Eur J Pediatr (1990) 149:493–495

European Journal of
Pediatrics


# Risk factors for fatal pulmonary interstitial emphysema in neonates

**C. Morisot, N. Kacet, M. C. Bouchez, V. Rouland, J. P. Dubos, C. Gremillet, and P. Lequien**

Service de Pédiatrie Néonatale, Hôpital Calmette, F-59037 Lille Cedex, France

**Abstract.** Among 315 infants treated for respiratory distress syndrome (RDS) over a 2 year period, 32 prematures were studied retrospectively with the diagnosis of pulmonary interstitial emphysema (PIE). Eighteen died. In this group, birth weight below 1600 g, need for oxygen above 0.6 on the 1st day and appearance of bilateral pulmonary interstitial emphysema within the first 48 h of life were significant risk factors, with a mortality rate of 94%. In order to recognize one or more early criteria predictive of fatal PIE, we compared ventilation parameters on day 1 between neonates with fatal PIE and those with the same birth weight and initial severity of RDS but without PIE treated during the same period. High positive inspiratory pressure on day 1 was found to be the most significant parameter associated with further appearance of fatal pulmonary interstitial emphysema. A cut-off level of 26 cm $H_2O$ was found to be discriminant. These criteria may be useful in selecting those neonates who might best benefit from a new therapy such as high frequency ventilation, before irreversible lesions appear.

**Key words:** Pulmonary interstitial emphysema – Respiratory distress syndrome – Neonatal mortality – High frequency ventilation

## Introduction

Pulmonary interstitial emphysema (PIE) is a severe complication of the respiratory distress syndrome (RDS) of prematurity. It causes an eruption of intrapulmonary gases outside the normal air passages; resulting in an endolymphatic air distribution and diffusion of air inside the connective tissue of the peribroncho-vascular sheets, interlobular septa, and the visceral pleura [16]. This abnormal collection of gases leads to life-threatening respiratory failure because pulmonary blood flow and ventilation are impaired. Gaylord and co-workers in 1985, in a study of premature infants with PIE, concluded that a birth weight of less than 1500 g and a peak positive inspiratory pressure of 25 cm $H_2O$ were the most significant variables to establish a predictive index of mortality of PIE [8]. In the last few years, high frequency ventilation (HFV) has been introduced as a new and effective treatment of PIE [6, 7, 11, 15]. On the other hand, it is logical to suggest that HFV must be preferably undertaken before appearance of radiological signs of PIE. However this is not innocuous [17] and it is therefore justified to select only patients at most risk. Following a design similar to Gaylord et al., we conducted a retrospective study to select infants at high risk for fatal PIE, before radiological lesions were present. Our study confirmed the findings of Gaylord et al.

*Offprint requests to:* P. Lequien

*Abbreviations:* $FiO_2$ = oxygen concentration in inspired air; HFV = high frequency ventilation; I/E = inspiratory-expiratory ratio; $PaCO_2$ = $CO_2$ pressure in arterial blood; $PaO_2$ = oxygen pressure in arterial blood; PEEP = positive end expiratory pressure; PIE = pulmonary interstitial emphysema; PIP = peak inspiratory pressure; RDS = respiratory distress syndrome

## Patients and methods

From 1 October 1984 to 30 September 1986, there were 1419 admissions, all outborn, to the Neonatal Intensive Care Unit of the University Hospital of Lille. Of these, 380 (27%) had RDS and 315 were mechanically ventilated. A time-cycled, pressure limited ventilator type Bourns BP 200, was used in all cases. Peak inspiratory pressure (PIP) was measured with the pressure manometer of the ventilator. It was at first limited to 20 cm $H_2O$, and progressively raised to maintain $PaCO_2$ between 40 and 55 Torr. All infants were ventilated with positive end expiratory pressure (PEEP) of 4 to 6 cm $H_2O$; $FiO_2$ was adjusted to control $PaO_2$ in the range 60 to 80 Torr. Initial inspiratory-expiratory (I/E) ratio was 1, and frequency was adapted to the spontaneous frequency of the newborn in a range of 30 to 60 bpm. Initial gas flow was 7 l/min.

Thirty-four infants had a discharge diagnosis of PIE based on the radiological criteria of Plenat et al. [16] and Campbell [2]. Case histories and chest X-rays were analysed for the following clinical parameters: birth weight, gestational age, highest PIP and $FiO_2$ in the first 24 h of life, age at the time of diagnosis of PIE (before or after 48 h of life), unilateral or bilateral location, incidence of pneumothoraces and/or pneumomediastinum, and incidentally time of death. Two patients died early (< 6 h) of massive intraventricular haemorrhage and were excluded. We studied initially all infants with PIE in order to find common criteria related to death. Second, in order to recognize one or more early criteria predictive of fatal PIE, we compared ventilation parameters on day 1 of the neonates with fatal PIE, with those of similar birth weight and

initial severity of RDS but without PIE, treated during the same period.

Data were expressed as means and standard deviations (SD). Differences between continuous variables were determined with use of the non parametric Mann and Whitney $U$ test. Categorical variables were compared by chi-square analysis. Statistical significance was accepted at the level of $P < 0.05$.

## Results

Thirty-two infants were studied. All were prematures (mean gestational age $30 \pm 2.8$ weeks, mean birth weight 1380 $\pm$ 420 g). There were 18 males, 14 females, all exhibited RDS, and were mechanically ventilated. They accounted for 11% of all the ventilated neonates with the diagnosis of RDS during the same period. Paralytic agent (pancuronium bromide) were used in 11 neonates. Fifteen of the 32 (45%) developed pneumothorax. PIE was more often bilateral (25/32). Unilateral PIE was located in six cases on the left side, and once on the right. Eighteen (58%) died from PIE from D1 to D21. In 12 infants it occurred before the 48th hour of life. Clinical outcome is summarized in Table 1.

Of the infants in the study group, 60% had a birth weight less than 1600 g, and it contributed to 90% of the mortality. Thus, it was felt that some data should be analysed separately to obtain a high predictive value for death. Table 2 shows the positive and negative predictive values of death for different parameters, isolated or in association. Therefore, a neonate, under mechanical ventilation, weighing less than 1600 g, with the need for $FiO_2 > 0.6$ in the first 24 h of life, and who has developed bilateral and early-onset PIE (< 48 h) should have a 94% risk of death.

The data of the 17 infants with birth weight less than 1600 g who died from PIE were compared to those of 48 other infants with same birth weights with RDS who were mechanically ventilated during the same period but remained free of PIE. In the first 24 h of life, they all needed oxygen concentrations $\geq 0.6$. PIP on day 1 was significantly different between those with PIE and the others (Table 3). It appeared that PIP during the first 24 h of life was indeed related to the appearence of fatal PIE: 15 of the 17 who developed fatal PIE were included in the group of 20 infants submitted to PIP exceeding 26 cm $H_2O$. On the other side, of the 45 ventilated with PIP below 26 cm $H_2O$, only 2 developed fatal PIE.

**Table 1.** Outcome of 32 infants with PIE in Neonatal Intensive Care Unit of the University of Lille during 24 months (values are mean $\pm$ SD)

| | | Died ($n = 18$) | Survived ($n = 14$) | $P$ |
|---|---|---|---|---|
| Birth weight (g)[a] | | 1180 $\pm$ 350 | 1632 $\pm$ 367 | <0.001 |
| Gestational age (weeks)[a] | | 28.8 $\pm$ 2.6 | 31.5 $\pm$ 2.3 | <0.001 |
| PIP max (24 h) (cm $H_2O$)[a] | | 33 $\pm$ 9 | 23 $\pm$ 3 | <0.001 |
| $FiO_2$ max (24 h) (%)[a] | | 94 $\pm$ 1 | 66 $\pm$ 1 | <0.001 |
| Neonates with pneumothoraces[b] | | 6 | 9 | NS |
| Onset of PIE[b] | $\leq 48$ h | 18 | 7 | <0.001 |
| | > 48 h | 0 | 7 | |
| Location[b] | Unilateral | 0 | 7 | <0.001 |
| | Bilateral | 18 | 7 | |

[a] Mann Whitney test
[b] $\chi^2$ analysis

**Table 2.** Positive predictive value (PPV) and negative predictive value (NPV) of death for clinical parameters, in 32 infants with PIE

| | PPV | NPV |
|---|---|---|
| Birth weight $\leq 1600$ g | 76% | 82% |
| Recognition of PIE $\leq 48$ h | 72% | 100% |
| Bilateral location of PIE | 72% | 100% |
| $FiO_2 \geq 0.6 < 24$ h | 65% | 83% |
| 1 + 2 + 3 + 4 | 94% | 93% |

**Table 3.** Outcome for 65 infants selected on birth weight below 1600 g and need for $O_2$ before 24 h $\geq 0.6$ during 24 months (values are mean $\pm$ SD)

| | Fatal PIE ($n = 17$) mean $\pm$ SD | Non fatal PIE ($n = 48$) mean $\pm$ SD | $P$ |
|---|---|---|---|
| Birth weight (g)[a] | 1155 $\pm$ 55 | 1180 $\pm$ 250 | NS |
| Gestational age (weeks)[a] | 28.6 $\pm$ 1.9 | 29.6 $\pm$ 1.9 | NS |
| PIP max < 24 h (cm $H_2O$)[a] | 32 $\pm$ 6 | 24 $\pm$ 3 | <0.001 |

[a] Mann Whitney test

In this population, (birth weight < 1600 g and $FiO_2 \geq 0.6$ before 24 h), when PIP during the first 24 h of life is superior to 26 cm $H_2O$, positive and negative predictive values for the appearence of severe PIE and death are 75% and 95% respectively.

## Discussion

This study allowed the recognition of sensitive criteria for predicting those neonates who were at high risk of death from PIE. These results were in agreement with those of Gaylord [8]. Diffuse, bilateral and symmetrical PIE was usually observed among premature babies with RDS on mechanical ventilation [9, 10, 12, 13].

Prevalence of PIE varies widely (Table 4). Two parameters must be considered when comparing different studies: the observed population, and the extent of the lesions. In our experience, PIE occurred, either unilaterally or bilaterally, in 32 of all the 315 ventilated neonates with RDS (11%). The frequency increased to 32% (21/65) when considering the 65 infants with a birth weight < 1600 g and oxygen requirement > 60%. In similar populations the frequency was 20% [9] and 32% [12].

In 78% of the patients in this study the lesions were bilateral similar to those of Gaylord et al.: 89% [8] and of Gregoire et al.: 66% [10]. They were surprisingly unilateral in 69% of cases reported by Plenat et al. [16].

Mortality rate when PIE is present is reported as high as 53%–67% in previous studies [8, 12, 16]. The observed rate was in the same range. An explanation for the lower values reported by Greenough et al. (24%) and Gregoire et al. (39%) [9, 10] could be due to differences in population selection.

Early appearance of bilateral PIE, before the 48th hour of life, attested the severity of the underlying parenchymal disease. It is a determinant parameter in mortality, as pointed out by others [11, 15, 17]. The need for an early recognition of the at-risk patients, before it appears or becomes apparent on

**Table 4.** Frequency and severity of PIE in the literature

| Author | Studied population | Total PIE (% of studied population) | Bilateral PIE (% of total PIE) | PIE mortality (% of total PIE) |
|---|---|---|---|---|
| Gregoire [10] | ? | 33 (?) | 22 (66%) | 13 (39%) |
| Hart [12] | Birth weight < 1500 g + RDS | 46 (32%) | – | 31 (67%) |
| Greenough [9] | Gestational age < 35 weeks + RDS ventilated | 41 (20%) | 35 (85%) | 10 (24%) |
| Gaylord [7] | Total admissions | 70 (3%) | 62 (89%) | 37 (53%) |
| Heneghan [13] | Total admissions | 58 (3%) | 47 (81%) | 22 (38%) |
| Our study | Total admissions | 34 (2%) | 25 (78%) | 18 (58%) |
| | RDS ventilated | 34 (11%) | 25 (78%) | 18 (58%) |
| | Birth weight < 1600 g + severe RDS | 21 (32%) | – | 17 (80%) |

the chest X-ray claims for other predictive parameters. The maximal PIP necessary for adequate gas exchange in the first hours of life was the most significant parameter associated with lethal PIE. However, it was difficult to demonstrate that the high PIP alone was responsible for PIE; it could not be excluded that "pre-radiological" histological lesions were present and accounted for the need of potentially traumatic ventilation. The proposed cut off point of 26 cm $H_2O$ needs explanation. Some values were just under or over this level in both groups. The difference between 25 and 27 cm $H_2O$ was too narrow to be truly determinative. This chosen value was theoretical and would have been adjusted for birth weight and gestational age. A larger group would have allowed us to verify the relationship between birth weight and PIP as stated by Gaylord et al. These authors demonstrated that a score combining birth weight (less than 1500 g) and highest PIP on the first day ($Z = BW - 27 \times PIP$) yielded a 81% confidence level to predict mortality when it was less than 393 [8].

It has been shown that conservative measures such as lowering PIP led to hypoxia and hypercapnic acidosis, even when $FiO_2$ was raised. Due to the severe prognosis of this complication, alternative aggressive modes of therapy have been attempted. Surgical pneumotomy [4], or lung puncture [14] have been successful but are very hazardous in such infants. Broncho-alveolar lavage combined with flexible bronchoscopy is not practicable in severely distressed patients [5]. Extra corporeal membrane oxygenation is not yet applicable to very low birth weight infants [1]. High frequency ventilation is an alternative method of treatment of PIE when conventional ventilation has been unsuccessful [6, 7, 11, 15]. The earlier it is started, the more efficient it would be, and it even would be more advisable to undertake HFV before radiological signs of alveolar rupture are present. However the main determinants of gas exchange of this new promising technique are not yet well understood [3]. Moreover, experimental studies have demonstrated tracheal and bronchial injuries [17]. This method of patient selection is proposed in order to utilize HVF only in those patients with a very high risk of fatal PIE. It is suggested that the method of patient selection could be a way to evaluate the safety and efficacy of early HFV without exposing to undue risks those neonates who would normally survive with conventional therapy.

*Acknowledgement.* We thank Françoise Brion for reviewing the manuscript.

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Received September 13, 1988 / Accepted September 19, 1989