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Predictors of outcome of prematurely born infants with pulmonary interstitial emphysema

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Short title: Outcome of pulmonary interstitial emphysema

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ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
I_{time}	Inflation time
MAP	Mean airway pressure
OI	Oxygenation index
$P_{A\text{-}a}O_2$	Alveolar-arterial oxygen gradient
P_aO_2	Partial arterial pressure of oxygen
P_aCO_2	Partial arterial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
PIE	Pulmonary interstitial emphysema
PIP	Peak inflation pressure
SpO_2	Transcutaneous oxygen saturation levels
VEI	Ventilation efficiency index
VR	Ventilation rate
V_T	Inspiratory tidal volume

ABSTRACT

Aim: To determine how oxygenation, ventilation efficiency and tidal volume requirements changed with the development of pulmonary interstitial emphysema (PIE) and whether in affected patients a composite gas exchange index predicted death or bronchopulmonary dysplasia (BPD).

Methods: Infants who developed PIE from 2010 to 2016 were identified. The oxygenation index, ventilation efficiency index, ventilation to perfusion ratio and inspiratory tidal volume were calculated before radiological evidence of PIE (pre-PIE) and at the worst PIE radiographic appearance (PIE-worst).

Results: Thirty infants, median (IQR) gestational age of 24.6 (24.3-26.7) weeks were assessed. Their age at pre-PIE was 11(6-19) days and 23 (13-42) days at PIE-worst. Compared to pre-PIE, at PIE-worst, the oxygenation index was higher [14.5 (10.7-19.2) versus 4.8 (3.1-6.1) respectively, $p<0.001$], ventilation efficiency index was lower [0.01 (0.01-0.11) versus 0.16 (0.13-0.19) respectively, $p<0.001$], ventilation to perfusion ratio was lower [0.15 (0.11-0.40) versus 0.26 (0.20-0.37), $p=0.033$] and tidal volume was higher [9.9 (7.2-13.1) versus 6.4 (5.5-6.8) ml/kg, $p=0.007$]. An oxygenation index >11.4 at PIE-worst predicted death or BPD with 80% sensitivity and 100% specificity.

Conclusion: Development of PIE was associated with poorer oxygenation and ventilation efficiency despite increased tidal volumes. The oxygenation index at PIE-worst predicted death or BPD.

Key words: pulmonary interstitial emphysema, premature, oxygenation index, ventilation efficiency index, ventilation to perfusion ratio, tidal volume.

KEY NOTES

• Despite advances in neonatal respiratory support, pulmonary interstitial emphysema (PIE) can still be a fatal condition in preterm infants.

• Development of PIE was associated with impairment of oxygenation and ventilation efficiency and increased tidal volume requirements.

• The oxygenation index when the PIE was worst predicted death or development of bronchopulmonary dysplasia.

INTRODUCTION

Pulmonary interstitial emphysema (PIE) is nowadays an uncommon, but often fatal condition in preterm infants (1). This condition develops from intrapulmonary air leak into the pulmonary interstitium and can cause respiratory failure secondary to impaired ventilation (2, 3). A high morbidity and mortality of PIE have been described (4, 5) but, since those reports, there have been many advances in respiratory support and routine use of antenatal corticosteroids and postnatal surfactant. The pathophysiology of impaired gas exchange due to PIE has not been described in the current era. We hypothesised that infants who developed PIE would have poorer oxygenation and ventilation efficiency compared to prior to its development and their tidal volume requirements would be increased because of a greater physiological dead space. Furthermore, we hypothesised that a composite gas exchange

index would predict death or bronchopulmonary dysplasia (BPD) development in infants with PIE. Our aim was to test those hypotheses.

METHODS

Study design and subjects

A retrospective review of the medical and nursing notes and chest radiographs of infants diagnosed with PIE between 1/1/2010 and 31/12/2016 at King's College Hospital (KCH) NHS Foundation Trust, London was undertaken. Infants with PIE were identified via the BadgerNet Neonatal Electronic Patient Record (Clevermed, Edinburgh, UK). Exclusion criteria included infants with chromosomal anomalies or pulmonary hypoplasia. The Research and Development department confirmed that the data collection was a service evaluation/audit and did not require research ethics approval. The study was registered with the Clinical Governance Department of King's College Hospital NHS Foundation Trust.

The nurses recorded hourly ventilatory settings, the fraction of inspired oxygen (F_IO_2), the inspiratory tidal volume (V_T) and transcutaneous oxygen saturation levels (SpO_2). A flow sensor was placed between the endotracheal tube and ventilator circuit and V_T was measured by integration of the flow signal. The V_T was routinely recorded from 1st September 2014 so this information was only available for a subgroup of infants. Four to six hourly arterial blood gas analysis was routinely performed. Ventilatory adjustments were made to keep the infants within the predefined criteria according to the Unit's protocol: pH 7.25 – 7.40, $PaCO_2$ 5-8 pKa, PaO_2 7-10 pKa.

Two-time endpoints were selected: the postnatal age corresponding to the last chest radiograph prior to the development of PIE (pre-PIE) and the postnatal age of the chest radiograph with the most widespread radiographical appearance of PIE (PIE-worst) (figure 1). The chest radiographs were independently reviewed by three neonatal clinicians (AG, PC, TD) and the diagnosis of PIE was confirmed in all. The following were collected from the medical notes: sex, gestational age at birth (weeks), birth weight (kg), positive blood cultures prior to the development of PIE, age at pre-PIE (days), postmenstrual age (PMA) at pre-PIE (weeks), age at PIE-worst (days), PMA at PIE-worst (weeks), antenatal steroids (yes/no), surfactant (yes/no), death before discharge from the neonatal unit (yes/no), BPD at 36 weeks PMA (yes/no), moderate BPD (only oxygen dependent at 36 weeks PMA), severe BPD (additionally required positive pressure support - an oxygen reduction test was not performed)(6)), home oxygen (yes/no), intraventricular haemorrhage grade III or IV (yes/no) and periventricular leukomalacia (yes/no). The incidence of BPD was compared to a gestational age matched group without PIE. The following were collected from the nursing charts at pre-PIE and at PIE-worst: partial arterial pressure of oxygen (P_aO_2), partial arterial pressure of carbon dioxide (P_aCO_2), F_IO_2, inflation time (I_{time}), mean airway pressure (MAP), peak inflation pressure (PIP), positive end-expiratory pressure (PEEP), ventilation rate (VR), V_T and SpO_2.

Premature infants who failed to stabilise with continuous positive airway pressure and infants who did not respond to positive pressure ventilation via face mask were intubated in the delivery room and given surfactant (7). Premature infants less than 32 completed weeks of gestation with respiratory distress who required intubation and ventilation in the delivery room were started on a PIP of 20-25 cm H_2O and an FiO_2 of 0.21-0.30 (8). Infants were ventilated on volume-targeted or pressure-controlled time-cycled ventilation with the

SLE5000 neonatal ventilator or the SLE2000 infant ventilator (SLE, Croydon, UK). The supplementary oxygen was modified to achieve SpO_2 values between 92 and 95% (9). Infants who required a PIP exceeding 25 cm H_2O were transferred to high frequency oscillation (HFOV). For infants on HFOV at PIE-worst, the MAP, I_{time}, PIP, PEEP and VR on conventional pressure-limited ventilation within eight hours of PIE-worst were recorded.

Calculation of gas exchange indices

The following composite gas exchange indices were calculated: oxygenation index (OI) = MAP x FiO_2 x 100/PaO_2 (10), ventilation efficiency index (VEI) = 3800 / delta PIP x RR x $PaCO_2$ (10, 11) and alveolar-arterial oxygen gradient ($P_{A-a}O_2$) (12). The $P_{A-a}O_2$ was derived from the following equation:

$$P_{A-a}O_2 = P_IO_2 – P_aCO_2/R – P_aO_2,$$

where P_IO_2 is the partial pressure of inspired oxygen and R the expiratory exchange ratio assumed to be 0.85. Using two paired values of F_IO_2 and SpO_2 corresponding to the highest and lowest value of SpO_2 six hours before the radiograph and using the fetal curve as a reference, we calculated for each infant the ventilation perfusion ratio (V_A/Q), the right shift of the oxyhaemoglobin dissociation curve and the percentage of right to left shunt (13, 14).

Statistics

Data were tested for normality with the Kolmogorov Smirnoff test and found to be non-normally distributed, hence data are presented as median (interquartile range) and differences assessed for statistical significance using the Mann-Whitney U rank sum test or χ^2 test as

appropriate. The performance of the demographics, respiratory and gas exchange indices in predicting death, BPD development or requirement for supplementary oxygen at home (home oxygen) were assessed by receiver operator characteristic curve analysis and estimation of the areas under the curve (AUC). The highest AUC indicated the best predictor for each outcome. The value that corresponded to the highest sensitivity and specificity was identified for each predictor. Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.)

RESULTS

During the study period, 4,681 infants were admitted to the neonatal unit at KCH. Thirty-eight infants were diagnosed with PIE; the medical notes were available for thirty. All infants were intubated within four hours after birth. The 30 included infants had a median (IQR) gestational age of 24.6 (24.3 – 26.7) weeks and a median (IQR) birth weight of 0.68 (0.63 – 0.81) kg and the non-included infants had a median gestational age of 24.7 (23.4 – 25.1) weeks (p=0.151) and a median (IQR) birth weight of 0.63 (0.55 – 0.68) kg (p=0.128). Nineteen of the thirty infants included (63%) and seven of the eight non-included infants survived to discharge from the neonatal unit (p=0.248). All of the infants developed PIE while being mechanically ventilated and 11(37%) had positive blood cultures prior to PIE development. In all infants the PIE was generalised and resolved in those who survived.

The included infants had their worst PIE chest radiograph at 23 (13 - 42) days (Table 1). Fifteen infants developed BPD (50%), thirteen went home on supplemental oxygen (43%) and twenty-five (83%) had the combined outcome of death before discharge or BPD at 36

weeks PMA. Seven of the infants had moderate BPD and eight had severe BPD. The incidence of BPD in the PIE group (50%) was significantly higher than that of the gestational age matched infants who did not develop PIE (128 infants of 420, 30%) (p= 0.026). None of the infants were supported by HFOV pre-PIE and two were supported by HFOV at PIE-worst.

The infants had significantly lower P_aO_2 and V_A/Q and higher F_IO_2, MAP, PIP, VR, P_aCO_2, $P_{A-a}O_2$, shift and right to left shunt at PIE-worst compared to pre-PIE (table 2). The median (IQR) OI was higher at PIE-worst [14.5 (10.7 – 19.2)] compared to pre-PIE [4.8 (3.1 – 6.1)], p<0.001, table 2, figure 2a and the median (IQR) VEI was lower at PIE-worst [0.01 (0.01 – 0.11)] compared to pre-PIE [0.16 (0.13 – 0.19)], p<0.001, table 2, figure 2b. The median (IQR) inspiratory V_T/kg was higher at PIE-worst [9.9 (7.2 – 13.1) ml/kg] compared to pre-PIE [6.4 (5.5 – 6.8) ml/kg], p=0.007 (data available for 12 infants) (table 2, figure 2c).

The change in PaO_2 (delta PaO_2) had the highest AUC in predicting death. The age at PIE-worst had the highest AUC for both BPD development and requirement for home oxygen (Table 3). The OI at PIE-worst had the highest AUC for the composite outcome for death or BPD (Table 3). Receiver operator characteristic curve analysis demonstrated that a reduction in P_aO_2 of 16 mmHg from pre-PIE to PIE-worst predicted death with 71% sensitivity and 70% specificity. Development of PIE before 24 days of age predicted BPD development with 67% sensitivity and 71% specificity and development of PIE before 16 days of age predicted home oxygen requirement with 84% sensitivity and 100% specificity. An OI exceeding 11.4 at PIE-worst predicted death or BPD with 80% sensitivity and 100% specificity.

DISCUSSION

We have demonstrated that the development of PIE in prematurely-born infants was associated with deteriorations in oxygenation and ventilation efficiency. In addition, there was an increase in tidal volume requirement. The oxygenation index at PIE-worst was the best predictor of death or BPD.

Early studies documented that low birth weight and a high peak inspiratory pressure during mechanical ventilation were risk factors for the development of PIE (2, 3). Gaylord et al. reported that a birthweight of less than 1500g and peak inflation pressures exceeding 25 cmH_2O during the first day after birth most accurately predicted mortality in infants with PIE (15). Similarly, Morisot et al, in a retrospective study found that PIP of more than 26 cmH_2O on the first day after birth was most significantly associated with the development of fatal PIE (3). In our cohort of premature babies who were routinely exposed to antenatal steroids and postnatal surfactant, ventilatory requirements were lower prior to the development of PIE (Table 2). Those results indicate despite the beneficial effects of antenatal steroids and postnatal surfactant, infants remain at high risk of PIE.

Although the majority of our infants were exposed both to antenatal corticosteroids and postnatal surfactant, they experienced gas exchange impairment when PIE developed. The presence of air in the interstitium reduces the compliance of the lungs by compression of the pulmonary parenchyma and also compresses the pulmonary vessels leading to reduced pulmonary blood flow (4). As a consequence, there is ventilation perfusion (V_A/Q) mismatch (12). This results in a decrease in ventilation efficiency and hypoxia and also an increase in

dead space ventilation (16, 17). As a result, increased tidal volumes are required to maintain carbon dioxide clearance as we have demonstrated in this study.

Previous studies have reported that PIE occurs early in the postnatal life of prematurely born infants at a mean age of two days and represents an early complication of respiratory distress syndrome (2). In our cohort, however, the median age at PIE-worst was 23 days. The majority had been exposed to both antenatal steroids and postnatal surfactant which might have altered the disease development. Indeed, other studies have reported late PIE developing after 12 days (18) and occurring as late as 75 days (1). It is possible that this 'late' radiographic phenomenon, which we have called PIE, might represent early evolving cystic changes. There is, however, no published evidence from post mortem studies to differentiate between PIE and the development of cystic BPD. As expected (1), the incidence of BPD was significantly higher in the PIE group than the gestational age matched infants without PIE.

Our study has strengths and some limitations. This is the first study in the current era of neonatal care to describe gas exchange abnormalities in PIE and explore the ability of composite gas exchange indices to predict respiratory morbidity and mortality. A limitation is the retrospective nature of our study, but given the rarity of the disease, a prospective design might have rendered the study logistically unfeasible. We were unable to locate the medical records of some infants with PIE. Those included compared to those not included in the study, however, did not differ significantly with regard to gestational age or birth weight and they had similar mortality rates.

In conclusion, we have demonstrated that PIE development is associated with impaired oxygenation and ventilation efficiency. The oxygenation index at PIE-worst was the best predictor of the composite outcome of death or BPD development.

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FIGURE LEGENDS

Figure 1: The chest radiograph on day two of life of an infant born at 25 weeks of gestation with a birth weight of 850 grams, before the development of PIE (a), and the chest radiograph of the same infant aged seven days corresponding to the worst radiographic appearance of PIE (b).

Figure 2: Boxplots of OI (a), VEI (b) and V_T (c) before the development of PIE (pre-PIE) and at the worst radiographic appearance of PIE (PIE-worst).

Table 1: Demographics of the affected infants

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

GA (weeks)	24.6 (24.3 – 26.7)
BW (kg)	0.68 (0.63 – 0.81)
Male sex	16 (53)
Age – pre-PIE (days)	11 (6 – 19)
PMA – pre-PIE (weeks)	27.7 (25.6 – 29.8)
Age - PIE worst (days)	23 (13-42)
PMA – PIE worst (weeks)	30.3 (26.5 – 32.1)
Antenatal steroids	29 (93)
Postnatal surfactant	30 (100)
Survived to discharge	19 (63)
BPD at 36 weeks PMA	15 (50)
Death or BPD at 36 weeks PMA	25 (83)
Home oxygen	13 (43)
IVH grade III or IV	4 (13)
PVL	5 (17)
PMA at discharge (weeks)	47.1 (41.0 – 50.0)

GA: gestational age, BW: birth weight, PMA: postmenstrual age, PIE: pulmonary interstitial emphysema, BPD: bronchopulmonary dysplasia, IVH: intraventricular haemorrhage, PVL: periventricular leucomalacia.

Table 2: Ventilator settings and pulmonary assessments according to pre-PIE and PIE-worst

Data are shown as median (interquartile range)

	Pre-PIE	**PIE-Worst**	***P* value***
P_aO_2 (mmHg)	62.2 (49.8 – 72.5)	41.4 (34.7 – 49.9)	<0.001
F_IO_2	0.44 (0.34 – 0.51)	0.75 (0.57 – 0.91)	<0.001
MAP (cm H_2O)	9 (9 – 10)	11 (10 – 13)	<0.001
I_{time} (sec)	0.37 (0.36 – 0.38)	0.38 (0.36 – 0.40)	0.289
PIP (cm H_2O)	19 (18 – 22)	24 (21 – 26)	<0.001
PEEP (cm H_2O)	5 (5 – 5)	5 (5 – 6)	0.125
VR (per minute)	50 (45 – 60)	60 (52 – 60)	0.011
P_aCO_2 (mmHg)	46 (41 – 53)	54 (50 -74)	0.001
OI	4.8 (3.1 – 6.1)	14.5 (10.7 – 19.2)	<0.001
VEI	0.16 (0.13 – 0.19)	0.01 (0.01 – 0.11)	<0.001
$P_{A-a}O_2$ (mmHg)	184 (115 – 236)	396 (271 – 526)	<0.001
V_T (ml) (*N*=12)	4.3 (3.7 -4.8)	7.3 (4.9 – 8.6)	0.001
V_T (ml/kg) (*N*=12)	6.4 (5.5 – 6.8)	9.9 (7.2 – 13.1)	0.007
V_A/Q	0.26 (0.20 – 0.37)	0.15 (0.11 – 0.40)	0.033
Shift (kPa)	28.2 (18.3 – 36.6)	45.5 (18.6 - 65.0)	0.018
Shunt (%)	13 (9 – 19)	19 (12 – 23)	0.014

P_aO_2: Arterial partial pressure of oxygen, F_IO_2: fraction of inspired oxygen, MAP: mean airway pressure, I_{time}: inspiratory time, PIP: peak inflation pressure, PEEP: positive end expiratory pressure, VR: ventilation rate, P_aCO_2: Arterial partial pressure of carbon dioxide, OI: oxygenation index, VEI: ventilation efficiency index, $P_{A-a}O_2$: Alveolar-arterial PO_2 difference, V_T: inspiratory tidal volume, V_A/Q: ventilation to perfusion ratio, Shunt: right to left shunt.

Table 3: Areas under the ROCs related to outcomes. The best predictors are marked with asterisks.

	Death	BPD	Home oxygen	Death or BPD
GA (weeks)	0.439	0.528	0.567	0.551
BW (kg)	0.524	0.600	0.550	0.696
Age of PIE-worst (days)	0.473	0.731*	0.933*	0.841
P_aO_2 at PIE-worst	0.439	0.431	0.117	0.116
F_IO_2 at PIE-worst	0.610	0.505	0.675	0.609
MAP at PIE-worst (mmHg)	0.626	0.492	0.633	0.638
P_aCO_2 at PIE-worst (mmHg)	0.449	0.513	0.475	0.580
OI at PIE-worst	0.658	0.533	0.867	0.884*
VEI at PIE-worst	0.422	0.574	0.550	0.435
$P_{A\text{-}a}O_2$ at PIE-worst (mmHg)	0.610	0.518	0.683	0.623
V_A/Q at PIE-worst	0.655	0.436	0.367	0.580
Shunt at PIE-worst (%)	0.465	0.497	0.458	0.493
Delta P_aO_2 (mmHg)	0.713*	0.673	0.427	0.275
Delta F_IO_2	0.469	0.542	0.545	0.522
Delta $P_{A\text{-}a}O_2$ (mmHg)	0.488	0.560	0.527	0.507
Delta OI	0.416	0.586	0.800	0.768
Delta VEI	0.634	0.643	0.491	0.428
Delta V_A/Q	0.638	0.512	0.527	0.348

GA: gestational age, BW: birth weight, P_aO_2: Arterial partial pressure of oxygen, F_IO_2: fraction of inspired oxygen, MAP: mean airway pressure, PaCO2: Arterial partial pressure of carbon dioxide, OI: oxygenation index, VEI: ventilation efficiency index, $P_{A\text{-}a}O_2$: Alveolar-arterial PO_2 difference, V_A/Q: ventilation to perfusion ratio, Shunt: right to left shunt, Delta P_aO_2: P_aO_2 at pre-PIE minus P_aO_2 at PIE worst, Delta F_IO_2: F_IO_2 at PIE-worst minus F_IO_2 at pre-PIE, Delta $P_{A\text{-}a}O_2$: $P_{A\text{-}a}O_2$ at PIE-worst minus $P_{A\text{-}a}O_2$ at pre-PIE, Delta OI: OI at PIE-worst minus OI at pre-PIE, Delta VEI: VEI at pre-PIE minus VEI at PIE-worst, Delta V_A/Q: V_A/Q at pre-PIE minus V_A/Q at PIE-worst.