

A comparison of indices of respiratory failure in ventilated preterm infants

N V Subhedar, A T Tan, E M Sweeney, N J Shaw

Abstract

Aim—To compare indices of respiratory failure in terms of their ability to predict adverse respiratory outcomes in preterm infants. The indices evaluated were: (a) the alveolar-arterial oxygen tension difference (A-aDO₂); (b) the ratio of arterial to alveolar oxygen tension (a/A ratio); (c) the oxygenation index (OI); (d) the fractional inspired oxygen concentration (FIO₂).

Methods—Details of respiratory support and arterial blood gas data in the first 24 hours of life were collected in ventilated infants below 34 weeks gestation. The worst single value of a particular index in the first 24 hours was chosen to quantify the severity of respiratory failure in each infant. Receiver operating characteristic curves were constructed and areas under the curve (AUC) calculated to compare the performance of the indices in predicting death from respiratory failure and/or the development of chronic lung disease (CLD).

Results—A total of 155 preterm infants were studied, of whom 35 (23%) died primarily from respiratory failure and 53 of the 120 survivors (44%) developed CLD. The overall performance of the four indices in predicting death from respiratory failure ranged from 0.77 (AUC for maximum FIO₂) to 0.88 (AUC for minimum a/A ratio). The corresponding AUCs for gestational age and birth weight were 0.75 and 0.76 respectively. In contrast, demographic variables tended to perform better than indices of respiratory failure in predicting CLD/death.

Conclusions—There was no evidence of a significant difference between the performance of the a/A ratio, A-aDO₂, and OI in predicting adverse respiratory outcomes. Use of the OI is recommended because of its ease of calculation.

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Keywords: respiratory distress syndrome; infant; premature; respiratory insufficiency; lung; arterial blood gas

In recent years, a number of different indices have been used to quantify the severity of respiratory illness in ventilated newborn infants. It has been suggested that calculated indices of respiratory failure may be better objective measures of hypoxaemic respiratory failure than the arterial oxygen tension (PaO₂) or the fractional inspired oxygen concentration

(FIO₂), which are closely related to each other and are operator dependent.¹

Commonly used parameters of respiratory failure include the alveolar-arterial oxygen tension difference (A-aDO₂), the ratio of arterial to alveolar oxygen tension (a/A ratio), and the oxygenation index (OI).²⁻⁴ Clinical trials of interventions for respiratory failure often use such parameters to select suitable infants,⁵ compare respiratory status in different groups after randomisation,^{6,7} and assess short term response.^{8,9} Although most experience with these parameters has been in term infants, they are being used increasingly in preterm neonates.¹⁰ In term infants, parameters of respiratory failure have been used to predict outcome in infants with respiratory failure¹¹; their value in preterm neonates with respiratory failure has not been systematically evaluated and remains unknown.

The aim of this study was to compare different parameters of respiratory failure in terms of their ability to predict adverse respiratory outcome in preterm infants.

Methods

Ventilated preterm infants below 34 completed weeks gestational age were considered eligible for the study if they met the following criteria.

- (1) They had received mechanical ventilation within six hours of birth and until at least 24 hours of age.
- (2) At least three arterial blood gas determinations had been performed within the first 24 hours of life from an indwelling arterial line.
- (3) No major congenital anomalies were present.

Routine clinical management during the period of study included the prophylactic use of artificial surfactant (pumactant; Britannia Pharmaceuticals Ltd, Redhill, Surrey, UK) in all ventilated preterm babies. Two doses of surfactant were given to all babies, at birth and again 12 hours later. Mechanical ventilation was provided with conventional mechanical ventilators; high frequency ventilation was not used. Inhaled nitric oxide and natural surfactant (poractant alfa; SeroPharmaceuticals Ltd, Middlesex, UK) were used in a few infants as part of randomised controlled trials running on the unit during the period of this study.

Supplemental oxygen was administered to maintain PaO₂ between 50 and 70 mm Hg in the acute phase of the respiratory illness. Subsequently, oxygen therapy was guided by pulse oximetry, aiming to maintain arterial oxygen saturation levels above 94%. Infants who

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Table 1 Patient characteristics

	Survivors (n=120)	Deaths (n=35)	p Value
Birth weight (g)	1176 (868–1479)	872 (730–942)	<0.0001
Gestation (weeks)	29 (26–30)	27 (25–27)	<0.0001
Male sex	77 (64)	28 (80)	0.08
Caesarean section	68 (57)	18 (51)	0.58
Antenatal steroids	97 (81)	32 (91)	0.20
Apgar score at 5 min	9 (1–10)	7 (2–10)	0.002
Surfactant	120 (100)	35 (100)	1.0
Patient trigger ventilation	10 (8)	0	0.12
Max PIP (cm H ₂ O)	22 (19–26)	32 (24–38)	<0.0001
Max PEEP (cm H ₂ O)	4 (4–4)	4 (4–5)	0.001
Max MAP (cm H ₂ O)	10.4 (8.9–12.6)	16.4 (12.0–19.5)	<0.0001
Max Paco ₂ (mm Hg)	48 (41–53)	55 (47–73)	0.0001
Max Fio ₂	0.68 (0.46–0.86)	1.0 (0.98–1.0)	<0.0001
Max A-aDo ₂ (mm Hg)	364 (205–494)	633 (584–645)	<0.0001
Min a/A ratio	0.14 (0.09–0.24)	0.05 (0.03–0.08)	<0.0001
Max OI	10.0 (5.6–19.1)	38.8 (22.0–98.9)	<0.0001

Data are expressed as median (interquartile range) or n (%).

PIP, peak inspiratory pressure; PEEP, peak end expiratory pressure; MAP, mean airway pressure; A-aDo₂, alveolar-arterial oxygen tension difference; a/A ratio, ratio of arterial to alveolar oxygen tension; OI, oxygenation index.

remained agitated despite opiate sedation and appeared to breathe asynchronously were managed with patient triggered ventilation. Neuromuscular paralysis was reserved for infants with severe respiratory failure and asynchronous respiration. Caffeine citrate was used to facilitate weaning from mechanical ventilation and extubation directly into head box oxygen. A course of postnatal corticosteroids was considered in any infant who remained ventilator dependent with Fio₂ above 0.30 beyond 7 days of age.

Details of respiratory support were gathered retrospectively from computerised blood gas data (which had been entered prospectively). For each arterial blood gas value entered within the first 24 hours of age, information about PaO₂, Paco₂, Fio₂, and mean airway pressure was collected at the same time, and values of A-aDo₂, a/A ratio, and OI were calculated.¹

Case notes were reviewed to obtain demographic details and outcome data. Respiratory outcomes collected included death and chronic lung disease, defined as oxygen dependency at 28 days and at 36 weeks postmenstrual age (CLD). Death certificates and/or postmortem examination reports were reviewed to classify the infants who died into two groups: (1) death primarily as a result of respiratory failure; (2) death from another cause, with co-existing respiratory disease. Infants in the first group were included in the study, and those in the second were excluded. Patient characteristics and respiratory support data were compared between groups of infants using univariate analysis (Mann-Whitney and χ^2 tests for continuous and categorical data respectively).

Receiver operating characteristic (ROC) curves were constructed, and the area under the curve (AUC) calculated to assess the overall performance of different parameters of respiratory failure as predictors of (a) death from respiratory failure and (b) a combined adverse respiratory outcome of CLD and/or death from respiratory failure.¹² The parameters evaluated were maximum Fio₂, maximum A-aDo₂, minimum a/A ratio, and maximum OI within the first 24 hours of life. AUC was also calculated for birth weight and gestational age for comparison. Further discriminant analysis was

performed by calculating the sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios for various thresholds of individual parameters. Statistical analysis was performed using the Arcus for Windows statistical package (Longman Software Publishing, Cambridge, UK).

Results

In total, 155 preterm infants met the study criteria. Of these, 35 (23%) died primarily from respiratory failure, and 53 of the 120 survivors (44%) had CLD. An additional 10 infants were receiving supplemental oxygen at 28 days, but not at 36 weeks postmenstrual age. The median age at death was 65 hours (interquartile range 16–384). Six infants were excluded because of “non-respiratory” deaths: three died from fungal septicaemia, two from Gram negative sepsis, and one from severe necrotising enterocolitis. The primary causes of “respiratory” death in infants included in the study were: respiratory distress syndrome in 25, pulmonary hypoplasia in three, and severe CLD in seven. Postmortem examinations were performed in 10 of the 35 infants who died.

A total of 1008 arterial blood gas determinations and corresponding ventilator settings were recorded; the median number of arterial blood gas determinations for each infant in the first 24 hours of life was seven (interquartile range five to eight). Table 1 shows the patient characteristics and respiratory data for surviving infants and those who died. Infants who died were significantly lighter and born after shorter gestation than those who survived. They also had significantly lower Apgar scores at five minutes. Respiratory support requirements and indices of respiratory failure were significantly higher during the first 24 hours in infants who ultimately died from respiratory failure. Maximum Paco₂ was also higher in this group. When all infants with an adverse respiratory outcome (CLD and/or death from respiratory failure) were compared with surviving infants without CLD, a similar overall pattern of differences in demographic and respiratory variables was observed (data not shown).

PREDICTION OF DEATH FROM RESPIRATORY FAILURE

Figure 1 shows the ROC curves for birth weight, maximum OI, and minimum a/A ratio for predicting death from respiratory failure.

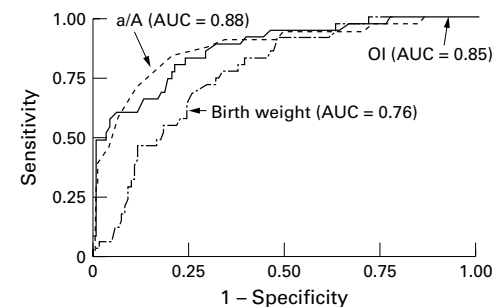


Figure 1 Receiver operating characteristic curves for prediction of death from respiratory failure. a/A, ratio of arterial to alveolar oxygen tension; OI, oxygenation index; AUC, area under curve.

Table 2 Performance of indices of respiratory failure for prediction of respiratory outcome

	Death		CLD/death	
	AUC	95% CI	AUC	95% CI
Gestational age	0.75	0.69 to 0.81	0.81	0.74 to 0.88
Birth weight	0.76	0.70 to 0.82	0.82	0.75 to 0.89
Maximum FIO_2	0.77	0.71 to 0.82	0.66	0.57 to 0.75
Maximum OI	0.85	0.80 to 0.90	0.69	0.60 to 0.78
Maximum A-aDO ₂	0.87	0.82 to 0.92	0.69	0.60 to 0.78
Minimum a/A	0.88	0.84 to 0.92	0.69	0.60 to 0.78

AUC, Area under the receiver operating characteristic curve; CLD, chronic lung disease; A-aDO₂, alveolar-arterial oxygen tension difference; a/A ratio, ratio of arterial to alveolar oxygen tension; OI, oxygenation index.

Table 3 Prediction of death from respiratory failure using minimum ratio of arterial to alveolar oxygen tension (a/A)

a/A ≤	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
0.02	0.11	0.99	0.80	0.79	13.71	0.89
0.06	0.63	0.93	0.73	0.90	9.43	0.40
0.10	0.91	0.66	0.44	0.96	2.68	0.13
0.14	0.94	0.51	0.36	0.97	1.92	0.11
0.18	0.94	0.32	0.29	0.95	1.38	0.18
0.22	0.97	0.26	0.28	0.97	1.31	0.11

Table 4 Prediction of death from respiratory failure using maximum oxygenation index (OI)

OI ≥	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
10	0.94	0.52	0.38	0.97	1.97	0.11
15	0.89	0.65	0.44	0.95	2.57	0.17
20	0.80	0.77	0.52	0.93	3.48	0.26
25	0.66	0.84	0.56	0.89	4.13	0.41
30	0.60	0.91	0.68	0.88	6.78	0.44
35	0.57	0.96	0.80	0.88	12.91	0.45

Table 2 shows the AUC for various parameters. The AUC for gestational age and birth weight were similar to each other, at 0.75 and 0.76 respectively. Although the AUC for OI, A-aDO₂, and a/A ratio tended to be higher, it was only the AUC for a/A ratio that was significantly different from those for birth weight and gestational age. The overall performance of the four indices of respiratory failure varied from 0.77 (AUC for maximum FIO_2) to 0.88 (AUC for minimum a/A ratio). The AUC for a/A ratio, OI, and A-aDO₂ tended to be larger than that for FIO_2 , but this was only statistically significant for the a/A ratio. There was no statistically significant difference between any of the other indices of respiratory failure. Tables 3 and 4 show the prognostic value of different thresholds of minimum a/A ratio and maximum OI within the first 24 hours for predicting death from respiratory failure.

PREDICTION OF CLD/DEATH FROM RESPIRATORY FAILURE

Table 2 shows the performance (AUC) of the various demographic variables and indices of respiratory failure in predicting CLD/death. The AUC for gestational age and birth weight were 0.81 and 0.82, respectively. The indices of respiratory failure tended to perform worse overall, with areas under the curve between 0.66 for maximum FIO_2 and 0.69 for the other three indices. There was no statistically significant difference between any of the indices of respiratory failure.

Discussion

In this study we have compared commonly used indices of hypoxaemic respiratory failure in terms of their ability to predict important adverse outcomes such as mortality from respiratory failure and CLD. The predictive performances of the three calculated parameters (a/A ratio, A-aDO₂, and OI) were broadly similar; we were unable to identify a single measure of respiratory status that outperformed all the others. However, calculated parameters tended to be able to predict death from respiratory failure more effectively than a simple measure of respiratory failure (FIO_2) or demographic variables such as birth weight and gestational age.

In contrast, there was no equivalent benefit in the prediction of the combined adverse respiratory outcome of CLD/death; demographic variables tended to perform better than indices of respiratory failure in this respect. The most likely explanation for these observations is that the development of CLD is much more closely associated with birth weight and gestational age than with the severity of respiratory disease. Other studies have also shown a poor relation between severity of respiratory disease and the development of CLD, the causes of which are many.^{13 14}

Indices of respiratory failure have been widely used as a measure of illness severity. However, calculation of these indices is not always straightforward, and a number of assumptions are necessary to simplify the equations used.² These indices have now largely been replaced by the OI, which is generally preferred because it is easier to calculate and also incorporates a measure of ventilator pressures.¹ We would recommend the use of the OI because of its simplicity and the lack of evidence suggesting superior performance using other parameters of oxygenation.

We studied a selected group of preterm infants who required respiratory support with conventional mechanical ventilation for at least 24 hours and had an arterial line in situ. We chose this group because it represents a typical population in whom indices of respiratory failure are used in clinical practice. However, our results cannot necessarily be extrapolated to predict outcome in other groups of newborn infants with respiratory disease or those managed using alternative ventilatory strategies.

The "worst" single value for each parameter was used to quantify respiratory status in the first 24 hours of life. Other summary measures that could have been used (to allow for repeated measurements in an individual) include the mean value or the "best" value during the same time period. Another approach would have been to test the performance of a parameter when persistently high or low over a period of time. We chose the worst single value because most clinicians are familiar with this type of threshold value, and a minimum level of respiratory illness severity can be assessed before the full 24 hour period has elapsed.

We have reported the predictive ability of the a/A ratio and OI at different severity thresholds

in this study. This information may be useful in research by allowing selection of subjects for randomised controlled trials. For example, an a/A ratio of ≤ 0.06 in a group of preterm infants managed with conventional ventilation would predict a risk of death from respiratory failure of 73%, and at the same time correctly identify 90% of survivors. This information would be helpful in targeting potentially toxic new treatments to a population with a high risk of mortality. It would also allow calculation of study sample sizes according to respiratory illness severity at trial entry. In clinical practice, a knowledge of respiratory status may also help to guide optimal timing of the changeover from conventional treatment to "rescue" treatments such as high frequency ventilation and inhaled nitric oxide.

In summary, our results suggest that calculated indices of respiratory failure are useful in that they provide more information about the risk of death from respiratory failure than demographic variables such as birth weight or gestational age. We found that the performances of the OI, a/A ratio, and A-aDo₂ were similar in terms of predicting respiratory mortality and/or CLD. For clinical and research purposes, the OI is likely to be preferred because of its ease of calculation.

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