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ABSTRACT

Objective To assess the predictive value of tidal volume (Vt) of spontaneous breaths at birth in infants with congenital diaphragmatic hernia (CDH).

Design Prospective study.

Setting Tertiary neonatal intensive care unit.

Patients Thirty infants with antenatally diagnosed CDH born at Hospital Sant Joan de Déu in Barcelona from September 2013 to September 2015.

Interventions Spontaneous breaths and inflations given in the first 10 min after intubation at birth were recorded using respiratory function monitor. Only expired Vt of uninterrupted spontaneous breaths was included for analysis. Receiver operating characteristics (ROC) analysis was performed and the area under the curve (AUC) was estimated to assess the predictive accuracy of Vt.

Main outcome measures Mortality before hospital discharge and chronic lung disease (CLD) at day 28 of life.

Results There were 1.233 uninterrupted spontaneous breaths measured, and the overall mean Vt was 2.8±2.1 mL/kg. A lower Vt was found in infants who died (n=14) compared with survivors (n=16) (1.7±1.6 vs 3.7±2.1 mL/kg; p=0.008). Vt was lower in infants who died during admission or had CLD (n=20) compared with survivors without CLD (n=10) (2.0±1.7 vs 4.3±2.2 mL/kg; p=0.004). ROC analysis showed that Vt ≤2.2 mL/kg predicted mortality with 79% sensitivity and 81% specificity (AUC=0.77, p=0.013). Vt ≤3.4 mL/kg was a good predictor of death or CLD (AUC=0.80, p=0.008) with 85% sensitivity and 70% specificity.

Conclusion Vt of spontaneous breaths measured immediately after birth is associated with mortality and CLD. Vt seems to be a reliable predictor but is not an independent predictor after adjustment for observed/expected lung to head ratio and liver position.

What is already known on this topic?

- Congenital diaphragmatic hernia (CDH) is associated with high morbidity and mortality.
- Observed/expected lung to head ratio and the position of the liver are the most widely used prenatal predictors of outcome in infants with CDH.

What this study adds?

- This is an evaluation of the predictive value of tidal volumes measured immediately after birth of infants with CDH.
- Tidal volume is correlated with observed/expected lung to head ratio and is therefore not an independent predictor of outcome.
- Tidal volume could be useful as a measure to confirm the antenatal prognosis of severe hypoplasia.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a fetal abnormality occurring in approximately 1 in 2500 live births.[1] Herniation of abdominal contents into the thoracic cavity through a hole in the diaphragm results in abnormal lung development, characterised as lung hypoplasia.[2] It is hypothesised that the pathogenesis of pulmonary hypoplasia is multifactorial, with genetic defects and/or environmental injury followed by compression of the lungs interfering with its growth.[3] The pulmonary vasculature is also underdeveloped, and this often results in pulmonary hypertension after birth.[4–6] Pulmonary hypoplasia and pulmonary hypertension are the main causes of mortality and morbidity in these infants.[1 7] Even in referral centres with extensive experience in the management of CDH, postnatal mortality rates vary from 10% to 35%.[8–13] In addition, 41% of the survivors are affected by chronic lung disease (CLD).[14]

The wide clinical spectrum and severity of CDH make the establishment of an individual prognosis challenging. Identifying infants at high risk of mortality and morbidity who may benefit from advanced therapies could help individualise treatment strategies after birth. Prenatal predictors to determine CDH severity have been defined, but they are generally not used to individualise postnatal management. These prenatal predictors are observed/expected lung to head ratio (O/E LHR) and the position of the liver.[15–17] Previous studies reported that a poor O/E LHR or a diagnosis of right-sided CDH is often associated with an early start of extracorporeal membrane oxygenation (ECMO) therapy.[16 18] Several studies have created postnatal mortality-predictive models. The Congenital Diaphragmatic Hernia Study Group model is based on birth weight, 5 min Apgar, pulmonary hypertension, major cardiac defects and chromosomal anomalies, and the Wilford Hall/Santa Rosa equation is based on blood gas measurements.[19–21] To date, no studies have examined tidal

volumes (Vt) of spontaneous breaths in the first minutes after birth as a predictive factor for adverse outcomes.

Vt in the first minutes after birth depends on lung compliance and lung volume, which vary considerably in infants with pulmonary hypoplasia.[22–24] We hypothesised that Vt of spontaneous breaths at birth reflects the severity of lung hypoplasia and could be used as a predictor of outcome. The secondary objective was to evaluate the added value of Vt to the currently used prenatal predictors of CDH severity.

METHODS

This observational prospective cohort study was performed at the tertiary neonatal intensive care unit of Hospital Sant Joan de Déu (HSJD) in Barcelona, Spain. From September 2013 to September 2015, all consecutive liveborn infants with antenatally diagnosed CDH were eligible for this study.

Data collection during stabilisation at birth

All patients were electively intubated in the first 10 min after birth, according to the European and Spanish guidelines of infants with CDH.[25 26] In some cases intranasal midazolam is given when intubation was hindered by the infant's movements. Muscle relaxants or other medications were not used in the delivery room. A T-piece device (Neopuff Infant Resuscitator; Fisher & Paykel Healthcare, Auckland, New Zealand) was used for manual ventilation. After intubation, a flow sensor was placed between the device and the endotracheal tube. Infants were started on ventilation support with a peak inspiratory pressure at 25 cm H_2O, positive end-expiratory pressure (PEEP) of 5 cm H_2O and inspiratory fraction of oxygen (FiO_2) of 0.3.

Flow and pressure waves were obtained from the Florian Respiratory Monitor (Acutronic Medical Systems, Hirzel, Switzerland), and inspired and expired Vt were calculated. The system also calculated the respiratory rate and minute volume. All these analogue output signals were subsequently collected and digitised at 200 Hz using the Spectra Software (Grove Medical, Hampton, UK). Simultaneously, video recording was used to help interpret the respiratory parameters during review for analysis. The umbilical cord was clamped early in all included infants. Measuring and recording respiratory parameters and video did not influence the process of resuscitation or management in the neonatal intensive care unit.

Analysis of the spectra recordings

Every breath and inflation measured during the first 10 min after intubation at birth were analysed and categorised into different breathing patterns: manual inflation, spontaneous breathing or spontaneous breath coinciding with manual inflation, as described before.[24] Vt of spontaneous breathing, during and in between inflations given or when only PEEP is temporarily given, was analysed.

Expired tidal volume (Vte) was used for analysis and displayed per kilogram of body weight. The Vt of infants who did not breathe spontaneously was defined as 0 mL/kg. Spontaneous breaths that were interrupted during expiration by a manual inflation were excluded. Interrupted spontaneous expirations were defined as the difference between spontaneous inspired tidal volume (Vti) and Vte of more than 20% ([Vti–Vt/Vti] × 100) when an inflation was given. Data were not blinded for the team. However, the respiratory function monitor (RFM) was measured for study purposes; there was no protocol for using RFM measurements at birth to guide respiratory support at birth.

Postnatal outcome

We used the endpoints mortality and 'death or CLD' for analysis. Mortality was defined as death before discharge. CLD was defined as oxygen dependency at day 28 of life. In our cohort, all non-survivors died before day 28 of life. The sample size of survivors was too small for a reliable analysis of the predictive value of Vt on CLD alone; therefore, we used the combined endpoint 'death or CLD'.

Postnatal treatment included the need for ECMO, high-frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO) during admission. The criteria for ECMO were defined as a persistent oxygen index greater than 35 or an alveolar-arterial gradient greater than 600 mm Hg. HFOV was used as rescue therapy in severe and persistent hypoxaemia and hypercapnia despite conventional ventilation. iNO was the first-choice therapy for pulmonary hypertension.

Statistical analysis

A convenience sample was recruited over a period of 2 years. Statistical analysis was performed using SPSS V.24.0. Data are presented as median (IQR), mean±SD or number (percentage). Outcome parameters were compared using Student's t-test for parametric comparisons, the Kruskal-Wallis for non-parametric comparisons for continuous variables and the χ^2 test for categorical variables. Univariable and multivariable analyses were performed using logistic regression analysis. Receiver operating characteristics (ROC) analysis was performed and the area under the curve (AUC) was estimated to assess the predictive accuracy of Vt and to determine the optimal cut-off values. Reported p values were two-sided, and a p value <0.05 was considered statistically significant.

RESULTS

During the study period, 40 infants with CDH were born alive at HSJD and 30 infants were included in this study (for baseline

Table 1 Patient characteristics

		Death			Death or chronic lung disease		
	All patients (N=30)	Yes (n=14)	No (n=16)	P value	Yes (n=20)	No (n=10)	P value
Male, n (%)	12 (40)	6 (43)	6 (38)	0.50	8 (40)	4 (40)	0.77
Birth weight (g), mean (SD)	2948 (544)	2769 (570)	3104 (484)	0.10	2809 (538)	3227 (459)	0.04
Gestational age (weeks), mean (SD)	38 (2.8)	38 (2.6)	38 (3.1)	0.99	37 (3.1)	40 (1.0)	0.009
Apgar score at 5 min, median (IQR)	8 (7–9)	7 (5–9)	8.5 (7–10)	0.03	8 (5–9)	9 (7–10)	0.045
CDH left, n (%)	29 (97)	13 (93)	16 (100)	0.28	19 (95)	10 (100)	0.47
Caesarean delivery, n (%)	6 (20)	3 (21)	3 (19)	0.86	5 (25)	1 (10)	0.33

CDH, congenital diaphragmatic hernia.

Table 2 Prediction of mortality

	Death		Univariable analysis		Multivariable analysis*	
Predictor	Yes (n=14)	No (n=16)	OR (95% CI)	P value	OR (95% CI)	P value
Vt, mean (SD)	1.7 (1.6)	3.7 (2.1)	0.57 (0.34 to 0.86)	0.02	0.67 (0.29 to 0.83)	0.13
O/E LHR (%), mean (SD)	31 (11)	47 (15)	0.90 (0.82 to 0.97)	0.01	0.90 (0.78 to 0.99)	0.07
Liver herniation, n (%)	10 (71)	6 (38)	4.2 (0.94 to 21.4)	0.07	2.0 (0.16 to 24)	0.60

*Analysis adjusted for Vt, O/E LHR and liver herniation.
O/E LHR, observed/expected lung to head ratio; Vt, tidal volume.

characteristics see table 1). There were ten infants excluded, in which no researcher was present at birth in eight infants and no informed consent was given by parents of two infants. The survival rate at hospital discharge was 53% (16/30). The median (IQR) day to death in infants who died was 7.5 (1–14) days. Ten infants (33%) survived without CLD. Twenty-two (73%) infants required HFOV, 19 (63%) infants received iNO and 10 (33%) infants required ECMO during admission. Of all 30 infants, there were 20 infants operated, of whom 13 underwent patch repair. There were no infants with congenital syndrome and four infants (13%) had a minor defect.

The mean (SD) time after birth at which measurement started was 68 (23) s. A total of 17.090 breaths and inflations were recorded in the first 10 min after birth (570±99 per patient). Spontaneous breathing was observed in 24 (80%) infants, with a mean Vt of 3.4±1.8 mL/kg and a median of 9 (4–18) breaths per minute. The mean FiO_2 was 55%±23% and the mean peripheral capillary oxygen saturation (SpO_2) was 72%±13%. Vt was positively correlated with FiO_2 (r=0.49, p=0.01) and negatively correlated with SpO_2 (r=−0.45, p=0.012).

A significantly lower number of spontaneous breaths were found in infants who died compared with infants who survived (3 (0–8) vs 10 (6–18) breaths per minute; p=0.037). In total, 1.967 spontaneous breaths were recorded, of which 734 (37%) breaths were interrupted by a manual inflation and excluded from further analysis. As such, a total of 1.233 uninterrupted spontaneous breaths were measured, with a mean Vt of 2.8±2.1 mL/kg and a median of 21 (7–60) breaths per infant.

Mortality

Infants who died before discharge had a significantly lower Vt when compared with infants who survived (1.7±1.6 vs 3.7±2.1 mL/kg; p=0.008) (figure 1). Furthermore, ROC analysis showed a fair predictive value of mortality (AUC=0.77, p=0.013). A Vt ≤2.2 mL/kg predicted mortality with a sensitivity of 79% and a specificity of 81%.

Univariable analysis showed that Vt was a significant predictor of mortality (OR 0.57 (95% CI 0.34 to 0.86); p=0.02), next to O/E LHR (OR 0.90 (95% CI 0.82 to 0.97); p=0.01) (table 2). However, multivariable analysis demonstrated that Vt and O/E LHR were not independent predictors of mortality and were correlated (r=0.47, p=0.07) (figure 2).

Death or CLD

Vt after birth was significantly lower in infants who died or had CLD compared with survivors without CLD (2.0±1.7 vs 4.3±2.2; p=0.004) (table 3). Using ROC analysis, the optimal cut-off value of Vt in predicting death or CLD (AUC=0.80, p=0.008) was ≤3.4 mL/kg with 85% sensitivity and 70% specificity.

Univariable analysis showed that death or CLD (ie, conversely, survival without CLD) was significantly associated with Vt (OR 0.53 (95% CI 0.29 to 0.83); p=0.01), O/E LHR (OR 0.88 (95% CI 0.79 to 0.95); p=0.007) and intrathoracic liver position (OR 9.3 (95% CI 1.7 to 75.7); p=0.02) (table 3). Multivariable analysis demonstrated that none of these variables were independent predictors for death or CLD.

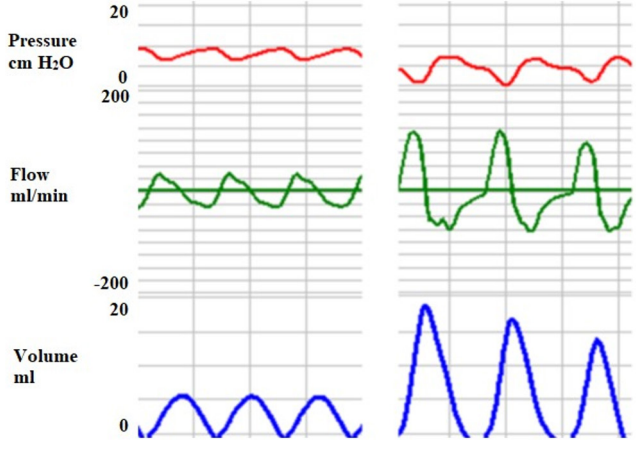

Figure 1 Two examples of three spontaneous breaths during stabilisation at birth. The first example (left) is of an infant who died before hospital discharge with a mean Vt of 2.1 mL/kg. The second example (right) is of an infant who survived with a mean Vt of 5.3 mL/kg.

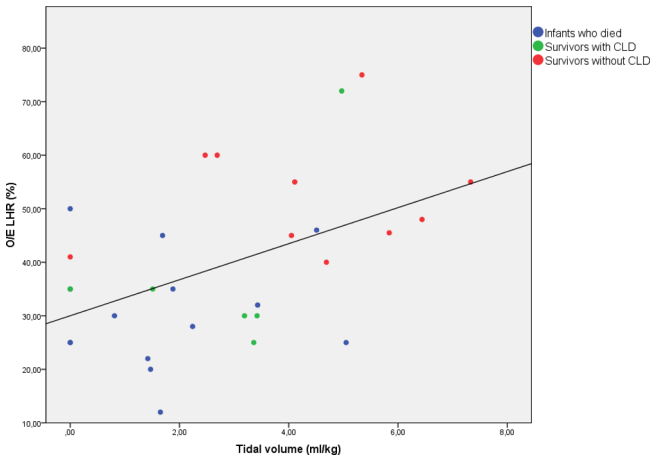

Figure 2 Correlation between O/E LHR and tidal volume (r=0.47, p=0.009). CLD, chronic lung disease; O/E LHR, observed/expected lung to head ratio.

Table 3 Prediction of death or CLD

	Death or CLD		Univariable analysis		Multivariable analysis*	
Predictor	**Yes (n=20)**	**No (n=10)**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Vt, mean (SD)	2.0 (1.7)	4.3 (2.2)	0.53 (0.29 to 0.83)	0.01	0.65 (0.34 to 1.1)	0.14
O/E LHR (%), mean (SD)	33 (13)	53 (11)	0.88 (0.79 to 0.95)	0.007	0.92 (0.80 to 1.0)	0.14
Liver herniation, n (%)	14 (70)	2 (20)	9.3 (1.7 to 75.7)	0.02	1.97 (0.11 to 32.6)	0.62

*Analysis adjusted for Vt, O/E LHR and liver herniation.
CLD, chronic lung disease; O/E LHR, observed/expected lung to head ratio; Vt, tidal volume.

Treatment

Univariable analysis showed that Vt was significantly associated with iNO therapy (OR 0.58 (95% CI 0.34 to 0.88); p=0.02) and HFOV (OR 0.29 (95% CI 0.08 to 0.60); p=0.01). There was no significant association between Vt and ECMO therapy (OR 0.79 (95% CI 0.53 to 1.12); p=0.25).

DISCUSSION

This prospective observational study in infants with CDH showed that Vt of spontaneous breaths measured during stabilisation at birth is associated with death, survival without CLD, and the need for iNO and HFOV therapy. Furthermore, the data demonstrated that Vt is correlated with O/E LHR and is therefore not an independent predictor of outcome. Vt immediately after birth could be useful as a measure to confirm the antenatal prognosis of severe hypoplasia.

To our knowledge, this is the first study that evaluated Vt of spontaneous breaths as an outcome predictor in infants with CDH. The predictive value of Vt during mechanical ventilation was investigated previously showing conflicting results. Dimitriou *et al*[27] did not observe differences in Vt prior to surgery between infants with unfavourable outcomes (death or CLD) compared with survivors without CLD. However, a more recent study performed at the same institution showed higher Vt and compliance in the first minute of resuscitation in infants who survived, similar to our observations with spontaneous breathing.[22] Nevertheless, Vt during ventilation is practitioner-determined and as such may not provide an accurate reflection of lung volume.

Interestingly, we found lower Vt values during spontaneous breaths than previously reported in a series of 12 infants with CDH in the study of te Pas *et al*[24] (3.8±1.9 vs 2.8±2.1 mL/kg). We speculate that this could be reflective of a difference in lung hypoplasia severity between these two cohorts. Compared with the results of te Pas *et al*[24], we found a higher mortality rate (47% vs 17%), which could be related to more severe degree of pulmonary hypoplasia and thus a lower Vt.

Pulmonary hypoplasia, characterised by abnormal airway and vascular development, is considered a main determinant of postnatal prognosis for infants with CDH. After birth, this results in small non-compliant lungs, with respiratory insufficiency and pulmonary hypertension.[28–30] Based on our results we speculate that Vt during spontaneous breathing can be used to estimate the degree of lung hypoplasia. This is also supported by previous observations by Cloutier *et al*[31] reporting a correlation between fractional lung masses and a pulmonary expansion index (measured by expiratory Vt over inspiratory pressure) in an ovine CDH model. In addition, in our study O/E LHR was correlated with Vt. Previous studies showed that LHR is associated with lung volume and therefore the likelihood of pulmonary hypoplasia.[32] In our study, a low Vt was indeed associated with mortality and CLD, hypothetically due to inadequate oxygenation. We speculate that this may have resulted in higher ventilation pressures and thus an increased risk of barotrauma.

Despite advances in neonatal care, postnatal morbidity and mortality rates remain high in infants with CDH.[8–14] To improve outcome, it is important to identify infants with severe CDH who may benefit most from advanced therapies. Early predictors such as Vt could be useful in identifying the sickest infants and thus providing individualised postnatal care. For instance, we observed lower Vt values in infants requiring iNO. We speculate that by using early predictors clinicians could anticipate the development of pulmonary hypertension and therefore start treatment accordingly in its early stages. The pulmonary vasculature in lung hypoplasia is highly reactive to hypoxia, and these infants may therefore benefit from alternative ventilation strategies to optimise oxygenation or the routine use of vasodilators. The VICI-trial (Ventilation in Infants with Congenital diaphragmatic hernia: an International randomised clinical trial) randomised infants with CDH to conventional ventilation or HFOV and did not show a difference in adverse outcomes (death or CLD). However, infants were not stratified based on the degree of lung hypoplasia, where HFOV may potentially have a protective effect.[33] The development of management strategies based on the patient's individual characteristics is relatively novel in neonatal intensive care medicine and may help improve outcomes of challenging conditions such as CDH.

The sample size of this single-centre study did not allow for a full validation of the findings. The relative rarity of CDH makes it challenging for specialised tertiary centres to recruit a vast number of patients. However, we found a significant association between Vt and postnatal outcome. Although Vt and O/E LHR are correlated, this multicollinearity did not affect its predictive value, as the correlation coefficient was lower than 0.7–0.8 and the variance inflation factor was below 2.[34] Also, spontaneous breathing was not observed in 6 out of 30 infants, which were included in this study. Absence of spontaneous breathing might predict severe pulmonary hypoplasia (four died before discharge and one had CLD). Excluding infants with no spontaneous breathing would result in selection bias, induced by the selection of infants who were relatively stable within the first minutes of life. In addition, eight infants received midazolam sedation in the first 10 min after birth. However, these infants were not sedated immediately after birth, so not all spontaneous breaths were influenced by this. On the other hand, we found a low spontaneous breathing rate (median of 9 breaths per minute). It is likely that respiratory effort is affected by midazolam sedation. Additionally, infants with CDH almost often undergo a transient period of hypoxia immediately after clamping of the cord, which inhibits breathing.

In conclusion, Vt is significantly lower in infants with CDH who died or had CLD. This would suggest that low Vt might be a reliable predictor of outcome, but it cannot act as an independent predictor after adjustment for O/E LHR and liver position.

Further research needs to clarify the independent predictive role of Vt to help to identify infants with severe disease who may benefit from advanced therapies.

Contributors AM collected data, analysed and interpreted the data, and drafted and revised the manuscript. CCC conceived the study, drafted and revised the study protocol, collected data, and revised the manuscript. MT contributed to the conception and design of the study and revised the manuscript. JC was involved in data collection. SCP analysed and interpreted the data and revised the manuscript. ABtP conceived the study, interpreted the data, and drafted and revised the study protocol and manuscript.

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