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Changes in Dead Space/Tidal Volume Ratio and Pulmonary Mechanics after Surfactant Replacement Therapy in Respiratory Distress Syndrome of the Newborn Infants

This study was performed to elucidate the mechanism of improved oxygenation after surfactant replacement therapy in respiratory distress syndrome (RDS) of the newborn infants. In 26 newborns with RDS, end tidal-CO_2 tension ($PetCO_2$), arterial blood gas analysis and pulmonary function tests were measured at baseline, 30 min, 2 hr and 6 hr after surfactant administration. The changes in dead space/tidal volume ratio (V_D/V_T ratio=($PaCO_2$-$PetCO_2$)/$PaCO_2$), oxygenation index and arterial-alveolar partial pressure difference for oxygen ((A-a)DO_2) were elucidated and correlated with pulmonary mechanics. Oxygenation index and (A-a)DO_2 improved, and V_D/V_T ratio decreased progressively after surfactant administration, becoming significantly different from the baseline at 30 min and thereafter with administration of surfactant. Pulmonary mechanics did not change significantly during the observation period. V_D/V_T ratio showed close correlation with OI and (A-a)DO_2, but not with pulmonary mechanics. These results suggest that decreased physiologic dead space resulting from the recruitment of atelectatic alveoli rather than improvement in pulmonary mechanics is primarily responsible for the improved oxygenation after surfactant therapy in the RDS of newborn.

Key Words: *Respiratory Distress Syndrome; Respiratory Dead Space; Tidal Volume; Pulmonary Surfactants; Respiratory Mechanics*

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INTRODUCTION

Respiratory distress syndrome (RDS) of newborn infants results primarily from a deficiency of pulmonary surfactant. It manifests as hypoxia and hypercarbia due to decreased lung compliance, increased atelectasis of alveoli and increased dead space. Surfactant replacement therapy is an established treatment for ventilation disoders induced by surfactant deficiency in neonates (1, 2). Intratracheal administration of exogenous surfactant in RDS rapidly improves oxygenation. The role of simultaneous improvement in lung mechanics in improvement of oxygenation is controversial (3). Many prospective studies have shown that surfactant replacement therapy improves gas exchange and decreases ventilatory requirement in the newborn infants with RDS (4-8). Studies with laboratory animals have shown that surfactant replacement therapy improves both gas exchanges and lung compliance (9, 10). Recently, a study using calf lung surfactant extract in preterm infants with RDS resulted in no significant improvement in pulmonary mechanics (minute ventilation, compliance of repiratory system, total lung resistance system) during mechanical breathing (11). Surfactant application leads to an improvement of gas exchange (ventilation/perfusion ratio, arterial PO_2, arterial/alveolar PCO_2 ratio) by increasing the functional residual capacity (FRC) (12).

Although oxygenation has been suggested to improve after surfactant replacement therapy in RDS due to increased recruitment of collapsed alveoli, decreased dead space, or improvement of pulmonary mechanics, exact mechanism still remains to be solved.

To determine the mechanism of the improved oxygenation after surfactant replacement therapy, the immediate effects on lung volume and pulmonary mechanics were analyzed in 26 newborns with RDS during mechanical ventilation. Because of difficulties in assessing pulmonary function, particularly the measurement of lung volume, we used end tidal CO_2 by capnometry in the current study. The aim of this work was to test the

hypotheses that recruitment of atelectatic alveoli rather than improved pulmonary mechanics is responsible for the improved oxygenation after surfactant treatment in RDS.

MATERIALS AND METHODS

Patients and study protocol

This study was performed in 26 infants who were randomly selected. All infants were admitted to the neonatal intensive care unit (NICU) at Samsung Medical Center and had clinical evidences of RDS requiring endotracheal intubation for mechanical ventilation. The diagnosis of RDS was made on the basis of history, physical examination, and the presence of typical roentgenogaphic finding. Their birth weights ranged from 950 g to 3,860 g (1,910 ±801 g) and their gestational age ranged from 27 to 38 weeks (32±3 weeks). Surfactant was administerd within 3 hr after delivery. The determination of arterial blood gas analysis (ABGA), end-tidal CO_2 tension ($PetCO_2$) and pulmonary mechanics was performed before and after surfactant administration in all patients.

Surfactant administration

All infants had surfactant therapy instituted according to a rescue protocol. The endotracheal tube was suctioned just prior to the administration of surfactant. Surfactant-TA (Surfacten™, Tokyo Tanabe, Japan) was given in a single dose (standard dose 120 mg/kg). To achieve more uniform distribution of the given surfactant in the lungs, each surfactant was injected for over 30 sec with the infant's position being changed for each aliquot (4 positions). Suctioning of the endotracheal tube was avoided for 3 hr after completion of surfactant instillation, unless clinically indicated. All infants were given the same method of conventional mechanical ventilation by a neonatal pressure-limited, time-cycled ventilator (Infant Star®).

Ventilatory equipment and care

Throughout the study period, ventilation setting was adjusted to maintain the arterial oxygen tension (PaO_2) between 50 and 80 mmHg, pulse oximeter reading between 90 and 95% (NELLCOR®), and arterial carbon dioxide tension ($PaCO_2$) between 35 and 55 mmHg. In the response to improvement of oxygenation, ventilator settings were adjusted with a reduction in inspired oxygen, followed by a reduction in ventilatory rate, and finally a reduction in peak inflation pressure. The level of positive end-expiratory pressure was set between 3 and 4 cmH_2O.

Measurement of pulmonary mechanics and clinical monitoring

Pulmonary function was measured bedside with a computerized system (BICORE CP-100®). Pulmonary mechanics, including measurement of dynamic compliance (C_{DYN}), resistance of the respiratory system (R_{RS}) and minute ventilation (V_E), was assessed before and 30 min, 2 hr, and 6 hr after administration of surfactant.

Samples of arterial blood were obtained anaerobically from indwelling arterial catheters (umbilical arterial line or radial arterial line). The mean airway pressure (MAP) and fraction of inspired oxygen (FiO_2) were recorded. Arterial blood gases were determined before, 30 min, 2 hr, and 6 hr after surfactant administration with blood gas analyzer (Ciba-Corning, MA, U.S.A.).

Dead space measurements

$PetCO_2$ was measured, analyzed and standardized with a known concentration of CO_2 on the expiratory side (mainstream) of the circuit's endotracheal tube connector using a NELLCOR®. $PetCO_2$ measurements and ABGA were simultaneously determined. The arterial end-tidal PCO_2 difference ($P(a\text{-}et)CO_2$) was obtained by subtracting the $PetCO_2$ from $PaCO_2$ of an arterial blood sample obtained during the sampling period. We then used the Bohr-Enghoff method to calculate the dead space/tidal volume ratio (V_D/V_T ratio) with the following equation (13).

$$V_D/V_T \text{ ratio} = P(a\text{-}et)CO_2/PaCO_2 \quad \cdots\cdots (1)$$

Oxygenation variables

The alveolar-arterial oxygen gradient ($(A\text{-}a)DO_2$) and oxygenation index (OI) were calculated using following equations, and their correlations with pulmonary mechanics were carried out.

$$(A\text{-}a)DO_2 = (P_B\text{-}47)FiO_2\text{-}PaCO_2/R\text{-}PaO_2 \quad \cdots\cdots (2)$$

(P_B: atmospheric pressure, R: respiratory quotient, assumed to be 0.8)

$$OI = FiO_2 \times MAP/PaO_2 \times 100 \quad \cdots\cdots (3)$$

Statistical methods

Data were given as mean ± standard deviations. Data were analyzed by paired t-test between before and after surfactant replacement therapy. A repeated measures analysis of variance (ANOVA) was used to assess whether changes over time were different among simultaneously obtained values. The correlation coefficient from linear regression method was used to assess the strength of the relationship between V_D/V_T ratio and OI or $(A\text{-}a)DO_2$. Statistical significance was given when p value was less than 0.05.

RESULTS

Changes in gas exchange

The changes in OI and (A-a)DO_2 after surfactant treatment are given in Fig. 1A&B. The OI and (A-a)DO_2 improved progressively after surfactant administration, becoming significantly different from the baseline at 30 min and thereafter with administration of surfactant ($p<0.001$).

The changes in V_D/V_T ratio after surfactant replacement are shown in Fig. 1C. The V_D/V_T ratio decreased progressively over time, also becoming significantly different from the baseline at 30 min and thereafter with administration of surfactant ($p<0.001$).

Pulmonary mechanics

Despite the significant improvement in gas exchange, no significant changes in pulmonary mechanics are demonstrated in Fig. 2. Dynamic compliance (C_{DYN}) seemed to decrease at 30 min, but the change was not significant. Statistically, there was no significant changes in minute ventilation (V_E) over time. After 30 min, resistance of the respiratory system (R_{RS}) increased, it increased significantly 2 hr after surfactant instillation ($p<0.05$). Decrease in resistance of the respiratory system (R_{RS}) was observed at 6 hr. Therefore, no statistically significant meaning was found in R_{RS} changes as other pulmonary mechanics.

Fig. 3 showed the relationship among OI, (A-a)DO_2 and V_D/V_T ratio. Changes in OI and (A-a)DO_2 showed close correlation with changes in V_D/V_T ratio (correlation coefficient $r=0.21$, $p<0.05$) but not with changes in pulmonary mechanics.

DISCUSSION

It has been described that surfactant treatment in animal experiments resulted in an improvement of oxygenation, pulmonary mechanics, and homogeneity of the ventilation (14-16). The improvement in oxygenation observed with the therapy is now well documented. However, the relationship between improvement in oxygenation and the lung mechanics is not clear. Pulmonary changes after surfactant treatment have been attributed to an increase in FRC as shown by several studies (2, 3, 12, 17-19). This increase in FRC has generally been discussed in terms of recruitment and stabilization of new alveolar units during expiration, resulting in increased lung distension (3).

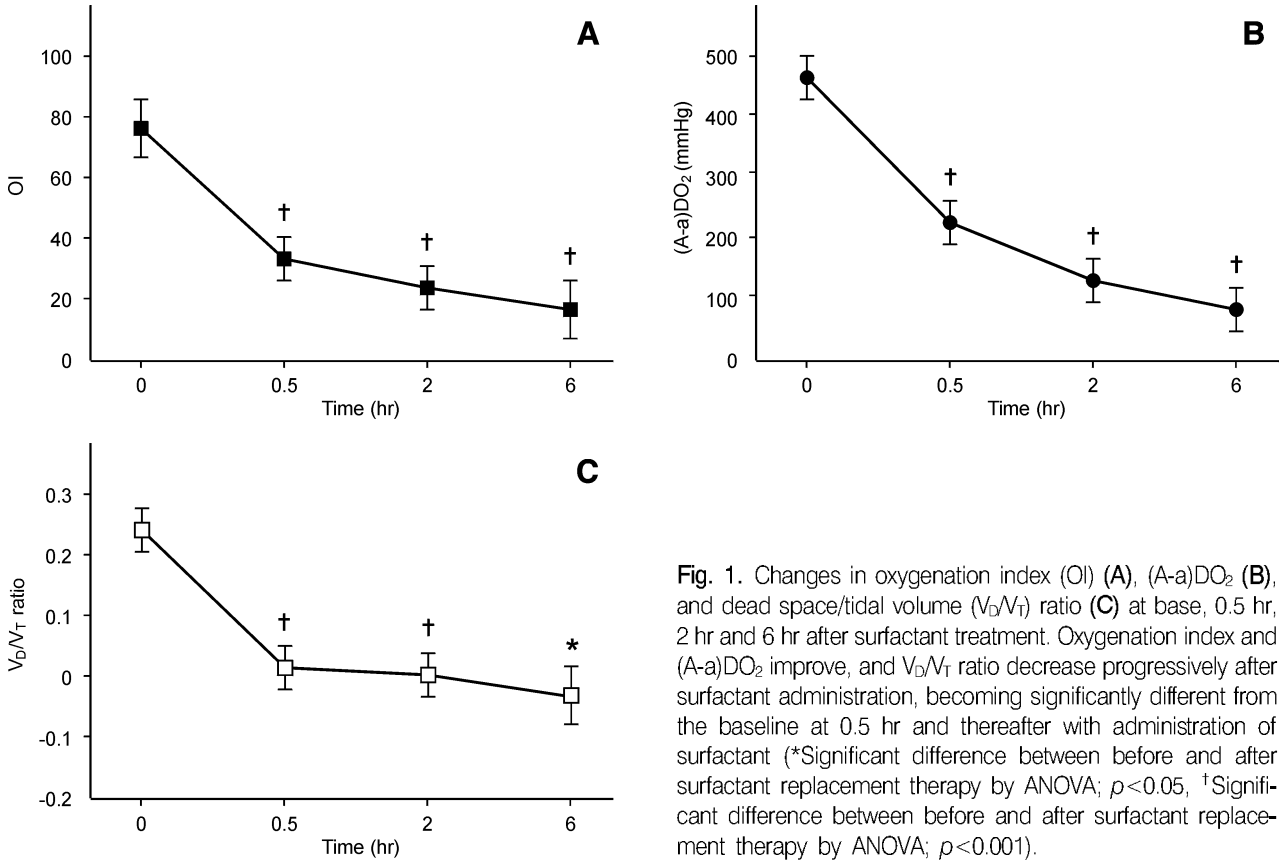

Fig. 1. Changes in oxygenation index (OI) (A), (A-a)DO_2 (B), and dead space/tidal volume (V_D/V_T) ratio (C) at base, 0.5 hr, 2 hr and 6 hr after surfactant treatment. Oxygenation index and (A-a)DO_2 improve, and V_D/V_T ratio decrease progressively after surfactant administration, becoming significantly different from the baseline at 0.5 hr and thereafter with administration of surfactant (*Significant difference between before and after surfactant replacement therapy by ANOVA; $p<0.05$, †Significant difference between before and after surfactant replacement therapy by ANOVA; $p<0.001$).

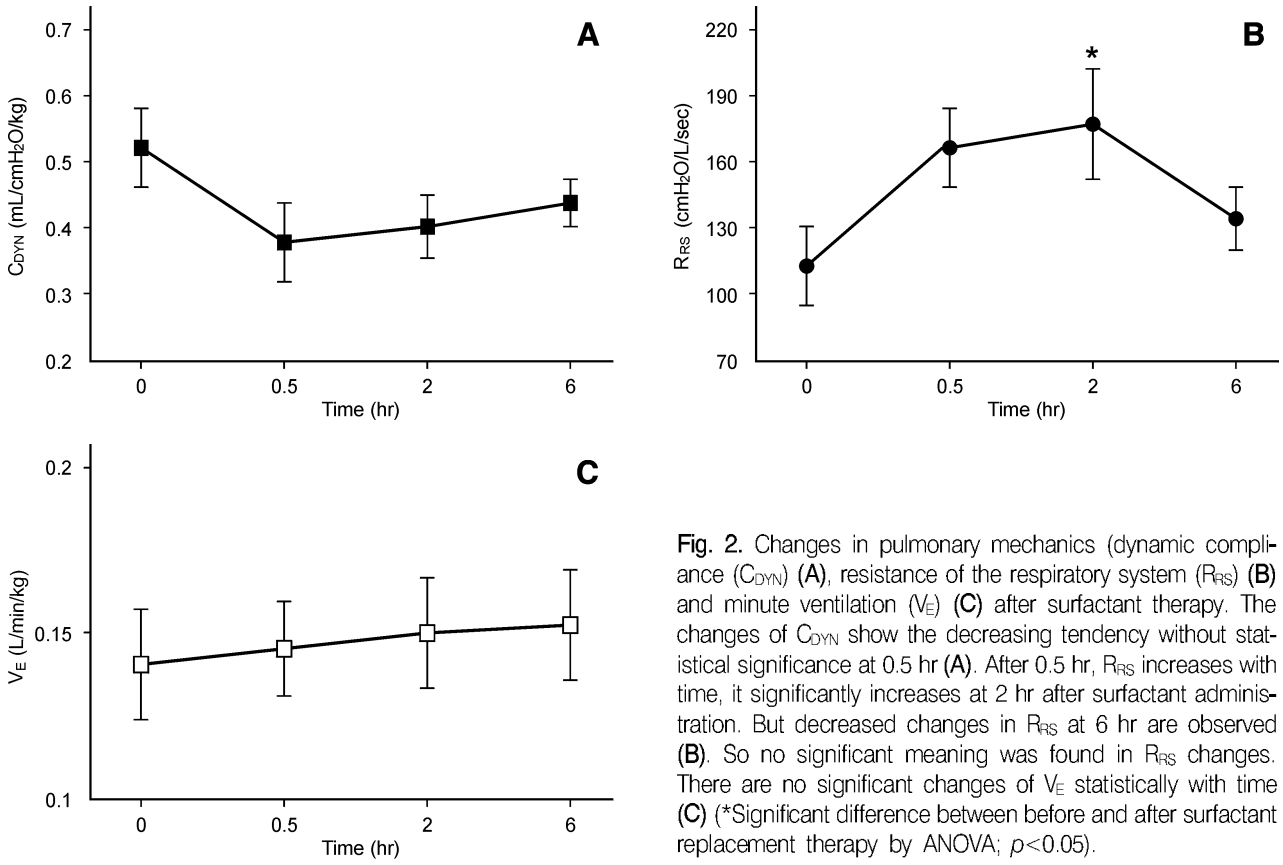

Fig. 2. Changes in pulmonary mechanics (dynamic compliance (C_{DYN}) (A), resistance of the respiratory system (R_{RS}) (B) and minute ventilation (V_E) (C) after surfactant therapy. The changes of C_{DYN} show the decreasing tendency without statistical significance at 0.5 hr (A). After 0.5 hr, R_{RS} increases with time, it significantly increases at 2 hr after surfactant administration. But decreased changes in R_{RS} at 6 hr are observed (B). So no significant meaning was found in R_{RS} changes. There are no significant changes of V_E statistically with time (C) (*Significant difference between before and after surfactant replacement therapy by ANOVA; $p<0.05$).

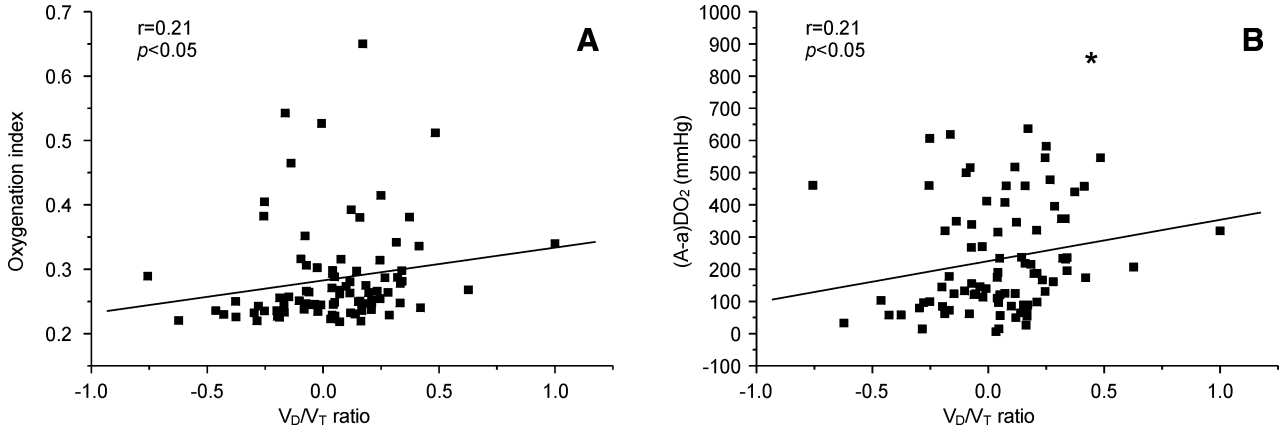

Fig. 3. Correlations between dead space/tidal volume (V_D/V_T) ratio and oxygenation index (OI) (A), and (A-a)DO_2 (B) after surfactant therapy, showing close correlation between parameters (r: correlation coefficient, $p<0.05$: significant difference between before and after surfactant replacement therapy by paired t test).

Cotton and colleagues (2) also have shown the recruitment of alveoli, measured as an increase in FRC as early as 30 min after surfactant administration, in a group of infants with RDS. They also observed a decrease in respiratory system compliance. They interpreted improvement of oxygenation as a result of stabilization of alveoli, not as a improved recruitment. They also interpreted increase in FRC as a result of stabilization of alveoli (2). A recruitment of previously atelectatic areas could be indicated by increased FRC (17-19), tidal volume (20), the arterial/alveolar PO_2 ratio (15, 21), and probably, decreased alveolar and physiologic dead space as well as by decreased V_D/V_T ratio or by reduced P(a-et)CO_2 (12).

Even though a new method for monitoring of efficacy of exogenous pulmonary surfactant replacement therapy would be offered, no one have determined the dead space

components in neonates with RDS and under pulmonary surfactant therapy. However, the dead space measurements are complicated; they require simultaneous volumetry and capnometry (12). To avoid these difficulties in assessment, we measured P(a-et)CO_2, which could provide a simple tool for long-time bedside monitoring in ventilated neonates. Assessment of pulmonary function in the sick, premature newborn infant needing intensive care has long been a challenge, not only because of the fragility of the newborns and their inability to cooperate, but also because of a limitation of available techniques (22).

We showed that the (A-a)DO_2 correlated closely with V_D/V_T ratio, possibly because both variables reflect the contribution of high ventilation/perfusion ratio (V_A/Q) regions. Thus, either V_D/V_T or (A-a)DO_2 can be used as the estimate of wasted ventilation (23).

Our results showed that OI and (A-a)DO_2 improved progressively after surfactant administration and became significantly different after 30 min. Six hr after surfactant administration, improvement in gas exchange was associated with a significant decrease in V_D/V_T ratio with time, and V_D/V_T ratio correlated closely with OI ($r=0.21$, $p<0.05$) and (A-a)DO_2 ($r=0.21$, $p<0.05$).

Some studies have reported that exogenous surfactant therapy in extremely premature infants with RDS improved dynamic compliance and gas exchange during mechanical breathing (24). Edberg and coworkers (25) found decreased compliance, increased resistance, decreased lung volume, and reduced gas mixing efficiency in very-low-birth-weight infants with RDS. However, on the other hand, some studies failed to demonstrate the significant changes in pulmonary mechanics during mechanical breathing; dynamic compliance, total pulmonary resistance, and tidal volume were not significantly altered 1 hr after therapy (19). Bowen and colleagues (1994) were unable to demonstrate a reduction in the arterial-alveolar N_2 tension difference with surfactant, indicating that ultimately the main effect of exogenous surfactant was not in optimizing the distribution of ventilation and perfusion in open air spaces but in the recruitment of new, previously collapsed air spaces (26).

From our study, pulmonary mechanics did not change significantly during the observation period. The dynamic compliance appeared to decrease at 30 min after surfactant therapy but increased with time. The respiratory resistance showed an increase at 2 hr ($p<0.05$), but decreased at 6 hr. OI and (A-a)DO_2 closely correlated with V_D/V_T ratio but not with pulmonary mechanics.

This observation suggests that surfactant replacement therapy produces an improvement in PaO_2, by recruitment of atelectatic alveoli with a balanced ventilation/perfusion ratio rather than by the redistribution of ventilation within already ventilated alveoli. Recruitment of atelectatic alveoli results in decreased physiologic dead space. We found that the V_D/V_T ratio, representing the amount of physiologic dead space, was the best indicator of the efficiency of the surfactant treatment for RDS infants.

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