity of disease[85]. In chapter 3 we report that a patch repair is associated with higher mortality and BPD rates.

Future perspectives

First, the optimal timing of surgical management should be studied. Clinical trials on this subject may also help to standardize criteria for physiological stabilization. Especially in ECMO-treated patients, it is important to determine what timing results in the best outcome: during or after ECMO treatment.

Furthermore, prospective clinical trials should evaluate possible benefits and disadvantages of the different surgical approaches, including long-term complications after patch repair and the use of biosynthetic patches. Lastly, future research regarding surgical repair should not only focus on mortality as an outcome measure, but also on the effect of timing on long-term pulmonary morbidity.

Strategies to reduce pulmonary morbidity in patients with congenital diaphragmatic hernia

Antenatal evaluation of predictive markers

Antenatal predictive markers of outcome, such as the lung-to-head ratio (LHR) measured by ultrasound and the fetal lung volume (FLV) determined by MRI, are frequently used in CDH. Both are dependent on the gestational age at measurement and nowadays are preferably expressed as the observed-to-expected ratio (O/E)[86-88]. Several studies, including the study in chapter 7, have reported the O/E LHR and the O/E FLV to be associated with survival[86,89]. There are only few reports on antenatal prediction of chronic lung disease in CDH. A study by Jani et al. reported the O/E LHR to be a good predictor for both chronic lung disease and duration of ventilation[90], whereas a study by Heling et al. did not demonstrate any correlation between LHR and postnatal ventilation parameters[91]. Another recent study by Deprest et al. showed that more than 75% of the patients who had an O/E below 25% were diagnosed with BPD[92]. However, these were retrospective studies, in which there was no standardized postnatal therapeutic approach, which may have a high impact on outcome as we demonstrated in chapter 6. In two studies, described in chapters 6 and 7, we found that the O/E LHR was associated with the occurrence of BPD. In chapter 4, we reported that LHR measurements were not associated with the severity of BPD. In that study, however, observed-to-expected ratios could not be determined. In chapter 7, we report that the O/E FLV is associated with chronic lung disease, mortality and need for ECMO.

Since both O/E LHR and O/E FLV measurements are used to predict outcome in CDH, it is important to determine the predictive value of these measurements. In chapter 7, we compared

the predictive value of single O/E LHR measurement and combined measurements of the O/E LHR and O/E FLV. Additional fetal MRI measurements of the O/E FLV may give a slightly better prediction of chronic lung disease and need for ECMO. With regard to mortality, additional MRI measurements did not improve predictive value. The role of fetal MRI measurement of the O/E FLV may therefore be debated.

Previous studies showed that an intrathoracic position of the liver is associated with mortality in CDH patients[90,93].

The defect size may then be larger, and consequently the degree of pulmonary hypoplasia may be larger. In this regard, the degree of liver herniation into the thorax may also be relevant[94]. We found that an intrathoracic position of the liver is associated with chronic lung disease (chapter 6), survival (chapter 7) and need for ECMO (chapters 6 and 7).

Since CDH patients do not only show pulmonary hypoplasia, but also maldevelopment of the pulmonary vessels, researchers have tried to find ways to evaluate the pulmonary vasculature. The prenatally measured main branch of the ipsilateral pulmonary vessel diameter was found to be related to mortality and respiratory morbidity[95-97]. Also, decreased lung tissue perfusion measured by the fractional moving blood volume on Doppler was associated with a lower O/E LHR and worse outcome[98]. Others applied a maternal hyperoxygenation test to predict pulmonary vascular reactivity[99-100]. This test measures the pulsatility index of the first branch of the contralateral pulmonary artery before and after administration of 60% oxygen to the mother. A less than 20% decrease of the pulsatility index was associated with an increased risk for neonatal pulmonary hypertension and mortality[99-100].

Antenatal intervention

Prenatal markers are not only important to predict outcome, but may also be used to estimate the need for fetal tracheal occlusion. In this procedure, a balloon is placed in the trachea at 26 to 28 weeks of gestation to prevent egress of lung fluid[101]. By raising the airway pressure, this manoeuvre increases the alveolar space and promotes maturation of the pulmonary vessels[101]. A fetal tracheal occlusion is indicated only when the O/E LHR is less than 28% and the liver is in an intrathoracic position[101]. Fetal tracheal occlusion resulted in an over 50% survival rate in high-risk isolated left-sided CDH patients, in whom the predicted survival rate was less than 20%[101-102]. In our study in chapter 4 the survival rate after fetal tracheal occlusion was 39%. Nevertheless, fetal tracheal occlusion may lead to preterm delivery in about one fourth of the cases. Preterm delivery in itself is independently associated with BPD and/or mortality by day 30 in patients with CDH (chapter 3).

To evaluate the effect of antenatal intervention, it is very important that those intervention studies are using a standardized postnatal treatment protocol, since we demonstrated that this had an impact on outcome. The FETO-trial evaluates the effect of antenatal intervention in high-risk patients with severe pulmonary hypoplasia. Fetal tracheal occlusion may have beneficial effects on pulmonary function[103]. In high-risk CDH patients it was associated with a 20-30% reduction of BPD[101]. The ongoing TOTAL-trial, which evaluates outcome in moderate risk CDH patients after

fetal tracheal occlusion, will also evaluate neonatal morbidity, especially BPD, as an outcome measure. However, in chapter 4 we report no significant differences in BPD incidence between patients who underwent a fetal tracheal occlusion and patients who did not. Up to now, it is not shown that fetal tracheal occlusion has a beneficial effect on pulmonary morbidity.

Future perspectives

It will be important to investigate if routine fetal lung imaging, by either MRI or ultrasound, can predict outcome of CDH. In chapter 8, we showed that fetal MRI has no clear role in this regard. Perhaps it would be possible to identify patients in whom an MRI will have additional predictive value, next to standard ultrasound measurements. MRI indeed provides better visualization in case of maternal obesity and a better view of the contralateral lung, the degree of liver herniation and possible other anomalies[101]. On the other hand, heart anomalies, which occur in about 20% of the CDH patients, may be better visualized in a dynamic way such as on ultrasound. Also, a focus should be placed on determining prenatal predictors of pulmonary hypertension, notably when the defect is non-isolated or right-sided. Finally, predictive markers could justify fetal tracheal occlusion in specific cases of CDH.

The importance of evidence-based medicine

Evidence based and standardized protocols are lacking in the field of CDH. This is due to the rarity of the disease and, consequently, the lack of randomized clinical trials. It goes without saying that centres that treat patients with CDH need to cooperate to build a larger database allowing to evaluate sufficient patient data, compare treatment strategies and enhance further research. Such cooperation has taken shape through the CDH study group, founded in 1995 and encompassing an important network of hospitals worldwide. The CDH study group meanwhile holds a large database, and data-mining has already led to important publications on outcome, surgical repair, ECMO treatment, mode of delivery and recently, as described in chapter 3, pulmonary morbidity.

Another initiative is the CDH-EURO Consortium, founded in 2006 as a European cooperative network of centres with expertise in treating infants with CDH. In chapter 4, data of this consortium were evaluated to describe severity of BPD in patients with CDH. A standardized treatment protocol proposed by the CDH-EURO Consortium, based upon levels of evidence and expert opinion, is described in chapter 5. In chapter 6 we reported that survival rates significantly increased from 67% to 88% after implementation of this protocol, which highlights the importance of standardized care. Furthermore, the consortium centres participate in the first randomized clinical trial comparing conventional ventilation and HFO as initial ventilation modes in CDH patients.

Future perspectives

In spite of the activities of the CDH Study Group and the CDH-EURO Consortium, research in CDH is still facing challenges. Also, analyses of retrospective data of the CDH-EURO consortium or CDH Registry have some important limitations, such as selection bias. CDH is a complex disease which

involves a continuum of care from prenatal diagnosis onwards. Moreover, long-term follow-up is necessary because secondary morbidity may present in later child- and adulthood. Cooperation between different specialists is important to guarantee multidisciplinary care at a high level as well research opportunities. To enable a valuable comparison of patient data of different centres, they all should use the same treatment protocol, notably when pre-and postnatal data are evaluated in the same context. In summary, multidisciplinary care, cooperation between centres, and standardized treatment protocols are important aspects to improve care for CDH patients. Moreover, prospective data-analyses and randomized clinical trials are badly needed to evaluate patient outcome and develop evidence-based standardized care.

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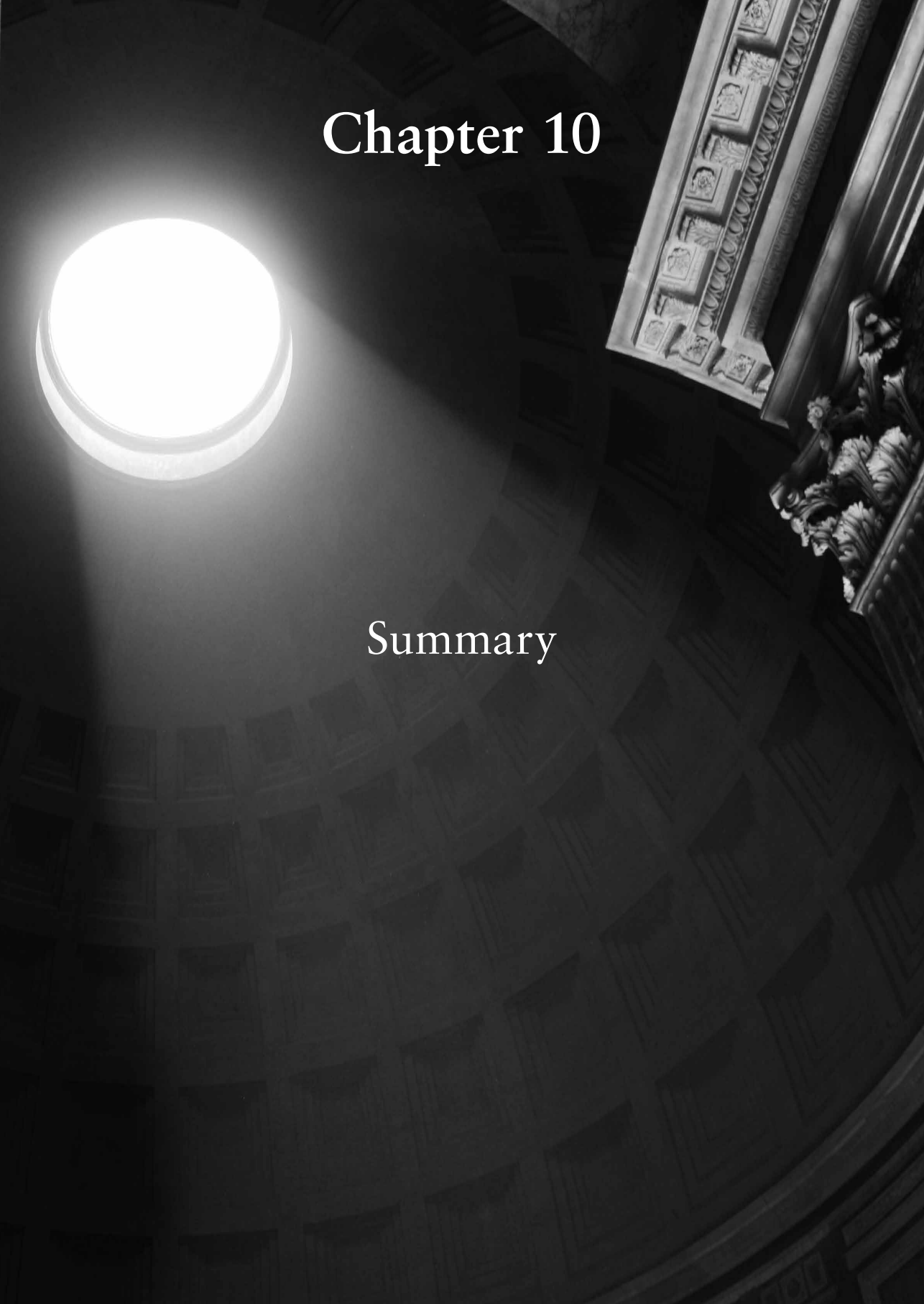
Chapter 10



Summary

Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm, which occurs in approximately 1 in 3,000 newborns[1]. The abdominal organs have moved into the chest cavity before birth, resulting in pulmonary hypoplasia and maldevelopment of the pulmonary vessels, and therefore pulmonary hypertension in a significant percentage of patients[2]. CDH is a life-threatening condition with a substantial mortality rate, depending on case selection. Those who survive initially are at risk of continued pulmonary, gastro-intestinal and neurological problems and should be followed closely[3].
After having identified different problems in the field of CDH (chapter 1), we describe pulmonary outcomes established by lung function measurements (chapter 2) in part I. In part II, we describe risk factors and severity of chronic lung disease (chapters 3 and 4). Strategies to improve survival and pulmonary outcome, including the role of a standardized treatment protocol (chapters 5 and 6), possible prenatal predictors of outcome (chapter 7) and a randomized clinical trial protocol regarding ventilation strategies (chapter 8) are described in part III.

PART I: Pulmonary outcome in survivors of CDH

Over the years, survival rates have increased with improvements in neonatal care, including 'gentle' ventilation strategies, delayed surgery and extra corporeal membrane oxygenation (ECMO) in selected patients[4-8]. However, survivors of CDH may develop secondary pulmonary morbidity, which may be caused by ventilator-induced lung injury, high concentrations of oxygen, pulmonary hypoplasia and pulmonary hypertension[9-12]. Recurrent respiratory infections, chronic lung disease, persistent pulmonary hypertension and asthmatic symptoms have been reported in 30-50 % of CDH survivors[3, 9, 12-16]. Moreover, survivors of CDH may show lung function abnormalities[17-18].
In chapter 2, we therefore aimed to describe pulmonary morbidity, defined as bronchopulmonary dysplasia, and lung function measurements during the first year of life in forty-three CDH survivors born at the Erasmus Medical Center. Bronchopulmonary dysplasia (BPD) according to the definition of Jobe and Bancalari entails oxygen dependency at day 28 or at 36 weeks postmenstrual age, depending on the gestational age at birth[10]. In our study, 41% of the patients were diagnosed with BPD. Lung function was measured at the ages of 6 and 12 months and expressed as functional residual capacity (FRCp) and forced expiratory flow at FRCp (V'maxFRC). The FRCp was generally above the expected range and the V'maxFRC was below the expected value. Both outcome measures did not change significantly from 6 to 12 months. Presence of BPD, ECMO-treatment, higher maximum mean airway pressure, and longer duration of ventilation were associated with significantly higher FRCp values. V'maxFRC was not associated with any of these characteristics. The FRCp values reported in our study may reflect hyperinflation. However, since FRCp values did not increase over time, there seems no progressive hyperinflation

of existing alveoli in the first year of life. Decreased maximal expiratory flows in our study may reflect abnormal airway size or alveolar architecture, which may be 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.

PART II: Prevalence, severity and risk factors for chronic lung disease

As described in chapter 2, survivors of CDH may suffer from BPD and show lung function anomalies. In chapter 3, we aimed to describe possible risk factors for BPD and early mortality, using patient data from the CDH Registry international database. In deviation from the above-mentioned definition, BPD was defined as oxygen dependency at day 30 of life, since data on oxygen dependency at day 28 were not available. Severity of BPD had not been recorded in the database. Risk factors were assessed separately for BPD and/or mortality by day 30, and for BPD and/or mortality by day 30. At day 30, 56% of the patients had either died or met the criteria for BPD. In infants who survived until day 30, the prevalence of BPD was 41%. The overall mortality rate was 31%. The following factors were associated with BPD and/or mortality by day 30: HFO as initial ventilation mode, right-sided defect, prenatal diagnosis, lower Apgar score at five minutes, cardiac anomaly, chromosomal anomaly, and lower gestational age. We could not but conclude that BPD and early death remain important problems in newborns with CDH, despite improvements in neonatal care. Surprisingly, HFO as initial ventilation strategy, believed to be effective in infants with CDH, was associated with a higher risk of a worse outcome. This may be explained by the fact that infants who received initially HFO were more severely ill from the start.

Since we could not take into account severity of BPD in chapter 3, we performed a study using such data from the CDH-EURO Consortium. In chapter 4, the presence and severity of BPD was determined for 368 patients. Severity of BPD at day 56 of life or at discharge, whichever comes first, was classified by the amount of supplementary oxygen (mild = no supplementary oxygen; moderate = oxygen 22-30%; severe = oxygen > 30% or mechanically ventilated)[10]. About half of the CDH patients with BPD had moderate or severe BPD. These were the most severely ill patients, with a significant longer duration of ventilation and higher need for ECMO therapy than patients with mild BPD. Multivariate analysis revealed that a vaginal delivery was the only independent risk factor for moderate to severe BPD. This might be explained by the fact that infants born by vaginal delivery were less often prenatally diagnosed and more often outborn, i.e. at home or outside a tertiary center. We speculate that ventilation strategies in those outborn infants may have been sub-optimal, for lack of experience with CDH patients, with high inspiratory pressures applied already in the delivery room.

The studies described in chapters 3 and 4 revealed that BPD was an important problem in survivors of CDH and that the initial ventilation mode was possibly associated with outcome.

PART III: Strategies to reduce mortality and pulmonary morbidity

Standardized care

Evidence-based therapy guidelines for CDH were lacking so far, partly because randomized clinical trials have not been performed, care has been decentralized, and individual centres treat relatively low numbers of patients[19]. In 2007 the international CDH-EURO Consortium, a collaboration between tertiary centres with an expertise in CDH, was therefore set up to exchange knowledge and to design research projects and standardized treatment protocols.

In chapter 6, we propose a protocol for standardized therapy of CDH patients based on a consensus statement developed by the members of the CDH-EURO Consortium. The statement was based on a summary of recent relevant literature. Five experts individually graded study design and methodological quality of the studies according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria[20]. Differences in opinion were solved by discussion until full consensus was reached. The final consensus statement, therefore, represents the opinion of all consortium members. This standardized treatment protocol allows for more valid comparison of patient data, enables benchmarking like in the Vermont Oxford Neonatal Network, and forms the basis for the VICI-trial (see below).

The protocol was first implemented in the Erasmus Medical Center and the University Hospital Mannheim. In chapter 7, we describe the impact of the protocol in these two centres. Survival rates significantly improved but prevalences of BPD and the use of ECMO therapy did not significantly change. Cooperation between different centres is key to develop effective protocols.

Prenatal prediction of outcome

Certain prenatal characteristics could determine postnatal outcome and possible need of prenatal surgical intervention. The most widely used prenatal predictor is the lung-to-head ratio (LHR), determined by ultrasound measurement[21-23]. Also, an intrathoracal position of the liver may foretell unfavourable outcome[24]. In addition, the fetal lung volume, measured by fetal MRI, was proposed to be a good predictor of mortality in patients with CDH[25]. Both lung-to-head ratio and fetal lung volume are dependent on the gestational age at measurement and are therefore best described as the observed-to-expected lung-to-head ratio and foetal lung volume (O/E LHR and O/E FLV)[26-27]. We aimed to determine if additional measurement of the O/E FLV by MRI gives a better prediction of chronic lung disease, early mortality, and need for ECMO therapy than does measurement of the O/E LHR by ultrasound only. We studied patients who all were treated according to the same standardized protocol. It appeared that chronic lung disease and need for ECMO therapy were slightly better predicted by combined measurement of the O/E LHR and the O/E FLV. Early mortality was very well predicted by measurement of the O/E LHR alone.

The clinical relevance and cost-effectiveness of additional MRI measurements may therefore be debated. Future research must be directed towards specific high-risk cases in which a fetal MRI may be of additional value. Meanwhile, measurement of the O/E LHR by ultrasound is a good method to predict outcome in fetuses with CDH.

Randomized clinical trial

RCTs in the field of CDH are urgently needed to develop evidence-based treatment strategies, which could help to reduce mortality and morbidity. One way to prevent chronic respiratory disease in CDH patients may be by optimizing ventilation strategies. To date, conventional ventilation is the most widely used initial ventilation mode in newborns with CDH, while in many institutions high frequency oscillatory ventilation (HFO) is used as rescue therapy. In some patients, however, HFO is used as the initial ventilation mode. The latter strategy may be effective to reduce mortality and chronic lung disease, because it promotes uniform lung inflation and may reduce barotraumas[28-31]. However, in our retrospective study in chapter 3, HFO as an initial ventilation mode was associated with worse outcome. This finding was occasion to set up the VICI-trial, in collaboration with the CDH-EURO Consortium. In this RCT, newborns with CDH are randomized to receive either conventional ventilation or HFO as initial ventilation mode. Primary outcome measures are BPD and mortality by day 28. To date, 88 patients have participated in the trial. The trial is still ongoing and therefore no results could be published in this thesis. However, the protocol of the VICI-trial has been submitted, and is described in chapter 8. In the general discussion, we discuss our findings and make recommendations for future studies.

The major findings and recommendations of this thesis are the following:

* Pulmonary morbidity is a major problem in CDH survivors and is reported in 30-40% of the patients.
* Lung function anomalies are present in survivors of CDH, especially in those treated with ECMO or ventilated for a long time.
* Long-term evaluation of pulmonary function is important in CDH survivors.
* The initial mode of ventilation may be associated with pulmonary morbidity and mortality.
* The VICI-trial, a randomized clinical trial which evaluates HFO and conventional ventilation as initial ventilation mode, will provide further information on the best initial ventilation mode to prevent mortality and pulmonary morbidity in infants with CDH.
* Moderate or severe pulmonary morbidity is present in almost half of the CDH survivors, especially in those who suffered from severe pulmonary hypertension.
* Standardized treatment significantly improve outcome in patients with CDH.
* Evidence-based medicine and randomised clinical trials, such as the VICI-trial, may lead to the development of standardized treatment protocols and are highly important in CDH research.
* Additional antenatal measurements of the observed-to-expected fetal lung volume by MRI gave a slightly better prediction of pulmonary morbidity than standard ultrasound measurements of the observed-to-expected lung-to-head ratio.
* Evaluation of antenatal measurements is necessary to identify high-risk CDH patients who may develop long-term morbidity.
* Cooperative networks for enhancement of research and evaluation outcome and treatment strategies are important.

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Appendices

Nederlandse samenvatting

Congenitale hernia diaphragmatica (CDH) is een ernstige aangeboren afwijking van het middenrif die voorkomt bij 1 op de 3000 pasgeborenen. Vanwege het defect in het middenrif, migreren de buikorganen voor de geboorte naar de borstholte. Dit verstoort de normale ontwikkeling van de longen en het longvaatbed, wat resulteert in pulmonale hypoplasie en pulmonale hypertensie in een deel van de patiënten. CDH is een aandoening met een grote kans op overlijden of pulmonale, gastro-intestinale en neurologische aandoeningen. Ongeveer 30-50% van de patiënten met CDH houden op de lange termijn longklachten, zoals luchtweginfecties, bronchopulmonale dysplasie (BPD), persisterende pulmonale hypertensie, of een slechte longfunctie.
In deel I van dit proefschrift wordt een overzicht van het ziektebeeld CDH gegeven (hoofdstuk 1) en worden longfunctiemetingen bij patiënten met CDH beschreven (hoofdstuk 2). In deel II wordt de prevalentie, de ernst en de risicofactoren van chronische longziekte beschreven (hoofdstuk 3 en 4). In deel III worden strategieën beschreven gericht op een grotere overlevingskans en het voorkómen van chronische longziekte, zoals gestandaardiseerde zorg (hoofdstuk 5 en 6), mogelijke prenatale predictoren voor overleving en morbiditeit (hoofdstuk 7) en een protocol voor een gerandomiseerde klinische studie naar beademingsstrategieën (hoofdstuk 8).
In hoofdstuk 2 beschrijven we longfunctiemetingen gedurende het eerste levensjaar van 43 patiënten met CDH. De metingen werden gedaan op de leeftijd van zes en twaalf maanden. De uitkomsten wijzen op hyperinflatie en beschadiging van de luchtwegen ten gevolge van mechanische beademing. Deze afwijkingen waren in het bijzonder aanwezig bij kinderen die behandeld waren met extra corporeale membraan oxygenatie (ECMO) en/of langdurige beademing.
Vervolgens onderzochten we in hoeverre BPD voorkwam bij een grote groep patiënten, hoe ernstig dit was, en wat de mogelijke risicofactoren waren. In hoofdstuk 3 beschrijven we dat 56% van de patiënten ofwel was overleden voor de 30e levensdag, ofwel was gediagnosticeerd met BPD op de 30e levensdag. De risicofactoren hiervoor waren: beademing begonnen met high-frequency oscillation (HFO), defect aan het middenrif rechts, diagnose al voor de geboorte gesteld, lage Apgar score, een bijkomende hart- of chromosomale afwijking, en een lagere zwangerschapsduur. In tegenstelling tot eerdere studies, was HFO in onze studie geassocieerd met een slechtere prognose. Een mogelijke verklaring hiervoor is dat HFO als eerste wordt toegepast in ziekere patiënten.
Gegevens betreffende de ernst van BPD waren niet beschikbaar voor de patiëntengroep die in hoofdstuk 3 beschreven werd. Daarom evalueerden we gegevens betreffende de ernst van BPD van centra die deelnemen in het CDH-EURO Consortium. In hoofdstuk 4 beschrijven we dat ongeveer de helft van de patiënten met CDH matige dan wel ernstige BPD heeft. Een vaginale bevalling was de enige significante risicofactor voor matige tot ernstige BPD. Dit kan mogelijk verklaard worden doordat deze kinderen minder vaak prenataal gediagnosticeerd zijn, vaker buiten een tertiair centrum worden geboren en dan wellicht niet goed beademd zijn.
In het laatste deel van dit proefschrift beschrijven we strategieën die mogelijk de overleving en morbiditeit kunnen verbeteren. In hoofdstuk 5 en 6 concluderen we dat gestandaardiseerde

zorg veelal ontbreekt voor kinderen met CDH – vooral omdat de aandoening zeldzaam is, gerandomiseerde klinische studies ontbreken en de zorg veelal niet gecentraliseerd is. Om tot betere behandeling te komen werd in 2007 het CDH-EURO Consortium opgericht, een samenwerkingsverband tussen een aantal Europese tertiaire centra met expertise op het gebied van CDH. In hoofdstuk 5, beschrijven we een protocol voor gestandaardiseerde zorg, dat ontwikkeld is door het CDH-EURO Consortium. In hoofdstuk 6, beschrijven we dat de overleving significant verbeterde na invoering van dit protocol, maar dat er nog evenveel BPD voorkwam en dat ECMO-therapie evenveel werd toegepast.

De prenatale lung-to-head ratio en longvolume kunnen helpen eventuele postnatale mortaliteit en morbiditeit te voorspellen. Over het algemeen wordt in geval van CDH de eerste standaard bepaald tijdens de zwangerschap d.m.v. een echo. Een MRI-scan om het foetale longvolume te meten kan mogelijk aanvullende informatie geven. In hoofdstuk 7 concluderen we dat gecombineerde metingen met behulp van echo en MRI postnatale BPD en de behoefte aan ECMO therapie iets beter voorspellen dan alleen maar een standaard echografische metingen. Wat betreft de mortaliteit was er geen verschil.

Zoals hierboven beschreven, is de initiële beademingsmodus bij CDH patiënten mogelijk geassocieerd is met mortaliteit en longziekte. Daarom is op initiatief van het CDH-EURO Consortium een gerandomiseerde studie naar twee initiële beademingsstrategieën (HFO en conventionele beademing) gestart. De studie loopt nog, dus resultaten kunnen nog niet worden gegeven. Het protocol is beschreven in hoofdstuk 8.

In het laatste hoofdstuk, de algemene discussie, bespreken we al onze bevindingen en geven we aanbevelingen voor toekomstig onderzoek.

Deze bevindingen zijn:

* Pulmonale morbiditeit komt voor bij 30-40% van de patiënten met CDH.
* Longfunctie afwijkingen komen voor bij patiënten met CDH, met name bij patiënten die behandeld zijn met ECMO en/of langdurig beademd werden.
* Evaluatie van de longfunctie op de lange termijn is belangrijk bij patiënten met CDH.
* De initiële beademingsmodus is mogelijk geassocieerd met mortaliteit en pulmonale morbiditeit.
* De VICI-trial, een gerandomiseerde studie die initiële conventionele beademing vergelijkt met initiële beademing met HFO, zal in de toekomst verdere informatie kunnen geven over de beste initiële beademingsmodus bij patiënten met CDH.
* Matige tot ernstige pulmonale morbiditeit is aanwezig bij bijna de helft van de CDH patiënten, en dan met name bij patiënten met ernstige pulmonale hypertensie.
* Een gestandaardiseerd behandelprotocol verlaagt de mortaliteit van patiënten met CDH.
* Evidence-based medicine en gerandomiseerde klinische trials op het gebied van CDH zijn erg belangrijk, aangezien zij kunnen leiden tot de ontwikkeling van gestandaardiseerde behandelprotocollen.
* Aanvullende antenatale metingen van het ‘observed-to-expected’ foetale longvolume door middel van MRI, hadden een iets hogere predictieve waarde ten aanzien van pulmonale

morbiditeit dan standaard echografische metingen van de ‘observed-to-expected’ lung-to-head ratio.

* Evaluatie van antenatale metingen is noodzakelijk om hoogrisico CDH patiënten te identificeren die mogelijk op de lange termijn pulmonale morbiditeit ontwikkelen.
* Samenwerking tussen centra is belangrijk voor de ontwikkeling van wetenschappelijk onderzoek en de evaluatie van behandelstrategieën.

Het beste wat je kunt worden, is jezelf

Dankwoord

Bij het tot stand komen van dit proefschrift waren vele mensen betrokken. Enkelen van hen wil ik graag in het bijzonder noemen.
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Many thanks to all members of the CDH-EURO Consortium. They have shown that cooperation is crucial to promote research and exchange knowledge. A nice example is the VICI-trial, in which most of the CDH-EURO Consortium centres are participating. Especially, I would like to thank the following members. Dr. Capolupo, dear Irma, it has been a great pleasure to write the

standardized treatment protocol together with you. Besides, you set up the VICI-trial in Rome and have been of great help in collecting data. But most of all, you are a very warm and friendly person and I enjoyed meeting you in Rome. Dr. A. van Heijst, beste Arno, en prof. K. Allegaert, beste Karel, hartelijk dank voor jullie hulp bij de dataverzameling en het tot stand komen van enkele van mijn artikelen. Dr. Gorett Silva, dear Maria, thanks to you we managed to have no fewer than six Portugese centres involved in CDH research! Thank you so much for all your help in setting up the VICI-trial in Portugal and collecting patient data.

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Liebe

Curriculum Vitae

Lieke van den Hout was born in Heerlen, the Netherlands, on April 7th 1981. Having finished secondary school at the Gymnasium Rolduc, Kerkrade, in 1999, she read law for one year because she did not draw a place in a medical faculty. In 2000, she could start her medical training at the University of Maastricht. As a medical student she worked at the departments of Internal Medicine (2001-2002) and Pulmonology (2003-2004) at the Krankenhaus Maria Hilf, Mönchengladbach, Germany, and spent two months at the children's Oncology department at the Universitetsjukhus in Linköping, Sweden (2003). In April 2004, she did her internship internal medicine at the Pretoria Academic Hospital, South Africa. She completed her final dissertation, on transitional healthcare in children with intellectual disabilities, at the departments of Pediatrics and Genetics at the University Hospital in Maastricht.

After obtaining the medical degree in 2006 she worked as a resident at the pediatric department of the Amphia Hospital in Breda. From 2008 onwards, she was a research fellow at the department of Paediatric Surgery and Intensive Care Medicine (Prof.dr. Tibboel) at the Erasmus MC-Sophia Children's Hospital in Rotterdam working on the research project presented in this thesis. In February 2011, she was appointed a resident (ANIOS) at this department. As from August 2009 she is taking a master's course in clinical epidemiology, which she will complete in September 2011. She is married to Evert-Jan de Jongste.

PHD Portfolio

Name PhD student:	Lieke van den Hout
Erasmus MC department:	Intensive Care and Pediatric Surgery
Research School:	Medisch Genetisch Centrum Zuid-West Nederland
PhD period:	February 2008-June 2011
Promotor:	Prof. Dick Tibboel
Co-promotor	Dr. Irwin Reiss

PhD training	**Year**	**Workload (hours)**
General academic skills		
Biomedical English Writing and communication	2009	80
Engels presenteren en discussiëren	2008	80
Cursus Good clinical practice	2008	40
Research skills		
Master of Science Program in Clinical Epidemiology, NIHES	2009-2011	12 months
Introduction to clinical trials, NIHES wintercourse	2009	25
Introduction to data-analysis, NIHES summercourse	2008	25
International conferences		
CDH-EURO Consortium meeting,Poster presentation	2011	16
European Society of Paediatric Research meeting (ESPR), Oral presentation	2010	24
CDH-EURO Consortium meeting, Oral presentation	2009	16
British Association of Paediatric Surgery, Oral presentation	2009	24
European Society Paediatric and Neonatal Intensive Care Medicine (ESPNIC),Oral and poster presentation	2009	24
Gesellschaft für Neonatologie und Paediatrische Intensivmedizin, Oral presentation	2009	16

Pediatric Academies Society meeting (PAS), Poster presentation	2009	40
Seminars and Workshops		
Postgraduate Course, CDH EURO-Consortium meeting	2011	8
Several workshops, Erasmus PhD Day	2010	8
Minicursus methodologie van patiëntgebonden onderzoek	2008	8
Teaching activities		
Several presentations on CDH for staff members and researchers	2008-2011	24
Several presentations on evidence-based medicine in CDH for nursing staff	2008-2011	24

List of publications

Publications related to this thesis

T. Schaible, K. A. Büsing, J. F. Felix, W.C.J. Hop, K. Zahn, L. Wessel, J. Siemer, K.W. Neff, D. Tibboel, I. Reiss, **L. Van den Hout**. Observed-to-expected fetal lung volume and observed-to-expected lung-to-head ratio as predictors for chronic lung disease in infants with congenital diaphragmatic hernia. *European Journal of Radiology, accepted*

L. van den Hout, M. Spoel, I.Reiss, C. Meeussen, S. Gischler, J.C. de Jongste, D. Tibboel, H. IJsselstijn. Lung function during the first year of life after repair of congenital diaphragmatic hernia: a longitudinal follow-up study. *Pediatric critical care medicine, accepted*

L. van den Hout, I. Reiss, J. Felix, W. Hop, D. Bohn, P. Lally, K. Lally, D. Tibboel. Risk factors for chronic lung disease and mortality in newborns with congenital diaphragmatic hernia. *Neonatology 2010;98(4):370-380.*

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L. van den Hout, T. Schaible, J. Siemer, T.E. Cohen-Overbeek, K. van de Ven, L. Wessel, D. Tibboel, I. Reiss*.* Actual outcome in infants with Congenital Diaphragmatic Hernia: the role of a standardized postnatal treatment protocol*. Fetal Diagnosis and Therapy 2011;29(1):55-63.*

L. van den Hout, I. Sluiter, S. Gischler, A. De Klein, R. Rottier, H. IJsselstijn, I.Reiss, D.Tibboel. Can we improve outcome of congenital diaphragmatic hernia? The CDH Euro-Consortium. *Ped surg Int 2009;25 (9):733-43.*

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L. van den Hout, D. Tibboel, S. Vijfhuize, W. Hop, I. Reiss. The VICI-trial: High frequency oscillation versus conventional mechanical ventilation in newborns with congenital diaphragmatic hernia: An international multicenter randomized controlled trial. Submitted.

E.D. Wilschut, R. Keijzer, R.J. Houmes, C.P. van de Ven, **L. van den Hout**, I. Sluijter, P. Rycus, N.M.A. Bax, D. Tibboel. Congenital Diaphragmatic Hernia: to repair on or off ECMO: that is the question. Submitted.

List of abbreviations

AUC	Area Under the Curve
BMC	Bone-Marrow derived stem Cell
BPD	Bronchopulmonary Dysplasia
cAMP	cyclic Adenosine Monophosphate
CDH	Congenital Diaphragmatic Hernia
CI	Confidence Interval
CLD	Chronic Lung Disease
cGMP	cyclic Guanosine Monophosphate
CMV	Conventional Mechanical Ventilation
CPAP	Continuous Positive Airway Pressure
ECMO	Extra Corporeal Membrane Oxygenation
ET	Endothelin
FLV	Fetal Lung Volume
FRCp	Functional Residual Capacity
FTO	Fetal Tracheal Occlusion
GER	Gastroesophageal Reflux
HFO	High Frequency Oscillation
ICAM	Intercellular Adhesion Molecule
I:E	Inspiration Expiration rate
iNO	inhaled Nitric Oxide
IPPV	Intermittent Positive Pressure Ventilation
LCI	Lung Clearance Index
LHR	Lung-to-Head Ratio
MAP	Mean Airway Pressure
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
O/E	Observed to Expected ratio
OI	Oxygenation Index
OR	Odds Ratio
PDE	Phosphodiesterase
PDGF	Platelet Derived Growth Factor
PEEP	Positive End Expiratory Pressure
PGE1	Prostaglandin E1
PGI2	Prostacyclin
PIP	Positive Inspiratory Pressure
PPHN	Persistent Pulmonary Hypertension of the Newborn
Pro-BNP	Pro-Brain Natriuretic Peptide
RA	Retinoic Acid

ROC curve	Receiver Operating Characteristic curve
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
SD	Standard Deviation
SE	Standard Error
SIGN	Scottish Intercollegiate Guidelines Network
SIMV	Synchronized Intermittent Mandatory Ventilation
SNAP	Score for Acute Neonatal Physiology
US	Ultrasound
VCAM	Vascular Cell Adhesion Molecule
VEGF	Vascular Endothelial Growth Factor
VILI	Ventilator Induced Lung Injury
V'maxFRC	Maximal expiratory flow at Functional Residual Capacity

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