Summary

In this thesis we describe the long-term morbidity of patients born with high risk congenital diaphragmatic hernia (CDH) and of patients born with esophageal atresia (EA). Congenital diaphragmatic hernia is a congenital malformation (birth defect) of the diaphragm with an incidence of approximately 1:2,500 live births and a mortality rate around 40-50%. Malformation of the diaphragm allows the abdominal organs to migrate into the chest, thereby impeding proper lung growth and development. Infants born with CDH experience respiratory failure due to pulmonary hypertension (i.e. restriction of the blood flow through the lungs) and pulmonary hypoplasia. Esophageal atresia is a congenital anatomic defect that is caused by an abnormal embryological development of the esophagus and affects 1 in 2,400 to 4,500 newborns. In EA the esophagus is divided into 2 blind-ended pouches, an upper and a lower, which may or may not communicate with the tracheobronchial tree through a fistulous tract called tracheo-esophageal fistula (TEF). Most patients have both EA and TEF and approximately 65% have other EA-associated congenital anomalies such as heart anomalies. CDH as well as EA are both major life threatening congenital anomalies needing surgical correction in the neonatal period. In the past decades new treatment strategies have been developed for CDH including extracorporeal membrane oxygenation (ECMO), which is an extracorporeal technique of temporary providing both cardiac and respiratory support to patients whose heart and lung are so severely diseased that they can no longer serve their function. In addition fetal tracheal occlusion (TO), which consists of occlusion of the fetal trachea by prenatal surgery, has been developed as an alternative strategy to promote fetal lung growth in CDH patients. Both techniques may improve mortality but, on the other hand, more severely affected patients are expected to have an increased chance of survival, which may affect long term morbidity. Children born with CDH and children born with EA have significant long-term morbidity due to pulmonary sequelae, gastro-intestinal problems and neurocognitive problems. Due to these sequelae health-related quality of life may be compromised.

The objectives of this study were to determine the incidence and severity of consequences of both CDH and EA on the longer term, assess its determinants and analyze the effects on health-related quality of life. We included all high risk CDH patients who were born in Amsterdam and Rotterdam, not treated with ECMO, who were, at the time of the study, between 6-18 years. Participating patients underwent pulmonary function testing, cardiopulmonary exercise testing and were asked to complete a questionnaire on gastro-intestinal problems. From patients originating from the Amsterdam cohort neurocognitive functioning and health-related quality of life were also assessed. Furthermore we assessed pulmonary function, exercise capacity and gas exchange together with health-related quality of life in adult CDH patients from Amsterdam. For EA we included all patients, treated in Amsterdam, with an age at the time of the study between 8-18 years. Participants
performed pulmonary function testing and maximal exercise testing. To investigate the role of gastro-esophageal reflux disease (GERD) on pulmonary function we compared the results of the EA patients with a control group consisting of patients with isolated GERD. In addition all EA patients were asked to complete questionnaires on gastro-intestinal symptoms and health-related quality of life.

**Pulmonary morbidity**

In chapter 2 and 3 we describe the pulmonary function and exercise capacity of 53 and 12 CDH survivors in childhood and adulthood, respectively. CDH patients in childhood, adolescence as well as in adulthood have mild obstructive pulmonary function impairment. For children and adolescents obstructive impairment may be related to GERD in early life. In all patients exercise capacity and gas exchange parameters were normal indicating that, at first, the majority of patients does not have physical impairment and, secondly, they are not at risk for developing long-term pulmonary vascular pathology. In chapter 6 we present the independent effects of EA and GERD on cardiopulmonary function by comparing pulmonary function and exercise capacity between patients with EA, patients with EA and GERD and patients with isolated GERD. We found that EA patients with and without GERD have restrictive pulmonary function impairment when compared to patients with only GERD. We hypothesize that this may be due to the fact that all EA patients underwent thoracotomy for EA repair. Based on these studies we propose that early GERD might be considered as an additional risk factor for the development of pulmonary injury in CDH as well as in EA. For CDH it is likely that a distorted airway architecture due to pulmonary hypoplasia and ventilator-induced lung injury play a more significant role in the development of airway disease. For EA recurrent respiratory infections due to tracheomalacia (a condition- which is inherent to EA and characterized by flaccidity of the tracheal support cartilage, which leads to tracheal collapse), and thoracotomy are likely to be more important in the development of airway disease in these patients.

**Gastro-intestinal morbidity**

In chapter 4 we analyse the perinatal and postnatal data of 69 CDH patients to identify variables predictive for early GERD. To examine the incidence of GERD 6-18 years after CDH repair 58 patients completed a standardized questionnaire on reflux symptoms. Patients who had a score indicating increased risk for GERD underwent further assessment. We found early GERD in 39% of the CDH patients with patch closure and intrathoracic position of the stomach being independent predictive variables. At follow-up 16% of the CDH patients has symptoms suggestive for late GERD, in 78% of them late GERD was confirmed. We could not identify predictive factors for late GERD. To prevent GERD-related complications in CDH patients we think that long-term follow-up for GERD in CDH survivors is mandatory.
Neurocognitive morbidity

In chapter 5 we assessed psychological and social functioning of 33 high risk CDH survivors aged 6-16 years. Although we found a normal IQ, CDH survivors appeared to be at risk for subtle cognitive problems, reflected in lower results for sustained attention. Learning difficulties were reported by 30% of the parents. We found that many CDH survivors have significant emotional and behavioral problems which may contribute to school failure. In contrast with other studies we did not find evidence for severe cognitive defects. No predictive variables could be identified.

Health-related quality of life

In addition to psychological and social functioning of CDH survivors chapter 5 also discusses health-related quality of life (HR-QoL) in CDH patients. HR-QoL was assessed with the Child Health Questionnaire (CHQ) and the Health Utilities Index (HUI). CDH patients had a reduced perception of health when compared to the reference population indicating that CDH survivors and their parents believe their health is poor and likely to worse. We found a lower HUI score on cognition, suggesting that CDH patients learn or remember school work more slowly than classmates and sometimes require special education. This is compatible with the results of the cognitive tests described in the same chapter. In chapter 7 HR-QoL of EA patient and its determinants such as concomitant anomalies and the presence of respiratory and/or gastro-intestinal symptoms were evaluated by using the CHQ for parents as well as for children. The domain General Health perception was significantly lower. According to parents this was negatively affected by age at follow-up and concomitant anomalies. According to EA patients themselves reflux symptoms reduced General Health perceptions. These results imply that health care workers as well as parents should be aware of the high incidence of EA and CDH-associated symptoms and the possible negative consequences for HR-QoL.

Conclusion

This long-term follow-up study of 2 life-threatening congenital anomalies, congenital diaphragmatic hernia and esophageal atresia, both needing surgical correction in the neonatal period, shows that CDH patients have mild obstructive pulmonary function impairment and a normal exercise capacity. We did not find evidence for (sub-clinical) pulmonary hypertension. EA patients have mild restrictive impairment 8-18 years after repair. Early GERD appears to play only a minor role in the development of pulmonary function impairment in both conditions. Despite screening for early GERD, CDH patients continue to be at risk for the development of GERD. Many patients underestimate their symptoms and consequently do not consult a physician, increasing the risk of GERD-related complications. Despite a normal IQ we found subtle cognitive problems in CDH survivors and an increased incidence of behavioral problems, which may contribute to school failure. Due
to these sequelae HR-QoL of both CDH and EA patients is compromised, represented by the fact that patients think their health is poor and likely to get worse. With the recent development and implementation of new treatment strategies, we think that it is very important to perform a prospective follow-up study of all patients to evaluate various treatment strategies, identify patients at risk and to provide good clinical care. By preventing CDH- or EA-related complications HR-QoL may be further optimized. Finally it should be realized that nowadays these patients will reach adulthood and need life-long care of a specialist.