Successful Direct Extubation of Very Low Birth Weight Infants From Low Intermittent Mandatory Ventilation Rate

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ABSTRACT. It is common practice to use endotracheal continuous positive airway pressure for various time periods up to 24 hours before attempting extubation in infants who are mechanically ventilated. A few studies in newborns have indicated that airway resistance is increased through small endotracheal tubes. This increases the work of breathing and the likelihood of subsequent ventilatory failure. In this study, 27 very low birth weight infants who were ½ to 28 days old at the time of extubation were randomly divided into two groups. One group of 13 study infants were extubated directly from intermittent mandatory ventilation rates of six to ten per minute, and the other 14 control infants were placed on continuous positive airway pressure through endotracheal tubes for six hours prior to an attempt to extubate. There was no difference between the two groups in gestational age, postnatal age, weight, or severity of lung disease at the time of extubation. All 13 study infants were successfully extubated without significant apnea or respiratory acidosis. Of the 14 control infants, only seven were successfully extubated; six infants had significant apnea and in one infant respiratory acidosis with pH 7.13 and P_{CO_2} 65 developed while receiving continuous positive airway pressure (13/13 *v* 7/14, $P < .005$). The seven infants who failed the preextubation trial of continuous positive airway pressure were later extubated from low intermittent mandatory ventilation rates without significant apnea or respiratory acidosis. Furthermore, slight CO_2 retention developed in the very low birth weight infants after six hours of continuous positive airway pressure but not after direct extubation (mean change $P_{CO_2} \pm SD$: 4.43 ± 3.87 *v* -0.23 ± 3.79 mm Hg, $P < .01$). This study demonstrates that the recommended preextubation trial of continuous positive airway pressure through an endotracheal tube is not only unnecessary but detrimental to very low birth weight infants, in whom more apnea and slight CO_2 retention develop probably because of increased airway resistance through small endotracheal tubes. *Pediatrics* 1987;80:409–414; *extubation, intermittent mandatory ventilation, very low birth weight infant, mechanical ventilation, continuous positive airway pressure, apnea, airway resistance.*

ABBREVIATIONS. CPAP, continuous positive airway pressure; VLBW, very low birth weight; IMV, intermittent mandatory ventilation

It is common practice to use continuous positive airway pressure (CPAP) of 2 to 3 cm H_2O for periods of up to 24 hours before attempting extubation in infants after mechanical ventilation.[1-8] Despite the lack of evidence to support its uses, this practice is recommended to ensure that the patient will not become exhausted without mechanical ventilation.[7] We observed several very low birth weight (VLBW) infants who were stable while receiving intermittent mandatory ventilation (IMV) rates of less than ten per minute, and who did not tolerate preextubation trials of CPAP, but who tolerated self-extubation from low IMV rates. It has been shown that airway resistance is significantly increased through small endotracheal tubes compared with infants' natural airways[9-11] and that ventilatory muscle fatigue can be caused by increased work of breathing resulting in ventilatory failure.[11-13]

We hypothesize that the use of CPAP via small endotracheal tubes for preextubation trials may increase airway resistance and critically increase work of breathing. This may cause ventilatory muscle fatigue and subsequent failure to extubate VLBW infants. Therefore, we studied the success

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rates of extubation with and without preextubation trials of CPAP.

MATERIALS AND METHODS

All infants with birth weights less than 1,250 g who were ventilated for more than 12 hours but less than 28 days were eligible for this prospective study. They were ventilated through endotracheal tubes of 2.5 mm by Bird Mark VII (Bird Corporation, Palm Springs, CA) or Sechrist (Sechrist Industries, Inc, Anaheim, CA) pressure-limited ventilators in a conventional manner with solid state electronic monitors to confirm ventilatory settings. Any infant who had a neuromuscular disorder or who was receiving CNS depressants was excluded from the study.

Infants were weaned from mechanical ventilators using usual clinical criteria until the following settings were obtained: flow rate $\leq$8 L/min, peak inspiratory pressure <16 cm H_2O, inspiratory time $\leq$0.5 seconds, positive end-expiratory pressure 3 cm H_2O ($\geq$1 kg trial weight) or 2 cm H_2O (<1 kg trial weight), and IMV rate six to ten cycles per minute. Only at the time when the attending neonatologist determined that the infant was ready for extubation was the patient randomly assigned to either the study or control group.

Thirteen infants were directly extubated from the low ventilatory settings (study) and 14 infants received preextubation trials of CPAP for six hours before extubation (control). The amount of CPAP used in each control infant was the same as that of the pretrial positive end-expiratory pressure. All control infants and ten study infants were randomized and placed on the test when they were determined to be stable at an IMV rate of six per minute and three other study infants at an IMV rate of eight or ten per minute. Patient characteristics are summarized in Table 1. During six hours following discontinuation of IMV, nursing staff were assigned

TABLE 1. Patient Characteristics

Patient Characteristic	Control Infants	Study Infants
Patients (No.)	14	13
Birth wt (mean g ± SD)	990 ± 118	1,085 ± 101
Trial wt (mean g ± SD)	963 ± 99	1,042 ± 108
Gestational age (mean wk ± SD)	28.5 ± 2.2	28.9 ± 1.7
Postnatal age (mean d ± SD)	7.1 ± 7.2	9.2 ± 8.5
Pretrial Pco_2 (mean mm Hg ± SD)	35.4 ± 7.8	38.1 ± 9.8
Pretrial Po_2/Fio_2 (mean mm Hg/% ± SD)	2.4 ± 0.95	2.85 ± 1.16
Patients theophylline used (n)	12	11

at all times to the infants for observation of apnea, bradycardia, and alteration in oxygen requirement determined by transcutaneous Po_2 monitoring to maintain the Pao_2 within the range of 50 to 70 mm Hg. Blood gases were analyzed either from blood obtained by heel stick or indwelling arterial catheter but not both for any infant at ½, one, and six hours and at least one more between one and six hours during the test period. A chest x-ray film was taken two hours after extubation.

ΔPco_2 was defined as the difference in Pco_2 compared with preextubation Pco_2, ie, ΔPco_2 = trial Pco_2 − pretrial Pco_2. Likewise, $\%Po_2/Fio_2$ was defined as (trial Po_2/Fio_2 ÷ pretrial Po_2/Fio_2) × 100.

Apnea was defined as a cessation of spontaneous breathing for $\geq$20 seconds by chest wall impedance. Bradycardia was defined as a heart rate of <100 beats per minute as measured by R-R interval. All bradycardia was considered to be associated with apnea.

The following criteria were used to initiate resumption of IMV: (1) two or more episodes of severe apnea/bradycardia requiring vigorous stimulation within 30 minutes, (2) any profound apnea/bradycardia that would respond only to intermittent positive pressure ventilation, or (3) respiratory acidosis with pH <7.3.

Infants who failed extubation in one arm of the study were reventilated at levels of support that provided normal blood gas values. They were again weaned to the study criteria. Patients were then assigned to the alternative treatment arm (crossover).

This study protocol was approved by The Research and Human Subjects Review Committee of Santa Clara Valley Medical Center. Informed consent was obtained from the parents of the infants. The numbers of successfully extubated infants were compared between the two groups using χ^2 analysis. The apnea density (episodes per hour) was also observed and compared between the two groups using t test and χ^2 analysis. The changes in respiratory rate, Pco_2, and the Po_2/Fio_2 during the six hours of the study, ie, during CPAP and after direct extubation, were analyzed using Student's t test.

RESULTS

Gestational age, postnatal age, weight, Pco_2, and alveolar-arteriolar O_2 gradient as measured by the Po_2/Fio_2 at the time of trial were similar between the two groups (Table 1). Birth weight but not trial weight of the study group infants was greater than that of the control group. All 13 infants directly extubated from IMV tolerated extubation according to the study protocol (Fig 1). Among 14 infants who first received CPAP via endotracheal tubes prior to extubation, seven tolerated the six-hour trial prior to extubation and subsequently tolerated extubation; significant apnea developed in six infants and significant respiratory acidosis with capillary pH 7.13 and Pco_2 65 mm Hg developed after two hours of CPAP in one infant (a change from pretrial capillary pH 7.34 and Pco_2 41 mm Hg). Thus, direct extubation was associated with a significantly higher rate of successful extubation (13/13 *v* 7/14, $\chi^2 = 8.7$, $P < .005$). All seven infants who could not be extubated were reventilated at the time failure criteria were met; of these seven infants, all eventually were successfully extubated directly from IMV. Three of the seven infants who could not be extubated from CPAP were able to be weaned to extubation criteria within 24 hours and successfully extubated directly from IMV. Their results when combined with above data also showed the same findings (16/16 *v* 7/14, $\chi^2 = 10.43$, $P < .002$).

No significant changes were noted in postextubation chest roentgenograms, and there were no significant changes in respiratory rates in any group during the trial. Changes in Pco_2 and the Po_2/Fio_2 ratio in both groups of infants between pretrial and trial measurements are shown in Table 2. No significant differences were noted in the absolute Pco_2 and Po_2/Fio_2 values between control and study infants. However, control infants who could not eventually be extubated from CPAP had higher Pco_2 values at ½ and one hour compared with infants who tolerated CPAP (45.8 ± 7.4 *v* 27.3 ± 0.6 mm Hg, $P < .05$; 45.4 ± 4.1 *v* 30.7 ± 6.4 mm Hg, $P < .03$, respectively) and with study infants (45.8 ± 7.4 *v* 36.8 ± 11.2 mm Hg, $P < .05$; 45.4 ± 4.1 *v* 37.2 ± 8.2 mm Hg, $P < .01$, respectively). The

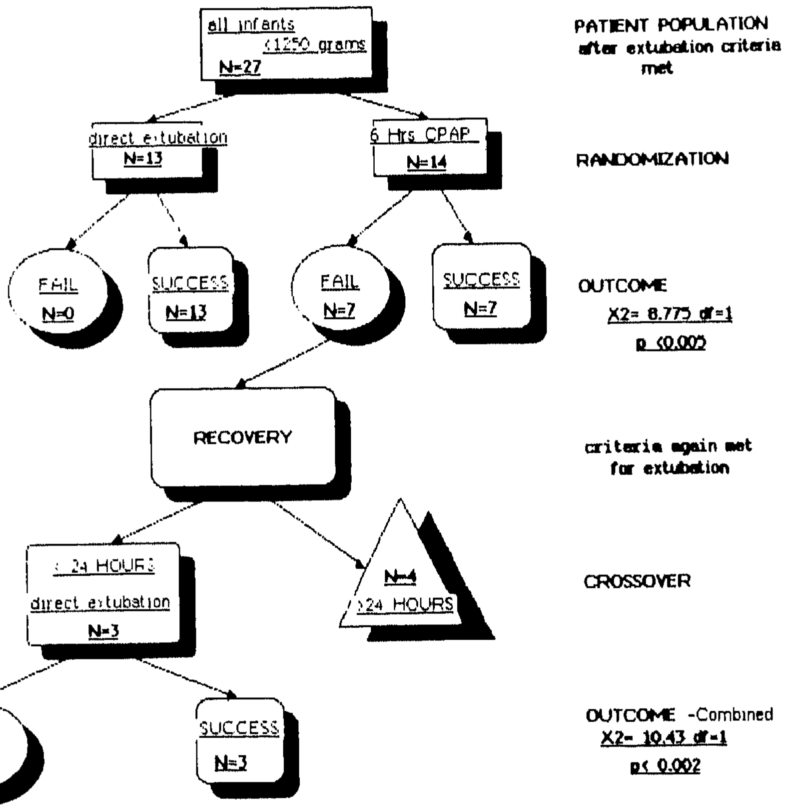

Fig 1. Experimental flow chart.

TABLE 2. Pco_2 and Po_2 to Fio_2 Ratio Changes Between Pretrial and Trial Measurements*

Hours	Control Infants			Study Infants		
	n	Pco_2 (mm Hg)	Po_2/Fio_2 (mm Hg/%)	n	Pco_2 (mm Hg)	Pao_2/Fio_2 (mm Hg/%)
Pretrial	14	34.7 ± 8.6	2.45 ± 0.94	13	38.1 ± 9.8	2.86 ± 1.16
½	10	40.2 ± 9.0	1.86 ± 0.48	10	36.8 ± 11.2	2.29 ± 0.84
1	10	41.2 ± 11.7	2.03 ± 0.58	11	37.2 ± 8.2	2.44 ± 0.97
6	6	36.7 ± 8.4	2.48 ± 1.24	10	37.4 ± 9.4	2.70 ± 1.39

* Results are means ± SD.

same trend could not be statistically demonstrated thereafter because only two control infants who could not be extubated from CPAP remained on CPAP beyond one hour of trial.

Because blood gas values were measured from either capillary or arterial specimens from each infant, relative differences in PCO_2 (ΔPCO_2) values and PO_2/FiO_2 ($\% PO_2/FiO_2$) ratios were also evaluated (Fig 2). As shown in Fig 2, the ΔPCO_2 values of the entire control group was significant at all intervals compared with pretrial PCO_2 values. Arterial ΔPCO_2 value in the control group was also significant at ½ and six hours after CPAP in spite of a limited number of arterial blood gas measurements. The differences were more pronounced when compared with the study group (at ½ hour $P < .001$, at one hour $P < .01$, and at six hours $P < .01$). Arterial ΔPCO_2 was also significantly larger in the control than in the study group at six hours ($P < .05$). The study group PCO_2 values were never elevated compared with pretrial values.

Although large alterations in alveolar-arterial O_2 gradient as measured by the $\% PO_2/FiO_2$ ratio were not seen, they were statistically different. The $\% PO_2/FiO_2$ decreased somewhat at ½ and one hour after extubation in study infants compared with pretrial values (Fig 2). This was confirmed by arterial blood gas measurement, which remained significantly low at six hours after extubation although less significantly. The control group $\% PO_2/FiO_2$ was decreased but not significantly at all times after initiation of CPAP via endotracheal tube, but a small number of arterial blood gas measurements showed significant decreases in $\% PO_2/FiO_2$ ratios at ½ hour after initiation of CPAP.

Apnea was the most common cause of respiratory failure during the CPAP trials (Fig 3). The incidence of apnea overall was not altered, but apnea

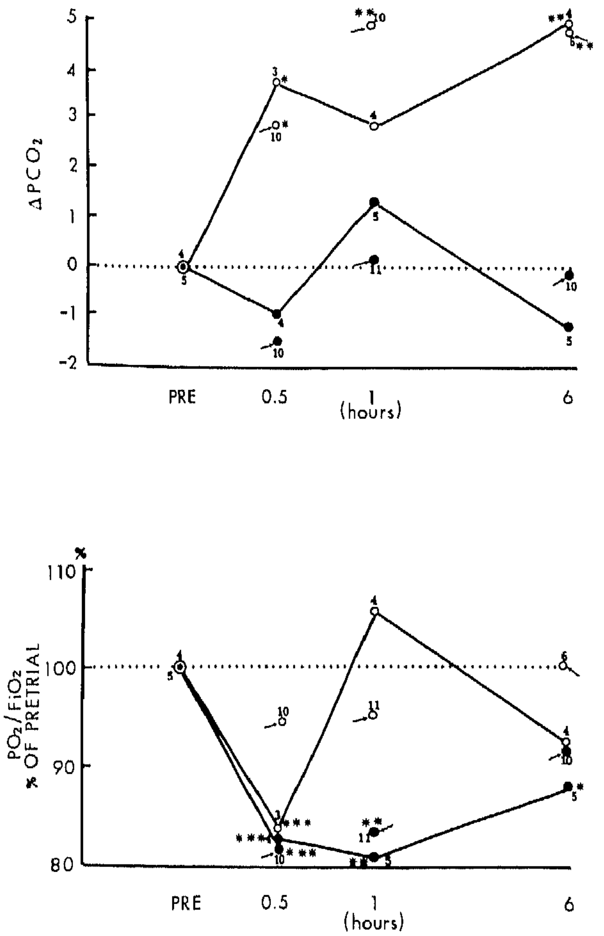

Fig 2. Mean ΔPCO_2 and $\% PO_2/FiO_2$ values, study v control infants. Top, ΔPCO_2 = trial PCO_2 − pretrial PCO_2. Bottom, $\% PO_2/FiO_2 = (PO_2/FiO_2 \div \text{baseline } PO_2/FiO_2) \times 100$. ○, continuous positive airway pressure via endotracheal tube prior to extubation; ●, direct extubation from low intermittent mandatory ventilatory rates; numerals, numbers of determinations at each time; circles connected with lines, values from arterial blood gas measurements; circles pointed by arrows, values from both arterial and capillary blood gas measurements. $^{*}P \leq .05$ compared with baseline value; $^{**}P < .01$ compared with baseline value; $^{***}P < .001$ compared with baseline value. PCO_2 of control group was significantly higher than that of study group during test period.

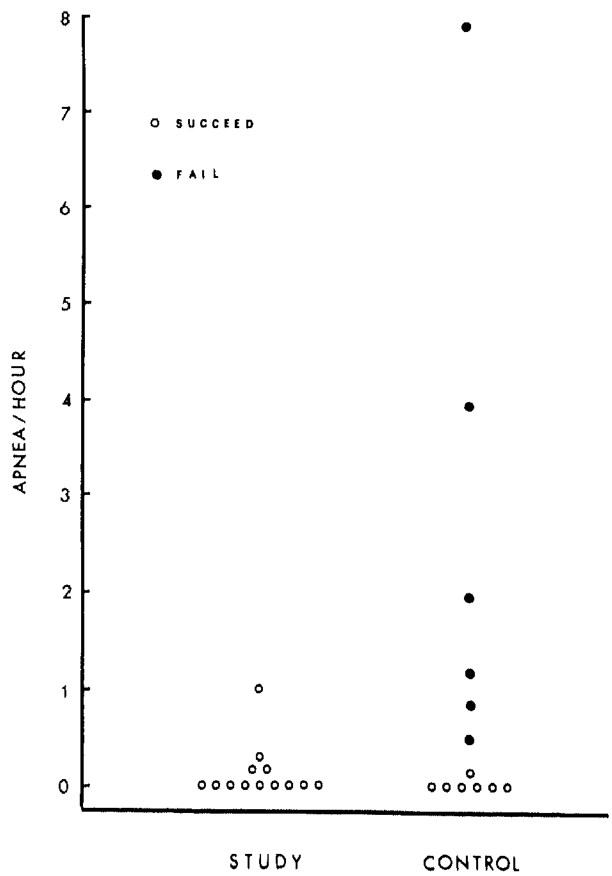

Fig 3. Apnea density, control v study infants. Number of moderate to severe apnea ($\chi^2 = 5.84$, $df = 1$, $P < .025$). Apnea density > 0.4 episodes per hour ($\chi^2 = 4.89$, $df = 1$, $P = .03$).

requiring any stimulation was more common in control infants. Apnea density greater than 0.4 episodes per hour was also more common in control infants.

Of 27 infants, 23 received therapeutic doses of theophylline prior to reaching study entry criteria. Of the four infants not receiving theophylline, two were assigned to the control group and the other two to the study group. Neither control infant could be extubated from CPAP, and both study infants tolerated direct extubation. If all infants who did not receive theophylline prior to the trial were excluded, the success rate would be still significantly different (11/11 *v* 7/12, $\chi^2 = 5.86$, $P < .02$).

Control infants who could not be extubated from CPAP had a greater birth weight than those control infants who could (mean birth weight 1,031 *v* 950 g; $t = 2.93$, $P < .001$) but were similar in weight to study infants.

DISCUSSION

The use of CPAP of two to three cm H_2O via endotracheal tube for a period of up to 24 hours before attempting extubation has been recommended for infants after mechanical ventilation.[1-8] This practice has been suggested to ensure that the patient will not become exhausted without mechanical ventilation.[7] The current study demonstrated that the recommended use of CPAP for a preextubation trial is not only unnecessary but detrimental to VLBW infants prior to extubation. CPAP via an endotracheal tube in VLBW infants was associated with mild CO_2 retention after six hours of CPAP even in those infants who tolerated the treatment. In infants who could not eventually be extubated after CPAP, the increase in PCO_2 value was dramatic during one hour of CPAP, but this could not be demonstrated thereafter because of limited numbers of blood gas measurements in control infants who remained on CPAP for more than one hour. These findings are consistent with previous studies by Fox et al[3] in spontaneously breathing infants before and after extubation. In one study, those infants who could not be extubated from CPAP tended to have higher PCO_2 values associated with a significantly higher airway resistance. In that study, those infants who failed extubation were considerably smaller than those who succeeded. The findings of our study duplicated the increase in PCO_2 seen in control infants who could not be extubated; even control infants who could be extubated had slightly elevated PCO_2 values. Elevated PCO_2 values during CPAP would suggest that CPAP increases airway resistance and the work of breathing.[9,10] We have not measured work of breathing in VLBW infants, but LeSouef et al[11] demonstrated that airway resistance is significantly increased through endotracheal tubes compared with newborn infants' natural airways which increased diaphragmatic work.[11]

In our study, all VLBW infants were either placed on CPAP or directly extubated from IMV rates of six to ten per minute. This sudden removal of IMV was initially suggested by Gregory,[5] which may be more aggressive treatment than that used by others who use IMV rates of less than six per minute before preextubation trials of CPAP.[4,14] We do not believe that our method of weaning of VLBW infants from IMV of six to ten breaths per minute significantly altered the success rate of extubation between the two groups, because we used the same weaning method from IMV in both groups of infants after they were determined to be stable in similar ventilatory settings. In addition, they were randomly assigned to either group only when the primary physician determined that they were ready to be extubated.

Absolute values of PO_2/FIO_2 during the trials did not differ significantly from pretrial values in this study. However, in our VLBW infants low $\%PO_2/FIO_2$ values were found during the entire six hours after direct extubation but not during CPAP via an endotracheal tube except at 30 minutes after initiation of CPAP when arterial $\%PO_2/FIO_2$ values were low. This is contrary to the results of previous studies on larger newborn infants whose PO_2 values were unchanged during small amounts of CPAP compared with that after extubation.[1,2] The results of this study suggest that, in VLBW infants, even CPAP of 2 to 3 cm H_2O may prevent subsegmental ventilation/perfusion abnormalities which may be associated with the lowered functional residual capacity and lowered PO_2/FIO_2 ratios. Further study is warranted to determine "physiologic" CPAP of VLBW infants by comparing functional residual capacity during IMV with low positive end-expiratory pressure and after extubation.

Failure of VLBW infants to tolerate CPAP was caused most frequently by apnea rather than respiratory acidosis. It is not possible to compare this finding with previously published studies because the criteria for extubation failure were not mentioned.[1-4] Because the elevation of PCO_2 was modest even in most control infants who were not to be extubated from CPAP, we speculate that the proximate cause of apnea in infants failing low amounts of CPAP via endotracheal tubes is an increased work of breathing due to increased airway resistance.[11] Those infants in whom the work of breathing is critically increased would presumably fail because of fatigue of the ventilatory musculature.[11-13]

In summary, this study demonstrates a deleterious effect of CPAP when applied via an endotracheal tube in VLBW infants. CPAP produces an increase in Pco_2 which is associated with apnea and with respiratory failure. Direct extubation is associated with a decrease in Po_2/Fio_2 ratio and an increase in alveolar-arterial O_2 gradient. Clinically, this can be compensated by a small increase in Fio_2. We believe that the effect of CPAP is to increase airway resistance and work of breathing, which in some instances is sufficient to produce ventilatory muscle fatigue and apnea. Thus, our recommendation and current practice is to directly extubate all infants weighing less than 1,250 g from IMV of six breaths per minute rather than after a trial of CPAP via the endotracheal tube.

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CONFUSING ± SIGN

We suggest that all journals discontinue the use of the ± sign; in all instances it should be clearly indicated whether SD or SE is quoted; the SE should not be used to indicate the variability of a set of observations; and the reporting of appropriate ranges or confidence intervals should be shown directly.

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From Altman DG, Gardner MJ: Presentation of variability. *Lancet* 1986;2:639.