Exosurf Rescue Surfactant Improves High Ventilation-Perfusion Mismatch in Respiratory Distress Syndrome

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Summary. Objective: To assess ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch of the high type, following rescue surfactant therapy for respiratory distress syndrome. **Hypothesis:** Surfactant therapy reduces such mismatch. **Design:** Randomized, double-blind, placebo-controlled study, assessing $\dot{V}_A/\dot{Q}$ with the arterial-alveolar difference of CO_2 tension ($P_{(a-A)CO_2}$). This difference was determined with capnometry and arterial blood gases, using the equation: $P_{(a-A)CO_2}$ equals arterial CO_2 minus alveolar CO_2 partial pressure. **Setting:** A level III nursery. **Patients:** Ten intubated infants with respiratory distress syndrome. **Intervention:** Infants were randomized to each receive two doses of surfactant or two doses of air placebo. **Results:** $P_{(a-A)CO_2}$ improved after surfactant and worsened after placebo ($P = 0.0021$), comparing slopes of 12-hr regression lines. A similar pattern occurred with oxygenation. These changes in $P_{(a-A)CO_2}$ and in oxygenation were minimally correlated within the surfactant group. **Conclusion:** Exosurf rescue surfactant reduced $\dot{V}_A/\dot{Q}$ mismatch of the high type, over several hours. Pediatr Pulmonol. 1994; 18:279–283. © 1994 Wiley-Liss, Inc.

INTRODUCTION

Surfactant therapy has reduced mortality in premature infants by treating or preventing respiratory distress syndrome (RDS).[1] Surfactant treatment commonly improves oxygenation within 0–2 hr[1-5] and improves lung compliance later.[5-7] Little has been published about how surfactant therapy affects alveolar ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$). We hypothesized that rescue surfactant therapy would improve $\dot{V}_A/\dot{Q}$ mismatch of the high type.

The lung model assessed by this study involves high $\dot{V}_A/\dot{Q}$ regions of the lung.[8-11] Ideally $\dot{V}_A/\dot{Q}$ is close to 1.0 in most lung regions. In diseased lungs there can be mismatches involving high $\dot{V}_A/\dot{Q}$ regions, low $\dot{V}_A/\dot{Q}$ regions, or both. Both types of mismatch can occur simultaneously in RDS.[12] Regions of high $\dot{V}_A/\dot{Q}$ contribute to increased dead space. If dead space becomes excessive, CO_2 retention results. Regions of low $\dot{V}_A/\dot{Q}$ can act as small venoarterial shunts. Blood perfusing such regions can be incompletely oxygenated with decreased CO_2 removal.

This study monitored the arterial-alveolar difference of CO_2 tension ($P_{(a-A)CO_2}$). This is defined as $P_{(a-A)CO_2} = P_{aCO_2} - P_{ACO_2}$, which relates the partial pressure of arterial CO_2 (P_{aCO_2}) and the partial pressure of alveolar CO_2 (P_{ACO_2}).[8-11] The P_{aCO_2} was measured with arterial blood gases, and P_{ACO_2} was assessed with capnometry. The $P_{(a-A)CO_2}$ value is a widely accepted gauge of high $\dot{V}_A/\dot{Q}$

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lung regions[8-11] and is minimally influenced by low $\dot{V}_A/\dot{Q}$ regions.[12] For assessing high $\dot{V}_A/\dot{Q}$ mismatch, $P_{(a-A)CO_2}$ is much more reliable than P_{aCO_2} because the latter is influenced by right-to-left shunting and other factors. The normal range for $P_{(a-A)CO_2}$ may be as narrow as 0–2 mm Hg in healthy adults,[10] but may be as wide as 0–12 mm Hg in healthy premature infants.[13] In this study, analysis focused on $P_{(a-A)CO_2}$ changes over time rather than absolute levels.

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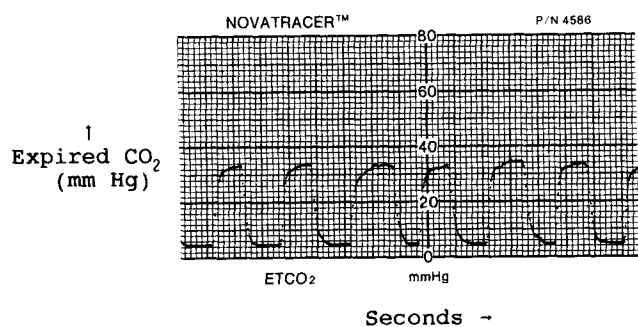
Fig. 1. A capnometric tracing of partial pressure of CO_2 during tidal breathing (plateaus at end-expiration approximate alveolar P_{CO_2}).

Fig. 2. Regression line of $P_{(a-A)CO_2}$ arterial-alveolar CO_2 pressure [$aADCO_2$ ($P_{(a-A)CO_2}$ in the text)] on time after treatment dose in one patient.

MATERIALS AND METHODS

Ten premature infants with RDS were monitored for respiratory parameters, to compare the response to surfactant with the natural course of RDS between 2 to 48 hr of age. All 10 patients were born in 1989 and cared for at the University of Michigan Medical Center. They were a subset of the 1656 infants in two randomized double-blind multicenter trials conducted by the manufacturer of Exosurf (Colfosceril Palmitate, Cetyl Alcohol, Tyloxapol: made by Burroughs-Wellcome Co., Research Triangle Park, North Carolina).[2,3]

These 10 infants were selected from a consecutive series of infants admitted to the hospital. The selection was solely based on meeting two criteria: (1) enrollment in one of these Exosurf trials,[2,3] and (2) having continuous monitoring of the partial pressure of end-tidal CO_2 (P_{etCO_2}). Exosurf was dosed endotracheally in a dose of 5 mL/kg (67.5 mg phospholipid/kg). Control infants received a doses of 5 mL/kg sham air. The first treatment dose was given to enrolled infants with significant RDS, who met certain requirements,[2,3] including age $\leq$24 hr, the need for mechanical ventilation, and a ratio of <0.22 between the partial pressure of arterial oxygen (P_{aO_2}) and the partial pressure of alveolar oxygen (P_{AO_2}). One repeat dose of Exosurf or air was given to all 10 patients $\geq$12 hr after the first dose. The ventilation techniques usually maintained a P_{aCO_2} of 35–50 mm Hg during this study's evaluation periods.

The following were concurrently measured with capnometry and other methods: P_{etCO_2},[14] fraction of inspired oxygen (F_{iO_2}), mean airway pressure (MAP), P_{aO_2}, and P_{aCO_2}. Data sets of these 5 measurements were obtained when clinicians ordered arterial blood gases. The blood samples were obtained from indwelling arterial catheters, usually umbilical catheters at 8–10 level thoracic vertebrae. Capnometry measured partial pressure of expired CO_2. Pressure of expired CO_2 at end-expiration (Fig. 1) approximates P_{ACO_2} if adequate gas mixing has occurred. The readings of P_{etCO_2} were made on the Novametrix
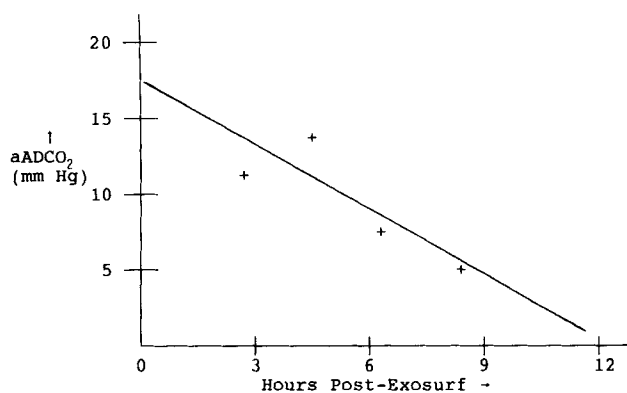
1260 capnometer with a mainstream infrared design (Wallingford, Connecticut).[15] These measurements are noninvasive and the instruments provide graphic printouts. Printouts were obtained for almost all of the data sets, which demonstrated good plateaus of P_{etCO_2} (Fig. 1). The plateau occurs after the mixing of expired gases when $P_{etCO_2} \cong P_{ACO_2}$. The capnometer was calibrated daily using its internal system, using one gas with zero CO_2 and another with a known CO_2 concentration.

Values for $P_{(a-A)CO_2}$ and for three parameters of oxygenation [$P_{(A-a)O_2}$, P_{AO_2}/P_{aO_2}, and oxygenation index (OI)] were calculated for each data set. The OI is defined as (fraction of inspired oxygen) $\times$ (100 $\times$ MAP)/P_{aO_2}.[16] The ratio P_{AO_2}/P_{aO_2} rather than P_{aO_2}/P_{AO_2} was used so that changes in the three oxygenation parameters would match in direction. Standard equations were used including the alveolar air equation for determining P_{AO_2} and $P_{(A-a)O_2}$.[10] A respiratory exchange ratio of 0.8 was used, since the patients were not yet receiving intravenous lipids.[10]

The timed data sets were statistically analyzed if they met all of the following criteria: (1) data obtained 0–12 hours following a dose of surfactant or air, (2) existence of $\geq$3 sets during the 12 hr interval, and (3) data appearing reliable by visual assessment, to exclude sets with an outlier $P_{(a-A)CO_2}$ (3 sets of 67 were thus excluded). Since individual doses were separated by $\geq$12 hr (Exosurf protocol[2,3]), none of these 12 hr postdose intervals had overlapping data sets. Therefore, each data set within one such interval was statistically analyzed for only that interval's dose (Fig. 2). Negative $P_{(a-A)CO_2}$ was not an exclusion criterion. Five of the final 64 data sets had such values, ranging from −1 to −3 mm Hg. This phenomenon may have indicated calibration error or lack of a steady state within the lungs. A negative $P_{(a-A)CO_2}$ can occur during exercise.[17]

Regression lines for $P_{(a-A)CO_2}$ were plotted against time over the 12 hr postdose intervals (Fig. 2). The X-axis was

TABLE 1—Population Characteristics

	Exosurf	Control	P
n (male, female)	5 (4,1)	5 (4,1)	
Inborn:outborn	3:2	4:1	
Gestational age[1] (weeks)	31.1 ± 2.7	29.8 ± 1.9	0.41
	(26.5–33.0)	(28.0–33.0)	
Birth weight[1] (g)	1614 ± 523	1516 ± 428	0.75
	(850–2120)	(1160–2108)	
High frequency jet ventilation[2]	20%	40%	
Mortality[2,3]	20%	20%	

[1]Continuous data given as mean ± SD (range).
[2]Occurred after this study's evaluation.
[3]Each from respiratory causes.

TABLE 2—Timing and Conditions for Evaluated Doses

	Exosurf	Control
n (dose 1,dose 2)	8 (3,5)	7 (2,5)
Hours, postnatal age[1]		
At dose 1	10.3	5.5
	(4.6–14.1)	(3.7–7.2)
At dose 2	25.8	17.4
	(14.1–36.4)	(14.5–20.3)
Respiratory parameters[1]		
$P_{(a-A)CO_2}$ (mm Hg)	6.5	8.9
$P_{(A-a)O_2}$ (mm Hg)	251	357
P_{AO_2}/P_{aO_2}	3.4	5.6
OI	5.3	8.1

[1]Mean (range).
[2]Means of line intercepts at dosing time (Fig. 2); OI,oxygenation index.

TABLE 3—Hourly Changes in Respiratory Parameters[1]

	Exosurf	Control	P
$P_{(a-A)CO_2}$/hr (mm Hg/hr)	−0.63	+0.39	0.0021
$P_{(A-a)O_2}$/hr (mm Hg/hr)	−9.3	+3.7	0.011
P_{AO_2}/P_{aO_2}/hr	−0.08	+0.15	0.095
OI/hr	−0.17	+0.33	0.052

[1]Means of slopes of regression; for abbreviations see text.

TABLE 4—Correlations Between Changes of $P_{(a-A)CO_2}$ and Other Respiratory Parameters[1]

	Exosurf		Control	
Parameters	r	P	r	P
$P_{(A-a)O_2}$	−0.22	0.60	+0.47	0.29
P_{AO_2}/P_{aO_2}	−0.21	0.62	+0.83	0.02
OI	−0.12	0.78	+0.71	0.07

[1]For abbreviations see text.

calibrated to the nearest minute, and the Y-axis to the nearest mm Hg or to ≥ 2 decimal places. Although linear representation might oversimplify the changes in $P_{(a-A)CO_2}$ and in oxygenation, it makes it possible to assess mutual correlations between these changes.[18] We used the Pearson r-coefficient to quantitate these correlations.[18] All P-values were two-tailed.

For each patient in this study, parents gave written informed consent for treatment with either Exosurf or placebo, and for data collection and analysis.

RESULTS

The 10 infants in this study were randomized to receive or to not receive Exosurf. The two resulting groups were fairly similar by the data in Table 1; they had a combined gestational age of 30.5 ± 2.3 weeks and birth weight of 1565 ± 478 g (mean ± SD). Table 2 gives estimates for $P_{(a-A)CO_2}$ and for oxygenation parameters at the times of dosing. Instead of a potential of 20 doses 15 were evaluated to meet the requirement of ≥ 3 data sets per dose. Table 2 also shows the mean postnatal ages at each of the 15 doses assessed in this study. Exosurf doses were given

at an average of about 7 hr later than placebo doses. This difference was likely a chance variation, but does not invalidate the outcome data.

Table 2 does not provide preintervention "baseline" comparisons. Many of the evaluated doses were second doses, thus the differences in the respiratory parameters reflect whether or not surfactant had previously been given. The groups were too small for reliable comparisons for only the first dose. The disparities in Table 2 regarding postnatal ages and respiratory parameters do not invalidate the outcome data presented in Tables 3 and 4. The outcome comparisons involve the changes during 12 hr postdose intervals, rather than absolute values. All of these intervals were within the first 2 days of life, presumably the early worsening phase of RDS.

During the 12 hr posttreatment intervals, $P_{(a-A)CO_2}$ usually decreased after surfactant doses and usually increased after air doses. Regression lines for $P_{(a-A)CO_2}$ on time demonstrated such patterns following 7 of the 8 surfactant doses evaluated and following 6 of the 7 air

doses evaluated ($P < 0.05$ by chi square). A total of 64 data sets were analyzed, i.e., a mean of 4.3 sets per dose (range, 3 to 8). Data spanned over 5 to 10 hr per dose, for determining regression lines. These lines showed changes in $P_{(a-A)CO_2}$: The slopes of the lines for $P_{(a-A)CO_2}$ averaged -0.63 mm Hg/hr following surfactant and $+0.39$ mm Hg/hr after air ($P = 0.0021$; Table 3). These data support that Exosurf reduced high $\dot{V}_A/\dot{Q}$ lung regions for several hours.

Trends for oxygenation ($P_{(a-A)CO_2}$, P_{AO_2}/P_{aO_2}, OI) were similar to the trends for $P_{(A-a)O_2}$ (Table 3). Oxygenation improved following surfactant and worsened following air; with the respective slopes of regression lines being significantly different by P-values of 0.01 to 0.1. Even though these overall trends were similar, patients receiving surfactant lacked strong correlations between the slopes of regression lines for $P_{(a-A)CO_2}$ and for oxygenation changes ($r \cong -0.1$ to -0.2, Table 4). In patients receiving air, correlations between these two items were moderately positive ($r \cong +0.5$ to $+0.8$; Table 4).

During this study, the main clinical problem of each patient was RDS (specifically, the early worsening phase of RDS). Up to 12 hr after the second dose, no infant had a pneumothorax and no infant was started on high frequency jet ventilation. The P_{etCO_2} can change dramatically with an acute event such as a pneumothorax,[14,16] however, clinically all 10 infants appeared to have RDS without such events throughout the study intervals.

DISCUSSION

Our main finding was that rescue Exosurf lowered $P_{(a-A)CO_2}$ in patients with RDS compared to untreated controls. Findings of this study might not be relevant to other surfactants preparations since their effects sometimes vary.[19] Unlike most other surfactants, Exosurf is entirely synthetic and lacks proteins.[2] We could find only one study similar to ours (in abstract form) which showed no consistent changes in $P_{(a-A)CO_2}$ for 2 hr following rescue surfactant.[20] That study evaluated Beractant, a modified bovine surfactant which contains proteins (Survanta, Ross Laboratories, Columbus, Ohio). The fact that we used a different surfactant probably did not account for the dissimilar study results. The differences were more likely due to the much longer than 2 hr long evaluation intervals in our study. Also, 8 of the 15 patients of Bowen et al.[20] were nonresponders in whom surfactant did not significantly improve oxygenation. Our results concur with those authors' conclusion that surfactant does not appear to increase lung regions of high $\dot{V}_A/\dot{Q}$, however, by our results, surfactant reduces high $\dot{V}_A/\dot{Q}$ lung regions over several hours.

Publications about the effects of surfactant on lung physiology can be categorized by the following functions (partial listing): oxygenation,[2–5] lung compli-

ance,[5–7,21,22] other aspects of lung mechanics,[5,21] blood flow patterns,[4,22–26] gas exchange,[27,28] and other issues.[29] Surfactant effects on $\dot{V}_A/\dot{Q}$ have been studied relatively little, although some studies have noted widely varying P_{aCO_2} levels.[4,23–26] The P_{aCO_2} of mechanically ventilated patients can usually be normalized by adjustments of the ventilator; therefore P_{aCO_2} alone may not correctly assess the lung's ability to remove CO_2. In a preliminary analysis of our study's patients $P_{(a-A)CO_2}$, but not P_{aCO_2} or P_{etCO_2}, consistently had positive correlations with MAP.[30] Since MAP is a rough gauge of ventilation requirements,[31] ventilation was assessed best with $P_{(a-A)CO_2}$.

Trends in $P_{(a-A)CO_2}$ of healthy premature infants[13] and in patients with RDS not treated with surfactant had been investigated.[12,32] Tori et al. (see their Fig. 6) provided information regarding $P_{(a-A)CO_2}$ changes during the early phase of RDS.[32] Progressive worsening of $P_{(a-A)CO_2}$ was observed in 6 of 6 individual patients with RDS: those for whom 2 or more $P_{(a-A)CO_2}$ values were obtained within the first 2 to 2-1/2 days of life (spacing between values was about 1/2 to 2 days). This trend of worsening $P_{(a-A)CO_2}$ was thus similar to the pattern of our control group.

Our findings were consistent with studies by Krauss and Auld and others who showed that both high and low $\dot{V}_A/\dot{Q}$ lung regions can occur simultaneously in RDS.[12,32] Regions of low $\dot{V}_A/\dot{Q}$ are important causes of poor oxygenation,[12,32] but other causes include anatomic right-to-left shunts[33] and diffusion block.[32] To demonstrate regions of low $\dot{V}_A/\dot{Q}$ requires specialized analyses such as the arterial-alveolar difference of nitrogen.[8–12,20,32] Our study did not include such an analysis, but we did show simultaneous occurrence of high $P_{(a-A)CO_2}$ and impaired oxygenation in RDS. Our findings were consistent with current knowledge that surfactant therapy in RDS almost always improves oxygenation.[1–5]

It is surprising that minimal correlations were found between the effects of surfactant on $P_{(a-A)CO_2}$ and on oxygenation (Table 4). This was the case regardless of which of the 3 oxygenation parameters was matched to $P_{(a-A)CO_2}$. Control infants had moderately positive correlations for these same parameters. The explanation of the minimal correlations in the surfactant group is probably related to different mechanisms involved in improving oxygenation and in improving $P_{(a-A)CO_2}$.

Surfactant improves oxygenation by increasing lung volume in underaerated regions[1,5,21] and by other mechanisms.[29] All of these appear to mainly involve lung regions with $0 \leqslant \dot{V}_A/\dot{Q} < 1$. Therefore the effects of these mechanisms on $P_{(a-A)CO_2}$ would be minimal.[8–11] Pulmonary underperfusion is one cause of high $\dot{V}_A/\dot{Q}$ regions. Accordingly, relief of hypoxemia might reduce high $\dot{V}_A/\dot{Q}$ regions by countering vasoconstriction, or by allowing MAP to be reduced (a high MAP would tend to

collapse compliant pulmonary vessels). Alternatively, surfactant might normalize high $\dot{V}_A/\dot{Q}$ regions by reducing regions of the lung which are overventilated. Our data are more consistent with the assumption that rescue Exosurf normalizes high $\dot{V}_A/\dot{Q}$ regions mainly by reducing overventilation.

In conclusion, Exosurf rescue therapy for RDS reduced high $\dot{V}_A/\dot{Q}$ mismatch over several hours, as shown by reductions in $P_{(a-A)CO_2}$. The exact mechanisms for this improvement were not determined by this study. Such mechanisms did not appear linked to the improved oxygenation caused by the surfactant. We speculate that the principal mechanism in reducing $P_{(a-A)CO_2}$ following surfactant is reduction of overventilation. Future study into clarifying the mechanisms of surfactant effects could help reveal the causes for differences between the results with various surfactants.

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