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# Neonatal pneumothorax in congenital diaphragmatic hernia: Be wary of high ventilatory pressures

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## ABSTRACT

**Background** Patients with congenital diaphragmatic hernia (CDH) require invasive respiratory support and higher ventilator pressures may be associated with barotrauma. We sought to evaluate the risk factors associated with pneumothorax in CDH neonates prior to repair.

**Methods** We retrospectively reviewed newborns born with CDH between 2014 and 2019 who developed a pneumothorax, and we matched these cases to patients with CDH without pneumothorax.

**Results** Twenty-six patients were included (n=13 per group). The pneumothorax group required extracorporeal life support (ECLS) more frequently (85% vs 54%, p=0.04), particularly among type A/B defects (31% vs 7%, p=0.01). The pneumothorax group had higher positive end-expiratory pressure (PEEP) within 1 hour of birth (p=0.02), at pneumothorax diagnosis (p=0.003), and at ECLS (p=0.02). The pneumothorax group had a higher mean airway pressure (Paw) at birth (p=0.01), within 1 hour of birth (p=0.01), and at pneumothorax diagnosis (p=0.04). Using multiple logistic regression with cluster robust SEs, higher Paw (OR 2.2, 95% CI 1.08 to 3.72, p=0.03) and PEEP (OR 1.8, 95% CI 1.15 to 3.14, p=0.007) were associated with an increased risk of developing pneumothorax. There was no difference in survival (p=0.09).

**Conclusions** Development of a pneumothorax in CDH neonates is independently associated with higher Paw and higher PEEP. A pneumothorax increases the likelihood of treated with ECLS, even with smaller defect.

### Key messages

**What is already known on this topic**

⇒ The concept of gentle ventilation has been used to improve outcomes in congenital diaphragmatic hernia.
⇒ Despite the use of gentle ventilation, there remains a 10%–23% rate of pneumothorax.
⇒ There is an increased risk of mortality when a pneumothorax develops preoperatively.

**What this study adds**

⇒ Elevated mean airway pressures and peak inspiratory pressures are risk factors for developing pneumothorax.
⇒ Development of pneumothorax is associated with increased use of extracorporeal life support.
⇒ Children with type A and B defects who develop a pneumothorax are more likely to use extracorporeal life support.

**How this study might affect research, practice or policy**

⇒ As high-frequency modes of ventilation become more frequently used in children with congenital diaphragmatic hernia, guidelines that address these ventilatory settings will be important to avoid pneumothorax while continuing to improve outcomes.

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a complex condition occurring in 1 in 3000 live births.[1] Severe pulmonary hypoplasia and persistent pulmonary hypertension are major contributors to mortality and long-term morbidity. Advances in neonatal care including standardized protocols for gentle ventilation and permissive hypercapnia; application of rescue modalities, such as high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV); and utilization of extracorporeal life support (ECLS) have been tried to improve outcomes.[2–5] Despite these interventions, there remains a high risk of morbidity and mortality in neonates with CDH.[6 7]

Gentle ventilation and lung-protective approaches have been described as strategies to limit the barotrauma to the hypoplastic lungs of patients with CDH.[8–10] Low positive end-expiratory pressure (PEEP) helps to prevent overdistention of the lung and facilitates improved lung compliance and decreased pulmonary vascular resistance.[11 12] Other studies have looked at the use of HFJV as an effective means of delivering adequate ventilation and oxygenation in infants exhibiting hypercarbia and hemodynamic instability on conventional mechanical ventilation (CMV).[13] HFJV uses small, high-velocity breaths delivered through a valve into

the breathing circuit while coupled to a conventional ventilator to deliver PEEP, thereby allowing for optimal lung expansion while mitigating the risk of lung injury by avoiding high tidal volumes.[2 13 14] Despite varying protocols using gentle ventilation, patients with CDH develop pneumothorax at an alarming rate (10.5%–23%) with an increased risk of mortality.[15–17] Risk factors contributing to the development of preoperative pneumothorax in CDH are not clear. Recent studies have found large diaphragmatic defects and higher mean airway pressures have been associated with developing a pneumothorax. The purpose of the study was to determine the institutional incidence and risk factors contributing to developing a pneumothorax in neonates with prenatally diagnosed CDH. We hypothesize that a higher mean airway pressure (Paw) is associated with increased risk of pneumothorax.

## METHODS

### Patient population

All patients with prenatally diagnosed CDH born between June 2014 and December 2019 were identified. Newborns who received either CMV or HFJV and developed a pneumothorax before surgical repair were selected for study. Pneumothorax was diagnosed based on the radiology reports abstracted from the patients' electronic medical records. Owing to the small number of patients and the inability to compare ventilator pressure measurements, newborns who received HFOV were excluded. Cases were matched (1:1) with a patient with CDH who did not develop a pneumothorax prior to surgical repair (control) by gestational age, laterality of defect (left sided), liver position, and CDH study group defect type (A through D).[18] To prevent potential bias based on changes in management strategies over time, cases were matched with controls who were born no more than 4 months apart. Patients with postnatally diagnosed CDH were not included given the potential variability in postnatal care that could have impacted the development of pneumothorax.

### Data collection

Perinatal, ventilation, and outcome data were collected. Perinatal variables included sex, gestational age at birth, birth weight, observed/expected lung to head ratio (o/e LHR) by ultrasound, observed/expected total lung volume (o/e TLV) by fetal MRI, 1 and 5 min Apgar scores, CDH defect size as classified by CDH study group classification,[19] and presence of cardiac anomalies. Ventilation variables included mode of ventilation, peak inspiratory pressure (PIP), PEEP, and Paw. The PIP, PEEP, and Paw were recorded at four time intervals: at birth, within 1 hour of birth, prior to pneumothorax (or 1–8 hours for patients without pneumothorax), and prior to ECLS (or highest value prior to surgical repair for patients who did not receive ECLS). Outcome variables included nitric oxide use, ECLS use, repair status, survival, and home oxygen use.

### Statistical analysis

Data were collected and stored in Microsoft Excel (Microsoft, Redmond, Washington). Sample characteristics are reported as number of observations and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. Comparisons between categorical variables used Fisher's exact test. Continuous variables were treated as non-parametric and were compared using the Mann-Whitney U test/Wilcoxon rank-sum test. Mixed effects regression analysis was used to compare ventilation data by group and postnatal event while accounting for within-patient repeated measures. Ventilation setting data are reported as mean with confidence interval (CI). During HFJV, a conventional ventilator is used in tandem with the jet ventilator and contributes to both PIP and PEEP. Because of this, CMV settings and HFJV were analyzed separately. All patients had CMV settings whereas only those who had HFJV would have data for the HFJV subset analysis. Multiple logistic regression analysis with cluster robust SEs (to account for patient-level repeated measures) was used to assess the relationship between meeting criteria for pneumothorax, Paw, and PEEP. Results of the analysis are reported as ORs with 95% CIs. All analyses were conducted in STATA V.16.1 (STATACorp, College Station, Texas) with a two-tailed p value <0.05 considered to be significant.

## RESULTS

### Demographics

During the study period, 79 newborns had an antenatally diagnosed CDH of which 15 (16%) developed a pneumothorax prior to surgical repair (figure 1). Two patients were excluded because they received HFOV prior to developing a pneumothorax. The 13 cases that met the inclusion criteria were then matched with 13 control patients who did not develop a pneumothorax. There were no differences in prenatal factors including o/e LHR (p=0.33), o/e TLV (p=0.45), gestational age (p=1.00), or side of the CDH defect (p>0.99) (table 1).

Diagnosis of pneumothorax occurred at a median of 110 min (IQR 66, 180) following birth. The pneumothorax was ipsilateral to the CDH defect in 31% (4/13), contralateral to the defect in 31% (4/13), and bilateral in 38% (5/13). Overall, the pneumothorax group was treated more frequently with nitric oxide (100% vs 38%, p=0.001) and ECLS (85% vs 46%, p=0.04) (table 1). Median time from birth to ECLS was similar between the pneumothorax group and the control group [7 hours (2–13) vs 9 hours (9–9), p=1.00]. Among the subgroup of less severe patients with a type A/B defect, those who developed a pneumothorax were more likely to require ECLS (31% vs 7%, p=0.01) and nitric oxide (31% vs 7%, p=0.01) (table 2). There was no difference in duration of ventilation (p=0.08) or survival among this subgroup of type A/B defects who developed a pneumothorax versus those who did not (75% vs 100%, p=0.26).

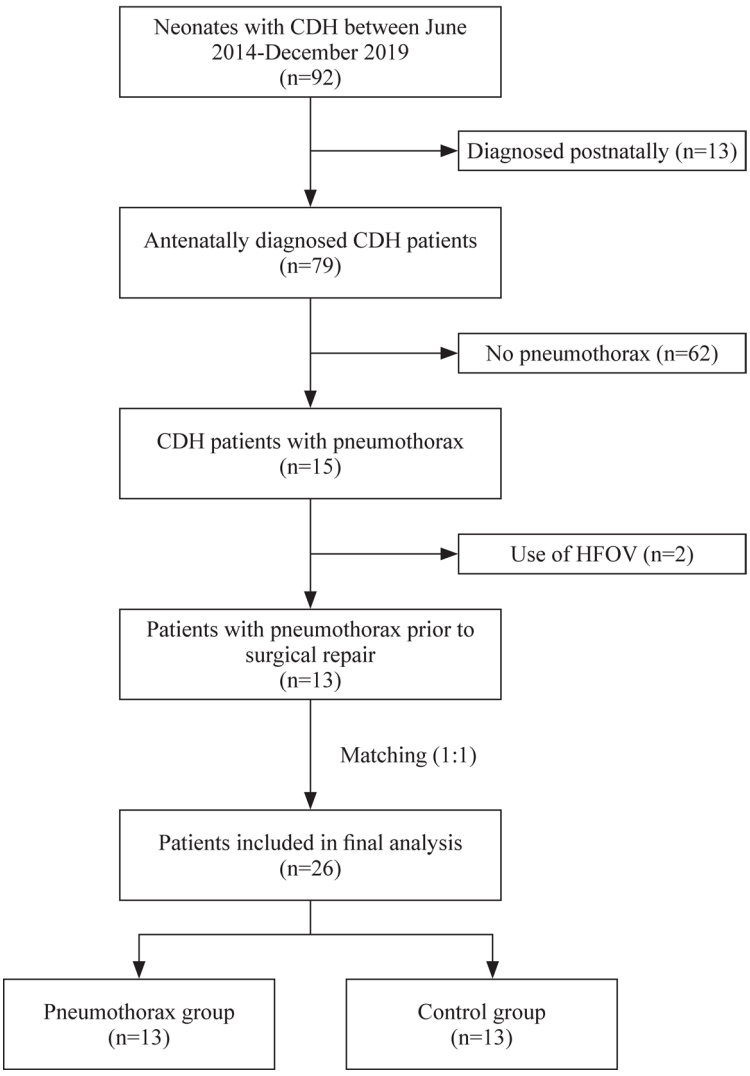


**Figure 1** Study flow diagram of the enrollment process. We identified 92 patients with congenital diaphragmatic hernia (CDH). After matching for defect type, liver position, gestational age within a 4-month time period, our final study population was 26 patients. HFOV, high-frequency oscillatory ventilation.

## Ventilation data

HFJV was more common among cases at the time of pneumothorax (77% vs 31%, p=0.03) (table 3). When analyzed as a whole, the pneumothorax group had a higher mean PIP at pneumothorax [36 $cmH_2O$ (95% CI 32 to 40) vs 27 $cmH_2O$ (95% CI 23 to 31), p<0.002] and at ECLS [40 $cmH_2O$ (95% CI 36 to 44) vs 30 $cmH_2O$ (95% CI 25 to 35), p=0.001] (figure 2). PEEP was also significantly higher in the pneumothorax cases compared with controls within 1 hour of birth [8.5 $cmH_2O$ (95% CI 7 to 9.5) vs 6 $cmH_2O$ (95% CI 5 to 7), p=0.02], at pneumothorax [8.5 $cmH_2O$ (95% CI 7 to 9.5) vs 6 $cmH_2O$ (95% CI 5 to 7), p=0.003], and at ECLS [9.5 $cmH_2O$ (95% CI 8 to 10.5) vs 7 $cmH_2O$ (95% CI 6 to 8.5), p=0.02]. Paw was higher in the pneumothorax group at birth [13.4 $cmH_2O$ (95% CI 11.7 to 15) vs 10 $cmH_2O$ (95% CI 8.5 to 11.8), p=0.01], within 1 hour of birth [13.9 $cmH_2O$ (95% CI 12.3 to 15.6) vs 11 $cmH_2O$ (95% CI 9.4 to 12.6), p=0.01], and at pneumothorax diagnosis [13.4 $cmH_2O$ (95% CI 11.8 to 15) vs 11.1 $cmH_2O$ (95% CI 9.5 to 12.7), p=0.04].

Next, CMV settings were compared in pneumothorax cases versus controls. There were no differences in PIP at any of the time periods between the two groups. However, PEEP was significantly higher in cases compared with controls at pneumothorax [8.2 $cmH_2O$ (95% CI 7.2 to 9.2) vs 6.2 $cmH_2O$ (95% CI 5.1 to 7.4), p=0.01] and at initiation of ECLS [9.3 $cmH_2O$ (95% CI 8.2 to 10.4) vs 6.6 $cmH_2O$ (95% CI 5.3 to 8.0), p=0.002]. In the subset of patients who received HFJV, those who developed a pneumothorax had a significantly higher HFJV PIP compared with the control group at birth [37 $cmH_2O$ (95% CI 33 to 41) vs 30 $cmH_2O$ (95% CI 26 to 35), p=0.02]. There was no difference in the HFJV PEEP between the two groups at any time interval.

Associations between pneumothorax, PEEP and Paw after multivariate analysis of risk factors are reported in table 4. When controlling for gestational age, defect type, and liver position, a statistically significant effect was detected between PEEP and pneumothorax [2.2 (1.2–3.8), p=0.007] and between Paw and pneumothorax [1.8 (1.06–3.0), p=0.03].

Table 1 Perinatal demographics

| | Pneumothorax group (n=13) | Control group (n=13) | P value |
|---|---|---|---|
| **Perinatal variables** | | | |
| Female sex* | 8 (62) | 4 (31) | 0.12 |
| Gestational age (wk)† | 38.9 [37.7, 39.9] | 39.1 [38.1, 39.6] | 1.00 |
| Birth weight (kg)† | 3.3 [2.9, 3.6] | 3.2 [3.0, 3.4] | 0.49 |
| o/e LHR by ultrasound† | 35 [27, 39] | 46 [27, 67] | 0.33 |
| o/e TLV by fetal MRI† | 21 [20, 23] | 24 [17, 39] | 0.45 |
| Apgar score 1 min† | 4 [1, 6] | 6 [3, 7] | 0.19 |
| Apgar score 5 min† | 7 [5, 8] | 8 [7, 8] | 0.23 |
| Left-sided CDH* | 12 (92) | 12 (92) | 1.00 |
| Liver up* | 7 (54) | 7 (54) | 1.00 |
| Defect type* | | | 0.80 |
| A/B | 4 (31) | 5 (38) | |
| C/D | 6 (54) | 6 (46) | |
| Died prior to repair | 3 (23) | 2 (15) | |
| Cardiac anomalies* | 6 (46) | 6 (46) | 1.00 |
| **Outcome variables** | | | |
| Time to pneumothorax (min)† | 110 [66, 180] | – | – |
| Side of pneumothorax* | | | |
| Ipsilateral only | 5 (38) | – | – |
| Contralateral only | 4 (31) | – | – |
| Bilateral | 4 (31) | – | – |
| Use of nitric oxide* | 13 (100) | 5 (38) | **0.001** |
| Use of ECLS* | 11 (85) | 6 (46) | **0.04** |
| Duration of ECLS (days)† | 10.5 [4, 20] | 13 [6, 14] | 0.67 |
| Repaired* | 10 (77) | 11 (85) | 0.93 |
| Duration of ventilation (days)† | 21 [13, 31] | 15 [7, 37] | 0.64 |
| Survival to discharge* | 6 (46) | 11 (85) | 0.09 |
| Discharged on home oxygen* | 3 (23) | 4 (31) | 0.42 |

P-value ≤0.05 is considered statistically significant.

*Data presented as proportion (%).
†Data presented as median [IQR].
CDH, congenital diaphragmatic hernia; ECLS, extracorporeal life support; IQR, Interquartile range; o/e LHR, observed/expected lung to head ratio; o/e TLV, observed/expected total lung volume.

## Outcome

Overall survival to discharge was 65% (16/26) with no difference in survival between the pneumothorax group and the control group (p=0.09) (table 1). There was no difference in duration of ECLS (p=0.67), duration of mechanical ventilation (p=0.64), or the proportion who were discharged on home oxygen (p=0.42) (table 1).

## DISCUSSION

The purpose of our study was to determine our institutional incidence and risk factors contributing to developing a pneumothorax in neonates with prenatally diagnosed CDH. Pneumothorax occurred in 16% of our patients, which is consistent with previous literature.[16 17] Among newborns with CDH, we found that higher PEEP and Paw settings were associated with the development of a pneumothorax after controlling for gestational age, CDH defect size, and liver position. In addition, we found that pneumothorax was associated with being treated with ECLS prior to surgical repair, most notably in those with smaller defect sizes (A or B defect).

As operative management of CDH has evolved during the last several decades, so have the resuscitative efforts immediately following birth. Past hyperventilation strategies have been shown to damage the already hypoplastic lungs of patients with CDH, further delaying adequate oxygenation and contributing to subsequent ventilator-induced lung injury (VILI).[20] Given that lung oxygenation is a crucial factor in decreasing pulmonary vascular resistance and in improving pulmonary blood flow

Table 2 Outcomes for small defect subgroup (type A/B)

| | Pneumothorax group (n=4) | Control group (n=5) | P value |
|---|---|---|---|
| Highest $pCO_2$ at 1 hour of birth* | 53 [42, 57] | 41 [39, 74] | 1.00 |
| Use of nitric oxide† | 4 (100) | 1 (20) | **0.01** |
| Use of ECLS† | 4 (100) | 1 (20) | **0.01** |
| Duration of ventilation (days) | 20 [18, 97] | 9 [7, 15] | 0.08 |
| Survival to discharge† | 3 (75) | 5 (100) | 0.24 |

P-value ≤0.05 is considered statistically significant.

*Data presented as median [IQR].
†Data presented as proportion (%).
ECLS, extracorporeal life support; IQR, Interquartile range; $pCO_2$, partial pressure of carbon dioxide.

with benefits to both survival and long-term outcomes, ventilator management strategies play a critical role in the survival of a patient with CDH.[8 12 14] As such, there has been a transition during the past 30 years towards favoring and standardizing the concept of gentle ventilation.[21] By allowing permissive hypercapnia, lower pH, lower levels of oxygen, lower ventilator pressures and decreasing the use of neuromuscular blockers and sedatives, gentle ventilation attempts to reduce the risk of barotrauma and VILI.[5] Even in the era of gentle ventilation, 10.5%–23% of newborns with CDH will develop a pneumothorax.[10 15 17] In our population, pneumothoraces occurred 53% of the time on the ipsilateral side of the CDH defect, suggesting both sides are at risk. In comparison, the literature reports a 62%–100% rate of developing an ipsilateral pneumothorax.[16 17]

By combining the ventilation data from the patients on CMV and HFJV, we found significant differences in both PIP and PEEP at multiple time intervals. Theoretically, the PIP delivered by CMV may not be equivalent to the PIP generated by HFJV.[14] Given the difference between the two modes of ventilation, combining PIP data from CMV and HFJV may lead to bias. For this reason, we performed a subgroup analysis for CMV settings and another for HFJV settings. In the subgroup analysis, PEEP levels generated by CMV were higher in the pneumothorax group at pneumothorax and at ECLS. HFJV PIP was only significantly higher in the pneumothorax group at birth. We suspect that this may reflect a type II error based on small sample size.

We attempted to identify the perinatal risk factors associated with the development of pneumothorax. After controlling for gestational age, left-sided defect, CDH defect size, and liver position, our multiple logistic regression found increased PEEP and Paw were associated with the development of a pneumothorax. Guevorkian *et al*[22] reported in a randomized cross-over study of 17 infants that a PEEP of 2 $cmH_2O$ compared with 5 $cmH_2O$ following surgical repair resulted in improved respiratory mechanics in patients with mild to moderate CDH (o/e LHR 35±13). The 2010 CDH EURO Consortium Consensus recommended similar initial PEEP levels of 2–5 $cmH_2O$, while a recent systematic review by the American Pediatric Surgical Association Outcomes and Evidence-based Practice Committee suggested parameters for CMV including PIP≤25 $cmH_2O$ and PEEP levels of 3–5 $cmH_2O$.[23 24] Regarding Paw, in a multi-institutional study of 495 neonates with CDH of whom 52 developed a pneumothorax, Masahata *et al*[16] found higher Paw was associated with developing a pneumothorax with an OR of 1.172 (95% CI 1.022 to 1.345), which is consistent with previous literature.[25] With the findings of our study, we conclude PEEP greater than 5 $cmH_2O$ and Paw greater than 13 $cmH_2O$ at any time should be avoided to limit the risk of pneumothorax. We acknowledge the PEEP in both groups is higher than these recommendations and is due to the local practice of teams managing our patients with CDH. We have modified our institutional protocols to reflect these recommendations.

While other studies have shown ECLS is more frequently applied in patients with pneumothorax, the higher frequency of patients with smaller defects (types A and B) on ECLS in the pneumothorax group compared with the control group is concerning.[16] With a similar max $pCO_2$ following delivery and time to ECLS from birth, patients with smaller defects who developed pneumothorax did not initially appear to be clinically worse than the control group. We were unable to show a mortality difference between the two groups which may be due to the sample size. However, Masahata *et al*[16] showed a lower rate of survival in those who developed a pneumothorax compared with those without.

Our study has several limitations. This single institution study is retrospective and may not be generalizable to a broader CDH population. The data available from chart review lacked specific details required to analyze the pressures used during the initial resuscitation and stabilization immediately after birth while patients were being ventilated with a manual T-piece resuscitator, which can be set to not exceed a specific pressure. Given the limited sample size, we also were unable to identify a difference in survival or whether receiving HFJV increased the odds of developing a pneumothorax. Regarding the variability in ventilator modes and settings found in our study,

Table 3 Ventilation data

| | Pneumothorax group (n=13) | Control group (n=13) | P value |
|---|---|---|---|
| High-frequency jet ventilation* | | | |
| At birth | 7 (54) | 5 (38) | 0.43 |
| Within 1 hour of birth | 10 (77) | 6 (46) | 0.11 |
| At pneumothorax | 10 (77) | 4 (31) | **0.03** |
| At ECLS | 10 (77) | 6 (46) | 0.35 |
| **Combined data** | | | |
| Peak inspiratory pressures ($cmH_2O$)† | | | |
| At birth | 32 [28 to 36] | 27 [23 to 31] | 0.05 |
| Within 1 hour of birth | 33 [29 to 37] | 27 [24 to 31] | 0.05 |
| At pneumothorax | 36 [32 to 40] | 27 [23 to 31] | **<0.002** |
| At ECLS | 40 [36 to 44] | 30 [25 to 35] | **0.001** |
| PEEP ($cmH_2O$)† | | | |
| At birth | 7.5 [6 to 8.5] | 6 [4.5 to 7] | 0.06 |
| Within 1 hour of birth | 8.5 [7 to 9.5] | 6 [5 to 7] | **0.02** |
| At pneumothorax | 8.5 [7 to 9.5] | 6 [5 to 7] | **0.003** |
| At ECLS | 9.5 [8 to 10.5] | 7 [6 to 8.5] | **0.02** |
| Mean airway pressure ($cmH_2O$)† | | | |
| At birth | 13.4 [11.7 to 15] | 10 [8.5 to 11.8] | **0.01** |
| Within 1 hour of birth | 13.9 [12.3 to 15.6] | 11 [9.4 to 12.6] | **0.01** |
| At pneumothorax | 13.4 [11.8 to 15] | 11.1 [9.5 to 12.7] | **0.04** |
| At ECLS | 13.2 [11.5 to 14.8] | 14.9 [13.3 to 16.6] | 0.14 |
| **Conventional ventilation‡** | | | |
| Peak inspiratory pressures ($cmH_2O$)† | | | |
| At birth | 25 [20 to 30] | 24 [20 to 29] | 0.78 |
| Within 1 hour of birth | 24 [20 to 27] | 24 [20 to 27] | 0.85 |
| At pneumothorax | 25 [22 to 29] | 22 [18 to 26] | 0.17 |
| At ECLS | 24 [20 to 28] | 23 [19 to 28] | 0.80 |
| PEEP ($cmH_2O$)† | | | |
| At birth | 6.0 [4.5 to 7.5] | 5.5 [4.3 to 6.8] | 0.63 |
| Within 1 hour of birth | 8 [6.7 to 9.3] | 6.6 [5.5 to 7.6] | 0.08 |
| At pneumothorax | 8.2 [7.2 to 9.2] | 6.2 [5.1 to 7.4] | **0.01** |
| At ECLS | 9.3 [8.2 to 10.4] | 6.6 [5.3 to 8.0] | **0.002** |
| **High-frequency jet ventilation§** | | | |
| Peak inspiratory pressures ($cmH_2O$)† | | | |
| At birth (7/5 pts) | 37 [33 to 41] | 30 [26 to 35] | **0.02** |
| Within 1 hour of birth (9/5 pts) | 38 [34 to 42] | 32 [28 to 37] | 0.05 |
| At pneumothorax (10/4 pts) | 40 [36 to 43] | 36 [31 to 41] | 0.19 |
| At ECLS (10/6 pts) | 40 [37 to 44] | 35 [31 to 40] | 0.06 |
| PEEP ($cmH_2O$)† | | | |
| At birth (7/5 pts) | 8.5 [7.3 to 9.7] | 7.4 [5.9 to 8.9] | 0.25 |
| Within 1 hour of birth (9/5 pts) | 8.9 [7.6 to 10.3] | 7.6 [6.2 to 9.1] | 0.19 |
| At pneumothorax (10/4 pts) | 8.8 [7.6 to 9.9] | 7.6 [6.0 to 9.1] | 0.22 |
| At ECLS (10/6 pts) | 9.3 [8.2 to 10.4] | 7.9 [6.4 to 9.3] | 0.12 |

Continued

Table 3 Continued

| | Pneumothorax group (n=13) | Control group (n=13) | P value |
|---|---|---|---|

P-value ≤0.05 is considered statistically significant.
*Data presented as proportion (%).
†Data presented as mean [CI].
‡Includes all patients.
§Includes only patients who were on HFJV (pneumothorax group/control group).
CI, Confidence interval; ECLS, extracorporeal life support; HFJV, high-frequency jet ventilation; PEEP, positive end-expiratory pressure; pts, patients.

institutional protocols are in place to guide resuscitation and ventilator management; however, management of the patient remains open to the multidisciplinary team caring for the patient and accounts for variability.

In conclusion, development of pneumothorax in CDH prior to surgical repair is independently associated with higher PEEP and Paw levels at multiple time intervals. Furthermore, developing a pneumothorax was found to increase the likelihood of receiving ECLS, particularly for less severe defect types. While continuing gentle ventilation protocols to minimize variability of care, additional research is needed to fully understand the risk factors that contribute to the development of pneumothorax in CDH during the preoperative neonatal period in hopes of increasing case management and survival outcomes for patients with CDH.

**Contributors** NR made substantial contributions to the conception or design of the work, to the acquisition of data, to the analysis of data, and to the interpretation of data for the work. GAN made substantial contributions to the acquisition of data. AGK made substantial contributions to the conception or design of the work, and to the acquisition of data. NM made substantial contributions to the analysis of data, and to the interpretation of data for the work. EEP is the guarantor of the study, made substantial contributions to the conception or design of the work, to the acquisition of data, analysis of data, and to the interpretation of data for the

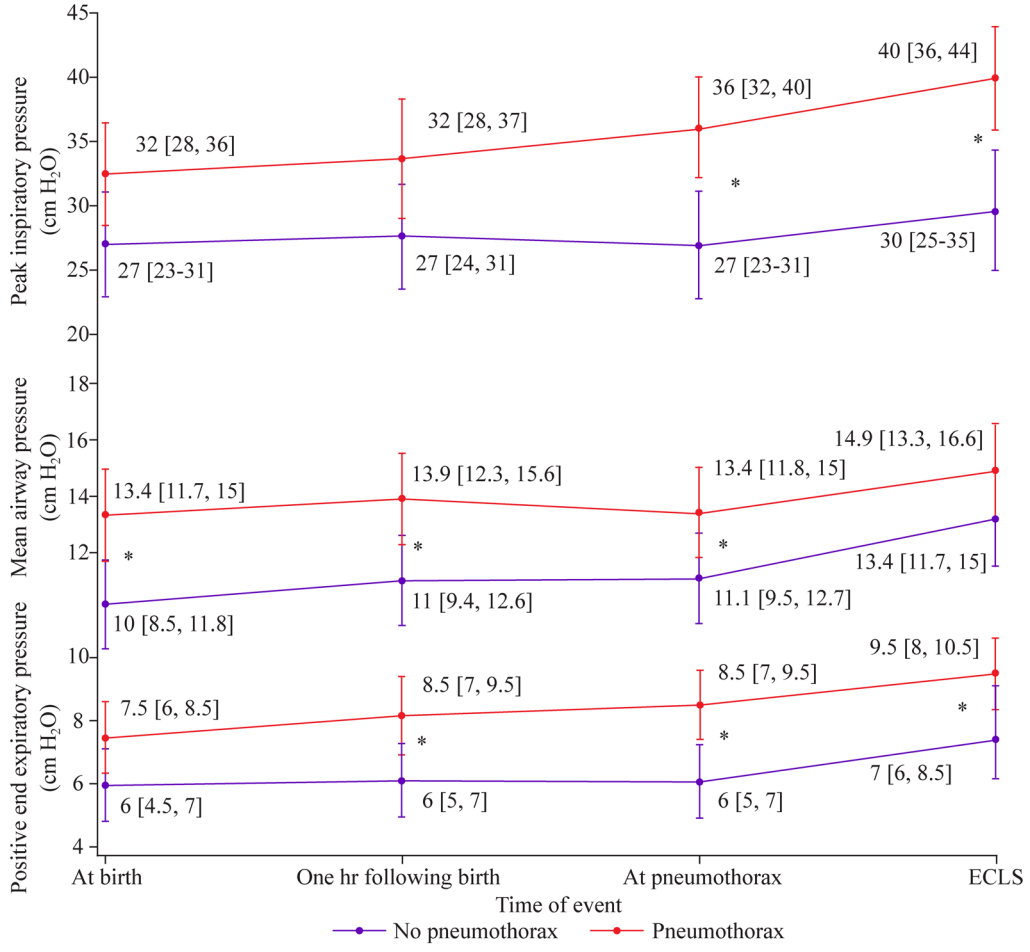


Figure 2 Ventilation settings [peak inspiratory pressures, mean airway pressures, and positive end-expiratory pressure (PEEP)] of patients with pneumothorax and those without pneumothorax recorded at birth, within 1 hour of life, at pneumothorax diagnosis (or 1–8 hours for patients without pneumothorax), and pre-extracorporeal life support (ECLS). Values on the graph are reported as mean [CI]. *Indicates p<0.05. CI, Confidence interval.

Table 4 Multivariate analysis of risk factors for developing pneumothorax

| | OR | SE | 95% CI | P value |
|---|---|---|---|---|
| Gestational age (wk) | 0.78 | 0.17 | 0.51 to 1.19 | 0.26 |
| C/D defect type | 0.92 | 1.5 | 0.04 to 22.7 | 0.95 |
| Liver up position | 0.41 | 0.69 | 0.01 to 11.4 | 0.60 |
| Mean airway pressure | 1.65 | 0.38 | 1.05 to 2.59 | **0.03** |
| PEEP ($cmH_2O$) | 1.77 | 0.37 | 1.2 to 2.68 | **0.007** |

P-value ≤0.05 is considered statistically significant. Likelihood Ratio $\chi^2$=−29.3, n=61 observations, p=0.015.
CI, Confidence interval; OR, Odds ratio; PEEP, positive end-expiratory pressure; SE, Standard error.

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