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Radiological changes after therapeutic use of surfactant in infants with respiratory distress syndrome

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Abstract The aims of this study were to determine the incidence of typical chest radiography findings – (1) uniform improvement, (2) asymmetrical improvement, (3) no improvement or (4) interstitial emphysema – after therapeutic use of surfactant and to analyse clinical course and outcome. Chest radiographs of 138 infants of very low birth weight treated with surfactant were analysed. Twenty-eight infants with a diagnosis other than typical respiratory distress syndrome (RDS), i. e., sepsis, congenital pneumonia and congenital malformation, were excluded. In 110 patients with clinical and radiological evidence of typical RDS (median gestational age 28 weeks, median birth weight 1070 g) adequate chest radiographs from before and within 72 h after surfactant treatment were available. The time of surfactant application ranged between 1 and 12 h after birth. The most common finding after surfactant treatment was uniform or asymmetrical improvement of pulmonary aeration (80 of 110 patients). Patients with uniform clearing had the best long-term outcome. Asymmetrical clearance was often localised on the right side or in central regions of the lung, and usually disappeared after retreatment with surfactant without clinical significance. In 11 patients no change in aeration was found and retreatment was absolutely ineffective. Development of pulmonary interstitial emphysema after surfactant treatment was a grave prognostic sign: 73 % of these infants died within the first 2 weeks of life compared with 10 % of those with uniform or asymmetrical improvement of ventilation.

Introduction

The effectiveness of surfactant replacement therapy in preterm infants with respiratory distress syndrome (RDS) has been established in several studies [1–5]. Surfactant is instilled either directly after birth (prophylactic treatment) or during the following few hours (therapeutic use) when symptoms of RDS develop. Posttreatment chest radiographs help to assess the effectiveness of surfactant therapy and to set appropriate ventilator parameters. Usually the radiographs show a remarkable improvement in lung aeration, but asymmetrical focal improvement of aeration and development of pulmonary interstitial emphysema (PIE) have also been described [6–10]. The aims of this study were to determine the incidence of typical chest radiograph findings – (1) uniform improvement, (2) asymmetrical improvement, (3) no improvement or (4) interstitial emphysema – after therapeutic use of surfactant and to analyse the clinical course and outcome in infants with RDS and birth weight of less than 1500 g.

Materials and methods

During the study period from 1 September 1990 to 31 August 1994 a total of 138 infants with RDS and a birth weight below 1500 g were admitted to our neonatal intensive care unit. Twenty-eight infants

Table 1 Relationship between type of radiographic response after surfactant application and clinical data (FiO_2 fraction of inspiratory oxygen, *PDA* patent ductus arteriosus, *PTX* pneumothorax, *RDS* respiratory distress syndrome)

	Uniform improvement	Asymmetrical improvement	No improvement	Interstitial emphysema
Number of patients	42	38	11	19
Gestational age (weeks)	28.7 ± 2.3	28.5 ± 2.1	27.1 ± 2	27 ± 1.8
Birth weight (g)	1088 ± 274	1081 ± 267	1020 ± 358	934 ± 262
Antenatal administration of corticosteroids	32 (76 %)	25 (68 %)	5 (45 %)	10 (53 %)
Severe RDS on initial chest radiograph (grade III or IV)	29 (69 %)	28 (74 %)	11 (100 %)	17 (89 %)
Mean FiO_2 before surfactant administration	72.1 %	77.3 %	85 %	93 %
Patients with more than one surfactant application	10 (23.8 %)*[a]	28 (73.6 %)*[a]	9 (82 %)	16 (84 %)
PTX on posttreatment chest radiograph	1 (2.3 %)	3 (8 %)	0	9 (47 %)*[b]
PDA	10 (24 %)	15 (39 %)	2 (18 %)	6 (31 %)
Severe intracranial haemorrhage (grade III or IV)	6 (14 %)	7 (18 %)	4 (36 %)	15 (79 %)*[b]
Surviving patients	40 (95 %)*[c]	32 (85 %)*[c]	4 (36 %)	5 (27 %)
Duration of mechanical ventilation (days)	8.5 (1–33)	10.5 (1–42)	11.5 (6–17)	18 (14–46)
Spontaneous breathing at day 28 with FiO_2 = 21 %	29/40 (73 %)	20/32 (63 %)	2/4 (50 %)	1/5 (20 %)

* $P < 0.01$
[a] Significant difference between infants with uniform and asymmetrical improvement
[b] Significant difference when compared with the other groups taken together
[c] Significant difference between infants with uniform or asymmetrical improvement and the rest

with clinical or radiological diagnosis of sepsis (n = 17), congenital pneumonia (n = 6) and congenital malformation (n = 5) were excluded to prevent mixed effects, especially between treatment of surfactant deficiency and changes of infectious origin. To study the influence of surfactant administration on radiographic appearance (Table 1), 110 patients with typical clinical and radiological diagnosis of RDS were selected, for whom adequate chest radiographs from before and 72 h after treatment were available. Inclusion criteria for infants of birth weight less than 1500 g with RDS were (1) need for mechanical ventilation, (2) a fraction of inspiratory oxygen concentration (FiO_2) of more than 0.4 to maintain an arterial oxygen tension of 50–70 mmHg and (3) the need for a positive end-expiratory pressure greater than 3 cm H_2O.

A natural surfactant extracted from bovine lungs (Alveofact; Thomae, Biberach, Germany) was instilled via a small nasogastric tube, which was inserted into the endotracheal tube with the tip just above the carina. Surfactant was given as bolus (initial dose 100 mg/kg body weight, retreatment dose 50 mg/kg body weight). Depending on the clinical situation, up to four doses were given. Median gestational age (GA) was 28 weeks (range 23–33 weeks) and median birth weight was 1070 g (range 340–1490 g). Severity of RDS prior to surfactant instillation was graded from I to IV. The time of pretreatment radiographs ranged between 30 min and 8 h (median 2 h) after birth. The time of surfactant application ranged from 60 min to 12 h (median 3.5 h) after birth. Timing of posttreatment radiographs was based on the clinical situation, the first being taken usually 4–6 h after surfactant replacement. Both pretreatment and the first posttreatment chest radiographs were compared and grouped according to extent and distribution of radiographic improvement of aeration. PIE and other air leaks were noted when present. Two independent observers evaluated the radiographs without knowledge of the clinical situation. If there was a discrepancy in their initial assessment, they tried to find a consensus.

Radiographic findings and clinical data were statistically analysed using the chi-squared test and Student's *t*-test.

Results

Pretreatment radiographs showed mild or moderate RDS in 25 and severe RDS (grade III or IV) in 85 of our patients. There was a good correlation between severity of RDS seen in pretreatment chest radiographs and pretreatment FiO_2 ($P < 0.01$).

Radiographic findings

Changes in pulmonary aeration were graded into four types: (1) uniform improvement, (2) asymmetrical improvement, (3) no improvement and (4) interstitial emphysema. The most common findings after surfactant instillation were uniform (n = 42) or asymmetrical (n = 38) improvement of aeration of the lungs. In 19 patients the typical pattern of PIE was present, and the remaining 11 patients showed no improvement of pulmonary aeration (Table 1).

Uniform improvement

The degree of uniform improvement of pulmonary aeration after surfactant administration was quite variable. Most of these patients (31/42) showed almost complete normalisation of lung aeration after a single surfactant dose (Fig. 1) or only discrete streaky residues remained, whereas in the remaining 11 patients – usually infants with severe RDS – a pattern of mild

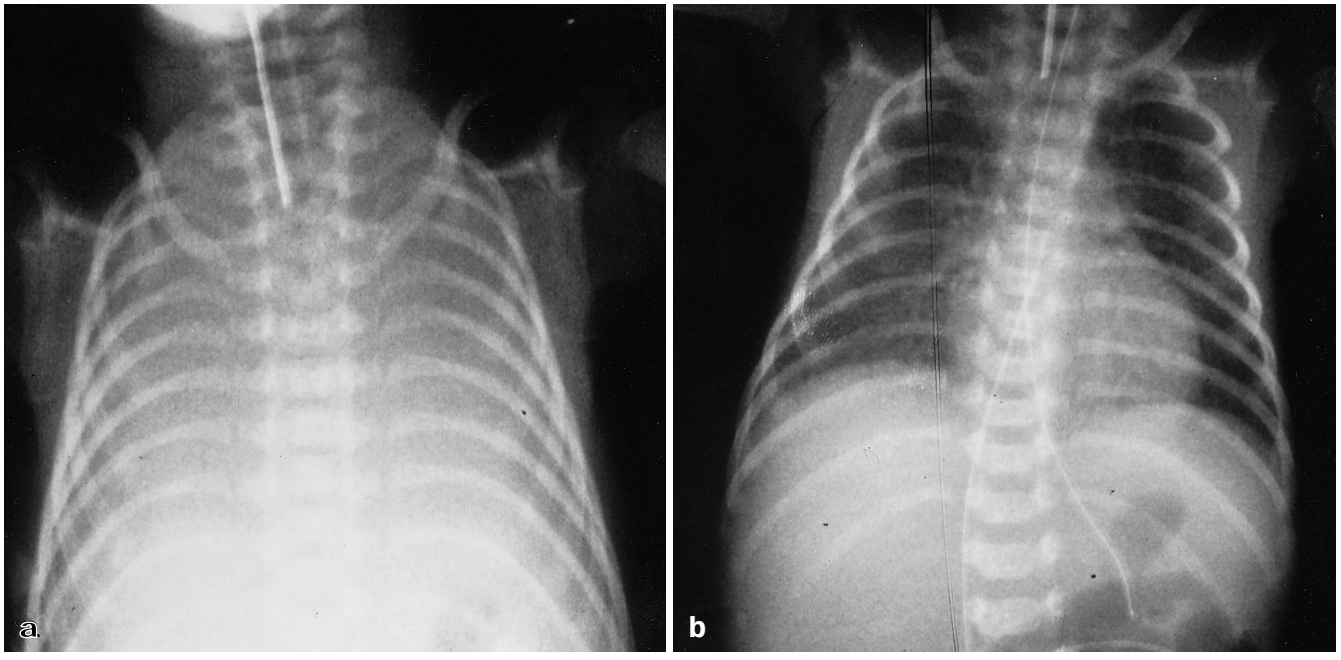


Fig. 1 a, b Preterm infant [gestational age (GA) 26 weeks, 820 g] with severe respiratory distress syndrome (RDS): chest radiographs **a** before and **b** 4 h after surfactant instillation show uniform and complete improvement of aeration

RDS with hypoinflation and granularity of the lungs was still present after a single dose of surfactant. Complete normalisation of lung aeration in all these patients was found in the posttreatment chest radiographs following the second dose of surfactant. Only one case of pneumothorax (PTX) was noted and severe intracranial haemorrhage was found in six patients. Ninety-five percent of the patients with uniform improvement survived: 29 of these 40 infants were breathing spontaneously at day 28 of life without the need for supplementary oxygen.

Asymmetrical/focal improvement

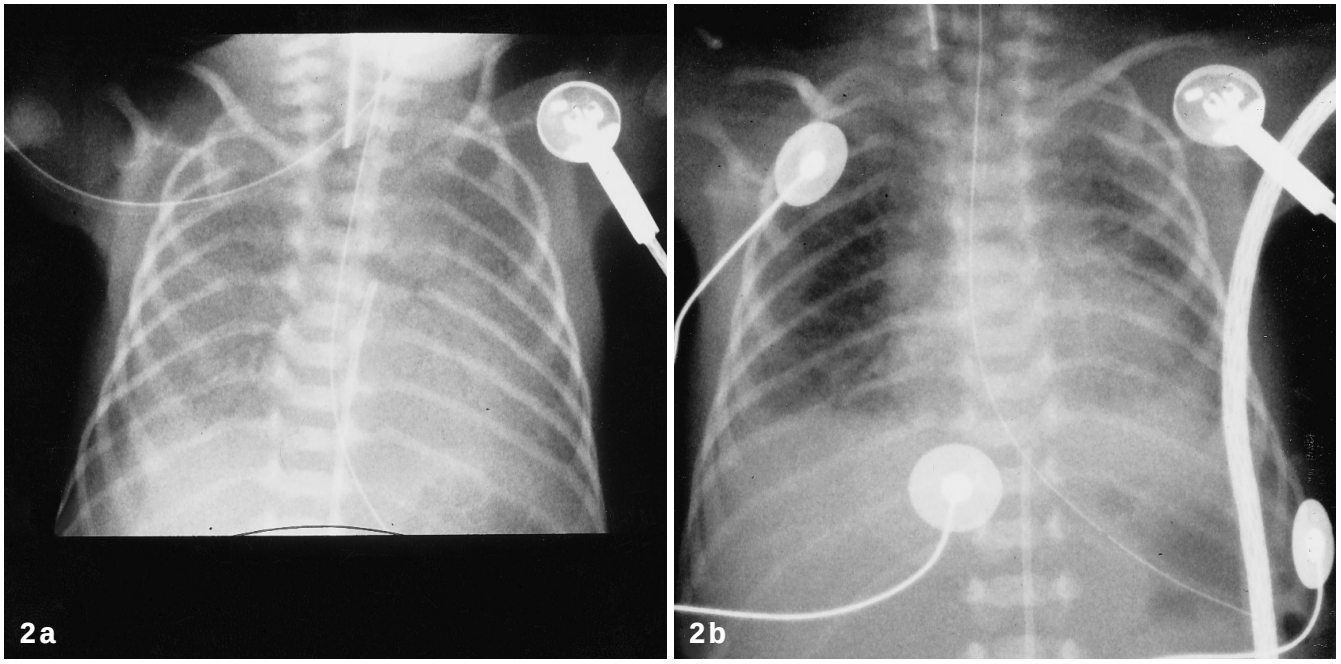
Asymmetrical or focal improvement of aeration was often more pronounced in the central or upper regions of the right lung (Fig. 2). These asymmetrical findings disappeared within a few days, often after instillation of a retreatment dose of surfactant (27/38 patients). In two patients pretreatment radiographs showed a malpositioned endotracheal tube in the right mainstem bronchus as a potential cause for overdistension of the right lung. Furthermore, in six patients we found that the bevel of the endotracheal tube was positioned just above the carina nearly obstructing the left main bronchus. Therefore, we hypothesise that malinstillation of surfactant into the right lung may occur when a small nasogastric tube is used for the instillation technique (Fig. 3). The incidence of PTX (3/38), intracranial haemorrhage (7/38), patent ductus arteriosus (PDA, 15/38) and mortality (6/38) tended to be higher than in the group of uniform improvement of aeration, but these differences were not statistically significant.

Both uniform and asymmetrical clearance were combined with a rapid reduction of oxygen requirement. Relapse after initial improvement did occur, with subsequent surfactant applications being less effective. Nearly 50 % of the 80 patients with initial radiographic improvement showed some degree of vascular engorgement on chest radiographs on day 3 or 4 after surfactant treatment as a sign of left-to-right shunting. Because of cardiac enlargement and perihilar oedema indicating PDA in 10 patients surgical ligature was performed. In 15 patients closure of PDA was achieved with indomethacin.

There were no statistically significant differences in GA, birth weight or severity of RDS between the two groups. Antenatal administration of corticosteroids tended to be higher in both groups with improvement of aeration, but differences were not statistically significant compared with the groups with no improvement or interstitial emphysema.

No improvement

Eleven patients showed no improvement of aeration in posttreatment chest radiographs. Subsequent surfactant applications were absolutely ineffective.



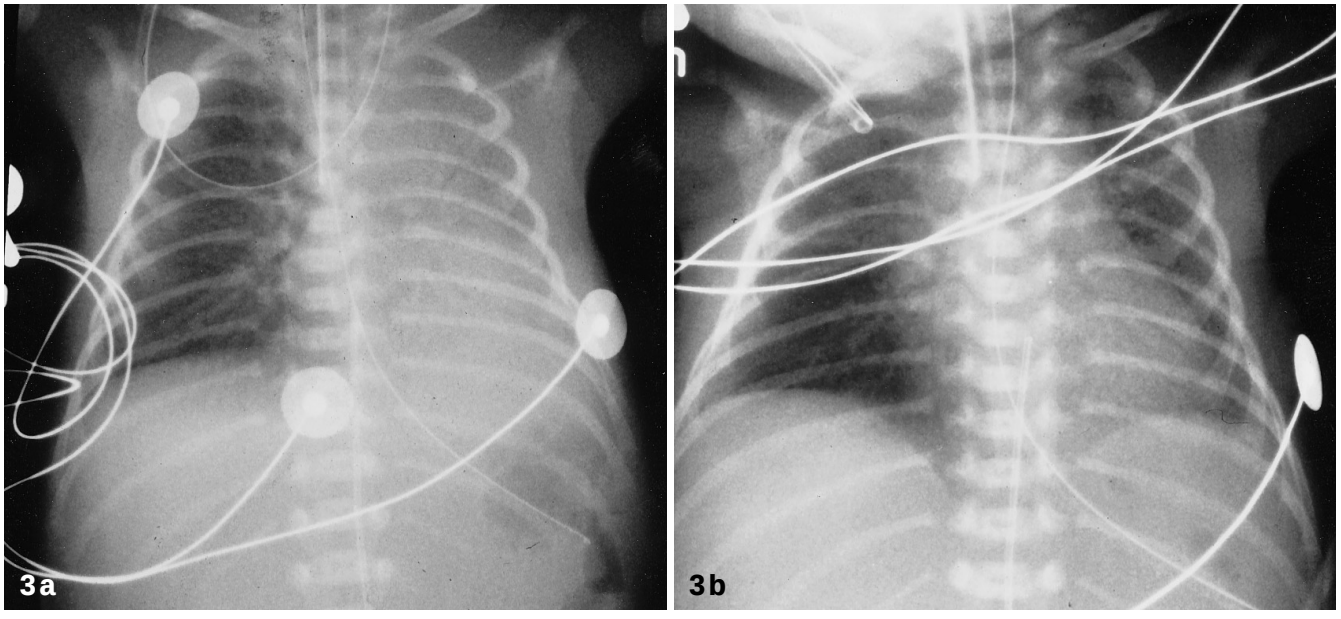


Fig. 2 a, b Preterm infant (GA 28 weeks, 920 g) with severe RDS: chest radiographs with typical severe RDS **a** before and **b** after surfactant treatment. Clearing is more pronounced in the central regions

Fig. 3 a, b Chest radiographs in a preterm infant (GA 29 weeks, 1320 g): **a** improved aeration of the right and underaeration of the left lung after surfactant instillation following malapplication into the right lung; **b** complete clearing after retreatment with surfactant

Interstitial emphysema

Development of PIE after surfactant treatment (Fig. 4) was a grave prognostic sign. Most of the patients developed PTX (10/19) and severe intracranial haemorrhage (16/19); 73 % of the infants with PIE after surfactant treatment (14/19) died within the 1-month of life, compared with 10 % (8/80) in the groups with initial improvement of aeration on the first posttreatment chest radiograph. As expected, the surviving five patients had to be ventilated mechanically for a long period (3 weeks or more). Among the surviving patients of the other three groups there was no clear correlation be-

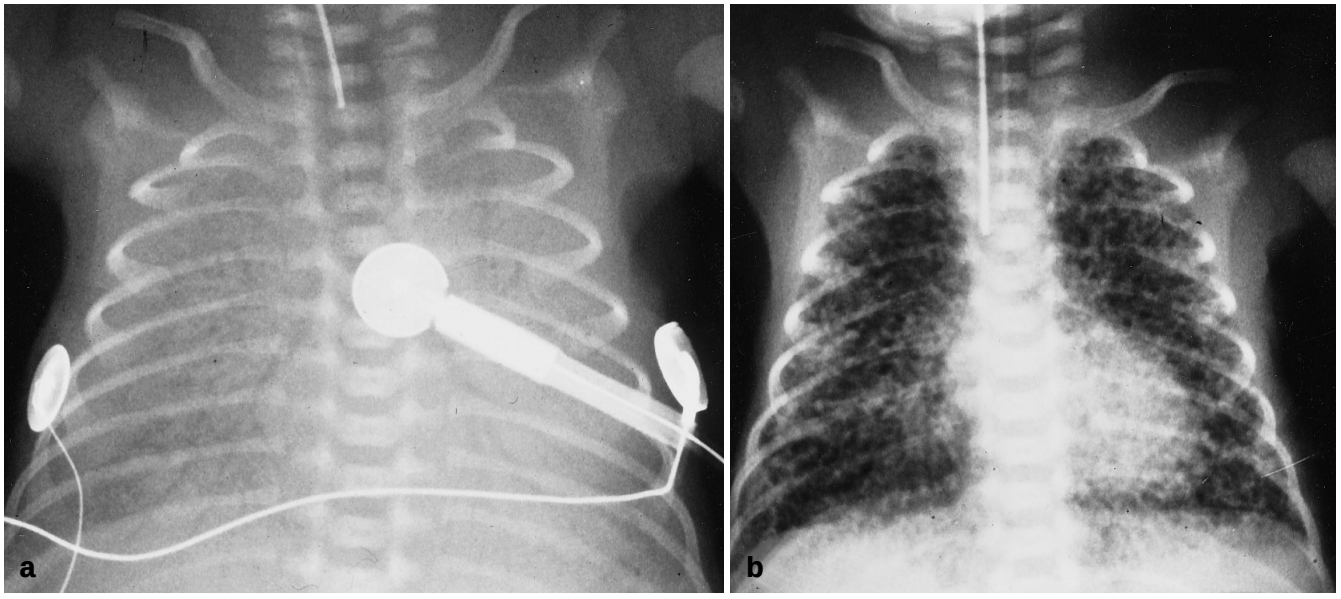


Fig. 4 a, b Preterm infant (GA 29 weeks, 1210 g) with severe RDS: chest radiographs **a** before and **b** 24 h after surfactant treatment show severe pulmonary interstitial emphysema after surfactant treatment

tween the type of initial radiographic response after surfactant treatment and the duration of mechanical ventilation. The clinical parameters best predicting long-term outcome – survival, duration of artificial ventilation, development of intracranial haemorrhage – were birth weight and GA.

Discussion

The effectiveness of surfactant replacement in infants with RDS is undisputed and has been shown by several studies. Improved oxygenation, decreased ventilator requirement and improved survival have been reported after intratracheal administration of surfactant in preterm infants with hyaline membrane disease [1–5]. These clinical patterns are accompanied by remarkable improvement of aeration of the lung on posttreatment chest radiographs seen in 42 out of our 110 study patients (38 %). Similar results were published by Bick et al. (35 %, 46/130 [7]). In contrast, Clarke et al. [8] found no evidence of RDS on posttreatment radiographs in 49 % of 80 patients treated prophylactically with surfactant. This higher incidence of homogeneous clearing in studies with prophylactic replacement of surfactant might be due to the fact that a significant number of infants without RDS and with normal ventilation were treated [9]. Nearly as often as homogeneous clearing we found asymmetrical or focal improvement of aeration after surfactant therapy. Asymmetrical clearing has been reported by several authors: Clarke et al. [8] found asymmetrical or central clearing in 22 % of 80 infants treated prophylactically with surfactant and Bick et al. [7] found an incidence of 35 % in a study group of 130 patients treated therapeutically with surfactant. The incidence in our study group was similar (34 %). In summary, about 70 % of infants with RDS treated with surfactant (72 % in our study, 69 % in the study of Bick et al. [7], 71 % in the study of Clarke et al. [8]) showed homogeneous or asymmetrical improvement of aeration with rapid reduction of oxygen requirement after surfactant treatment. As expected, patients with uniform clearing had the best long-term outcome: 72 (90 %) of our 80 patients survived, and 49 (62 %) of our surviving infants were breathing spontaneously at day 28 of life without the need for supplementary oxygen. Disproportionate aeration usually resolved within 3–5 days, often after retreatment with surfactant.

There are three explanations for this asymmetrical improvement of aeration: (1) we speculate that asymmetrical improvement of aeration after surfactant treatment might be the result of maldistribution [6, 8]. Maldistribution due to a malpositioned endotracheal tube was seen only in two cases but in six of our patients malapplication might have occurred. In the pretreatment chest radiographs we found the tip of the endotracheal tube just above the carina; therefore, malapplication of surfactant into the right main bronchus via the nasogastric tube inserted into the endotracheal tube during the replacement procedure is possible (Fig. 3). (2) Focal clearing might be due to administration of an insufficient amount of surfactant, making further applications necessary [11]. (3) Regional differences in aeration are a well-known phenomenon in infants with RDS not treated with surfactant [12, 13]. Often the dependent regions of the lungs are less venti-

lated. Atelectasis and fluid collection in these dependent regions of the lungs temporarily inhibit the surfactant effect and may cause overdistension of well-aerated anterior and upper regions of the lungs. Thus, selective aeration of the anterior and upper regions of the lungs before surfactant replacement might explain the picture of central clearing seen after surfactant replacement.

Development of PIE after surfactant replacement is a grave prognostic sign. More than 70 % of our patients with PIE died within the first 2 weeks of life. Our results confirm the relationship between development of air leaks and poor clinical outcome described by other authors [14–16]. However, poor clinical outcome can only in part be explained by the slightly lower GA and lower birth weight of these patients compared with the two groups with improved aeration after surfactant. Rather, these findings might arise from erroneous adjustment of ventilator parameters. Furthermore, it could not be excluded that "pre-radiological" histological lesions [14] were present. At least it is still possible that interstitial emphysema developed during the time between the pretreatment radiograph and the initiation of surfactant replacement. Bronchiolar epithelial disruption may cause release of plasma proteins into the airways, as well as leakage of surfactant into the interstitium, and might prevent success of surfactant treatment [17]. Both release of plasma proteins and leakage of surfactant might explain the cases of unusually severe interstitial emphysema after surfactant treatment (Fig. 4 b).

In conclusion, our results show that: (1) about 38 % of infants with RDS show complete improvement after surfactant treatment with good correlation to clinical data; (2) asymmetrical or focal air disturbances are frequent (34 %), but usually resolve after retreatment with surfactant without causing any significant clinical problems; and (3) development of interstitial emphysema after surfactant treatment is a grave prognostic sign, emphasising the sensitivity of the immature lung to barotrauma. Therefore, early chest radiographic monitoring of the therapeutic effect of surfactant, especially when retreatment doses of surfactant are given, might prevent overinflation and help in setting appropriate ventilator parameters, improving outcome.

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