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Surfactant Substitution in Ventilated Very Low Birth Weight Infants: Factors Related to Response Types

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ABSTRACT. We investigated factors that may influence the response to surfactant substitution. Thirty-five very low birth weight infants with respiratory distress syndrome were treated with Curosurf at 3–12 h of age. From the changes in oxygenation, the therapeutic response was categorized as rapid and sustained, rapid with relapse, or poor. Phospholipids and surfactant protein A were quantified in gastric aspirate samples obtained immediately after birth. They showed that 16 infants had accelerated lung maturity, despite clinical and radiologic signs of respiratory distress syndrome. Ten of them had suffered from birth asphyxia or connatal infection. Nevertheless, 12 of these 16 infants responded rapidly to surfactant substitution. Poor response was seen in four infants with connatal infection. Of 19 infants with immature lung profile, 18 showed a rapid initial response to surfactant substitution. Dynamic compliance of the respiratory system or arterial blood pressure before substitution, the ultrastructure of the surfactant preparation, or persistence of the ductus arteriosus did not influence the response type, but fraction of inspired oxygen was higher before surfactant substitution in infants with poor response. Prognosis was related to short-term response: Of 17 infants who showed a rapid and sustained response, none died, whereas eight of 18 infants with relapse after rapid initial response or poor response died ($p < 0.05$). We conclude that surfactant substitution may be beneficial not only in babies with primary surfactant deficiency but also in other pulmonary disorders that are common in very low birth weight infants. The type of response may be of prognostic value. (*Pediatr Res* 30: 591–596, 1991)

Abbreviations

RDS, respiratory distress syndrome
ARDS, adult respiratory distress syndrome
C_{RS}, dynamic compliance of the respiratory system
AUTC, area under the time curve
FiO_2, fraction of inspired oxygen
PDA, persistent ductus arteriosus
SP-A, surfactant protein A
PG, phosphatidylglycerol
L/S, lecithin/sphingomyelin ratio

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The efficacy of surfactant rescue treatment has been demonstrated in numerous controlled trials (1). However, the response to surfactant administration can be variable. Fujiwara *et al.* (2) found that 6% of preterm infants did not respond to surfactant treatment; Hallman *et al.* (3) observed a poor response in 8% and Charon *et al.* (4) in 22% of surfactant-treated infants. Relapse after an initially favorable response to surfactant replacement was reported by the same authors in varying incidences [11% (4), 16% (2), and 56% (3)]. The definitions used for relapse and poor response, however, were different, as were the explanations for their occurrence. The aim of our study was to relate types of response after surfactant substitution in clinically and radiologically diagnosed RDS to the biochemical pattern of the infants' surfactant at birth and to evaluate other factors that may influence this response.

PATIENTS AND METHODS

Between September 1988 and June 1990, 36 very low birth weight infants were enrolled into a surfactant rescue study carried out at our department. Entry and exclusion criteria are summarized in Table 1. The study protocol was approved by the local Ethics Committee. Written informed parental consent was obtained.

Standard patient management. Babies were mechanically ventilated with the aim of achieving arterial oxygen tensions of 5.9–9.2 kPa (45–70 mm Hg) and carbon dioxide tensions of 5.3–6.6 kPa (40–50 mm Hg) (5). Oxygen and carbon dioxide tensions were monitored transcutaneously and verified by arterial blood sampling. Blood pressure was monitored by oscillometry (Dinamap; Criticon, Tampa, FL).

Surfactant preparation, dose, and administration. The surfactant (Curosurf) used in this study was prepared from minced pig lungs by a combination of chloroform-methanol extraction and liquid-gel chromatography (6). The vials were stored at −20°C until use. After thawing at room temperature, an initial dose of 200 mg/kg (2.5 mL/kg) was instilled as described (5). Depending on the response (see below), up to two repeat doses of 100 mg/kg (maximum total dose 400 mg/kg) were allowed within the first 72 h of life.

Surfactant analysis. Gastric aspirate was obtained from each infant at birth to analyze phospholipids and SP-A concentrations.

Table 1. *Entry and exclusion criteria of surfactant rescue trial*

Entry criteria
Birth wt 700–1499 g
Gestational age 25–31 completed wk
Reticulogranular pattern and air bronchogram in chest film
Need for artificial ventilation with $FiO_2 \geq 0.40$
Postnatal age <12 h
Informed parental consent
Exclusion criteria
Prolonged rupture of membranes >3 wk
Obvious major congenital malformation
Grade III–IV intracerebral hemorrhage

Phospholipids were quantified by two-dimensional thin-layer chromatography as described elsewhere (7). The SP-A concentration was measured by a noncompetitive sandwich ELISA using a mouse MAb against human SP-A (generously provided by Byk-Gulden, Konstanz, Germany) as the first antibody and a rabbit polyclonal anti-human SP-A antibody as the second one. Complexes were visualized after incubation with a third, peroxidase-labeled goat anti-rabbit IgG antibody (8, with minor modifications).

C_{RS}. In all infants, C_{RS} was measured before surfactant application and 1, 6, and 24 h thereafter. As described recently (9), inspiratory and expiratory air flow was measured with a heated pneumotachograph (Fleisch 00, Metabo, Epaepalinges, Switzerland; Validyne MP 45 differential pressure transducer, H. Sachs Elektronik, Hugstetten, Germany) at the proximal end of the endotracheal tube, amplified and integrated to tidal volume (Pulmonary Mechanics Computer Model 6; Buxco Electronics Inc., Sharon, CT). Airway pressure was measured at the inlet of the endotracheal tube (Validyne DP 45-24 pressure transducer; H. Sachs Elektronik) and recorded simultaneously by a four-channel strip chart recorder (Schwarzer US 266; Cambridge Instruments GmbH, München, Germany). C_{RS} was calculated from expiratory tidal volume and airway pressure difference between inspiration and expiration at zero flow. The results were corrected for body weight. Measurements with a leakage exceeding 15% of the tidal volume were discarded. A previous study has documented satisfactory reproducibility of measurements with this technique (9).

Electron microscopic examination. Samples from 37 vials of Curosurf used in 25 infants in the present study were fixed with 1.25% glutaraldehyde, embedded in 2% agarose at 37°C, post-fixed for 2 h with 1% osmium tetroxide in 0.1 M cacodylate pH 6.9, washed with H_2O, blockstained with 1% aqueous uranyl acetate overnight, dehydrated with ethanol, and embedded in Epon (Roth, Karlsruhe, Germany). Ultrathin sections were stained with lead citrate and examined at 60 kV in a Philips EM 201 or CM 10 electron microscope (Philips, Eindhoven, Netherlands) (10).

Statistical procedures. Fisher's exact test was applied to evaluate differences in nominal data in each group. The Mann-Whitney U test or, for three groups, the Kruskal-Wallis test was used to evaluate differences in continuous variables. Statistical significance was defined as $p < 0.05$. All calculations were done with the SPSS statistical package (SPSS Inc., Chicago, IL).

As a summarizing parameter of oxygen requirement after surfactant administration, we determined the AUTC for FiO_2 of each infant from the time of surfactant substitution to 96 h afterward (Fig. 1). Values of this parameter could theoretically range from 0 h (no additional oxygen during 96 h) to 76 h (FiO_2 = 1.0 for 96 h).

Definitions. A surfactant pattern was regarded as "immature" if, in the gastric aspirate, L/S was < 2.7 (7), PG was not detectable, and SP-A concentration was < 0.3 μg/mL. (In our hands, with this cut-off value, infants with RDS can be distinguished from non-RDS infants with a sensitivity of 87% and a specificity of 81%). "Pure surfactant deficiency" was defined as an immature surfactant pattern in the absence of any other lung disorder. The surfactant pattern was regarded as "mature" if at least one of the following three criteria were fulfilled: L/S ratio ≥ 2.7, PG present, and SP-A concentration ≥ 0.3 μg/mL.

Birth asphyxia was assumed to be present in case of severe acidosis with an umbilical arterial pH ≤ 7.10 at birth (11, 12).

Connatal infection was diagnosed retrospectively if two out of three of the following criteria were fulfilled: positive blood cultures or surface swabs obtained shortly after birth, immature to total blood neutrophil ratio ≥ 0.20 (13), and C-reactive protein concentration during the first 24 h > 10 mg/L (14).

PDA was diagnosed from clinical (15), echocardiographic (16), and Doppler-ultrasonographic (17) signs. These examinations were routinely carried out on the 4th d of life and thereafter

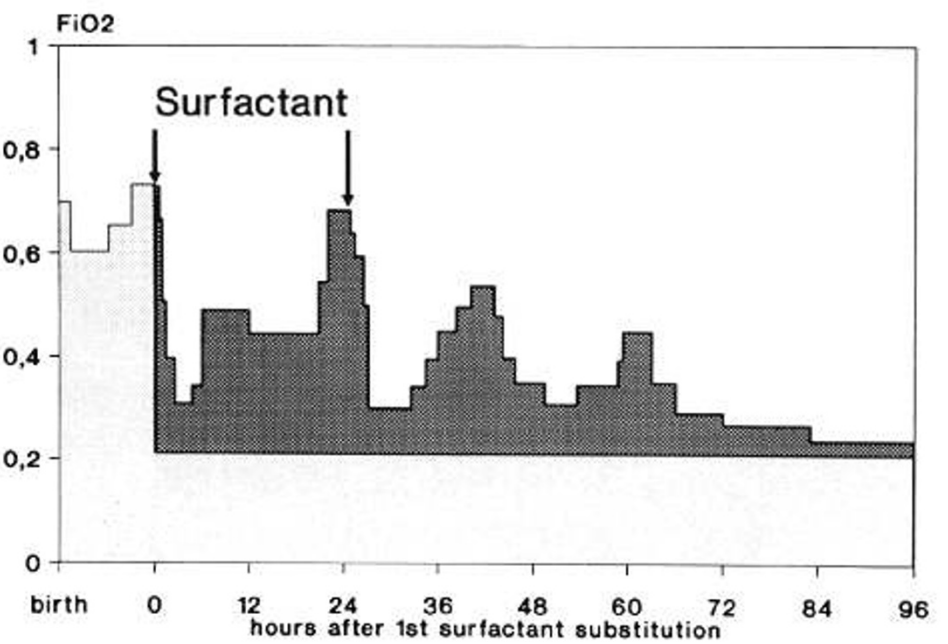

Fig. 1. AUTC for FiO_2 (example). The dark-shaded area is calculated from the course of FiO_2 between the time of the first surfactant application (*arrow on left*) and 96 h afterward. Ninety-six h × 0.21 is subtracted in each case (*dotted area*). The area represents the need for additional oxygen after surfactant substitution. This baby relapsed and was retreated after 24 h (*arrow on right*).

Table 2. *Characteristics of patients [absolute numbers (N) or mean ± SD] according to surfactant pattern at birth**

Parameters	Immature (n = 19)	Mature (n = 16)
Boys/girls (N)	11/8	7/9
Prenatal steroids (>12 h) (N)	9	12
Premature rupture of membranes (N)	9	5
Birth wt (g)	1093 ± 253	1118 ± 221
Gestational age (wk)	27.3 ± 1.7	28.2 ± 1.9
Age at treatment (h)	5.5 ± 2.6	6.6 ± 3.1
FiO_2 before substitution	0.81 ± 0.14	0.78 ± 0.17

* Differences between the groups are not statistically significant.

Table 3. *Surfactant profile and neonatal disorders*

Surfactant profile/ neonatal disorder	n	Surfactant profile* L/S	PG present (n)	SP-A (μg/mL)
Immature				
Pure surfactant deficiency, no complicating factors	15	<1 (<1–2.2)	ND	0.05 (0–0.2)
Birth asphyxia	3	2.1 (<1–2.1)	ND	0.05 (0–0.07)
Connatal infection	1	2.15	ND	0.03
Mature				
No complicating factors	7	3.0 (<1–10)	1	0.5 (0.01–6.6)
Birth asphyxia	2	3.4 (2.7; 4.1)	ND	1.6 (1.6; 1.7)
Connatal infection	7	3.2 (<1–4.2)	1	1.0 (0.01–2.1)

* Values are medians and range; ND, not detected.

whenever indicated. The PDA was regarded hemodynamically significant and treated if need for intermittent mechanical ventilation was prolonged, had to be reinstituted, or was reinforced (15).

We defined response types by the relative change of supplemental oxygen requirement. Response was regarded as "rapid" if additional oxygen supply could be reduced by 50% within 1–6 h after surfactant substitution. A rapid initial response followed by increasing oxygen requirements up to >0.60 within 8–60 h after surfactant substitution was interpreted as a "relapse," and a second or third surfactant dose was given. The term "sustained" was used for a rapid response without relapse.

If supplemental oxygen could not be lowered by at least 50% within 6 h after surfactant administration, the response was classified as "poor." In this case, repeated doses of surfactant were not given.

RESULTS

Thirty-five of the 36 infants enrolled in the study were evaluated; in one infant, gastric aspirate for surfactant analysis was lost.

Nineteen infants revealed an immature surfactant pattern, and 16 infants showed a mature surfactant pattern. The characteristics of these infants are listed in Table 2. Table 3 shows the results of surfactant analysis in gastric aspirates.

A deterioration in oxygenation or persistent carbon dioxide elevation did not occur after surfactant supplementation in either the infants with immature or in those with mature surfactant patterns.

Oxygenation after surfactant substitution. After surfactant substitution, mean FiO_2 improved rapidly, regardless of the infants' lung maturity (Fig. 2).

The AUTC for FiO_2 was 26.6 ± 12.8 h (mean ± SD) in infants with immature surfactant pattern compared with 31.6 ± 24.6 h in infants with mature lung profile (NS).

In the majority of infants in the mature group, additional lung disorders could be diagnosed according to the criteria given above; in the immature group, four infants had additional pulmonary problems apart from surfactant deficiency (Table 3).

Infants with connatal infection or birth asphyxia had a trend toward higher oxygen need after surfactant substitution [AUTC for FiO_2: 31.1 h (median), range 8.0–77.9 h; n = 13] than infants with pure surfactant deficiency (21.4 h, 8.6–48.2 h; n = 15, NS) and infants with a mature surfactant pattern and no complicating factors (13.4 h, 6.5–70.3 h; n = 7, NS).

Response types after surfactant substitution. The types of response were not equally distributed among the infants with different types of neonatal disorders (Table 4). Poor response was mainly seen in infants with unrecognized connatal infection.

Those 13 babies who relapsed after rapid initial response received a second surfactant dose 22 h (median; range 10–51 h)

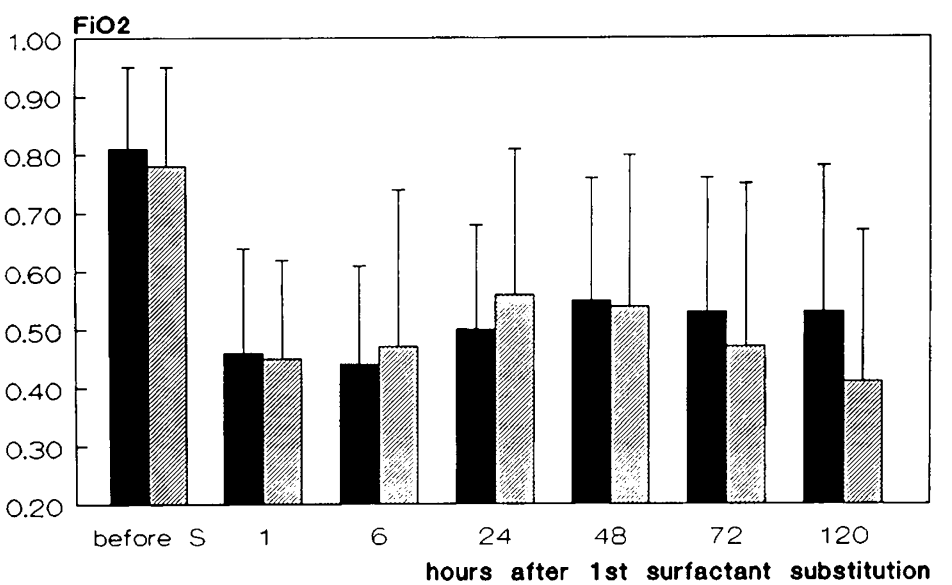

Fig. 2. Oxygenation before and after first surfactant substitution. FiO_2 (mean + SD) in 19 infants with immature (*black bars*) and 16 infants with mature (*gray bars*) surfactant profiles. *S*, surfactant application. Time axis is discontinuous.

Table 4. *Type of response in relation to surfactant profile and neonatal disorder*

	Type of response/surfactant profile* (number of cases)					
	Rapid, sustained		Rapid, relapse		Poor	
Neonatal disorder	I	M	I	M	I	M
Pure surfactant deficiency	8	0	6	0	1	0
Connatal infection	0	3	1	0	0	4
Birth asphyxia	0	2	3	0	0	0
Mature profile, no complicating factor	0	4	0	3	0	0

* I, immature; M, mature.

after the first one. Twelve to 28 h later, four of them were treated a third time (median time interval 17 h).

The type of response was not related to systolic or mean arterial blood pressure before or 1 h after surfactant substitution. In infants with a poor response, mean arterial blood pressure 1 h after surfactant substitution (36.8 ± 8.0 mm Hg) was not different from that of infants who relapsed (36.7 ± 4.5 mm Hg) or showed a sustained response (34.0 ± 6.4 mm Hg).

The quality of response to surfactant substitution was not related to gestational age, mode of delivery, vitality at birth as evaluated by Apgar scores, postnatal age, grading of RDS severity by chest x-ray, mean airway pressure, or C_{RS} (Fig. 3) before treatment. There was, however, a higher ($p < 0.05$) initial oxygen need in those infants who developed a poor response [FiO_2 = 1.0 (median), range 0.9–1.0, n = 5] compared with infants showing a rapid, sustained response (FiO_2 = 0.80, 0.45–1.0, n = 17) or a relapse after a rapid initial response (FiO_2 = 0.75, 0.55–1.0, n = 13).

The type of short-term response was related to the outcome at d 28: None of the infants with rapid, sustained response died, whereas eight of 18 infants who relapsed or responded poorly died ($p < 0.05$). Adverse outcome in relation to the type of response is summarized in Table 5.

There was no relation between the type of response and the occurrence of a PDA on d 4 or the development of hemodynamically significant PDA that became evident between d 4 and 12 of life (Table 6). There was also no relation between hemodynamically significant PDA and surfactant profile (data not shown).

C_{RS} did not increase within 24 h after surfactant therapy irrespective of the type of response (Fig. 3). We could not discriminate between immature and mature lung profiles nor one lung disorder from another using measurements of C_{RS}. It also did not help to predict the response to surfactant therapy. However, those 12 infants who survived and did not need supplemental oxygen on d 28 showed higher C_{RS} values before surfactant replacement (0.35 ± 0.11 mL/cm H_2O/kg) compared with 23 infants who were in oxygen on d 28 or died (0.27 ± 0.09 mL/cm H_2O/kg; $p < 0.05$). With a cutoff value of 0.30 mL/cm H_2O/kg, sensitivity was 64% and specificity 83%.

There was no correlation between FiO_2 and C_{RS} before surfactant substitution.

Electron microscopic examination of the Curosurf samples showed large multilamellar structures with diameters between 0.5 and 3 μm and small, uni- or oligolamellar vesicles with diameters of 0.1–0.5 μm (Fig. 4). There were no differences in the ultrastructural appearance of surfactant samples that could be related to the clinical response to replacement therapy.

DISCUSSION

Our study was designed to identify factors influencing the response to surfactant therapy. Therefore, we evaluated surfactant profiles in very low birth weight infants who fulfilled the customary clinical and radiologic criteria for diagnosis of RDS. As reported by others (18), infants below 32 wk of gestation may have accelerated surfactant maturity. In the present study, changes in oxygenation after surfactant substitution were not related to the degree of surfactant maturation estimated from biochemical parameters. Obviously, factors other than surfactant deficiency can play a role in the course of respiratory failure.

Hjalmarson (19) classified some pulmonary disorders in preterm infants that can mimic RDS but are not caused by surfactant deficiency. Infants with connatal infection may present with symptoms indistinguishable from RDS (19). This problem was also encountered in a recent Exosurf trial (20). Surfactant administration to infants with pulmonary infection presently is not recommended because killing of group B streptococci by pulmonary macrophages may be impaired after surfactant admin-

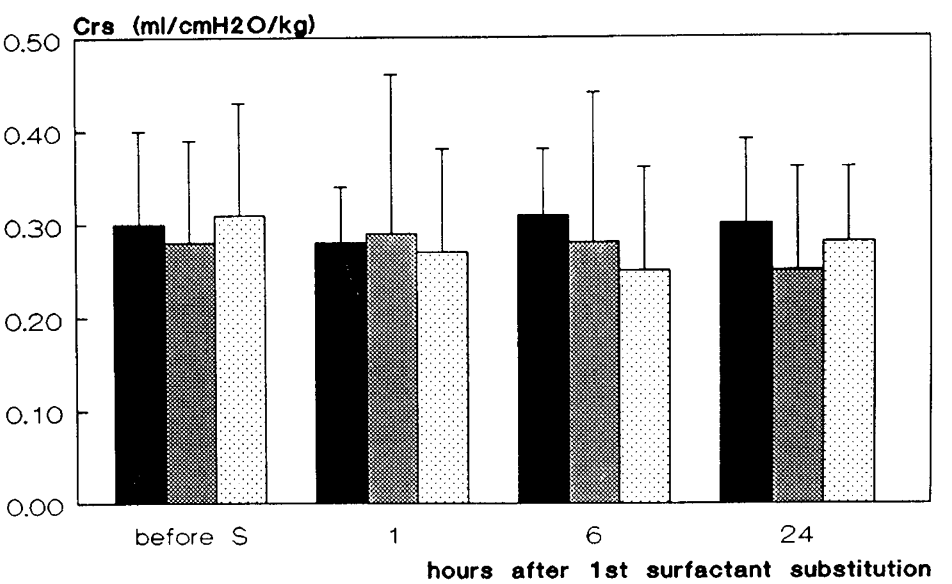

Fig. 3. C_{RS} before and after first surfactant substitution in different types of response (mean + SD). *Black bars*, 17 infants with rapid, sustained response. *Dark-shaded bars*, 13 infants with relapse after rapid response. *Dotted bars*, five infants with poor response. *S*, Surfactant application. Time axis is discontinuous.

Table 5. *Prognostic value of the response type*

Outcome (d 28)	Response type: Rapid, sustained	Response type: Rapid with relapse or poor
$FiO_2 = 0.21$	9	3
$FiO_2 > 0.21$	8	7
Death	0	8

Table 6. *Type of response and PDA*

Type of response	PDA: Hemodynamically significant	PDA: Insignificant
Rapid, sustained	7	10
Rapid, relapse	6	7
Poor	1	4

istration (21). However, connatal pulmonary infection often cannot be excluded readily in preterm infants, particularly if surfactant is administered soon after birth.

Another disorder must be considered in RDS patients with mature or nearly mature surfactant patterns. Faix *et al.* (22) described a clinical and radiologic picture resembling RDS in term neonates after birth asphyxia. They concluded that these infants suffered from ARDS. An increased alveolar membrane permeability typical of ARDS (23) may occur in very low birth weight infants. The protein-rich fraction of lung effluents from preterm infants with RDS but normal phospholipids has been found to inhibit the surface tension lowering capacity of lung lavage fluid from normal newborns (18). We speculate that in those infants of our study who had suffered from birth asphyxia, an ARDS-like mechanism lead to the clinical and radiologic picture of surfactant deficiency. Relapse or poor response in connatal infection or birth asphyxia may be due to surfactant-inactivating enzymes released by leukocytes (24) or surfactant inhibition by proteinaceous fluid leaking into the alveoli (25).

The infants with clinical and radiologic characteristics of RDS but with signs of accelerated surfactant maturation (see Table 3) seem to be a heterogenous group. In some of them, there was evidence of "incomplete" surfactant maturation with borderline SP-A concentration and low L/S ratio, or an L/S ratio just above the cutoff value associated with low SP-A concentration. Other infants in this group improved rapidly during the 1st day of life; their course resembles that of infants with "pulmonary maladaptation" (19), which can mimic RDS during the first hours of life. Surprisingly, although these infants did not suffer from primary surfactant deficiency, they nevertheless seemed to benefit from supplementation of exogenous surfactant. We speculate that exogenous surfactant improves liquid clearance from the alveoli (26) or reverses secondary damage of the surfactant system that can occur because of artificial ventilation with high oxygen concentrations (27).

Half of our infants with pure surfactant deficiency relapsed. In these babies, one dose of exogenous surfactant as given in most of the controlled trials of surfactant substitution may not suffice. Hallman *et al.* (28) found it necessary to retreat infants with severe RDS in about 50% of the cases. In their study, the half-life of PG was about 30 h in infants of 25 to 30 wk gestational age. Solimano *et al.* (29) pointed out that in ventilated lambs the clearance of exogenous surfactant from the airways increased with the severity of RDS. In addition, high concentrations of inhibitory proteins leaking into the airways contribute to surfactant dysfunction in neonatal RDS (30). These observations suggest that the efficacy of surfactant therapy may be further improved if repeat doses are supplied should RDS not resolve after one dose. This hypothesis is currently being tested in controlled clinical trials organized by the Collaborative European Multicenter Study Group.

Contrary to data presented by others (4), the finding of a PDA was not, in our study, related to the response to surfactant substitution.

Our C_{RS} measurements confirm the observations of Davis *et al.* (31) and of Couser *et al.* (32), who found no increase of C_{RS} after surfactant supplementation in ventilated infants. In our experience, measurement of C_{RS} does not help to differentiate between types of lung disorders in the first hours of life, nor does it help to determine the need for surfactant substitution, as suggested by others (33). C_{RS} measurements might be of prognostic value when survival and oxygen dependency on d 28 are considered, although specificity and sensitivity are not good enough to allow use of this parameter alone as a means of evaluating the prognosis of a preterm infant.

Electron microscopic examination of Curosurf was carried out to exclude the possibility that the vesicle size of the surfactant

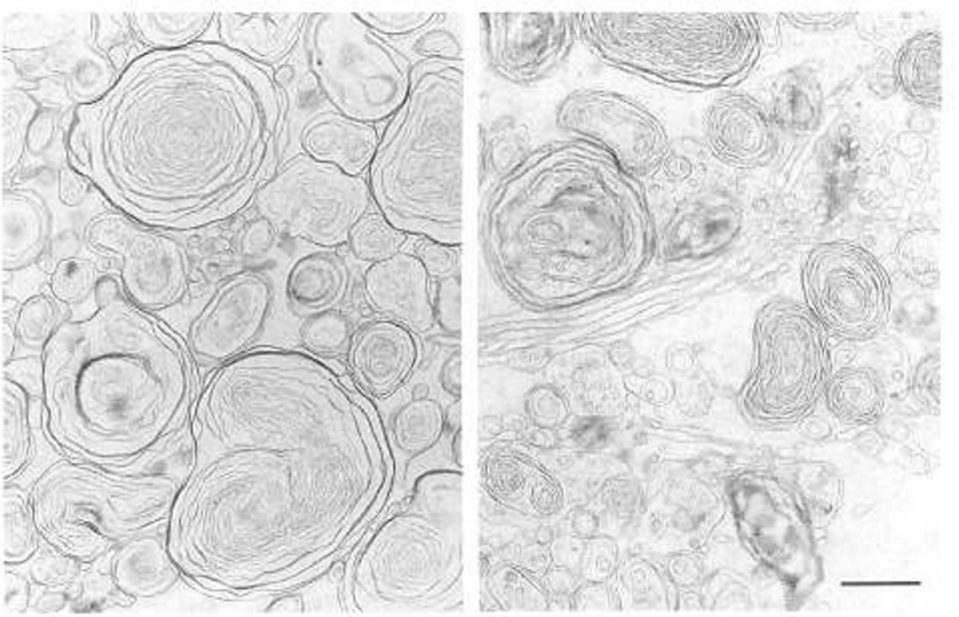

Fig. 4. Electron microscopic appearance of two Curosurf samples. The electron micrographs show large (0.5–3 μm in diameter) multilamellar structures and small (0.1–0.5 μm in diameter) uni- or oligolamellar vesicles. *Bar* represents 1 μm.

preparation would differ from vial to vial. Variations in vesicle size related to functional activity have previously been described for artificial mixtures of surfactant lipids (10).

Conclusions. From recordings of FiO_2, typical patterns of response to surfactant substitution can be recognized in very low birth weight infants presenting with the clinical and radiologic features of RDS. The quality of response is less influenced by the degree of lung maturity than by the presence of additional pulmonary disorders. Rapid initial response, sustained or with relapse, may be seen in infants with primary surfactant deficiency without complicating factors, as well as in babies with birth asphyxia or accelerated lung maturation. Poor response is suggestive of some additional pulmonary disorder such as infection. Relapse or a poor response are related to poor outcome, as are low initial values of C_{RS}.

Surfactant substitution may be beneficial not only in primary surfactant deficiency (pure neonatal RDS) but also in other pulmonary disorders that are common in very low birth weight infants.

From this study, however, no conclusions can be drawn about whether it is advisable to give surfactant to infants with lung disorders other than primary surfactant deficiency. To clarify this matter, RDS should be clearly distinguished from other pulmonary disorders in future clinical trials of surfactant substitution. Rapid, reliable, and readily available methods for surfactant phospholipid or apoprotein analysis and unequivocal diagnostic markers for other neonatal pulmonary diseases are desirable.

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