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ORIGINAL ARTICLE

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Prediction of outcome in congenital diaphragmatic hernia

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Abstract The case records of 59 patients with congenital diaphragmatic hernia (CDH) who presented between 1984 and 1997 were studied retrospectively. Included in the study were infants born with CDH who required respiratory support within the first 6 h of life. Twenty-three were excluded from the study for various reasons; 36 were enrolled in the study; the male-to-female ratio was 18:18. Twenty-nine hernias were left-sided and 7 were right-sided. All patients were ventilated using conventional techniques. Arterial blood gases were measured on average 1.76 h following admission and the initial period of resuscitation (range 1–4 h). Three formulae were applied in an attempt to predict outcome: ventilation index against PCO_2, alveolar-arterial oxygen gradient, and a newly derived formula from this institution (Red Cross formula) that comprises respiratory rate × PCO_2 × FiO_2 × mean airway pressure/PaO_2 × 6000. Seventeen patients (47.2%) survived and 19 died (52.8%); 21 became stable enough to undergo surgery. The average time from presentation until surgery was 1.98 days (range 6 h to 4 days). The Red Cross formula, with a 100% predictive value for mortality, 85% predictive value for survival, and an overall predictive value of 91.6%, appeared to be superior to the other formulae studied. The availability of a highly accurate predictive formula may facilitate management of this frequently lethal disease.

Key words Congenital diaphragmatic hernia · Ventilatory parameters · Blood gases · Survival

Introduction

Congenital diaphragmatic hernia (CDH) remains a challenge to clinicians, with high mortality despite better understanding of the pathophysiology of the condition and the advent of the new therapeutic modalities, extracorporeal membrane oxygenation (ECMO) and nitric oxide (NO) [2, 3]. Emphasis is now on pre-operative stabilization and delayed repair, having acknowledged that the degree of underlying pulmonary hypoplasia (PH) determines eventual outcome. The roles of ECMO and NO are as yet poorly defined in the management of these patients, and it remains to be proven whether either of these modalities will significantly improve survival and which, if any, patients actually benefit from their application [3, 12].

A number of formulae have been used in an attempt to predict outcome, differentiating survivors from non-survivors with lethal PH [7, 12]. In 1984 Bohn et al. introduced the concept of the ventilation index (VI), which was defined as the product of the mean airway pressure (MAP) and respiratory rate (RR) [2]. The VI, when correlated with partial pressure of CO_2, was found to be a reliable indicator of survival using conventional management and has now become the most widely-accepted predictive formula [1]. Bohn et al. further suggested that VI is an indication of the severity of PH [3]. The alveolar-arterial (A-a) oxygen gradient (A-aDO_2) has also been used to reliably predict outcome, as shown by Bohn [1, 6]. In our population, however, we have found that VI used in isolation does not accurately predict outcome. Ventilatory manipulations always involve a change in inspired oxygen fraction (FiO_2), and it is our contention that oxygenation is an important predictive factor under these circumstances. We therefore carried out a retrospective study to assess the predictive value of arterial blood gases (ABGs), combining CO_2 and O_2 partial pressures and ventilatory settings in comparison to the standard formula in use.

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Materials and methods

In the 13-year period 1984–1997, 59 patients with CDH were admitted to Red Cross Children's Hospital neonatal intensive care

unit (ICU). All these infants were born in obstetric units not attached to Red Cross Hospital. All infants included in the study had respiratory distress within the first 6 h of life and required respiratory support. Twenty-three were excluded from the study on the basis of delayed presentation (7), other lethal congenital abnormalities such as univentricular heart and left ventricular atrophy (2), proven septicaemia and disseminated intravascular coagulation (5), and inadequate data (9).

All patients had been intubated either at birth or on arrival to the ICU, and conventional intermittent positive pressure ventilation was initiated. The stomach was decompressed with a nasogastric tube. An attempt was made to insert an arterial cannula, and a chest radiograph was done to check the position of the endotracheal tube and exclude a pneumothorax. All patients received either pancuronium and sedation with fentanyl or fentanyl alone. The first ABG obtained following initiation of resuscitation was measured on average 1.76 h (range 1–4 h) following admission. This was used as the index blood gas analysis for the predictive formulae.

Three formulae were applied in an attempt to predict outcome: (1) VI against PCO_2 [2]; (2) A-a DO_2 [1, 6]; and (3) the "Red Cross" formula: $RR \times PCO_2 \times MAP \times FiO_2/PaO_2 \times 6{,}000$. The final formula was constructed as the numerator containing variables that show an inverse relationship to outcome and PaO_2 as the only denominator. The formula was then divided by 6,000 to make it equal to 1 when all variables contain normal values.

Results

Thirty-six patients were eligible for the study with an equal male-to-female ratio; 29 had left-sided and 7 had right-sided hernias. Seventeen patients (47.2%) survived and 19 died (52.8%). The average gestational age was 36.9 weeks with a range of 29–41 weeks ($n = 22$). Twenty-one patients stabilized to a point where surgery could be carried out. The average time from presentation until surgery was 1.98 days with a range of 6 h to 4 days. Fifteen patients died preoperatively, having failed to stabilize, at an average of 1.7 days and range of 6 h to 8 days. This group of infants demonstrated refractory hypoxemia in association with severe right-to-left shunting. Nine out of 19 patients who died had postmortem examinations carried out, which verified PH as the sole significant cause of death.

Predictive values of the various formulae are compared in graph form. Our own formula successfully separated survivors from non-survivors by drawing an arbitrary line horizontally at the level of 5 in the graph (Fig. 1): 100% of the patients ($n = 16$) above this level died and 85% ($n = 20$) of those below this level survived. The outcome was accurately predicted in 33 of 36 patients, giving an overall predictive value of 91.6%.

The outcome was incorrectly predicted in only 3 patients; 2 had been antenatally diagnosed and all had presented at birth with severe respiratory distress and required immediate and aggressive ventilatory support. Figure 2 shows how our formula applied to one of these infants over a period of time, inclusive of the first two very early ABG results from the referring institution. Although the initial ABGs, if taken into account, accurately predict non-survival, there are no other distinguishing clinical prognostic features of this group. This pattern is representative of all 3 patients (Fig. 2).

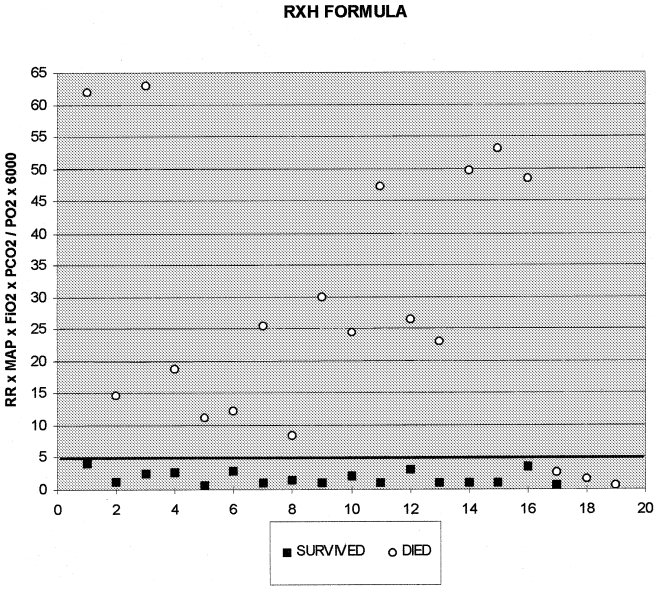

Fig. 1 Predictability of outcome using Red Cross (RXH) formula (*RR* respiratory rate, *MAP* mean airway pressure, FiO_2 inspired oxygen fraction)

When the formula using A-a DO_2 was applied to our population, a horizontal line drawn at the level of 60 shows optimum predictive value (Fig. 3): 88.8% of the patients ($n = 18$) above this level died and 83.3% of those below this level survived ($n = 18$). This gives an overall predictive value of 86.1%. These results are comparable with Bohn's results published in 1987 [1]. The success of this formula is indicative of the importance of variables reflecting oxygenation.

Using Bohn's formula, which divides patients into four groups, we were able to predict 90.9% survival in

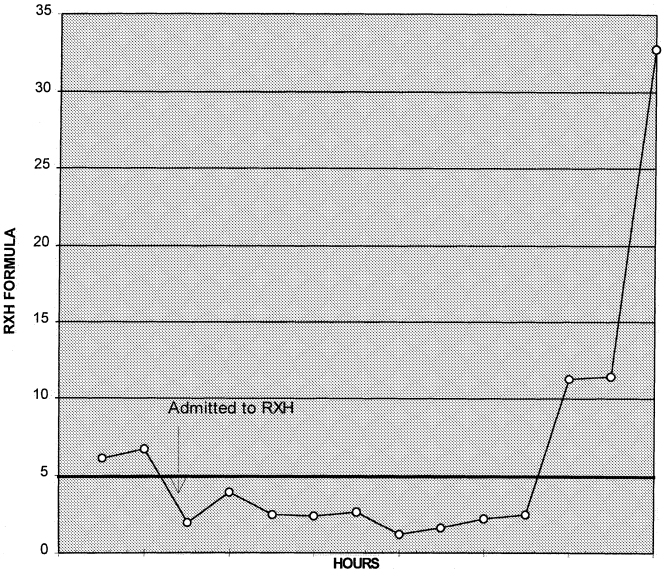

Fig. 2 Trend over time: Red Cross Hospital (RXH) formula in falsely predicted survivor

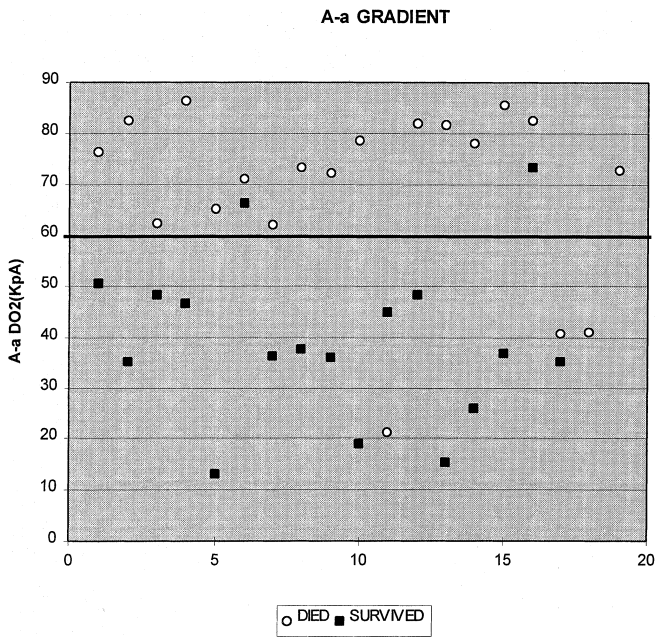

Fig. 3 Predictability of outcome using alveolar-arterial oxygen (A-a) Gradient

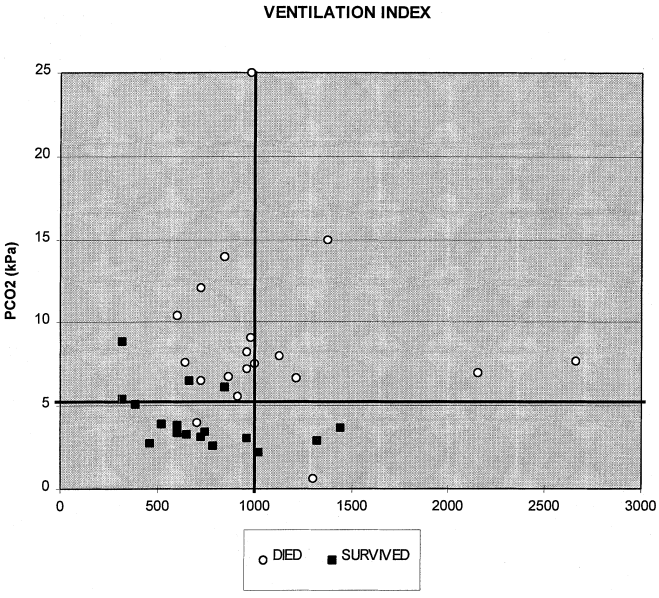

Fig. 4 Predictability of outcome using ventilation index versus PCO_2

the "low-risk" group ($n = 11$) and 100% mortality in the high-risk group ($n = 5$). However, the majority (55.5%) of our population fell outside of these two categories ($n = 20$) (Fig. 4, Tables 1 and 2).

Discussion

Over the past decade, emphasis in the management of CDH has shifted from the urgent repair of the diaphragmatic defect to allow time for optimal stabilization of the patient. This is in recognition of the fact that delayed repair does not increase mortality and that the main determinant of survival is the degree of underlying PH and associated pulmonary hypertension. In addition, it is recognized that pulmonary function, rather than improving post-operatively, actually worsens due to decreased lung compliance and increased pulmonary vascular tone [2, 3, 13]. The average age at surgery in our study group was 1.98 days, the reason for this short interval being the infants included in the study prior to the appreciation of preoperative stabilization in the mid 1980s.

Although our overall survival of 49% of 59 infants with CDH is comparable to that of other published series, when applying the Bohn formula to our population it is clear that its overall predictive ability is considerably poorer than would be expected [2, 11, 15]. This may be due to the inclusion of earlier patients in the series who were perhaps less aggressively managed, as is suggested by the large number of infants who fell into the low VI, high PCO_2 group. It is possible that with a continuing, consistent approach to management we may see an improvement in the predictive value of this formula when applied to our population. Infants who fell within the low VI, high PCO_2 group in our study had a mortality of 75% ($n = 16$). Correspondingly, no infants from Bohn's second study fell within this category, but the first series he published showed a substantial number of infants within this group [1, 2].

Table 2 Average arterial blood gas results

	pH	PO_2	PCO_2
Died	7.11	8.25	8.75
Survived	7.42	20.95	4.29
Total	7.25	13.85	6.79

Table 1 Average values of ventilatory settings (*RXH* Red Cross Hospital, *VI* ventilation index, *RR* respiratory rate, *MAP* mean airway pressure)

Patients	A-a gradient	RXH value	VI	RR	MAP	FiO_2
Died (19)	68.2	34.81	1088	76	14.1	91.05
Survived (17)	36.39	1.7	734	61	11.9	65.33
Total (36)	54.17	20.2	932	69.38	13.9	79.7

Bohn has shown in both of his series that high VI and high PCO_2 can distinguish those infants with severe PH and indicate non-survival of 100% and 90%, respectively [1, 3]. This correlates well with our figures, which also showed 100% mortality in this group. For infants in the low-risk group with low VI and PCO_2, survival in our population was comparable to that in Bohn's study, with 90.9% versus 86% survival.

Our results indicate that the outcome of patients with CDH can be predicted with varying accuracy within the first few hours following admission depending on which formula is applied. When Dimitriou used maximum VI and modified VI (peak inspiratory pressure × ventilator rate × PCO_2/1,000) within the first 6 h of life, there was no significant difference in poor and good outcome groups [4]. Our formula, which combines PCO_2, PO_2, and ventilatory settings, had a superior predictive value in this population than either of the others studied: overall 100% predicted mortality and 85% predicted survival.

The derivation of the formula was based on the observation that inspired PO_2 concentrations and arterial PO_2 were significant variables along with VI and PCO_2. The construction of the formula was based on the numerator combining the variables that show an inverse relationship to outcome; i.e., the greater the value, the worse the outcome. The final value was multiplied by 1/6000 in order to minimize the range of results. Inclusion of variables reflecting oxygenation may give a more comprehensive picture of other coexisting lung pathology in addition to PH, which may impact on outcome. This may account for the improved predictive value of our formula.

Using our formula over a period of time from admission, we have been able to demonstrate that a number of the non-survivors enter the so-called ''honeymoon period'', which is indicated by an improvement in condition after an initial period of instability. The remainder of non-survivors show no sign of improvement, are consistently unstable, and die. The correlation between the honeymoon period and the severity of PH has been examined in other series and indicates that those infants who undergo a honeymoon period have less severe PH than those who do not [7]. In our population to date, none of the infants who entered a honeymoon period ultimately survived.

The 3 infants who were predicted survivors but died all had early, initial ABGs from referring institutions that when plotted fell above the discriminating value of 5. Subsequent values obtained following admission to Red Cross Hospital fell below this value, and this pattern would be in keeping with an infant who has severe PH but has entered the honeymoon period.

Reliable prediction of outcome and lethality of underlying PH may help guide management decisions, which in some centers, in addition to the timing of surgery, include the use of high-frequency oscillatory ventilation (HFOV), NO, and ECMO. In this way, use of resources may be optimized and individual patients treated as appropriately as possible.

HFOV has been used in some infants who in other centers would be considered eligible for ECMO, and outcome is comparable [11, 12, 14]. It remains to be seen whether NO will make a significant improvement in outcome in CDH; published data so far are few in number and report tachyphylaxis and a rather inconsistent response [10, 14]. NO in combination with HFOV has been used with possibly additive beneficial effects as optimum lung volumes and alveolar ventilation are achieved, ensuring optimal delivery of the inhalational vasodilator and minimizing intrapulmonary shunting [8].

The use of ECMO in infants with CDH remains controversial, and it has been suggested that a positive response to NO will select out those patients who would benefit from ECMO, non-responders being those with lethal PH [9]. However, other published series, although small, have reported survival with ECMO following failed NO response [5]. Overall, the standardization of patient selection for ECMO programs remains poor, making comparisons of results between institutions and conclusions regarding its efficacy difficult. The development of a highly accurate, discriminating formula that distinguishes those infants with lethal PH may facilitate the rational use of ECMO in addition to guiding decisions regarding the timing of surgery.

In conclusion, the degree of PH is the main factor in determining the outcome in infants with CDH. Delayed surgical repair with preoperative stabilization forms the cornerstone of current management. HFOV, NO, and ECMO may play a role in management when conventional techniques fail, however, this has not as yet been clearly defined. Identification of those patients who would benefit from the application of these modalities is important, both in terms of appropriate treatment for the patient's individual needs as well as to guide the allocation of valuable resources, particularly ECMO. A highly accurate predictive formula may assist in the management of infants with CDH in regard not only to the timing of their surgical repair, but also to the use of ECMO.

From our study, it appears that oxygenation is an important factor that must be considered in addition to other variables in trying to predict outcome. Our formula, which takes variables regarding oxygenation into account, seems to reliably predict outcome when applied in the first 4 h after admission. Further studies are required to confirm the improved predictive value of this formula.

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