Citation for published version (APA):
Resuscitation of infants with congenital diaphragmatic hernia

Anthony O’Rourke-Potocki¹, Kamal Ali², Vadivelam Murthy¹, Anthony Milner¹,
Anne Greenough¹,³

¹Division of Asthma, Allergy and Lung Biology, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, King’s College London, London, United Kingdom
²Neonatal Intensive Care Centre, King’s College Hospital NHS Foundation Trust, London, United Kingdom
³NIHR Biomedical Research Centre at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London, United Kingdom

Address for correspondence: Professor Anne Greenough, Neonatal Intensive Care Unit, 4th Floor Golden Jubilee Wing, King’s College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom. Tel: 0203 299 3037; fax: 0203 299 8284
Email: anne.greenough@kcl.ac.uk

Key words: Congenital diaphragmatic hernia; resuscitation; compliance

Word count: 2573
ABSTRACT

Objective: To determine whether the respiratory response to resuscitation in infants with congenital diaphragmatic hernia as measured by a respiratory function monitor differed between those who did and did not survive.

Design: Observational study.

Setting: Tertiary perinatal centre.

Patients: Thirty-eight infants born at 34 weeks of gestation or greater and diagnosed antenatally with a CDH.

Interventions: Expiratory tidal volume (VTe), peak inflation pressure (PIP) and end tidal carbon dioxide level (ETCO₂) were simultaneously recorded during resuscitation using a respiratory function monitor. Oxygen saturation was also monitored.

Main outcome measures: Mortality related to the median VTe, PIP, compliance (VTe divided by PIP) and ETCO₂ levels in the first and last minute of recorded resuscitation and the maximum oxygen saturation.

Results: The median gestational age, birth weight and duration of resuscitation of the eleven infants who died did not differ significantly from those who survived. During the first minute of recorded resuscitation, the VTe (median 1.89 versus 2.68 ml/kg) (p=0.009)), the ETCO₂ (median 11.7 versus 41.7 mm Hg) (p=0.023)) and the compliance (0.06 versus 0.08 ml/cmH₂O/kg) (p=0.018)) were lower in the non survivors. In the last minute, the PIP was higher (32.5 versus 30.3 cm H₂O) (p=0.03)), the VTe (3.22 versus 4.66 ml/kg) (p=0.003)) and compliance (0.10 versus 0.15 ml/cmH₂O/kg) (p=0.004)) were lower in the
non survivors. The maximum oxygen saturation achieved in the labour suite
was lower in the non survivors (93% versus 100%) (p=0.037).

**Conclusions:** Infants with CDH who did not survive responded less well even to
initial resuscitation.
INTRODUCTION

Congenital diaphragmatic hernia (CDH) affects approximately 1 in 3000 infants.[1] Herniation of abdominal contents into the thoracic cavity in utero causes defects in pulmonary development and abnormal morphology of the pulmonary vasculature.[2] In the immediate postnatal period, the risks of developing severe respiratory distress and pulmonary hypertension are very high and the majority of infants are symptomatic at birth. The key principles of successful delivery room resuscitation are to establish adequate preductal arterial saturation and to avoid progressive hypercapnia.[3] Initial management in the delivery room is based on the Guidelines of the International Consensus on Cardiopulmonary Resuscitation and Emergency Care Science with Treatment Recommendations,[4] European Resuscitation Council,[5] and the American Heart Association.[6] Immediate intubation is recommended to reduce the risk of pulmonary hypertension due to prolonged acidosis and hypoxia which might result from delayed intubation.[7] The evidence on which the recommendation was based, however, was graded D (non-analytic studies, that is case reports, case series and/or expert opinion).[7]

There is a scarcity of data describing how infants with CDH respond to resuscitation protocols and whether their response correlates with outcomes. A low Apgar (two or less) at five minutes was reported to be associated with 60% survival to discharge.[8] Respiratory function monitoring is now available for use in the labour suite.[9] Such monitoring has demonstrated that CDH infants may spontaneously breathe at birth, although only 12 infants were included in the study.[10] Manual ventilation was mostly asynchronous, but when spontaneous
breaths coincided with manual inflations greater tidal volumes were achieved.[10] The authors, therefore, hypothesized that improving synchrony between spontaneous and delivered breaths could improve the respiratory support delivered to CDH infants. Their results, however, were not related to longer term outcomes.[10] We have demonstrated, using respiratory function monitoring, that CDH infants have a low compliance at birth and administration of a neuromuscular blocking agent further reduced their lung compliance [11], but whether a low compliance predicts outcome has not been tested. The aims of this study were to analyse the results of respiratory monitoring in the labour suite to determine whether the response to resuscitation differed between those who did and did not survive and if the results predicted survival.

METHODS

The study was conducted at King’s College Hospital between 2011 to 2015. All infants born at 32 weeks of gestation or greater and diagnosed antenatally with a CDH were eligible for entry into the study. Ethical approval was given by the Outer London Ethics Committee. The committee required parental consent only for the analysis of the data; this was obtained once the mother was transferred to the postnatal ward.

Resuscitation Protocol

None of the infants underwent face mask resuscitation. The infants were intubated with a Cole’s shouldered endotracheal tube as soon as possible after birth. Respiratory monitoring using a respiratory function monitor began as soon as the infants were intubated. Positive pressure ventilation was delivered
via a t-piece device attached to the endotracheal tube. The continuous-flow, pressure-limiting device (Neopuff Infant Resuscitator, Fisher and Paykel Healthcare, Auckland, New Zealand) had a built-in manometer and positive end expiratory pressure (PEEP) valve. At the start of resuscitation, the blow off valve was set at 30 cmH₂O and the "blow off" pressure level was only increased if there was a need to deliver higher pressures to achieve adequate ventilation. The unit protocol was that the first five inflations via the endotracheal tube were to be with an inflation pressure of 20 cmH₂O, "ie" a peak inspiratory pressure of 25 cmH₂O with a PEEP of 4-5 cmH₂O was used throughout all resuscitations. The first five inflations were to be maintained for two to three seconds.[5] The infant’s condition was then to be reassessed. The inflation pressure was increased if chest wall expansion was thought inadequate. A PEEP of 4–5 cm H₂O and a flow of 8 litres/min were used throughout all resuscitations. A neuromuscular blocking agent (pancuronium bromide) was routinely given intravenously as soon as possible after intubation. Following pancuronium administration, clinicians increased the inflating pressure as necessary to ensure adequate chest wall rise and the inspired oxygen was increased to try and maintain the preductal oxygen saturations at least at 95%. The clinicians attending the resuscitations had all been trained in newborn life support and had received the Resuscitation Council (UK) Newborn Life Support provider certificate. They all had at least three to six years paediatric experience. They had also been trained to operate the respiratory function monitor. All infants were subsequently supported on time cycled, pressure limited ventilation.
**Monitoring Equipment**

The respiratory function monitor used was an NM3 respiratory profile monitor (Philips Respironics). The monitor was connected to a Laptop (Dell Latitude) with customised Spectra software (3.0.1.4, Grove Medical, London, UK). The NM3 respiratory profile monitor has a combined pressure, flow and carbon dioxide (CO\(_2\)) sensor (dead space 0.8 ml) which was placed between the t-piece and the endotracheal tube connector. The flow and pressure measurements were made using a fixed orifice differential pressure pneumotachometer. Respired gas flowing through the flow sensor caused a small pressure drop across the two tubes connected to the sensor. The pressure drop was transmitted through the tubing to a differential pressure transducer located inside the monitor. Gas flow was digitally integrated by the NM3 monitor to obtain volume. One of the tubes was also connected to a second pressure transducer to measure airway pressure. The NM3 monitor was automatically calibrated for flow, pressure and CO\(_2\) according to the factory-stored calibration in the monitor. The pressure transducer was automatically ‘zeroed’ to correct for changes in ambient temperature. According to the manufacturer’s information and confirmed by in vitro studies in our laboratory, the accuracy of the flow sensor was ±3% and the airway pressure was ±2%. The software compensated for higher oxygen concentrations, such that gas density and viscosity effects did not cause significant errors in flow or volume measurement, again confirmed by in vitro studies in our laboratory. During the resuscitation, the respiratory function monitor was set to display tidal volume, flow and inflation and PEEP. Dynamic lung compliance was calculated by dividing the change in expiratory volume by the peak pressure minus the PEEP of the previous inflation. Expiratory tidal
volumes were used in the calculation to reduce any errors due to leaks around the endotracheal tube. In a previous study [12], we reported minimal or no leaks around Cole’s shouldered endotracheal tubes. Continuous oxygen saturation monitoring was routinely used in the resuscitation of infants with CDH. The probe was attached to the right hand i.e. preductal.

**Analysis**

Analysis was made of the first and last minute of the respiratory function recording during resuscitation. Traces were excluded if there was a large leak (>75%) throughout the recording. In addition, inflations were excluded if there was a leak >75% or the tidal volume could not be measured accurately due to artefact.

**Statistics**

The data were tested for normality using the Kolmogorov-Smirnov test and found to be not normally distributed. Differences between those who did and did not survive, therefore, were assessed for statistical significance using the Mann-Whitney U test or Chi-square test as appropriate. Receiver operateure curves (ROC) were constructed to determine the sensitivity and specificity of tidal volume, ETCO$_2$ and compliance levels in the first and last minutes of recorded resuscitation in predicting survival. Analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL).
RESULTS

During the study period, there were forty-three infants with CDH who had respiratory function recordings. Five infants were excluded as the demographic details for three infants were not available (and hence their outcomes were not known), one infant had been ventilated for an unknown period of time before respiratory function monitoring was commenced (who survived) and resuscitation for the fifth infant was discontinued in the labour suite (who died).

Eleven of the thirty eight infants included in the analysis died. There were no significant differences in the demographics of the survivors and non-survivors, except a greater proportion of non-survivors had received antenatal corticosteroids and more required high frequency oscillatory ventilation (HFOV) and or inhaled nitric oxide (NO) (Table 1). Five of the 27 survivors (18.5%) were oxygen dependent at 28 days. The time to reach an oxygen saturation of >90% or a heart rate > 150 seconds did not differ significantly between the groups (Table 2). The maximum saturation achieved during resuscitation, however, was significantly lower in the non survivors (p=0.037) (Table 2).

A total of 1508 inflations were analysed in the first minute of recorded resuscitation. The median VTe (p=0.009), compliance (p=0.018) and ETCO$_2$ (p=0.023) levels were lower in the non-survivors (Table 2). A tidal volume of greater than 2.1 ml/kg predicted survival with a sensitivity of 87% and specificity of 87%, a compliance of greater than 0.007 ml/cmH$_2$O/ kg predicted survival with a sensitivity of 88% and a specificity of 87% and an ETCO$_2$ of greater than 25 mm Hg predicted survival with a sensitivity of 76% and specificity of 70%.
In the last minute of recorded resuscitation 1385 inflations were analysed. The median VTe (p=0.003) and compliance (p=0.004) were lower in the non-survivors, despite use of higher peak inflation pressures (p=0.03) (Table 3). A tidal volume of > 3.8 ml/kg predicted survival with a sensitivity of 85% and a specificity of 90% and a compliance > 0.12 ml/cmH₂O/kg was predictive with a sensitivity of 85% and a specificity of 90%, but ETCO₂ levels were not predictive of survival.

**DISCUSSION**

We have demonstrated that infants with CDH who did not survive had a poorer response even to initial resuscitation as evidenced by significantly a lower median tidal volume, compliance and ETCO₂ levels in the first minute of recorded resuscitation. Furthermore, during the last minute of resuscitation despite the peak inflating pressures being significantly higher in the non-survivors, the median tidal volume and compliance remained significantly lower than in the non-survivors. In addition, the maximum oxygen saturation achieved during resuscitation was significantly lower in the non-survivors. A tidal volume of > 3.78 ml/kg and a compliance of > 0.12 ml/cmH₂O/kg in the last minute of recorded resuscitation had a sensitivity of 85% and a specificity of 90% for prediction of survival. Those results likely reflect non-survivors had a greater degree of pulmonary hypoplasia.

Although the ETCO₂ levels were significantly lower in non-survivors during the first minute of respiratory function recording, there was no significant difference
between the two groups during the last minute. This suggests the groups had similar levels of pulmonary vasodilation at the end of resuscitation.[13] Our results of low ETCO$_2$ levels in non-survivors compared to survivors in the first minute of resuscitation suggest a significant ventilation/perfusion mismatch in the non-survivors at the start of resuscitation. In the first 24 hours, however, non-survivors with CDH have been shown to have higher arterial CO$_2$ levels compared to survivors presumably due to pulmonary hypoplasia.[14]

Both groups of infants had very stiff lungs, but particularly so in the non-survivors (Tables 3 and 4), hence the infants required high pressures to cause chest wall expansion. A healthy infant at term has a compliance of 2.0 ml/cm H$_2$O/ kg. All of the infants received neuromuscular blockade and we have previously shown that this reduces lung compliance necessitating higher peak inspiratory pressures.[11] King’s College Hospital NHS Foundation Trust is a referral centre for fetal tracheal occlusion (FETO) and approximately one third of the population studied had had FETO. Those infants were born at an earlier gestational age (data not shown), as we have previously demonstrated.[14] There was, however, no significant difference in the proportions of infants who had undergone FETO and who did and did not survive (Table 1), which may reflect improvements in the lung to head ratio following FETO.

The median duration of the recordings did not differ significantly between the two groups. In both groups, respiratory recordings were commenced as soon as possible after intubation. All infants remained intubated when transported to the neonatal unit. It is likely respiratory function monitoring ceased only when
the infant was moved from the resuscitaire to the transport incubator. Hence, we speculate it was not that better results were achieved in those who survived because they were resuscitated for longer.

Previous studies have demonstrated the five minute Apgar score [15-17] differed significantly between those who did and did not survive. In this study, the Apgar scores at one and five minutes, however, did not differ significantly between the two groups. The Apgar score provides a method for reporting the status of newborn infants immediately after birth. The American Academy of Paediatrics has commented Apgar scores alone do not predict mortality.[18] We cannot comment on the previous findings [10] which highlighted that CDH infants may spontaneously breathe at birth, as respiratory recordings only began once the infants were intubated. A neuromuscular blocking agent was given immediately after intubation so we also cannot comment on the interaction of spontaneous respiration and manual inflations.[10]

Even in the first minute of recorded resuscitation, the peak inflating pressures were higher than those our protocol recommends for the first five inflations and in the previous [7] and updated [19] CDH Euro Consortium statement. The clinicians, however, were instructed to increase the inflation pressures to ensure adequate chest wall rise and despite the high pressures used, few of the infants had excessive tidal volumes. The very low compliance of these infants explains why the infants needed high pressures. Administration of a neuromuscular blocking agent at resuscitation reduces the respiratory compliance of CDH infants.[11] Whether lower pressures are required in CDH infants who are not
paralysed from birth merits study. It is important in this patient group to use as low pressures as possible as they are at very high risk of developing pneumothoraces.

There are strengths and some limitations to our study. To our knowledge, this is the largest series reported of CDH infants who had undergone respiratory monitoring during resuscitation in the labour suite. We were able to simultaneously assess tidal volume and peak inflating pressure and hence calculate compliance. The very low compliance level of the non-survivors suggests they died of pulmonary hypoplasia, furthermore a greater proportion required HFOV. Indeed, a number of studies have demonstrated an association between pulmonary hypoplasia and mortality in infants with CDH.[20] In addition, inhaled NO use was greater in the non-survivors suggesting they had more severe pulmonary hypertension. Unfortunately post-mortem data were not available for all the infants. We analysed the first minute of recorded resuscitation, not the first minute of resuscitation. Respiratory recordings were made once the infant was intubated, but as this was attempted immediately after intubation, the first minute of recording likely reflected the infant’s condition very close to birth. The tidal volume, compliance and ETCO$_2$ levels during the first minute of recording were predictive of outcome. We did not calculate the oxygenation index, which has been shown to be the best predictor of outcome both in the first 24 hours in a single centre [21] and in a multicentre study, as we did not undertake arterial blood gas analysis in the labour suite.[22] We, however, did demonstrate a significantly lower maximum oxygen saturation level in the labour suite in the non-survivors.
In conclusion, we have demonstrated that infants with CDH who subsequently died had a poorer response to even initial resuscitation. In addition, survival was predicted by a low tidal volume and compliance during initial resuscitation. We suggest that the results of respiratory function monitoring during resuscitation of infants with antenatally diagnosed CDH might be useful in predicting survival.
ACKNOWLEDGEMENTS

**Funding:** The research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

**Competing interests:** None to declare.

**Contributor statement:** AG, AM and KA designed the study. VM collected the data. AO’R and KA analysed the data. All authors were involved in producing the manuscript and approved the final version.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article to be published in Archives of Disease in Childhood editions and any other BMJPLG products to exploit all subsidiary rights, as set out in our licence “http://adc.bmjournals.com/ifora/licence.dtl”.
What is already known on this topic

- Infants with congenital diaphragmatic hernia can have severe pulmonary hypoplasia.
- Key to successful resuscitation of CDH infants is to establish adequate preductal arterial saturation and avoid progressive hypercapnia.

What this study adds

- CDH infants who did not survive responded less well to even initial resuscitation than those who survived.
- Non-survivors had significantly lower tidal volumes (VTe) and exhaled carbon dioxide (ETCO₂) levels.
- The maximum oxygen saturation achieved in the labour suite was significantly lower in non-survivors.
REFERENCES


Table 1: Demographics according to survival

The data are presented as median (range) or percentage

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>27</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age</strong>&lt;sup&gt;(wks)&lt;/sup&gt;</td>
<td>38.6 (32-41)</td>
<td>35.7 (32.7-39.9)</td>
<td>0.140</td>
</tr>
<tr>
<td><strong>Birth weight</strong>&lt;sup&gt;(gms)&lt;/sup&gt;</td>
<td>2790 (1380-3976)</td>
<td>2756 (1674-3760)</td>
<td>0.427</td>
</tr>
<tr>
<td><strong>Gender</strong>&lt;sup&gt;(male)&lt;/sup&gt;</td>
<td>70.4%</td>
<td>54.5%</td>
<td>0.351</td>
</tr>
<tr>
<td>FETO</td>
<td>40.7%</td>
<td>36.4%</td>
<td>0.802</td>
</tr>
<tr>
<td><strong>Antenatal steroids</strong></td>
<td>40.7%</td>
<td>81.8%</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Apgar 1 minute</strong></td>
<td>7 (1-9)</td>
<td>6 (1-8)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Apgar 5 minutes</strong></td>
<td>7 (3-10)</td>
<td>7 (2-9)</td>
<td>0.32</td>
</tr>
<tr>
<td>HFOV</td>
<td>22.2%</td>
<td>72.7%</td>
<td>0.003</td>
</tr>
<tr>
<td>Inhaled NO</td>
<td>44.4%</td>
<td>100%</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Duration of recording</strong>&lt;sup&gt;(seconds)&lt;/sup&gt;</td>
<td>847 (144-1649)</td>
<td>787 (515-1690)</td>
<td>0.857</td>
</tr>
</tbody>
</table>
Table 2: Heart rate and oxygen saturation by survival

The data are presented as median (interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non Survivors</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to saturation &gt;90% (seconds)</td>
<td>205 (83, 296)</td>
<td>317 (95, 491)</td>
<td>0.726</td>
</tr>
<tr>
<td>Maximum saturation during resuscitation (%)</td>
<td>100 (96, 100)</td>
<td>93 (85, 97)</td>
<td>0.027</td>
</tr>
<tr>
<td>Time to heart rate &gt;150 (seconds)</td>
<td>124 (68, 206)</td>
<td>154 (44, 273)</td>
<td>0.848</td>
</tr>
</tbody>
</table>
Table 3: First minute respiratory recording data according to survival

The data are presented as median (range)

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>P value</th>
<th>AUROC*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak inflation pressure (cmH₂O)</strong></td>
<td>31 (26-48)</td>
<td>32 (25-39)</td>
<td>0.657</td>
<td>0.451</td>
</tr>
<tr>
<td><strong>Inflation time (secs)</strong></td>
<td>0.7 (0.4-1.9)</td>
<td>0.7 (0.5-1.0)</td>
<td>0.975</td>
<td>0.505</td>
</tr>
<tr>
<td><strong>VTe (ml/kg)</strong></td>
<td>2.7 (0.1-17)</td>
<td>1.9 (0.8-5.9)</td>
<td>0.009</td>
<td>0.748</td>
</tr>
<tr>
<td><strong>Compliance (ml/cmH₂O/kg)</strong></td>
<td>0.1 (0.003-0.8)</td>
<td>0.06 (0.03-0.17)</td>
<td>0.018</td>
<td>0.807</td>
</tr>
<tr>
<td><strong>ETCO₂ (mmHg)</strong></td>
<td>41 (0.2-65.6)</td>
<td>11.7 (0.5-44.9)</td>
<td>0.023</td>
<td>0.781</td>
</tr>
</tbody>
</table>

*Area under the ROC
Table 4: Last minute respiratory recording data by survival

The data are presented as median (range)

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>P value</th>
<th>AUROC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak inflation pressure (cmH$_2$O)</td>
<td>30 (26-45)</td>
<td>33 (28-39)</td>
<td>0.03</td>
<td>0.726</td>
</tr>
<tr>
<td>Inflation time (secs)</td>
<td>0.6 (0.4-1.4)</td>
<td>0.8 (0.2-1.7)</td>
<td>0.48</td>
<td>0.412</td>
</tr>
<tr>
<td>VTe (ml/kg)</td>
<td>4.7 (2.1-8.9)</td>
<td>3.2 (0.9-15.4)</td>
<td>0.003</td>
<td>0.333</td>
</tr>
<tr>
<td>Compliance (ml/cmH$_2$O/kg)</td>
<td>0.2 (0.07-0.34)</td>
<td>0.1 (0.02-0.5)</td>
<td>0.004</td>
<td>0.811</td>
</tr>
<tr>
<td>ETCO$_2$ (mmHg)</td>
<td>56 (6.6-75.9)</td>
<td>61.7 (18.1-95.5)</td>
<td>0.13</td>
<td>0.807</td>
</tr>
</tbody>
</table>

*area under the ROC