Journal of Pediatric Surgery 50 (2015) 739–743

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Persistent hypercarbia after resuscitation is associated with increased mortality in congenital diaphragmatic hernia patients ☆

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ARTICLE INFO

Article history:
Received 21 January 2015
Accepted 13 February 2015

Key words:
Congenital diaphragmatic hernia
Hypercarbia
Prenatal imaging
Arterial blood gas
Mortality

ABSTRACT

Background: Within congenital diaphragmatic hernia (CDH) care, there have been attempts to identify clinical parameters associated with patient survival, including markers of postnatal pulmonary gas exchange. This study aimed to identify whether postnatal pulmonary gas exchange parameters correlated with CDH patient survival.
Methods: A retrospective review was performed of isolated CDH neonates treated at a single institution from 1/2007 to 12/2013. Patient demographics, prenatal imaging, and postnatal clinical parameters, including arterial blood gas values within the first 24 hours of life, were collected.
Results: Seventy-four patients with isolated CDH were identified. Fifty-seven had fetal MRI. Overall, 30-day patient survival was 85%. Sixteen infants (22%) required ECMO within 24 hours. Mean initial $PaCO_2$ in nonsurvivors was higher, and infants who remained hypercarbic postresuscitation (72 ± 19 mmHg) had a worse prognosis than those who resuscitated to a normal $PaCO_2$ (39 ± 1.6 mmHg) ($p < 0.001$). Prenatal fetal lung volumes measured by MRI were not strongly correlated with $PaCO_2$ levels.
Conclusion: CDH nonsurvivors are unable to maintain sufficient pulmonary gas exchange during the first 24 hours of resuscitation. Furthermore, prenatal fetal lung volumes are weakly correlated with actual pulmonary gas exchange. These data may be useful for patient counseling during the resuscitative phase of CDH care.

1. Background

Congenital diaphragmatic hernia (CDH) is a rare congenial anomaly that is present in 1 in 3000 live births [1–3]. The reported mortality rate for this disease is 20–50%, depending on the series [4–6]. Historically, patients with severe CDH were treated with immediate surgical repair. However, as understanding of the disease has evolved, the timing of CDH surgery has shifted to a delay in repair with a focus on preoperative pulmonary resuscitation and stabilization. Patient survival during the resuscitative period is largely dependent on the severity of pulmonary hypoplasia and pulmonary hypertension, and this area has been the focus of increasing research efforts. Although prenatal imaging parameters have been used as predictors of pulmonary morbidity and mortality, there currently exists no postnatal measurement to accurately determine pulmonary function. This paradigm has led to increased efforts to define clinical variables that serve as markers of pulmonary hypoplasia to predict patient prognosis. As such, attention has been directed to preoperative arterial blood gases (ABGs) as a potential indicator of pulmonary function. One of the initial studies to examine this relationship was published in 1991 by Price et al. using the Extracorporeal Life Support Organization database [7]. In this study, they reported that a low PaO_2 on ABG was found to be associated with increased mortality in CDH patients.

After this initial study by Price et al., other studies began evaluating ABGs for prognostication and found an association between the ability to resuscitate to a normal $PaCO_2$ level and higher survival [4,8]. Salas et al. reported a cutoff of $PaCO_2$ of 60 mmHg that was associated with or predictive of survival in their patient cohort. Although these studies are limited as one was performed in the era of minimal preoperative stabilization before operative intervention [4] and the other reviewed ABGs only at a specified time point [8], these studies suggest the importance of $PaCO_2$ as a potential marker for pulmonary hypoplasia. The identification of potential predictive variables of severe pulmonary hypoplasia can be central in the clinical decision making for CDH patients. This is especially crucial in instances when the clinician is evaluating a CDH patient and deciding whether ECMO or surgery will confer any benefit given the severity of the pulmonary hypoplasia. Therefore, the objective for this study was to evaluate prenatal imaging parameters and laboratory trends that may serve as markers for pulmonary hypoplasia to delineate if any one parameter was associated with increased 30-day mortality. Specifically, we hypothesize that postnatal $PaCO_2$ provides an accurate measure of pulmonary function and ventilatory capacity and, as such, is useful in predicting 30-day mortality in infants with isolated CDH.

☆ Disclosures: The authors have no disclosures of funding or financial support to disclose with regard to the preparation of this manuscript.
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http://dx.doi.org/10.1016/j.jpedsurg.2015.02.028
0022-3468/

2. Methods

2.1. Patient population

Neonates included in this study were patients with isolated congenital diaphragmatic hernias that were evaluated within the first 24 hours of life at a single large academic center. The study time period was from January 2007 to December 2013. The majority of patients were inborn; however, patients transferred from outside institutions were included if the patient arrived within 24 hours of birth. Patients were excluded from the study if they had concomitant congenital heart disease, major congenital anomalies such as omphaloceles, known genetic syndromes (Trisomy 13, 18, and 21), or Fryns syndrome.

2.2. Prenatal imaging measurements

The measurements for prenatal imaging parameters have been described in previous studies from our institution [9,10]. In brief, the total fetal lung volume (TFLV) was calculated using MR images. Lung volumes were measured in axial planes by standard volumetric technique. Observed-to-expected total fetal lung volume (O/E-TFLV) was calculated by dividing the measured TFLV by the mean expected TFLV reported in the literature at the respective gestational age of each fetus. The ultrasound derived lung-to-head ratio (LHR) was measured using two-dimensional ultrasonography by multiplying the two longest perpendicular diameters of the contralateral lung at the level of the four-chamber view of the heart and dividing this by head circumference. Quantification of liver herniation was evaluated by measuring volumes of the herniated liver and the total liver in coronal planes on MR images and %LH was obtained by calculating the ratio of herniated liver volume to total fetal liver volume.

2.3. Neonatal CDH management protocol

A standardized management protocol [11] was utilized to direct care in all cases to attempt optimal cardiopulmonary stability prior to CDH repair. To summarize, the protocol entails immediate endotracheal intubation and gentle mechanical ventilation. High-frequency oscillatory ventilation (HFOV) was initiated when criteria for transition from conventional mechanical ventilation to HFOV were met. Pulmonary vasodilators such as nitric oxide were initiated for patients with severe pulmonary hypertension. Extracorporeal membrane oxygenation (ECMO) was used for patients with severe pulmonary or cardiac compromise refractory to medical management.

2.4. Study design and clinical variables

The study was a retrospective chart review. Patient demographics collected included, gestational age, side of defect, and survival at 30 days. Pulmonary data were collected for all ABGs obtained within the first 24 hours of life or prior to the initiation of ECMO, whichever was reached first. After collecting all appropriate ABG measurements, the best $PaCO_2$ was defined as the value closest to the normal physiologic range (Texas Children's Hospital reference value: 27–40 mmHg), and this was documented for each patient and used for analysis. Trends for PaO_2 were also collected. As a recent study reported that initial $PaCO_2$ > 60 mmHg was a marker for poor survival [12], we also performed an analysis using a threshold of $PaCO_2$ > 60 mmHg in our patient population to determine mortality outcomes.

2.5. Statistical analysis

Patient survival was calculated at 30 days of life. Prenatal imaging parameters and postnatal laboratory measurements for both groups were evaluated using a comparison of means with a student's *t* test. A Pearson correlation coefficient was calculated to assess the relationship between best $PaCO_2$ and prenatal imaging variables of significance on univariate analysis. Data are represented as mean ± standard error of the means. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Study population

Seventy-four neonates met inclusion criteria for the study. Patients that were evaluated at the Texas Children's Hospital (TCH) Fetal Center were diagnosed at an average gestational age of 24.7 ± 6.4 weeks. Of the 74 neonates, 84% (n = 63) of patients had isolated left sided congenital diaphragmatic hernia and 77% (n = 57) had prenatal imaging. There were no differences between survivors and nonsurvivors with regard to gestational age at diagnosis, gender, inborn status, or side of diaphragmatic defect (Table 1).

3.2. Patient outcomes

Twenty-two percent of the patients (n = 16) required ECMO within the first 24 hours of life. The 30-day mortality rate was 15% (n = 10) in our cohort. The mean initial $PaCO_2$ was higher in nonsurvivors than those who survived (121 ± 20 vs. 68 ± 4 mmHg, p < 0.001) and the mean initial PaO_2 was significantly lower in nonsurvivors than in survivors (36 ± 5.4 vs. 55 ± 3.3, p = 0.032). After resuscitative efforts, neonates who did not survive had an average best $PaCO_2$ in the hypercarbic range (72 ± 19 mmHg) while survivors had best $PaCO_2$ within physiologic range (39 ± 1.6 mmHg) (p < 0.001) (Fig. 1). There was no significant difference between the best PaO_2 between survivors and nonsurvivors (Table 2). Furthermore, when followed over a 24-hour time continuum, survivors and nonsurvivors were able to reach an average physiologic range of $PaCO_2$, but nonsurvivors were unable to maintain that lower range (Fig. 2).

3.3. Association of neonatal survival with $PaCO_2$

Patients were stratified by initial $PaCO_2$ of less than or greater than 60 mmHg, 36 infants had $PaCO_2$ > 60 mmHg and 38 infants had $PaCO_2$ < 60 mmHg. Of the patients with $PaCO_2$ > 60 mmHg, 22% (n = 8) were nonsurvivors compared to 5.3% nonsurvivors (n = 2) with initial $PaCO_2$ < 60 mmHg (p = 0.033) (sensitivity 20%, specificity 44%, PPV 5%, NPV 78%).

Patients were then restratified based on best $PaCO_2$ with a cutoff value of 60 mmHg. Of the 8 infants with best $PaCO_2$ > 60 mmHg, 50% (n = 4) were nonsurvivors compared to the 9.1% nonsurvivors with a best $PaCO_2$ < 60 mmHg (p = 0.001) (sensitivity 60%, specificity 6%, PPV 9%, NPV 91%).

3.4. Prenatal imaging and association with postnatal $PaCO_2$

In the 57 patients with prenatal imaging, there were no differences in LHR between the survivors and nonsurvivors. However, there was a significant difference in the percent of liver herniation (18% ± 2.6 vs. 31% ± 1.2, p = 0.024) and O/E-TFLV (0.39 ± 0.02 vs. 0.23 ± 0.04) between survivors and nonsurvivors (Table 2). Despite the difference in imaging parameters and 30-day outcomes, there was no strong

Table 1
Characteristics and outcomes of CDH patients who survived or died at 30 days of life.

Clinical factors	Survived (N = 64)	Died (N = 10)	p-Value
Gestational age at diagnosis, weeks (mean ± SEM)	25 ± 0.89	23.3 ± 2.5	0.507
Male, n (%)	38 (60)	6 (60)	1.0
Inborn status, n (%)	55 (87)	9 (90)	0.727
Left CDH, n (%)	52 (83)	8 (80)	0.761