

Predictors of survival in infants with congenital diaphragmatic hernia - systemic oxygenation status versus dynamic compliance of the respiratory system

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Objective. To compare whether early measurement of blood gases and/or dynamic compliance of the respiratory system (CRS_{dyn}) predicts outcome in high-risk infants with unilateral congenital diaphragmatic hernia (CDH).

Patients and methods. A retrospective study was performed at Tygerberg Children's Hospital between January 1992 and August 2001. High-risk infants with unilateral CDH, who presented with respiratory distress within 6 hours of birth, were included. Patients with other lethal congenital abnormalities were excluded. The first arterial blood gas value after endotracheal intubation was documented and the arterial-alveolar oxygen tension (a:A) ratio was calculated. CRS_{dyn} was measured within 24 hours of birth. The ability of these measurements to predict outcome (survival or death during the newborn period) was determined.

Results. Seventeen of 40 infants with CDH were categorised as high risk and included in the study. Eight of them (47%) survived the neonatal period. The best single predictors of outcome were, in order, partial pressure of oxygen in arterial blood (PaO_2), a:A ratio and dynamic compliance of the respiratory system standardised for body weight ($CRS_{dyn/kg}$). The specificity and sensitivity at a PaO_2 cut-off of 19.3 kPa were 7/8 (95% confidence interval (CI): 0.473 - 0.997) and 9/9 (95% CI: 0.634 - 1.000) respectively. Results for a:A ratio were cut-off 0.321, specificity 6/8 (95% CI: 0.349 - 0.968), and sensitivity 9/9 (95% CI: 0.634 - 1.000). Results for $CRS_{dyn/kg}$ were cut-off 0.259, specificity 6/8 (95% CI: 0.349 - 0.968), and sensitivity 9/9 (95% CI: 0.634 - 1.000). A linear discriminant function based on the 3 best single predictors was found to be no more effective than the first PaO_2 .

Conclusions. Early oxygenation status predicts outcome better than the $CRS_{dyn/kg}$ in infants with unilateral CDH. However, both measurements predict outcome with high accuracy.

Despite advances in prenatal and postnatal diagnosis and management of congenital diaphragmatic hernia (CDH), high mortality rates, exceeding 40%, are still reported.¹ In high-risk infants, i.e. those presenting with symptoms within 6 hours of life, pulmonary hypoplasia, associated pulmonary hypertension and severe disturbances in intrapulmonary ventilation/perfusion ratios, are the most important factors determining survival.²

Since 1970 numerous authors^{3,4} have tried to clarify the postnatal functional-reversible and structurally fixed factors such as blood gases and ventilatory indexes (compromise in ventilation/perfusion), echocardiography (pulmonary hypertension, cardiac abnormalities) and lung mechanics

Key words

CDH = congenital diaphragmatic hernia;
 CRS_{dyn} = dynamic compliance of the respiratory system;
 $CRS_{dyn/kg}$ = dynamic compliance of the respiratory system standardised for body weight;
 PaO_2 = partial pressure of oxygen in arterial blood;
 $PaCO_2$ = partial pressure of carbon dioxide in arterial blood;
 a:A ratio = arterial-alveolar oxygen tension ratio;
 CMV = conventional mechanical ventilation;
 FRC = functional residual capacity;
 IQR = interquartile range.

(lung volume and distensibility), in guiding management and predicting outcome in infants suffering from isolated CDH. In many of the studies the threshold values of variables used to determine outcome in CDH are often of low specificity and therefore none consistently predicts fatal pulmonary hypoplasia. Determining risk factors or predictors of mortality while avoiding hyperventilation through an approach of 'gentle' ventilation, confuses the picture even more.

We hypothesised that two bedside measurements obtained early after birth might assist in defining fatal pulmonary hypoplasia. The first measurement is the arterial blood gas from which the arterial-alveolar oxygen tension (a:A) ratio is calculated. This measurement is a composite measure of diffusion limitations, shunting and ventilation-perfusion match. The second measurement, the dynamic compliance of the respiratory system (CRS_{dyn}), reflects lung distensibility. We reasoned that a combination of these 2 measurements could result in better risk stratification and therefore assist the clinician to guide therapy and give parents more appropriate information regarding prognosis in infants with a unilateral CDH.

Patients and methods

To examine the potential effectiveness of the bedside measurements as predictors of survival we retrospectively studied all infants diagnosed with a CDH admitted to the neonatal intensive care unit (NICU) at Tygerberg Children's Hospital, a unit that does not offer extracorporeal membrane oxygenation (ECMO) support. Between 1 January 1992 and 31 August 2001, consecutive infants with unilateral CDH without associated lethal abnormalities were included in the final analysis if they complied with all of the following criteria: presented within 6 hours of birth with respiratory distress (high risk); required endotracheal intubation and assisted ventilation; the first post-intubation blood gas reading was available; and a CRS_{dyn} was measured within 24 hours of birth.

A cut-off postnatal age of 24 hours was selected in order to include infants from referral hospitals in the region as well as to minimise the effects of postnatal physiological changes and interventions on respiratory compliance. Delayed surgical repair was carried out after stabilisation of affected infants with CDH.

Data collection and management

The following demographic data were collected: gestational age, birth weight, gender, side of the CDH and place of birth (inborn or outborn). Arterial blood gas values and ventilator parameters included the first blood gas values (pH, partial pressure of oxygen in arterial blood (PaO_2) and partial pressure of carbon dioxide in arterial blood ($PaCO_2$)), initial ventilator settings (respiratory rate, peak inspiratory pressure (PIP), and positive end-expiratory pressure (PEEP)) and tidal volume. In our study we aimed to collect the pre-ductal PaO_2 values. However folders did not always include a record of whether pre- or post-ductal PaO_2 measurements had been used. Variable concentrations of oxygen were administered to infants, but oxygen saturation was kept at a range of 87 - 92%.

A ventilation index (VI) was calculated according to the following formula: $VI = \text{respiratory rate} \times PIP$. The a:A ratio was calculated as follows: $a:A \text{ ratio} = PaO_2/PaCO_2$, where the

PaO_2 is the alveolar oxygen tension derived from: $(\text{fractional oxygen requirement} (FiO_2) \times 760 - 47) - PaCO_2/0.8$.

The determination of CRS_{dyn} was part of the standard ventilatory management protocol of infants with respiratory compromise. Measurements were performed before surgery and while the infants were nursed supine with the head in the midline position. Measurements were done using hot-wire anemometry (Neonatal Volume Monitor (NVM-1), Bear Medical Systems, Riverside, Calif.). After placing the sensor, 5 minutes was allowed for stabilisation. Parameters that were constantly monitored and displayed included inspiratory and expiratory tidal volume (V_{texp}), minute ventilation, respiratory rate, inspiratory and expiratory time and percentage tube leakage. The CRS_{dyn} was then derived from the following formula: $(V_{texp}/PIP-PEEP)$. The average of 3 CRS_{dyn} measurements, taken at 1, 3 and 5 minutes, was used and then standardised for birth weight. The transpulmonary pressure as reflected by the difference between PIP and PEEP was derived from the ventilator. This method of determining compliance has previously been validated against the single-breath occlusion technique.⁵ The NVM-1 system was calibrated for volume using an air-filled syringe and found to be accurate to within 5%. None of the ventilators were calibrated before use and accuracy of displayed PIP and PEEP were not determined.

Routine prenatal ultrasonography was not performed on all pregnant mothers. Postnatally, infants with CDH were managed according to a standardised protocol. Conventional mechanical ventilation (CMV) was the primary mode of ventilation (time-cycled, pressure limited). All infants were paralysed and received a continuous infusion of fentanyl (5 - 10 $\mu\text{g}/\text{kg}/\text{h}$) and dopamine (2.5 $\mu\text{g}/\text{kg}/\text{min}$). The choice of switching from CMV to high-frequency oscillatory ventilation, administering of inhaled nitric oxide or rescue exogenous surfactant replacement therapy was left to the discretion of the attending physician. Infants treated with rescue postnatal surfactant received treatment only after the first series of CRS_{dyn} were determined. The primary approach to delayed surgical repair included the use of a subcostal slide procedure where diaphragmatic repair was under mild to moderate tension. Synthetic reconstruction of the diaphragm was considered when a subcostal slide procedure was not feasible. Postoperative paralysis was continued for 3 - 5 days. The underwater drain, placed during surgery, was removed between 5 and 10 days after surgery. No suction control device was connected to the drain.

Arterial saturations were monitored pre-ductally. Although attempts were made to confirm a suspected diagnosis of pulmonary hypertension using echocardiography, the results of these measurements were only available for 6 infants and are therefore not reported.

Currently no method appears to have sufficient clinical accuracy for predicting the outcome of an individual infant with CDH.



Outcome

The outcome measure was survival of the neonatal period.

Statistics

Comparisons of the survivor versus non-survivor group, with regard to ratios such as male/female, were made using tests appropriate for contingency tables. The medians of quantitative variables were compared using the Mood test for difference of medians.⁶ The results of Mood tests of the variables PaO₂, PaCO₂, CRS_{dyn}, a:A ratio and VI were used as a guide to identifying clinically useful discriminators of survival. The specificity, sensitivity and area under the receiver operator curve (ROC) were calculated as indicators of the efficacy of the predictors. A linear combination of predictors was examined by discriminant analysis.

Results

Seventeen of 40 neonates presenting with CDH during the study period were eligible for analysis as per set-out criteria. Eight of them (47%) survived the neonatal period. Mortality was associated with refractory respiratory failure (N = 8) associated with documented pulmonary hypertension (N = 3), preoperative pneumothoraces (N = 5) and postoperative nosocomial sepsis (N = 1). Two infants had associated gut malrotation and 1 infant had an atrial septal defect and imperforate anus. Surgical correction was performed in only one of the infants in the non-surviving group. Two infants developed transient chylothorax after surgery.

The clinical characteristics of survivors and non-survivors are given in Table I. There were no statistically significant differences between the groups with regard to gestational age, birth weight, gender, side of the hernia or whether the infants were inborn or transferred. Although the difference is not significant, a greater proportion of non-survivors received surfactant treatment. The CDH was detected by prenatal ultrasonography in 10 of 17 infants. Of these, 6 infants were in the non-survivor group and 4 in the survivor group. Ventilator parameters, blood gas results and lung function measurements for surviving and non-surviving neonates are summarised in Table II. Significant differences were found between the medians of survivors and non-survivors in first PaO₂, a:A ratio, expiratory tidal volume and dynamic compliance of the respiratory system standardised for body weight (CRS_{dyn/kg}).

TABLE I. CLINICAL CHARACTERISTICS OF SURVIVORS AND NON-SURVIVORS

Characteristics	Survivors (N = 8)	Non-survivors (N = 9)
Gestation (weeks) (median (IQR))	38 (2.5)	36.5 (4.5)
Birth weight (kg) (median (IQR))	2.52 (0.89)	2.7 (0.53)
Surfactant (%)	1 (12.5)	5 (55.5)
Male/female (N)	6/2	6/3
Sidedness (L/R) (N)	4/4	5/4
Inborn/outborn (N)	4/4	6/3

p > 0.05 (the between-group difference was not significant with regard to any of the clinical characteristics).

The diagnostic value and predictive capacity of variables are shown in Table III, which gives details for optimal cut-off values, proportion for correct classifications, sensitivity, specificity, area under the ROC curve and its estimated standard error for several variables. The best single predictors of outcome were, in order, PaO₂, a:A ratio and CRS_{dyn/kg}. The specificity and sensitivity at a PaO₂ cut-off of 19.3kPa were 7/8 (95% confidence interval (CI): 0.473 - 0.997) and 9/9 (95% CI: 0.634 - 1.000) respectively. Results for a:A ratio were cut-off 0.321, specificity 6/8 (95% CI: 0.349 - 0.968), and sensitivity 9/9 (95% CI: 0.634 - 1.000). Results for CRS_{dyn/kg} were cut-off 0.259, specificity 6/8 (95% CI: 0.349 - 0.968), and sensitivity 9/9 (95% CI: 0.634 - 1.000). A linear discriminant function based on the 3 best single predictors was found to be no more effective than first PaO₂.

Discussion

The incidence of CDH is between 1 in 2 000 and 1 in 5 000 live births. It usually presents in the newborn with respiratory distress.¹ It is associated with high morbidity and mortality, with the primary causes of respiratory insufficiency being severe pulmonary hypoplasia in combination with pulmonary hypertension.⁷ In our study we assessed commonly used indexes of respiratory failure in terms of their ability to predict survival in high-risk infants with unilateral CDH. In these infants we showed that the first post-intubation PaO₂ value is a better predictor of outcome than the a:A ratio or CRS_{dyn} measured within the first 24 hours of life. Our findings are in keeping with those of others^{3,8} who showed that 31 - 53% of

TABLE II. FIRST BLOOD GAS RESULTS, a:A RATIO, VENTILATION INDEX, TIDAL VOLUME AND RESPIRATORY SYSTEM COMPLIANCE VALUES OF SURVIVORS AND NON-SURVIVORS

Parameter median (IQR)	Survivors (N = 8)	Non-survivors (N = 9)	p-value
First pH	7.37 (0.18)	7.26 (0.27)	0.229
First PaO ₂ (kPa)	38.9 (34.3)	6.9 (7.6)	0.002
First PaCO ₂ (kPa)	4.35 (1.4)	5.5 (2.8)	0.457
a:A ratio	0.467 (0.34)	0.087 (0.096)	0.002
Ventilation index	1 360 (555)	1 608 (1 301)*	0.614
Tidal volume (ml/kg)	6.03 (2.12)	4.33 (1.51)*	0.046
CRS _{dyn} (ml/cmH ₂ O/kg)	0.344 (0.247)	0.170 (0.101)	0.030

*Indicates one missing value, i.e. N = 8.

TABLE III. AREA UNDER ROC CURVE, ITS ESTIMATED STANDARD ERROR, OPTIMAL CUT-OFF, PROPORTION CORRECT CLASSIFICATIONS, SENSITIVITY AND SPECIFICITY

Variable	AUC (standard error)	Cut-off	Proportion correct	Sensitivity (%)	Specificity (%)
PaO ₂ (kPa)	0.92 (0.08)	19.3	16/17	100.0	87.5
pH	0.66 (0.15)	7.27	12/17	55.6	87.5
PaCO ₂ (kPa)	0.69 (0.15)	6.45	12/17	55.6	37.5
a:A ratio	0.90 (0.09)	0.321	15/17	88.9	87.5
Tidal volume (ml/kg)	0.73 (0.13)	5.029	13/16	87.5	75
CRS _{dyn} (ml/cmH ₂ O)	0.83 (0.11)	0.79	15/17	100	62.5
CRS _{dyn} (ml/cmH ₂ O/kg)	0.91 (0.06)	0.259	15/17	100	75

*In case of PaCO₂ observed value smaller than cut-off = classified alive.

high-risk infants with CDH die if they present with clinical respiratory distress within 6 hours of birth.

Estimation of the severity of pulmonary hypoplasia in these high-risk infants with CDH remains a challenge. Uncertainty exists regarding the exact relationship between functional disturbances of gas exchange or lung mechanics and acquired images of lung volumes or actual morphometric measurements of lung volume in infants with isolated CDH. Current concepts suggest that survival is associated with a minimum lung volume above 40 - 45% of the expected.⁷

Establishing the role of pulmonary hypertension in the outcome of infants with CDH is technically challenging. Few studies have quantified the contribution of the pulmonary vascular bed to outcome in infants with CDH.³ At term, respiratory compromise in unilateral CDH in the absence of other lethal congenital abnormalities is due to a reduction in lung mass, number and size of the pulmonary arteries and, albeit contentious, primary or secondary surfactant dysfunction and/or deficiency.⁹ Although many interventions such as high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO) assist in treating pulmonary hypertension in infants with isolated CDH, the challenge of the co-existing pulmonary hypoplasia remains.³

Predicting outcome should therefore be feasible by determining an index of lung expansion, i.e. dynamic compliance of the respiratory system (CRS_{dyn}), since a direct correlation can be demonstrated between CRS_{dyn} and lung volume in spontaneously breathing healthy infants.¹⁰ This relationship has also been documented in mechanically ventilated infants with isolated CDH.¹¹ Lung hypoplasia is usually associated with pulmonary hypertension, often resulting in a severe compromise in systemic oxygenation. As a consequence many studies have focused on the degree of compromise in systemic oxygenation by assessing the predictive capacity of blood gases, determined initially or early, within 24 hours, or before surgery.^{2,3,8,12} In infants with CDH a pH < 7, PaCO₂ > 60 mmHg (8 kPa) and postductal PaO₂ < 50 mmHg (6.6 kPa) predict an unfavourable prognosis.¹² A 'best' PaO₂ value below 80 - 100 mmHg (10.6 - 13.3 kPa) has previously been shown to be predictive of severe pulmonary hyperplasia (PH), and PH, as reflected by postmortem data (lung weight to body weight ratio, LW/BW), has been related to poor blood gas values.^{2,13} The observation in this study that a single first post-intubation PaO₂ value < 18 kPa (< 135 mmHg) may be a sensitive discriminator of outcome is in agreement with Germain and co-workers¹³ who found that all of their surviving infants had a PaO₂ > 135 mmHg. The a:A ratio cut-off value of 0.321 was the second most sensitive and specific marker. This is in

agreement with Bohn *et al.*,¹⁴ who has also used it as a reliable marker to predict outcome.

The question whether respiratory tests independent of the influence of pulmonary hypertension, such as lung compliance and lung volume measurements, may assist prognostication remains unresolved. If the argument is followed that a reduction in lung mass, in conjunction with surfactant dysfunction and/or deficiency, results in diminished respiratory compliance, the postnatal outcome of infants with CDH may be more reliably predicted by studies that focus on tests aimed at determining lung volumes and measures of lung expansion.^{8,11} In the present study dynamic respiratory compliance was measured during mechanically assisted ventilation. Dynamic lung compliance was calculated by relating driving ('transpulmonary') pressure to expired flow and volume. The derived compliance therefore indirectly reflects lung volume, i.e. at least for a specific tidal volume. Since the relationship between dynamic lung compliance and lung volume is non-linear, with compliance increasing with increasing lung size, we speculate that the low compliance in the non-survivors in this study probably represents too low a lung mass and possibly lung volume required for survival.¹⁰

The advantage of measuring compliance soon after birth, preferably within 6 hours, avoids the influence of many confounding variables on lung compliance. The role of CRS and functional residual capacity (FRC) as tools in the decision-tree for the management of CDH and as predictors of outcome has been reported previously.¹⁴ A low lung compliance and low FRC independently correlates with survival, but in comparison with FRC, CRS_{dyn} has been shown to be a more useful measurement.¹⁵ In isolated CDH, the reported range of lower cut-off values for CRS_{dyn} for the prediction of survival with or without ECMO varies between 0.15 and 0.2 ml/cmH₂O/kg.^{4,11,16} It appears that the majority of infants with initial preoperative lung compliance values between 0.18 ml/cmH₂O/kg and 0.25 ml/cmH₂O/kg may have sufficient lung tissue to survive without ECMO.^{4,8} This is corroborated in the current study in that none of the survivors had a CRS_{dyn} below 0.2 ml/cmH₂O/kg. Dynamic respiratory compliance values between 0.11 and 0.18 ml/cmH₂O/kg probably represent a 'grey' zone that includes the group of infants with severe respiratory compromise associated with suprasystemic pulmonary hypertension and who could benefit from early ECMO, providing the technology is available. In this subgroup of infants, ECMO or inhaled nitric oxide seems to 'buy' time during which pulmonary vascular resistance and right ventricular systolic pressure decrease.⁷

Respiratory scoring systems often reflect both the amount of ventilator support and respiratory compromise of a particular

infant and although the sensitivity of all of the above tests/indices in predicting outcome in CDH has been somewhat reduced by the availability of ECMO in First-World countries, they may still have relevance for units without ECMO facilities. In our study we showed that the best single predictors of outcome were, in order, PaO₂, a:A ratio and CRS_{dyn}. Like others,³ we showed that blood gas derangement as reflected by the PaO₂ and a:A ratio is still an important predictor of outcome. This is not surprising, considering the complex pathophysiology present in CDH. Alveolar hypoplasia, associated pulmonary hypertension and disturbed surfactant function reflect on blood gas results, indices of intrapulmonary and extrapulmonary shunt and lung mechanics. Criticism levelled against the use of blood gases and blood gas-derived indices in predicting outcome pertains to the fact that these variables may be more significantly influenced by variables such as ventilator settings, FiO₂ adjustments, haemodynamic factors and inconsistencies in the site of blood sampling than, for instance, measuring lung mechanics. Fewer systemic physiological and other confounders influence dynamic respiratory system compliance measurements. The main determinant of distensibility of the lung, while receiving assisted ventilation, is the difference between ventilator peak inspiratory pressure and positive end-expiratory pressure. The present study used the expired tidal volume in the calculation of compliance in order to circumvent the effect of air leak around the airway tube and volume lost to air trapping.

Some criticism is in order. The driving pressure was not standardised in the present study because it was felt that such a practice would have been difficult to defend in the light of varying degrees of respiratory compromise in the infants. Furthermore, ventilator settings were not calibrated, i.e. accuracy of displayed PIP and/or PEEP checked against a standard. The blood gas determination was not synchronised with the measurement of CRS_{dyn} and pulmonary arterial pressure measurements were not available for every infant included in the study.

In summary, we showed that the first PaO₂ value and to a lesser extent, a:A ratio, after intubation is a useful test to determine outcome in infants with unilateral CDH. In terms of predicting outcome, these parameters performed slightly better than the CRS_{dyn/kg}. In the non-survivors, the low CRS_{dyn} value probably reflects the combined effects of a lack of lung mass and surfactant inefficiency, while both alveolar hypoplasia and accompanying pulmonary hypertension (pulmonary hypoperfusion) may account for the raised arterial PaCO₂ levels and compromise in systemic oxygenation of these infants. Whether improved identification of the true high-risk-for-mortality infant may be achieved by combining blood gas results, lung compliance values, the ratio of pulmonary artery pressure to systemic arterial pressure and technology assessing the contribution of wasted ventilation (dead-space/intrapulmonary shunt),

requires a prospective study. At this moment in time, abovementioned indexes can only be used as guidance tools in the counselling of parents. Currently no method appears to have sufficient clinical accuracy for predicting the outcome of an individual infant with CDH. Further studies are required before any definitive measurements can be advocated for making life-or-death decisions.

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