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Congenital diaphragmatic hernia: a single-centre experience at Kepler University Hospital Linz

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Summary Congenital diaphragmatic hernia (CDH) is found in about 1 of 3000 live births and is often complicated by pulmonary hypoplasia and alteration of the pulmonary arterial wall with resulting pulmonary hypertension. Since 2005, with the fusion of the children's hospital and the maternity clinic of the Kepler University Hospital Linz, affected neonates have been treated according to a standard protocol at our perinatal centre. Some prenatally measured parameters have been used to predict mortality, e.g., observed-to-expected lung-to-head ratio or lung volume measurements by nuclear magnetic resonance imaging. We performed a retrospective chart review of 67 newborns with CDH treated at our institution to detect any predictors of hospital mortality from parameters routinely collected within the first 24 h of life. The term "liver up" was identified as a predictor of hospital mortality; OR 9.2 (95% CI 1.9–51.1, $p=0.002$, sensitivity 79%, specificity 71%). In addition, the need for application of high-frequency oscillatory ventilation during the first 24 h was associated with mortality; OR 44.4 (95% CI 6.3–412.1, $p=0.001$, sensitivity 85.7%, specificity 88%).

Keywords Congenital diaphragmatic hernia · Extracorporeal membrane oxygenation · Neonatal disorders · Neonatal intensive care · Neonatal mortality

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Angeborene Zwerchfellhernie: Einzelzentrum-Erfahrungsbericht des Kepler Universitätsklinikums Linz

Zusammenfassung Eine angeborene Zwerchfellhernie tritt bei einem von 3000 Neugeborenen auf und ist oft mit einer Hypoplasie und Verdickung der Pulmonalarterien mit begleitender pulmonaler Hypertonie verbunden. Seit dem Jahr 2005 werden die betroffenen Neugeborenen an dem Perinatalzentrum der Klinik der Autor(inn)en nach einem Standardprotokoll behandelt. Dies wurde durch die Zusammenlegung der Frauen- und Kinderklinik des Kepler Universitätsklinikums Linz ermöglicht. Einige pränatale Parameter werden zur Vorhersage der Mortalität herangezogen, wie z. B. das beobachtete im Vergleich zum erwarteten Größenverhältnis der Lunge zum Kopfumfang oder Lungenvolumenmessungen durch Magnetresonanztomographie. Es wurde eine retrospektive Datenanalyse aus den Krankengeschichten von 67 betroffenen Neugeborenen durchgeführt, um einen Vorhersagewert der Krankenhausmortalität aus routinemäßig in den ersten 24 h erhobenen Werten zu ermitteln. Der Wert „Leber im Thorax" wurde als Vorhersagewert der Krankenhausmortalität ermittelt; Odds Ratio (OR): 9,2 (95%-Konfidenzintervall [95%-KI]: 1,9–51,1; $p=0{,}002$, Sensitivität 79 %, Spezifität 71 %). Zusätzlich war auch die Notwendigkeit einer Hochfrequenzbeatmung in den ersten 24 h mit der Krankenhausmortalität assoziiert; OR: 44,4 (95%-KI: 6,3–412,1; $p=0{,}001$, Sensitivität 85,7 %, Spezifität 88 %).

Schlüsselwörter Kongenitale Zwerchfellhernie · Extrakorporale Membranoxygenierung · Neugeborenenerkrankungen · Neugeborenen Intensivmedizin · Neugeborenensterblichkeit

Introduction

This report summarises the results of a retrospective chart review performed to show the details and the outcome of babies born with congenital diaphragmatic hernia (CDH) at Kepler University Hospital Linz. A standard treatment protocol for prenatally diagnosed CDH was introduced in 2005 at our hospital. At that time, the children's hospital and the maternity clinic were connected within the same building to constitute the perinatal centre. Since then, the babies have been delivered by caesarean section at 38 weeks of gestation in the children's operating theatre by experienced obstetricians and obstetric anaesthetists. Immediately after birth, the new-borns were supported by paediatric anaesthetists and surgeons, including the following procedure: intubation without prior mask ventilation, nasogastric tube to avoid distention of the bowel and compromise of mechanical ventilation, insertion of an intravenous line and a right radial arterial line, haemodynamic stabilisation by volume and inotropes if needed, and, finally, chest X-ray. Thereafter, the babies were referred to the paediatric ICU, where monitoring and treatment were continued according to current guidelines at that time. Conventional mechanical ventilation was the initial mode of ventilation. An ultrasound was performed to rule out malformations of other organs and an echocardiography to assess cardiac malformations, heart function or pulmonary hypertension. Nitric oxide (NO) and high frequency oscillatory ventilation (HFO) were available throughout the study period, and extracorporeal membrane oxygenation (ECMO) was introduced in 2009. These methods were applied according to clinical guidelines. Surfactant was not used routinely, but later in the course at the discretion of the attending intensivist. The target values for haemodynamic support were within the normal range for neonatal age, urine output >1 ml/kg/h, lactate <5 mmol/l. Inotropes and vasopressors including vasopressin as well as stress dose hydrocortisone were given according to the patients' needs.

Methods

Babies treated for congenital diaphragmatic hernia (CDH) between 2005 and 2020 were included in the retrospective analysis. The study was approved by the local ethics committee and informed consent was waived due to the anonymised data analysis. Routine parameters were collected from the patients' medical records. Statistical analysis was performed by PASW statistic software package (IBM SPSS Statistics 20; IBM Vienna, Austria). Binary variables were compared by Fisher's exact test, continuous variables were compared by Mann–Whitney *U*-test between survivors and non-survivors. For evaluation of parameters collected within the first 24 h to predict hospital mortality, a univariate logistic regression analysis was performed, sensitivity and specificity as well as positive and negative predictive values were assessed. Data are presented as numbers and percentages or medians and IQRs. A p-value of <0.05 was considered statistically significant.

Results

From January 2005 to December 2020, 67 new-borns with CDH were treated at our hospital. Demographic data are shown in Table 1. 76% were delivered by caesarean section and 67% were detected by prenatal ultrasound. Most of them were born at our perinatal centre. 81% of the babies had surgery after a median delay of 3 (2–6) days to allow resolution of pulmonary hypertension. An abdominal approach was used in all cases. In 33%, a patch repair was necessary. No child was operated on extracorporeal membrane oxygenation (ECMO). One child required reoperation at the age of 3 years due to a relapse of his right-sided hernia (Table 1).

A total of 30 patients (45%) had concomitant congenital malformations. 20 of them (67%) needed surgery at the time of correction of the CDH or thereafter (Table 2).

Overall survival rate of our patient cohort was 75%. After the implementation of ECMO at our institution in 2009, survival increased to 80%. Since that time, 28% of the babies with CDH were treated on ECMO and 54% of ECMO-treated patients survived. The median duration of ventilation of the entire cohort was 14.5 days; the median length of intensive care stay was 26.5 days, and the median length of hospital stay was 38.5 days (Table 3).

Causes of death were as follows: 6 patients died on ECMO—2 from sepsis due to necrotising enterocolitis and pneumonia, 2 due to circulatory problems, 1 from heart failure, and 1 from cerebral haemorrhage. 8 patients who were deemed without a chance of survival due to very low lung volumes and concomitant malformations were supported by comfort care, 3 patients

Table 1 Demographic data (numbers and percent)

Male, *n* (%)	44 (66)
Left, *n* (%)	55 (82)
Gestational age, week (median, IQR)	34 (37–39)
Birth weight, kg (median, IQR)	3.08 (2.54–3.19)
Caesarean section, *n* (%)	51 (76)
Referral from external, *n* (%)	18 (27)
Prenatal diagnosis, *n* (%)	45 (67)
Surgery, *n* (%)	54 (81)
Age at repair, days (median, IQR)	3 (2–6)
Patch repair, *n* (%)	18 (33)
Isolated CDH, *n* (%)	37 (55)
Concomitant malformations, *n* (%)	30 (45)

Table 2 Associated malformations

Malformation	Patients *n*	Surgery	Survival	Characteristics
Pulmonary sequestration	2	Simul-taneous	Yes	–
LADDs bands	2	Simul-taneous	Yes	–
Intestinal malrotation	8	Simul-taneous	Yes	–
Intestinal malrotation	1	Delayed	Yes	–
Omphalocele	2	Delayed	Yes	Tracheostomy
Meckel diverticulum	1	No	No	–
Bowel strangulation	1	Delayed	Yes	–
Small bowel volvulus	1	Delayed	Yes	–
Trisomy 9, LADDs bands	1	Simul-taneous	No	–
TAPVC	1	No	No	–
ASD II, pulmonary stenosis	1	No	Yes	–
Hypoplastic aortic arch, ISTHA, ASD, VSD	1	Simul-taneous	Yes	–
Mitral regurgitation	1	No	Yes	–
Hypoplastic aortic arch, ISTHA	1	Simul-taneous	Yes	ECMO
Hypospadias, ISTHA, ASD II	1	No	Yes	–
Dextrocardia	1	No	Yes	ECMO
VSD	1	No	Yes	–
Multiple cerebral malfor-mations	2	No	No	Comfort care
Factor VIII deficiency	1	No	Yes	ECMO

Associated anomalies: *patients n* numbers of patients. Surgery: *simultaneous* concomitant with the correction of the diaphragmatic hernia, *delayed* second intervention
LADDs bands, *TAPVC* total anomalous pulmonary venous connection, *ISTHA* aortic isthmus stenosis, *ASD* atrial septal defect, *VSD* ventricular septal defect, *ECMO* extracorporeal membrane oxygenation

Table 3 Survival and length of stay data in numbers and percent

Overall survival *n* (%)	50 (75)
Survival since ECMO institution *n* (%)	37 (80)
Patients on ECMO *n* (%)	13 (28)
ECMO survival *n* (%)	7 (54)
Ventilator days (median, IQR)	14.5 (6–26.25)
ICU LOS days (median, IQR)	26.5 (13–43.75)
Hospital LOS days (median, IQR)	38.5 (22.75–58.25)

ECMO extracorporeal membrane oxygenation, *LOS* length of stay, *ICU* intensive care unit

died weeks after surgery from pulmonary complications and heart failure.

Inhaled nitric oxide (NO) was available throughout the observation period at our hospital, and 37% of the patients were on NO treatment due to pulmonary hypertension. Almost half of these (48%) subsequently needed ECMO. NO was continued throughout the perioperative period if needed. Sildenafil was considered only postoperatively in the case of persistent increased pulmonary resistance. 50% of our surviving patients were on sildenafil treatment at hospital discharge, one was on home ventilation and oxygen therapy. Most of the sildenafil-treated patients received that therapy for 3 to 4 months after surgery.

High-frequency oscillatory ventilation (HFO) was applied in 31% of all babies. 85% of our ECMO patients were on HFO before that treatment (Table 4).

Prenatal lung-to-head ratio (LHR) measurements were available in 60% of our cohort and had been performed between weeks 20 and 38 of gestation. The results ranged from 0.6 to 4.66. There was also a wide range of observed-to-expected LHR (OE LHR) of 25 to 98% in our children. Magnetic resonance imaging (MRI)-based lung volumes were obtained in 26 patients (46%), lying between 14 and 59% at gestational weeks 26 to 37.

One child underwent foetal endoluminal tracheal occlusion (FETO) at an external centre and was subsequently treated by ECMO at our institution. The treatment history is summarised below:

After having been given the diagnosis of CDH, the child underwent FETO at Kings College, London, at 27 weeks gestational age. The balloon was removed by fetoscopy at 33 + 4 weeks gestational age in Munich. The baby boy was delivered by caesarean section (36 + 0) due to sustained uterine contractions at our hospital. His birth weight was 3710 g. After tracheal intubation, conventional ventilation failed, and the new-born was treated with inhaled NO and HFO. Nevertheless, after 5 days, extracorporeal veno-venous ECMO had to be established. Following an episode of CPR due to cardiac failure 1 day later, coarctation repair was performed; thereafter, veno-arterial ECMO was continued for 11 days leaving the chest open. The chest was closed 10 days after coming off ECMO. Correction of his CDH was possible on day 29 of life, using an abdominal patch. One day later, NO was discontinued. The abdominal wall was closed in the eighth week of life. The child was extubated on day 68. Pulmonary infections caused by *Klebsiella pneumoniae, Klebsiella oxytoca* and *Stenotrophomonas maltophilia* were treated accordingly. During his illness, the boy also suffered from cerebral haemorrhage grade IV on the right side and grade I–II on the left side. Due to persisting pulmonary hypertension, he was still on sildenafil and furosemide medication at hospital discharge. The follow-up examination in 2017 at 3 years of age presented a boy in good health, no residual gradient within the aorta, a height of 85 cm, and a weight of 11 kg.

To identify risk factors for hospital mortality, parameters recorded within the first 24 h of life were compared for difference between survivors and non-survivors. Non-survivors had their liver within the chest more often than survivors (78.6% versus 28.6%, $p = 0.001$), they had a lower "nadir oxygen saturation" (the lowest pulse oximetry saturation, SpO_2) within the first 24 h (70% versus 88%, $p = 0.03$) and were on HFO more often (85.7% versus 11.9%, $p = 0.001$). Fewer

Table 4 Characteristics of patients on extracorporeal membrane oxygenation

ECMO	Weight	Side	LHR	Liver up	Prosta-glandin	Inotrope/vasopressor	NO	HFO	Surfactant	Survived	Cause of death
1	2.80	Left	1.4	Yes	No	Yes	Yes	Yes	Yes	No	NEC
2	2.77	Left	2	No	No	Yes	Yes	No	No	Yes	–
3	3.20	Right	2.1	Yes	No	Yes	Yes	Yes	Yes	No	Circulatory
4	2.50	Left	1.6	Yes	No	Yes	Yes	Yes	Yes	Yes	–
5	2.50	Left	n. a.	Yes	Yes	Yes	Yes	No	No	Yes	–
6	3.69	Left	n. a.	No	Yes	Yes	Yes	Yes	Yes	Yes	–
7	3.07	Left	2.7	No	Yes	Yes	Yes	Yes	Yes	Yes	–
8	2.80	Right	n. a.	n. a.	Yes	Yes	Yes	Yes	Yes	No	Circulatory
9	1.90	Left	n. a.	No	Yes	Yes	Yes	Yes	Yes	Yes	–
10	2.59	Left	n. a.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–
11	2.67	Left	o/e42%	Yes	Yes	Yes	Yes	Yes	Yes	No	Heart failure
12	3.00	Left	o/e31%	Yes	Yes	Yes	Yes	Yes	Yes	No	Cerebral haemorrhage
13	2.00	Left	n. a.	Yes	No	Yes	Yes	Yes	Yes	No	Sepsis

LHR lung to head ratio, *o/e* observed to expected, *NO* inhaled nitric oxide, *HFO* high frequency oscillatory ventilation, *ECMO* extracorporeal membrane oxygenation

Table 5 Comparison of routine parameters between hospital survivors and non-survivors

Parameter	Unit	All	Hospital survivors	Hospital non-survivors	*p*-value
n	–	56	42	14	–
Male gender	*n* (%)	40 (71.4)	29 (69)	11 (78.6)	0.73
Birth weight	g	2800 (2500–3200)	2850 (2560–3330)	2800 (2360–3155)	0.49
Week of pregnancy	*n*	37 (36–38)	37 (36–38)	37 (35–38)	0.39
In utero diagnosis	*n* (%)	39 (69.6)	27 (64.3)	12 (85.7)	0.08
Referral after birth	*n* (%)	13 (23.2)	12 (28.6)	1 (7.1)	0.15
Birth mode	*n* (%)	–	–	–	0.2
Vaginal delivery	–	5 (8.9)	5 (11.9)	0	–
C-section	–	47 (83.9)	33 (78.6)	14 (100)	–
Vacuum	–	3 (5.4)	3 (7.1)	0	–
Unknown	–	1 (1.8)	1 (2.4)	0	–
APGAR 1 min	Points	6 (4–8)	7 (4–9)	6 (4–7)	0.26
APGAR 5 min	Points	8 (4.5–9)	9 (6–9)	8 (2–9)	0.41
APGAR 10 min	Points	8 (5.5–10)	9 (7–10)	8 (5–9)	1
Umbilical cord pH	–	7.31 (7.28–7.34)	7.32 (7.28–7.34)	7.3 (7.28–7.32)	0.36
Left-sided defect	*n* (%)	45 (80.4)	36 (85.7)	9 (64.3)	0.12
Liver up	*n* (%)	23 (41.1)	12 (28.6)	11 (78.6)	<0.001*
First $PaCO_2$	mm Hg	74 (62–88)	70 (57–81)	91 (71–110)	0.4
First SpO_2 preductal	%	94 (81–96)	95 (88–97)	85 (68–94)	0.07
Lowest SpO_2 first 24 h	%	84 (71–91)	88 (75–91)	70 (55–78)	0.03*
Additional defects	*n* (%)	26 (46.4)	23 (54.8)	3 (21.4)	0.1
Honeymoon	*n* (%)	40 (71.4)	35 (83.3)	5 (35.7)	0.001*
Catecholamines preoperative	*n* (%)	43(76.8)	30 (71.4)	13 (92.9)	0.049*
Nitric oxide	*n* (%)	22 (39.3)	13 (31)	9 (64.3)	0.06
HFO ventilation	*n* (%)	17 (30.4)	5 (11.9)	12 (85.7)	<0.001*
Surfactant	*n* (%)	10 (17.9)	5 (11.9)	5 (35.7)	0.1
Prostaglandin	*n* (%)	18 (32.1)	17 (40.5)	1 (7.1)	0.02*
ECMO	*n* (%)	8 (14.3)	5 (11.9)	3 (21.4)	0.39

C-section caesarean section, *$PaCO_2$* partial arterial carbon dioxide pressure, *SpO_2* arterial oxygen saturation, *HFO* high frequency oscillatory ventilation, *ECMO* extracorporeal membrane oxygenation
*Significant difference between hospital survivors and non-survivors

patients were on prostaglandin infusions (7.1% versus 40.5%, $p=0.02$) and fewer patients had a "honeymoon phase" (5% versus 35%, $p=0.001$) among non-survivors compared to survivors (Table 5).

Binary logistic regression was performed for prediction of hospital mortality. The term "liver up" was identified as a predictor of hospital mortality, OR 9.2 (95% CI 1.9–51.1, sensitivity 79%, specificity 71%, $p=0.002$) as well as application of HFO during the first 24 h, OR 44.4 (95% CI 6.3–412.1, sensitivity 85.7%, specificity 88%, $P=0.001$). The lowest saturation within the first 24 h (nadir SpO_2) below 88% was associated with an increased hospital mortality, OR 2.2 (95% CI 0.5–9.2, $p=0.36$) but not statistically significantly. If the eight cases in which no lowest SpO_2 values were documented were to be excluded, the nadir SpO_2 <88% was significantly related to hospital mortality (OR 200, 95% CI 1.6–12,913, $p=0.006$).

Discussion

The incidence of CDH is about 1:3000 in live births around the world. Survival is reported 70–80% (up to 90%) [1]. The data of our retrospective evaluation show similar results. There is often an association with reduced lung growth and vessel development leading to increased vascular resistance in CHD patients. In addition, a dynamic process of increased pulmonary vascular reactivity may be aggravated by hypoxia, hypercarbia, and acidosis. The latter may result from the inability to ventilate the babies using conventional techniques [2]. The resulting pulmonary hypertension is reported with worse survival and an increased need for ECMO in CDH patients. Treatment options are inhaled nitric oxide (NO) and sildenafil. We used NO perioperatively in our more severe cases. All patients of our cohort who subsequently needed ECMO had this inhaled treatment beforehand. We applied sildenafil only postoperatively in the cases of persistent pulmonary hypertension. As is well known, the authors of the VICI trial showed that the optimal initial ventilation strategy for CDH babies was conventional mechanical ventilation (CMV). The resulting recommendations for CMV are a PIP <25–28 cm H_2O, a PEEP of 3–5 cm H_2O, and a rate of 40–60 breaths/min. The inability to maintain $PaCO_2$ between 50 to 70 mm Hg with a PIP of 30 cm H_2O and a respiratory rate of 60 breaths/min should trigger HFO, limiting mean airway pressure (MAP) to 14–16 cm H_2O and a pressure delta (ΔP) from 30–40 cm H_2O. Otherwise, ECMO should be discussed [17, 18].

Though there are conflicting results about timing and route of delivery with the suggestion of reduced ECMO use after caesarean delivery, we plan an elective caesarean at the age of 38 weeks gestation at our institution [3–5].

Associated congenital anomalies are reported in 20% (cardiac) up to 25% (chromosomal, genitourinary) in the literature. The overall rate of concomitant malformations including intestinal malrotations in our patients was 45% [6, 7].

Several prenatal parameters have been developed to predict postnatal course and survival. Initially, lung-to-head ratio was proposed as a predictive value for survival. Measurement was recommended before 32 weeks of gestation to assess the need for foetal intervention, which is done before that age. With growing evidence of the exponentially increasing LHR during late pregnancy, the observed to expected (OE) LHR has been used more widely [8, 9]. Moreover, if LHR was measured before 25 weeks of gestation, no difference between survivors and non-survivors was detected [10].

Lung volume measurement by nuclear magnetic resonance imaging (MRI) has proved insensitive due to the unpredictable severity of pulmonary hypertension. But the extent of displacement of the liver or stomach into the thorax may indicate a larger defect and more complicated course [11]. 4 of 9 ECMO patients at our centre had their liver up. Interestingly, ECMO complications in terms of sudden interruption of backflow from the patient into the circuit occurred in the 2 patients with right-sided hernia. According to a study published in 2016, observed-to-expected MRI foetal lung volume and observed-to-expected ultrasound lung-to-head ratio are valuable prognostic parameters for survival, need for ECMO and development of chronic lung disease in left-sided CDH but not in right-sided CDH [12]. There was wide variation in the numbers of LHR, lung volumes, and particularly the timepoints of the examinations obtained in our patient cohort. But for all that, CDH pregnancies are regularly assigned to our prenatal clinic for close observation and delivery is scheduled to take place at our centre. An individual plan is made by obstetricians, paediatric surgeons and anaesthesiologists, including the decision for an ECMO standby. As a matter of course, this is not applicable to prenatally undiagnosed neonates.

There are some non-randomised reports concerning FETO. In 2001, Harrison and co-workers reported successful endoscopic tracheal occlusion in two foetuses with severe CDH [13]. In 2003, in a randomised trial of this technique, enrolment was stopped after 24 patients because of a high survival rate with standard care. Foetuses between 22 and 27 weeks with an LHR <1.4 had been included. Unfavourably, prematurity was higher in the interventional group [14].

According to a publication from 2009 concerning severe CDH, survival rate increased from 24.1 to 49.1% in left and from 0–35.3% in right CDH after FETO; 210 patients with LHR ≤1 had been included, and the procedure had been performed between 27–33 weeks of gestation [15]. Nevertheless, the medical history of our FETO patient was complicated by the need for ECMO. Through foetoscopic balloon occlusion of the trachea between the vocal cords and the carina at 27–29 weeks of gestation, accelerated lung growth is

expected. But this procedure may reduce the number of type-II pneumocytes and surfactant production. The balloon should be removed before gestational week 34 to allow an increase in the number of pneumocytes and surfactant production. At the moment, FETO is considered experimental and is not recommended aside from an ongoing multicentre trial (TOTAL trial) [16].

Wynn et al. report an overall hospital stay of 50 days after CDH repair. The result was lower in our cohort, with a median length of hospital stay of 38 days. The median age at repair was also slightly lower in our children. Presumably, the strategy to postpone surgery to allow resolution of pulmonary vascular reactivity was established later at our institution. Survival has improved by this strategy, which was introduced after the description of the so called "honeymoon", a period in the first 12–36 h after birth with adequate gas exchange and stable haemodynamics. But this period may be followed by respiratory and circulatory deterioration caused by a vasoconstrictive response of the hypoplastic pulmonary vascular bed [20]. Guidelines for the timing of surgery were published by the EURO CONSORTIUM [17]. The frequency of ECMO was 31.8% as reported by Wynn and 28% in our patients. The slightly lower rate may be due to the smaller number of our patients and the fact that ECMO was not available until 2009 at our centre.

A retrospective data analysis from Germany comprised patients between 2009 and 2013. The incidence of CDH was 2.73 per 10,000 live births, ECMO was used in 23.5%, overall mortality was 30.2% and hospital stay was 40 days. Though this analysis was performed based on insurance data with limited medical information, the authors report that very low birth weight, ECMO, persistent pulmonary hypertension and major additional malformations were risk factors for mortality within the first year of life [19].

Among the reported congenital malformations, such as chromosomal defects and genetic syndromes, structural heart defects may also be found in newborns with CDH and contribute to the pathophysiology of pulmonary hypertension. Besides the coincidence of congenial heart defects, there are minor structural abnormalities like diastolic dysfunction and borderline size of the left ventricle which lead to pulmonary venous hypertension and ineffectiveness of pulmonary vasodilators in the treatment of pulmonary hypertension. Echocardiography may reveal left-to-right shunting across an ASD and right-to-left shunting across the ductus Botalli as a hint for a left ventricular problem that has evolved through an embryonic blood flow pattern away from the foramen ovale towards the right ventricle in CDH babies [20, 21]. Therefore, milrinone might play a role by its lusitropic effect allowing better filling of the left ventricle. NO should be reserved for oxygenation difficulties due to right-to-left atrial shunting. These new insights in the role of cardiac dysfunction associated with CDH are the topic of clinical investigations and may also lead to an improvement in the care of these patients [22]. According to a retrospective multicentre evaluation, pulmonary hypertension medication was administered to 62.8% of CDH infants and 11.6% were discharged on this medication [23].

There is not only an impact of liver position but also of that of the stomach on subsequent morbidity and mortality of left-sided CDH. Equally, it seems more important than lung size itself, in that there were fewer patients with pulmonary hypertension in the "stomach down" group. A retrospective analysis comparing "stomach down" and "stomach and bowel" CDH patients is dealing with this subject [24].

There are certainly some limitations to our study, such as the retrospective design, the long observation period and the inhomogeneity of the group with and without additional malformations. To preclude major confounders in future studies, the development of a core outcome set for perinatal interventions for CDH is being planned. This should also guide future interventions and improve patient care [25].

Conclusion

In conclusion, the introduction of an interdisciplinary treatment protocol including timing, mode and place of delivery, adherence to current intensive care guidelines and introduction of an ECMO program made it possible to successfully treat congenital diaphragmatic hernia at our institution. "Liver up" and need for HFO were predictors of hospital mortality in our patient cohort.

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Author Contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Franz Hornath, Regina Greiner, Gudrun Huber, Julia Pernegger and Reza Zahedi. The first draft of the manuscript was written by Anna Hofer and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest A. Hofer, G. Huber, R. Greiner, J. Pernegger, R. Zahedi and F. Hornath declare that they have no competing interests.

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