Published in final edited form as:

J Pediatr Surg. 2010 April ; 45(4): 698–702. doi:10.1016/j.jpedsurg.2009.07.025.

Preliminary Observations of the Use of High-Frequency Jet Ventilation as Rescue Therapy in Infants with Congenital Diaphragmatic Hernia

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Abstract

Background/Purpose—Congenital diaphragmatic hernia (CDH) is associated with mortality of 10–50%. Several investigators have reported outcomes from centers using high-frequency oscillatory ventilation in their management of CDH, but there are no recent reports on use of high-frequency jet ventilation.

Methods—During the study period from January 2001 until August 2007, infants with CDH, who were cared for at Duke University Medical Center, received high-frequency jet ventilation as a rescue mode of high frequency ventilation. We compared actual survival with predicted survival for infants treated only with conventional ventilation versus those rescued with high-frequency jet ventilation after failing conventional ventilation.

Results—Survival for the 16 infants that received high frequency jet ventilation was predicted to be 63%; actual survival was 75%. Survival for the 15 infants that received only conventional ventilation was predicted to be 83%; actual survival was 87%. We observed no significant survival benefit for high-frequency jet ventilation, 8.0% (95 confidence interval; –22.0%, 38.1%, $p=0.59$).

Conclusions—Although our sample size was small, we conclude with consideration of the absolute results, the degree of illness of the infants, and the biologic plausibility for the intervention, that high-frequency jet ventilation is an acceptable rescue ventilation mode for infants with CDH.

Keywords

high frequency jet ventilation; congenital diaphragmatic hernia; survival

INTRODUCTION

The incidence of congenital diaphragmatic hernia (CDH) is 1 in 2000 to 5000 live births.¹ The survival rate of liveborn infants with CDH is variable and ranges from 63–93% at different centers.^{2,3} Although no well powered randomized controlled trials evaluating specific ventilatory strategies for CDH exist, therapies that minimize volutrauma and barotrauma are thought to improve outcomes.^{3–5}

Historically, ventilator-induced alkalosis was used in the management of pulmonary hypertension associated with CDH.⁵ High peak inspiratory pressures (PIP) and mean airway pressures (MAP) were used to reach targeted blood gases, which resulted in an increase in lung damage.^{6, 7} More recently, clinicians have taken a less aggressive approach in an attempt to improve long-term pulmonary outcomes and overall survival rates in patients with CDH.⁸ Current mechanical ventilation strategies emphasize protection of the lung by minimizing ventilator-induced lung injury from volutrauma, barotrauma and atelectotrauma. Successful strategies that have been reported include use of protocols of care to ensure consistency, permissive hypercapnia and limiting PIP.^{3-5, 9}

The physiologic rationale for the use of high frequency ventilation derives from its ability to ventilate at low tidal volumes with extremely short inspiratory time, thereby avoiding over-distention and lung injury. High frequency jet ventilation (HFJV) is a mode of high frequency ventilation that utilizes small, high velocity, rapid breaths delivered through a pinch valve coupled with the concurrent use of a conventional ventilator to deliver end expiratory pressure. Exhalation in HFJV is passive, and this mode of ventilation allows for the use of low airway pressures to adequately ventilate and oxygenate. There are several reports of the use of high frequency oscillatory ventilation (HFOV) in the management of CDH as a first line therapy, or as a rescue modality when conventional ventilation fails.^{3, 5, 10} However, there are no current reports, and only one report of 5 infants from 1985, outlining clinical outcomes following use of HFJV in patients with CDH.¹¹ The purpose of this study was to report our recent experience with HFJV used as a rescue mode of ventilation for patients with CDH and respiratory failure.

METHODS

We included all infants admitted to Duke University Medical Center Intensive Care Nursery with the diagnosis of CDH between January 2001 and August 2007. Patients were excluded from analysis if they had major congenital anomalies other than CDH or gestational age < 37 weeks. Patients with CDH received HFJV when conventional mechanical ventilation (CMV) failed. Failure of CMV was defined as requiring a PIP > 26 cmH₂O or MAP > 12 cmH₂O to achieve a PaCO₂ < 65 mmHg. Infants in the HFJV group were defined as infants requiring HFJV at any point in their care prior to discharge. Infants that never received HFJV were defined as the CMV group. During this epoch, we used synchronized, pressure-cycled, intermittent mandatory ventilation. Usual inspiratory times were set between 0.3 and 0.4 seconds, end expiratory pressures were in the range of 4–6 cmH₂O, and inspiratory pressures initially set at 20 – 25 cmH₂O depending on physical exam findings of air movement in the lung contralateral to the defect.

Criteria for use of extracorporeal membrane oxygenation (ECMO) included an inability to achieve > 85% preductal oxygen saturation, postductal PaO₂ > 30 mmHg, or a postductal pH > 7.25, after having reached a preductal oxygen saturation higher than 85% at some point in the clinical course. An oxygenation index > 40, rising serum lactate levels, oliguria, and poor perfusion as an indicators of respiratory failure and significant cardiovascular compromise were also considered in the decision to use ECMO. After ECMO treatment, each patient's initial mode of ventilation was determined based on clinical status.

For comparisons of survival among CDH infants who received only CMV and those who received CMV plus rescue HFJV, we used a Wilcoxon rank-sum test or Fisher's exact test where appropriate. To evaluate the effect of HFJV on outcome, we determined the excess survival for each infant based on the difference between actual survival (survived = 1, deceased = 0) and the predicted chance of survival which was calculated using the equation developed by the CDH Study Group in 2001 from an examination of a cohort of 322 infants

with CDH from 71 centers.¹² Predicted survival was calculated as follows: $\text{survival} = 1 - 1/(1 - e^{-x})$ where $x = 5.024 - 0.9165 * (\text{birth weight in kg}) - 0.4512 * (5 \text{ min APGAR})$. For example, a 3.0 kg infant with a 5 minute Apgar score of 4 would have a predicted survival of 38.5%. The excess survival for a surviving infant with a predicted survival of 38.5% would be calculated as follows: $1 - 0.385 = 0.615$. We then used linear regression to examine the relationship between the use of HFJV and excess survival.

Analysis was conducted using STATA 10 (College Station, Texas). The Duke University Institutional Review Board provided permission to conduct this analysis.

RESULTS

Thirty-one infants met inclusion criteria of gestational age ≥ 37 weeks and absence of other major congenital anomalies. Although the median birth weights of the HFJV and CMV groups were similar (Table 1), the patients that required HFJV during their care were initially more critically ill than the patients who only required CMV. Patients that required HFJV during their care had a lower median 5 minute APGAR score compared to the CMV group. The HFJV group received inhaled nitric oxide (iNO) therapy and ECMO more frequently than the CMV group.

Twenty-eight (90%) infants survived to surgical repair. Prior to repair, the mean and median number of days on HFJV were 3.6 and 0 (0, 5.5) days, respectively. The mean and median number of days on CMV prior to repair were 2.8 and 2 (1, 3.5) days, respectively. Following repair, the mean and median number of days on the HFJV were 2.4 and 0 (0, 1.5) days, respectively. The mean and median number of days on CMV following repair were 3.9 and 3 (1, 5) days, respectively. The longest duration of HFJV was 68 days by a 3.09 kg infant that did not survive.

The predicted survival based on the equation developed by the CDH study group of the entire cohort was 73%; however, 81% (25/31) of the infants survived to discharge (Figure 1). The predicted survival of the infants receiving only CMV was 83%, and 87% (13/15) of these infants survived to discharge. The predicted survival of the HFJV infants was 63%, and 75% (12/16) of these infants survived to discharge. Although the difference in actual survival vs. predicted survival was greater (12%) in the HFJV cohort compared to the conventional ventilation cohort (4%), this difference was not statistically significant, $p=0.59$. Use of linear regression to predict the excess survival by mode of ventilation showed no significant benefit for HFJV, 8.0% (95 confidence interval; -22.0%, 38.1%, $p=0.59$).

There was no statistical difference in survival when comparing patients with right-sided versus left-sided lesions (Table 2). Although not statistically significant, survival was lower for patients receiving HFJV or iNO and for Caucasian infants.

DISCUSSION

CDH remains a complex and challenging disease, and clinicians caring for newborns with CDH are often faced with multiple pathophysiologic challenges including hypoplastic and dysmature lungs and maldeveloped pulmonary vasculature.^{13, 14} Recent reports suggest improved survival from lung protective ventilation strategies, but there are no well-powered randomized clinical trials for testing any ventilatory strategies in these infants.⁹ High frequency ventilation allows for gas exchange at low ventilation volumes thereby decreasing iatrogenic pulmonary barotrauma. We believe the results of our current approach, which includes use of HFJV as a rescue strategy, add to the evidence supporting the lung protective approach.

In the one prior report of use of HFJV in 5 patients with CDH, only one survived.¹¹ There are no more recent reports of HFJV as rescue therapy for infants with CDH, but there are several reports demonstrating the effectiveness of HFOV.^{15–17} In one recent retrospective review of 111 CDH infants treated with early HFOV and presurgical stabilization, the survival rate was 69.4% using HFOV immediately after birth.¹⁷ Goal average HFOV ventilator settings were: MAP 13–15 cmH₂O, ΔP (amplitude) 30–40 cmH₂O, and frequency 10 Hz. The predicted survival using the same CDH Study Group equation used in our study was 69%, which was not different than their actual survival among the whole cohort of 69.4%. Low, moderate and high risk subgroups were individually examined, and again, no difference between observed and predicted survival was noted.

In the absence of definitive CDH-specific clinical trials or animal studies, we have used HFJV for CDH patients because of study results in other non-CDH animal models and patient populations with respiratory and cardiovascular diseases. In animal studies^{18–20} as well as reports from pediatric patients,²¹ cardiovascular parameters, including pulmonary vascular resistance, are improved on HFJV versus either conventional ventilation or HFOV. Although the evidence suggests that HFJV has advantages over HFOV, there is not a well-designed clinical trial comparing their use for CDH. Recent animal studies in the nitrofen-induced CDH model have demonstrated increased expression of vasoconstrictor substances versus vasodilators with 6 hours of conventional mechanical ventilation,²² but there have been no animal studies comparing effects of HFJV with either HFOV or CV on such potential pathophysiologic mechanisms of postnatal lung disease.²³ There are theoretical advantages of HFJV over HFOV for infants with CDH that could explain the improvement in pulmonary vascular resistance. First, in experimental animal and in adult clinical situations with non-CDH respiratory and cardiovascular diseases and injuries, lower pressures are required to achieve similar blood gases, and the lower pressure requirement is a likely mechanism that improves systemic and pulmonary venous return.^{20, 24} Secondly, and related to the need to maintain higher pressures with HFOV than HFJV, the expiratory phase of HFOV is active which could lead to airway collapse and atelectasis if inadequate mean airway pressure is maintained relative to the set amplitude. The expiratory phase is passive with HFJV, with the intra-alveolar pressure highest along the breathing circuit. Atelectasis is prevented by the concurrent application of positive end expiratory pressure by a conventional ventilator. The need for higher mean airway pressures to maintain lung function and optimal blood gases for HFOV compared with HFJV has been demonstrated in piglet models of both cardiac and respiratory failure,²⁵ but has yet to be demonstrated in a model of CDH. In addition, with HFOV routine inspiratory to expiratory ratio is 1:2, with a frequency of 10 Hz, one third of each cycle (minute) is spent with oscillatory pressures above the mean, while for two thirds of the equivalent period the pressure is below the mean. This contrasts with routine initial settings for HFJV of 7 Hz (420 breaths/minute) and an inspiratory time of 20 milliseconds, resulting in 86% of each cycle spent at the end expiratory pressure. With the vast majority of any “ventilatory minute” being maintained at the end expiratory pressure, resistance to cardiac filling or outflow is minimized. With the oscillator, higher airway pressures for more of any unit of time may result in compromised preload via increased intrathoracic pressures.^{26, 27} In both HFOV and HFJV, careful assessment of preload and cardiovascular support may obviate many of the cardiovascular response differences in the various ventilatory modes.²⁸ Animal studies have demonstrated a higher risk of gas trapping with HFJV than with HFOV under certain conditions.²⁹ During our study period, this was monitored closely with serial chest radiographs and arterial blood gas measurements.

We used the regression equation developed by the CDH study group to predict survival of infants in our cohorts with predicted survival of our CDH patients based on established methods of disease severity.¹² In 2003, Downard et al, compared actual with predicted

survival in a cohort of 39 patients with CDH over a two year time period.² They showed that the actual survival during the time period at their institution was significantly higher than predicted (94% vs. 68%), $p < 0.001$. A recent study from the Canadian NICU network described a cohort of 88 patients with survival significantly higher than that predicted by the CDH study group equation (83% vs. 62%), $p = < .01$.³⁰ This paper also showed a significantly higher actual survival in patients treated at institutions with more than 12 CDH admissions during the 22-month study period (90% vs. 77%), $p < 0.01$. Both high and low volume centers had similar predictive survival (61% vs. 63%), $p = 0.67$. The CDH Study group equation is an effective tool that allows for estimation of survival in the first 5 minutes of life for individual infants, and minimizes the effect of center specific treatments.^{31, 32} In addition, this method of predicting survival does not depend on clinical, laboratory or radiographic measurements. Previous work has shown the superior predictive ability of this equation versus two other mortality-predictive models which use clinical and/or laboratory data, namely, the Wilford Hall/Santa Rosa clinical predictive formula and the Canadian Neonatal Network predictive equation.³² The equation was developed as a way to estimate disease severity and estimate risk, independent of treatment and used appropriately, can be used by centers to evaluate predicted and actual survival.¹²

Because of the epochal differences in the CDH Study Group cohort and our cohort, we are limited in our ability to discern whether the observed versus predicted differences in survival result from refinements in multiple aspects of care over time. Unfortunately, the sample size of our cohort prevents us from knowing whether or not the absolute increase of 12% in observed compared with predicted survival was a reliable estimate. Although the actual survival of patients treated with HFJV was not significantly higher than predicted, these data suggest that HFJV is an acceptable method of ventilatory support for patients with CDH when conventional ventilation at a relatively high inspiratory pressure fails. We, like many others, await prospective randomized trials of the multiple hypothesized 'optimal' management strategies that appear to have led to improved survival for infants with congenital diaphragmatic hernia.

Abbreviations

CDH	Congenital diaphragmatic hernia
CMV	Conventional mechanical ventilation
ECMO	Extracorporeal membrane oxygenation
HFJV	High frequency jet ventilation
HFOV	High frequency oscillatory ventilation
iNO	Inhaled nitric oxide
MAP	Mean airway pressure
PIP	Peak Inspiratory pressure

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Figure 1.
 Predicted Survival for Each Infant*
 * calculated from CDH Study Group equation

Table 1**Cohort Demographics**

	HFJV (N=16)	CMV (N=15)	P-value
Male	38% (6/16)	67% (10/15)	0.16
Caucasian	63% (10/16)	33% (5/15)	0.21
BW (g) Median, IQR	3215 (3005, 3500)	3400 (3000, 3520)	0.55
5 minute APGAR, IQR	6 (5,7)	8 (8,9)	<0.001
Inborn	75% (12/16)	40% (6/15)	0.07
ECMO	38% (6/16)	7% (1/15)	0.08
iNO	63% (10/16)	14% (2/14)	0.01
Left-Sided CDH	69% (11/16)	67% (10/15)	0.60

HFJV – High frequency jet ventilation

CMV – Conventional mechanical ventilation

BW – Birth weight

IQR – Interquartile range

CDH – congenital diaphragmatic hernia

ECMO – Extracorporeal membrane oxygenation

iNO – Nitric oxide

Table 2

Survival to hospital discharge

	Survived	P-value
Overall	25/31 (81%)	
Sex		
Male	14/16 (88%)	0.3
Female	11/15 (73%)	
Race		
White	10/15 (67%)	0.37
Black	6/7 (86%)	
Hispanic	7/7 (100%)	
Asian	2/2 (100%)	
Inborn		
Yes	14/18 (78%)	0.5
No	11/13 (84%)	
Site		
Left	16/21 (76%)	0.35
Right	9/10 (90%)	
iNO		
Yes	8/12 (67%)	0.07
No	17/18 (94%)	
ECMO		
Yes	4/7 (57%)	0.11
No	21/24 (88%)	
HFJV		
Yes	12/16 (75%)	0.36
No	13/15 (87%)	