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*Clinical Study*

# Rescue High-Frequency Oscillatory Ventilation for Congenital Diaphragmatic Hernia: What about Lung Histopathology and Necropsy Findings?

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*Introduction*. It is not yet a resolved issue whether HFOV (high-frequency oscillatory ventilation), used as primary mode or as rescue ventilation, has benefit over conventional mechanical ventilation for CDH (congenital diaphragmatic hernia) patients treatment. *Purpose*. To evaluate the success rate of rescue HFOV for CDH, and the histological characteristics of the lungs, at the autopsy of the deceased patients. *Material and Methods*. Out of 80 CDH patients, 10 were treated with rescue HFOV. The success of HFOV, histological exam of the lungs of deceased patients, and data on the followup of discharged patients were assessed. *Results*. Rescue HFOV was started between two hours and four days of life. The success rate of rescue HFOV was 20% (2/10). Autopsy findings along with pulmonary hypoplasia included coarctation of aorta ($n = 1$), pneumonia ($n = 3$), meconium aspiration ($n = 2$), hyaline membranes ($n = 2$), severe muscular hypertrophy of medium and small diameter lung arteries ($n = 1$), severe lung hypoplasia ($n = 1$), pleural effusions ($n = 2$), haemorrhagic diatesis ($n = 2$), and signs of overwhelming sepsis ($n = 1$). The five-years follow up of the two survivors revealed normal growth and neurodevelopment. *Conclusions*. The results of this study support the idea that rescue HFOV may increase survival of CDH patients, when conventional mechanical ventilation fails.

## 1. Introduction

The underlying pathophysiology of Bochdalek congenital diaphragmatic hernia (CDH) is that of pulmonary insufficiency and persistent pulmonary hypertension secondary to pulmonary hypoplasia. The severity of CDH is related mostly to the degree of hypoplasia, which depends on the size of the defect, the presence of the liver in the chest, and how early in gestation the abdominal contents were displaced [1].

A standardized postnatal management of infants with CDH, the CDH EURO Consortium Consensus, has been proposed in 2010 [2]. The different centers treating CDH patients use different mechanical ventilation strategies, and most target the use of gentle ventilation and permissive hypercapnia. The actual recommendations include the use of high-frequency oscillatory ventilation (HFOV) if conventional mechanical ventilation (CMV) fails [3]. Although many centers use HFOV as the primary mode of ventilation, it is not yet a resolved issue whether this approach has benefit over CMV. The ongoing multicenter randomized controlled trial, VICI trial, will help to clarify which primary respiratory mode, CMV or HFOV, has the most benefit on CDH patients.

Our center uses HFOV as a rescue ventilation mode for CDH patients. We conducted a study in order to evaluate the success rate of rescue HFOV, and the histological characteristics of the lungs at the autopsy exam of the deceased patients in which rescue HFOV failed.

Table 1: Characteristics of the CDH population admitted between 1997 and 2010.

| | |
|---|---|
| Patients, *n* (%) | 80 (100) |
| Male, *n* (%) | 41 (51) |
| Female, *n* (%) | 39 (49) |
| Singleton, *n* (%) | 78 (98) |
| Multiple, *n* (%) | 2 (2) |
| Birthweight (g), median (min-max) | 2735 (880–3770) |
| 1500–2500 g, *n* (%) | 25 (31) |
| <1500 g, *n* (%) | 3 (4) |
| IUGR, *n* (%) | 2 (3) |
| Gestational age (weeks), median (min-max) | 38 (28–41) |
| Preterm (<37 weeks), *n* (%) | 21 (26) |
| Inborn, *n* (%) | 58 (73) |
| Outborn, *n* (%) | 22 (27) |
| Prenatal diagnosis, *n* (%) | 53 (66) |
| Postnatal diagnosis, *n* (%) | 27 (34) |
| C-section, *n* (%) | 50 (63) |

CDH: congenital diaphragmatic hernia; IUGR: intrauterine growth restriction.

## 2. Material and Methods

Cases of CDH were identified in our database, a tertiary referral centre for neonatal surgery. All neonates diagnosed with CDH from January 1997 to December 2010 were included. Analysed data were retrieved from maternal and infant medical records.

Since 2003, the management protocol of CDH has changed, and in 2010 the CDH EURO Consortium Consensus protocol has been adopted. Inhaled nitric oxide (INO, 20 ppm) was routinely used from 2003 after echocardiography and an oxygenation index (mean airway pressure × fraction of inspired oxygen × 100/partial arterial pressure of oxygen) over 20. Sildenafil has been used in infants with persistent pulmonary hypertension refractory to INO. A policy of delayed surgery after preoperative stabilization was practiced throughout the study period. Rescue HFOV was done using SensorMedics 3100A (Sensor Medics Corporation, Yorba, Linda, CA, USA), after a period of unsuccessful conventional mechanical ventilation.

The position of the liver, side of herniation, degree of pulmonary hypertension, settings of CMV before changing to HFOV, settings used on HFOV, effect of rescue HFOV on the respiratory status of the patient evaluated by blood gases samples, rate of success of HFOV and histological exam of the lungs, and other necropsy findings of those patients whose parents consented to autopsy were analyzed. Data on the followup of discharged patients who benefited from rescue HFOV were also evaluated.

Results are presented in absolute number and percentage of the total sample. Continuous variables are presented in median (minimum and maximum). Mann-Whitney test was used to compare two independent samples and a $P$ value $< 0.05$ was considered significant.

Table 2: Clinical characteristics of the CDH population admitted between 1997 and 2010.

| | |
|---|---|
| Resuscitation | |
| 5 minute Apgar score | |
| <7, *n* (%) | 16 (20) |
| 7–10, *n* (%) | 64 (80) |
| Admission | |
| Mechanical ventilation, *n* (%) | 70 (87.5) |
| Spontaneous ventilation, *n* (%) | 10 (12.5) |
| Arterial blood pH | |
| ≥7.35, *n* (%) | 25 (31.3) |
| <7.35, *n* (%) | 55 (68.7) |
| Anomalies | |
| Chromosomal anomaly (amniotic fluid study), *n* (%) | 2 (3.7) |
| 45, X0 *n* (%) | 1 (1.8) |
| 47, XX, +i(9) (pter-p10::p10-pter).ish i(9) (wcp9+) *n* (%) | 1 (1.8) |
| Other major congenital anomaly, *n* (%) | 3 (5.6) |
| Esophageal atresia, *n* (%) | 1 (1.8) |
| Cystic hygroma of the neck, *n* (%) | 1 (1.8) |
| Coarctation of aorta, *n* (%) | 1 (1.8) |
| Nonimmune hydrops fetalis, *n* (%) | 1 (1.8) |
| Evolution | |
| Pulmonary hypertension | |
| Mild (<40 mmHg), *n* (%) | 19 (23.7) |
| Moderate (40–60 mmHg), *n* (%) | 27 (33.8) |
| Severe (>60 mmHg), *n* (%) | 34 (42.5) |
| HFOV, *n* (%) | 10 (12.5) |
| INO, *n* (%) | 18 (22.5) |
| Sildenafil, *n* (%) | 15 (18.7) |
| Inotropic support, *n* (%) | 42 (52.5) |
| ECMO, *n* (%) | 1 (1.2) |
| Need for paralysis, *n* (%) | 20 (25) |
| Preoperative pneumothorax, *n* (%) | 7 (8.7) |
| Surgery, *n* (%) | 58 (72.5) |
| Day of surgery, median (min-max) | 4 (1–42) |
| Side of hernia | |
| Right, *n* (%) | 11 (13.8) |
| Left, *n* (%) | 68 (85) |
| Bilateral, *n* (%) | 1 (1.2) |
| Intrathoracic liver, *n* (%) | 22 (20) |
| Duration of NICU stay (days), median (min-max) | 14 (1–167) |
| Deceased, *n* (%) | 41 (51.2) |
| Discharged, *n* (%) | 39 (48.7) |

CDH: congenital diaphragmatic hernia; ECMO: extracorporeal membrane oxygenation; INO: inhaled nitric oxide; HFOV: high frequency oscillatory ventilation; NICU: neonatal intensive care unit.

The study was approved by the institutional research ethics board.

Table 3: Data of the 10 patients that used rescue HFOV.

| | |
|---|---|
| Gender (male/female) | 5/5 |
| Birthweight (g), median (min-max) | 2710 (2125–3400) |
| Gestational age (weeks), median (min-max) | 38 (36–40) |
| Inborn, *n* (%) | 8 (80) |
| Side of hernia | |
| Left, *n* (%) | 7 (70) |
| Right, *n* (%) | 2 (20) |
| Bilateral, *n* (%) | 1 (10) |
| All liver intrathoracic, *n* (%) | 4 (40) |
| Left hepatic lobe intrathoracic, *n* (%) | 2 (20) |
| Persistent pulmonary hypertension | 10 (100) |
| Moderate, *n* (%) | 1 (10) |
| Severe, *n* (%) | 9 (90) |
| INO, *n* (%) | 7 (70) |
| Sildenafil, *n* (%) | 7 (70) |
| ECMO, *n* (%) | 1 (10) |
| Surgery, *n* (%) | 6 (60) |
| Deceased, *n* (%) | 8 (80) |
| Discharged, *n* (%) | 2 (20) |

ECMO: extracorporeal membrane oxygenation; HFOV: high-frequency oscillatory ventilation; INO: inhaled nitric oxide.

Table 4: Median ventilation settings, $PaCO_2$, OI, and arterial pH before (CMV) and after staring on HFOV.

| CMV | HFOV |
|---|---|
| Frequency—70/min (30–75) | Amplitude—50 (27–90) |
| Inspiratory pressure—25 (22–30) $cmH_2O$<br>Mean pressure—11 (7–15) $cmH_2O$ | Continuous distending pressure (CDP)—16 (12–21) $cmH_2O$ |
| $FiO_2$-1 | $FiO_2$-1 |
| $PaCO_2$ median (min-max) 80 (70–110) | $PaCO_2$ median (min-max) 45 (35–65), $P = 0.001$ |
| OI median (min-max) 23 (6–30) | OI median (min-max) 24 (7–32), $P = 0.785$ |
| pH median (min-max) 7.12 (7.0–7.25) | pH median (min-max) 7.25 (7.20–7.40), $P = 0.02$ |

CDP: continuous distending pressure; CMV: conventional mechanical ventilation; $FiO_2$: fraction of inspirited oxygen; HFOV: high-frequency oscillatory ventilation; OI: oxygenation index; $PaCO_2$: partial pressure of arterial carbon dioxide.

## 3. Results

A total of 80 newborns with CDH were treated at our institution during the considered period. The demographics of patient population are reported in Table 1, and the clinical characteristics in Table 2. Rescue HFOV was used in ten patients, Table 3. HFOV was started between two hours and four days of life. The reason for rescue HFOV from CMV was hypercapnia ($PaCO_2 > 60$ mmHg) in five patients (50%) and hypercapnia plus hypoxia ($PaCO_2 > 60$ mmHg plus preductal saturation < 80%) in five patients (50%). Ventilation settings and indexes before and after HFOV are reported in Table 4. After starting on rescue HFOV there was no benefit over oxygenation in any patient, and there was a significant decrease of $PaCO_2$ values, although not to normal values (45 and 60 mmHg) in three patients, and a decrease of $PaCO_2$ values to normal values in five patients. Two (20%) patients survived and were discharged. The rate of success of rescue HFOV in this subgroup of ten patients was 20% (2/10).

The histological findings of the six patients whose parents consented to necropsy are reported in Table 5.

Clinical neonatal characteristics and followup of the two survivors of CDH after rescue HFOV are reported on Table 6.

## 4. Discussion

Our center's overall survival of CDH was 49% until 2003. Since 2003, the overall survival has raised to 67% with the implementation of new protocols of treatment. HFOV is used as rescue ventilation and according to the results of our study, two patients out of ten (20%) benefited from this respiratory mode.

Many studies in the literature reported that HFOV for preoperative stabilization and for intra- and postoperative respiratory treatment of CDH has been shown to be effective and associated with a superior survival rate when compared

Table 5: Histological findings of the six patients whose parents consented to necropsy.

| Patient | Characteristics | Necropsy findings |
|---|---|---|
| 1 | Male; 38 weeks GA; 3010 g BW; inborn; left CDH; normal fetal echocardiography; started HFOV on hour 2 of life because of hypercapnia and hypoxia; INO; deceased on day 2 of life. | Coarctation of aorta; lung hypoplasia; bilateral pneumonia; exuberant aspect of hyaline membranes; presence of meconium in alveolar spaces. |
| 2 | Male; 36 weeks GA; 2125 g BW; inborn; left CDH; started HFOV on hour 5 of life because of hypercapnia and hypoxia; deceased on day 1 of life. | Lung hypoplasia; liver up; presence of meconium and hyaline membranes in alveolar spaces; small ascitis (15 mL), right pleural (6 mL), and pericardial (1 mL) effusions. |
| 3 | Female; 39 weeks GA; 2520 g BW; inborn; bilateral CDH; liver up; started HFOV on hour 2 of life because hypercapnia and hypoxia; INO; ECMO. Operated on day 2; deceased on day 17 on ECMO. | Severe bilateral lung hypoplasia; bilateral pneumonia; generalized haemorrhagic diatesis; ischemic lesions most expressed over the brain, heart, and kidneys. |
| 4 | Male; 36 weeks GA; 2230 g BW; outborn; left CDH; liver down; changed to HFOV at hour 24 of life because of hypercapnia; surgery on day 5; deceased on day 11. | Severe left lung hypoplasia; bilateral pleural effusion; bilateral pneumonia; multiorganic lesions suggestive of overwhelming sepsis. |
| 5 | Male; 40 weeks GA; 3130 g BW; outborn; C-section because of fetal stress; meconium stained amniotic fluid; right CDH; liver up; started on HFOV on day one because of hypercapnia and hypoxia; surgery on day 2; deceased on D2. | Right lung hypoplasia with de structural malformation of the lower lobe; bilateral pleural effusion (R: 45 mL; L: 10 mL); bilateral lesions of pneumonia; significant meconium aspiration; focal pulmonary haemorrhage. |
| 6 | Female; 39 weeks GA; 2600 g BW; inborn; left CDH; left hepatic lobe up; started HFOV on day 1 of life because of hypercapnia; severe pulmonary hypertension; INO; surgery on day 2; deceased on day 14 of life. | Severe left lung hypoplasia; severe muscular hypertrophy of medium and small diameter lung arteries, characteristic of severe pulmonary hypertension. |

BW: birthweight; CDH: congenital diaphragmatic hernia; GA: gestational age; HFOV: high-frequency oscillatory ventilation; INO: inhaled nitric oxide.

Table 6: Clinical neonatal characteristics and followup of the two survivors of CDH after rescue HFOV.

| Patient | Neonatal period | Followup |
|---|---|---|
| 1 | Female; 38 weeks GA; 3400 g BW; inborn; left CDH; liver down; HFOV on day 1 because of hypercapnia; INO + sildenafil; surgery day 8 of life; ventilated for 28 days; discharged day 38. | 5 years old; pectus escavatum; normal growth (weight on centile 5, height centile 50 head circumference centile 75); normal neurodevelopment. |
| 2 | Female; 38 weeks GA; 2820 g BW; inborn; left CDH; liver down; started HFOV on day 2 of life because of hypercapnia; INO + sildenafil; surgery on day 14; ventilated for 35 days; discharged on D 46. | 5 years old; normal growth (centile 25–50) and neurodevelopment. |

BW: birthweight; CDH: congenital diaphragmatic hernia; GA: gestational age; HFOV: high-frequency oscillatory ventilation; INO: inhaled nitric oxide.

to CMV [4–10]. On the other hand, some other well-conducted studies did not show improvement in survival of CDH patients when HFOV was used as rescue or first intension respiratory mode [11–13]. Although some of these studies were performed years ago, in an era where therapies for pulmonary hypertension and CDH treatment protocols were limited, the comparison to CMV did favour HFOV in some studies, and did not in others. It is still an undefined issue whether HFOV has supremacy over CMV for CDH patients.

In our study, two patients benefited from rescue HFOV, and the five years followup does not show neurodevelopmental or other significant disabilities. The other eight patients to whom HFOV was offered as rescue respiratory mode did not survive. Looking at the necropsy findings of the six patients whose parents consented to necropsy we can understand why ventilation was unsuccessful. One patient with a coarctation of aorta not diagnosed prenatally, and other findings such as pneumonia, meconium aspiration, hyaline membranes, severe muscular hypertrophy of medium and small diameter lung arteries, severe lung hypoplasia, pleural effusions, and haemorrhagic diatesis, may explain the CMV and HFOV failure. It seems that the question is how are the lungs of the CDH patients? Are they hypoplastic without other histological findings that may worsen the outcome, or are there other findings that may worsen the diagnosis? In our small series, it seems that the other findings on the lungs, and in one case a coarctation of aorta, could be the explanation to the fatal outcome.

Two out of ten patients who were ventilated with HFOV had a good outcome, suggesting that these lungs probably did not present the ominous findings of the deceased patients. In these two patients rescue, HFOV proved to be superior to CMV.

Although limited by the small number of patients and the significant period of time considered (1997–2010) in which treatment strategies and protocols for CDH have changed, the results of this study support the idea that there is a role for HFOV in CDH, when used as rescue ventilation for selected patients or as first respiratory mode. Also, the results of this

study show that we cannot judge the efficacy of one strategy of ventilation, if we do not know the histopathological characteristics of the lung. The reason why in some studies HFOV was, or was not, superior to CMV, could be better explained if a necropsy study and histological assessment of the lung were done.

Other studies, related to other pathologies, have shown that the necropsy findings and histological assessment of the lungs may change the diagnosis in a significant number of cases [14, 15].

More studies are needed to establish which respiratory mode, CMV or HFOV, is better for first respiratory treatment of CDH patients. We hope that the ongoing VICI trial may clarify this issue. The results of this study support the idea that HFOV may increase survival of CDH patients, when conventional ventilation fails.

We suggest that all deceased CDH patients should have a necropsy study in order to identify other congenital malformations that may pass undetected on prenatal and postnatal evaluation, and the lung histological findings that may explain the failure of the respiratory mode. In randomized studies comparing CMV and HFOV, the necropsy study is of great importance and should be part of the study, when comparing the failure of each respiratory mode.

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