A Randomized, Controlled Trial Comparing Two Different Continuous Positive Airway Pressure Systems for the Successful Extubation of Extremely Low Birth Weight Infants

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ABSTRACT. *Objective.* **To determine whether the use of the Infant Flow continuous positive airway pressure (IF CPAP) system reduces the rate of extubation failure among extremely low birth weight (ELBW) infants (infants with birth weight <1000 g) when compared with conventional CPAP delivered with a conventional ventilator and nasal prongs.**

Methods. **A prospective, unmasked, randomized, controlled clinical trial was conducted in 162 eligible intubated ELBW infants who were hospitalized in 2 intensive care nurseries in Winston-Salem, North Carolina, between July 1997 and November 2000. Successful extubation was defined as no need for reintubation for any reason for at least 7 days after the first extubation attempt.**

Results. **The individual extubation success rates were 61.9% (52 of 84) in the conventional CPAP group and 61.5% (48 of 78) in the IF CPAP group. There were no significant differences in the extubation success rate in any birth weight subset between the 2 cohorts. The most common cause of extubation failure was apnea/bradycardia. Infants who were randomized to IF CPAP had fewer days on supplemental O_2 and shorter hospital stays.**

Conclusions. **Extubation failure is a common problem, occurring in nearly 40% of ELBW infants who require mechanical ventilation. IF CPAP was as effective but no more effective than conventional CPAP in preventing extubation failure among ELBW infants. New strategies are needed to identify predictors of extubation success and to treat apnea/bradycardia, the most common cause of extubation failure, thereby reducing the likelihood of prolonged intubation in this high-risk cohort of premature infants. *Pediatrics* 2003;112:1031–1038; *continuous positive airway pressure, extremely low birth weight, extubation, Infant Flow CPAP.***

ABBREVIATIONS. ELBW, extremely low birth weight; BPD, bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; IF, Infant Flow; BW, birth weight; FIO_2, fraction of inspired oxygen; NIPPV, nasal intermittent positive pressure ventilation.

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Prolonged intubation and mechanical ventilation of extremely low birth weight (ELBW) infants is associated with upper airway trauma and development of bronchopulmonary dysplasia (BPD).[1] Extubation of ELBW infants to nasal continuous positive airway pressure (NCPAP) has been shown to decrease the need for reintubation, thereby reducing these ventilator-associated risks.[2–4] CPAP has also been shown to reduce atelectasis, improve ventilation-perfusion matching, and reduce apnea of prematurity.[5,6]

Various systems for delivering CPAP are available, but there is little evidence for the superiority of one system over another.[7–10] The Infant Flow (IF) CPAP system (Electro Medical Equipment Ltd, Sussex, England), invented in Sweden in the 1980s by Moa and Nielson and approved for use in the United States in 1995, uses a dedicated driver and generator with unique fluid mechanics to adjust the gas flow throughout the respiratory cycle. The fluid flip action of the IF generator has been reported to assist spontaneous breathing and reduce the work of breathing by reducing expiratory resistance and maintaining a stable airway pressure throughout respiration.[11–14] However, published reports on the efficacy or superiority of IF CPAP have been confined to laboratory studies using a test lung or clinical studies of brief duration with measurements of pulmonary function as the only endpoints.[11–17] Nevertheless, this technologically novel device is gaining widespread acceptance in European and North American nurseries[18] without supporting evidence from randomized, controlled clinical trials of the efficacy or superiority of IF CPAP versus other CPAP delivery systems for facilitating extubation or preventing the need for mechanical ventilation.

The present study was designed to test the hypothesis that the use of the IF CPAP system will reduce the extubation failure rate, defined as no need for reintubation within 7 days of extubation, among ELBW infants by 50% (from 40% to 20%) when compared with conventional CPAP delivered by a mechanical ventilator and INCA prongs (Ackrad Laboratories, Inc, Cranford, NJ). Secondary outcome measures included death, survival without BPD, and the length of hospital stay.

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METHODS

A retrospective chart review of 30 infants who had birth weight (BW) ≤1000 g and were treated in 2 intensive care nurseries under the management of neonatologists from Wake Forest University School of Medicine demonstrated a 40% extubation failure rate, consistent with the published literature.[3,5,19,20] Power analysis indicated that a cohort of 162 infants would be needed to demonstrate a 50% reduction in extubation failure from 40% to 20%, with a power of 0.8 and an α-error of 0.05.

Patients, Randomization, and Study Criteria

A prospective, unmasked, randomized, controlled trial of IF CPAP versus conventional CPAP for successful extubation was initiated in 1997 in consecutive eligible ELBW infants in the intensive care nurseries at Brenner Children's Hospital and Forsyth Medical Center in Winston-Salem, North Carolina. Between July 1997 and November 2000, 162 ELBW infants were assigned using a table of random numbers and sealed opaque envelopes to either IF CPAP or conventional CPAP and stratified into 3 BW blocks as follows: ≤600 g, 601 to 800 g, and 801 to 1000 g. Randomization occurred after informed consent had been obtained from the infant's parent or legal guardian and close to the time of the infant's first extubation attempt. In the rare circumstance when an infant was randomized but not immediately extubated, the randomization card was marked with indelible ink and kept in the study notebook at the respiratory therapy desk in the nursery until extubation occurred. CPAP was delivered per randomization assignment with either IF CPAP or "conventional CPAP" using INCA prongs and a time-cycled, pressure-limited ventilator. Our study design precluded crossover between the CPAP delivery systems.

The primary endpoint was a reduction in the percentage of infants who failed extubation, defined as no need for reintubation for 168 hours (7 days). Secondary endpoints were death, survival without BPD, number of days on CPAP, days on supplemental oxygen, and length of hospitalization. Potential confounders of extubation success, such as necrotizing enterocolitis, patent ductus arteriosus, sepsis, and intracranial hemorrhage, were also compared between the 2 groups.

Study entry criteria included BW ≤1000 g, need for mechanical ventilation, first extubation attempt, and signed parental consent. Exclusion criteria included major chromosomal anomalies, known airway anomalies, neuromuscular disorders, other major congenital malformations, and participation in a concurrent randomized clinical trial. Regardless of gestational age or BW, the suggested criteria for a mandatory trial of extubation included respiratory stability for 12 to 24 hours on minimal ventilatory settings, defined as mean airway pressure ≤5 cm on conventional mechanical ventilation or ≤7 cm on high-frequency ventilation, with pH ≥7.25, P_{CO_2} ≤65 torr, and fraction of inspired oxygen (F_{IO_2}) ≤0.3. Infants could be extubated from higher levels of support at attending discretion. The study protocol included administration of methylxanthine therapy before extubation. Infants were extubated to CPAP of 4 to 6 cm H_2O and were to remain on their assigned CPAP device for a minimum of 24 hours. CPAP was discontinued when the infants were stable on CPAP of 4 cm H_2O and F_{IO_2} ≤0.3 and the patient was having <5 apneic episodes per day.

Extubation failure was defined as the need for reintubation and mechanical ventilation for any reason within 168 hours of initial extubation. Patients were reintubated when they exhibited arterial hemoglobin saturations <88% while receiving F_{IO_2} ≥0.50, arterial CO_2 ≥65 torr with arterial pH <7.25, the need for CPAP >8 cm of H_2O, or recurrent significant apnea or bradycardia requiring bag-mask ventilation or vigorous stimulation. Infants who deteriorated after CPAP was discontinued were placed back on their initially assigned CPAP system unless immediate reintubation and mechanical ventilation was deemed necessary. Infants who failed their initial extubation attempt and required reintubation were extubated on subsequent attempts to the CPAP system to which they were initially randomized.

Cranial ultrasounds were performed on all infants on days 7 and 42 of life or more frequently as clinically indicated. Cranial ultrasounds were read by radiologists who were masked to the infants' randomization assignment. Radiographs, blood cultures, and echocardiography were done when clinically indicated. Maternal and infant demographic data, birth history, chest radiographs, cranial ultrasound reports, pharmacy records, and respiratory data were collected.

Study Definitions

Air leaks were documented by evidence of pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema on chest radiograph. Patent ductus arteriosus was documented by echocardiography. Intraventricular hemorrhage was determined according to Papile's classification of cranial ultrasound findings of echodensity in the germinal matrix or ventricular extension. Periventricular leukomalacia was defined by development of periventricular cysts identified by cranial ultrasound. Sepsis was diagnosed by a positive blood culture or suggestive clinical and laboratory presentation resulting in a clinical decision to treat with antibiotics for at least 7 days despite the absence of a positive blood culture. Necrotizing enterocolitis was defined as stage 2 or higher as per modified Bell's criteria.[21] Retinopathy of prematurity was defined as per the international classification.[22] BPD was defined as an oxygen dependence at 36 weeks' postmenstrual age in association with characteristic radiograph changes.

Statistical Methods and Data Analysis

Patient characteristics were summarized using observed proportions and means, standard deviations, and ranges. Comparisons between categorical outcomes and patient characteristics between the 2 CPAP groups were tested using Fisher exact test. Comparisons between continuous measures between the 2 CPAP groups were tested using the *t* test. Time to reintubation among the infants with extubation failure in each CPAP group was depicted using Kaplan-Meier plots, and comparison of time on CPAP was tested using the log-rank statistics.

Ethics

The research protocol for this study was approved by the Institutional Review Boards of the Wake Forest University School of Medicine and Forsyth Medical Center. The procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

RESULTS

Between July 1997 and November 2000, 500 infants who were ≤1000 g at birth were admitted to the intensive care nurseries at Brenner Children's Hospital and Forsyth Medical Center (Fig 1). Of these, 162 infants fulfilled the study entry criteria and were enrolled in our study. Among the 338 nonenrolled infants, 33% (n = 103) died before their first extubation attempt, 23% (n = 78) were extubated before consent was obtained, 10% (n = 33) of parents refused participation, 25% (n = 87) were ineligible either because they were enrolled in a competing study (15%, n = 52) or they met the other ineligibility criteria (10%; n = 35). In 7% (n = 23), there were other reasons for nonenrollment (study enrollment ended before extubation, nares were too small, physician chose IF CPAP, error of enrollment, or consent deferred because of maternal illness or unavailability), and 4% (n = 14) of infants were transferred to another hospital (Fig 1).

Among the 162 patients enrolled, 84 infants were randomized to receive conventional CPAP and 78 infants were randomized to receive IF CPAP postextubation. There were no statistical differences between the 2 groups with regard to any of the baseline maternal characteristics (Table 1). Likewise, there was no significant difference in any of the baseline infant characteristics (Table 2).

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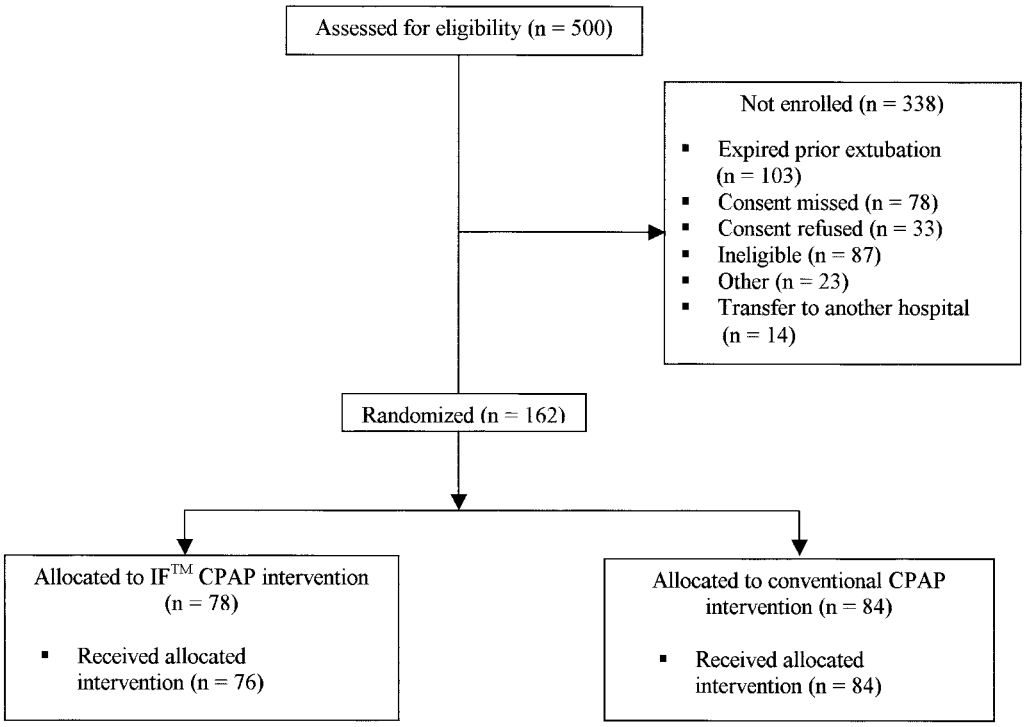

Fig 1. Flow diagram of ELBW infants who were screened and randomly assigned to the IF CPAP and conventional CPAP groups, adapted from the Consort Statement.[23] The number of infants excluded and the reasons for nonenrollment are provided. Two infants in the IF CPAP group did not receive the allocated treatment (1 infant died after randomization but before extubation, and 1 was extubated directly to nasal cannula). Statistical analysis was by "intention to treat."

TABLE 1. Maternal Baseline Characteristics

Maternal Characteristics	Conventional CPAP (n = 84)	IF CPAP (n = 78)
Age (y)		
Mean ± SD	26.7 ± 6.2	25.5 ± 6
Range	14–40	14–39
Ethnicity (n [%])		
White	39 (46%)	46 (59%)
Black	38 (45%)	28 (36%)
Asian	1 (0.1%)	1 (0.1%)
Hispanic	4 (0.5%)	2 (0.2%)
Other	2 (0.2%)	1 (0.1%)
Antenatal steroids (n [%])		
Complete	38 (45.2%)	36 (46.1%)
Incomplete	21 (25.0%)	16 (20.5%)
None	22 (26.2%)	21 (26.9%)
Unknown	3 (3.6%)	5 (6.4%)
Chorioamnionitis (%)	12 (15%)	11 (13%)
Preeclampsia/eclampsia (n [%])	22 (26%)	16 (20%)
Cesarean section (n [%])	46 (54.7%)	49 (62.8%)

SD indicates standard deviation.

Per study protocol, methylxanthine administration should have been given before the initial extubation attempt. However, 10 infants were extubated before methylxanthine administration. Of these 10 infants, all 3 in the IF CPAP group and 4 of the 7 infants in the conventional CPAP group were extubated successfully; the remaining 3 infants in the conventional CPAP group failed extubation because of a need for >8 cm H_2O CPAP to maintain arterial hemoglobin saturations above 88%.

To address other potential confounders of extubation failure, we compared the rates of other complications of prematurity. As shown in Table 3, the 2 groups were comparable with respect to their clinical outcomes. Fewer infants received bronchodilators in the IF CPAP group (8%) compared with conventional CPAP group (19%), which did reach statistical significance (P = .04).

The overall extubation success rate in the combined cohort was 61.7%. There were no significant differences between the infants who were randomized to the IF system and the conventionally delivered CPAP system with respect to the primary outcome variable of successful extubation. Among the infants in the IF CPAP group, 61.5% (48 of 78 patients) remained extubated, whereas in the conventional CPAP group, 61.9% (52 of 84 patients) were extubated successfully. Both of these results approx-

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TABLE 2. Infant Baseline Characteristics

Infant Characteristics	Conventional CPAP (n = 84)	IF CPAP (n = 78)
BW (g)		
Mean ± SD	755 ± 155	744 ± 123
Range	406–1000	440–985
Gestational age (wk)		
Mean ± SD	25.7 ± 2.0	25.9 ± 1.5
Range	22–31	23–29
Male sex (n [%])	35 (42%)	33 (42%)
Singleton (n [%])	63 (75%)	64 (82%)
CRIB score		
Mean ± SD	7.4 ± 4.4	7.9 ± 3.8
Range	1–17	1–16
Surfactant therapy (n [%])	82 (98%)	78 (100%)
1-minute Apgar score (mean ± SD)	4.2 ± 2.4	4.5 ± 2.5
5-minute Apgar score (mean ± SD)	6.5 ± 2.1	6.3 ± 2.2

CRIB indicates Clinical Risk Index for Babies.

TABLE 3. Clinical Outcomes in the Conventional CPAP and IF CPAP Groups

Outcome	Conventional CPAP (n = 84)	IF CPAP (n = 78)
PDA treated with indomethacin (n [%])	48 (59%)	43 (55%)
PDA ligation (n [%])	13 (15%)	6 (8%)
Sepsis (n [%])	70 (83%)	66 (85%)
Postnatal steroids for BPD (n [%])	53 (63%)	44 (56%)
Diuretics (n [%])	57 (68%)	46 (59%)
Bronchodilators (n [%])	16 (19%)	6 (8%)
NEC (n [%])	15 (18%)	18 (23%)
PIE (any grade; n [%])	17 (20%)	20 (26%)
Gross air leak (n [%])	10 (12%)	4 (5%)
ROP (n [%])	72 (86%)	60 (77%)
Surgery (n [%])	9 (11%)	6 (8%)
IVH (grades 1 and 2; n [%])	17 (20%)	13 (17%)
IVH (grades 3 and 4; n [%])	14 (17%)	11 (14%)
PVL (n [%])	5 (6%)	3 (4%)
Ventriculomegaly (n [%])	25 (30%)	24 (31%)

PDA indicates patent ductus arteriosus; NEC, necrotizing enterocolitis; PIE, pulmonary interstitial emphysema; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

imated our historical control finding of a 40% extubation failure rate among infants with BW ≤1000 g. Figure 2 is a Kaplan-Meier curve depicting the time

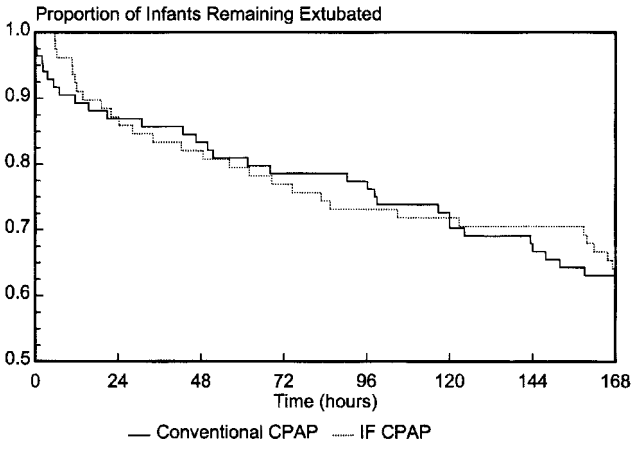

Fig 2. Kaplan-Meier curve depicting the time course of extubation failure among infants in each CPAP group who required reintubation within the first 7 days (168 hours). Approximately 40% of infants in both groups were reintubated by 168 hours. Almost 15% of all infants, or approximately 35% of infants who failed the first extubation attempt, required reintubation within 24 hours.

to reintubation among the infants who failed extubation in each CPAP group. There were no significant differences in the time to reintubation among the 2 groups.

Figure 3 shows the percentage of infants who were extubated successfully as a function of BW. We did not find any statistical differences between the 2 CPAP groups among the 3 BW categories: ≤600 g, 601 to 800 g, and 801 to 1000 g. The mean weight at extubation was higher among infants in the conventional CPAP group (828 ± 195 g vs 781 ± 135 g in the IF CPAP group), and infants in the conventional CPAP group were slightly older (mean age at extubation: 16.6 ± 19.1 days in the conventional CPAP group and 13 ± 13.3 days in the IF CPAP group), although these differences were not statistically significant.

We found no significant differences between the 2 CPAP groups as a function of extubation weight (Fig 4). Infants who weighed ≤600 g were as likely to be extubated successfully as infants who weighed 601 to 1000 g. Infants who weighed >1000 g at the time of extubation had a 92% likelihood of being extubated successfully.

As shown in Table 4, there were no significant

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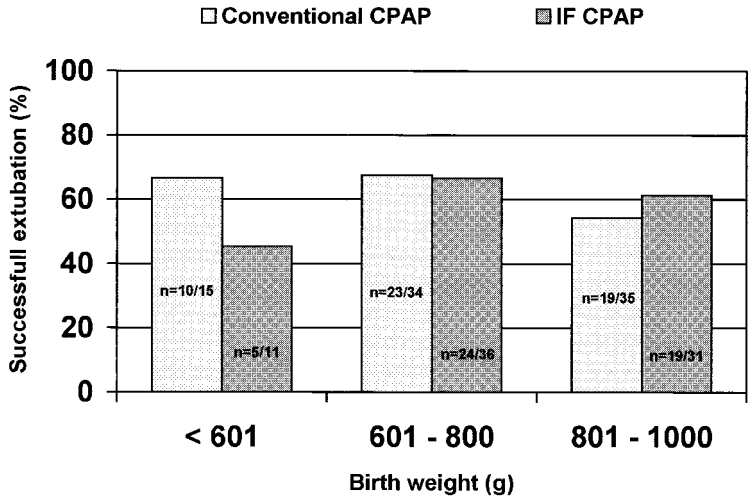

Fig 3. Successful extubation as a function of birth weight.

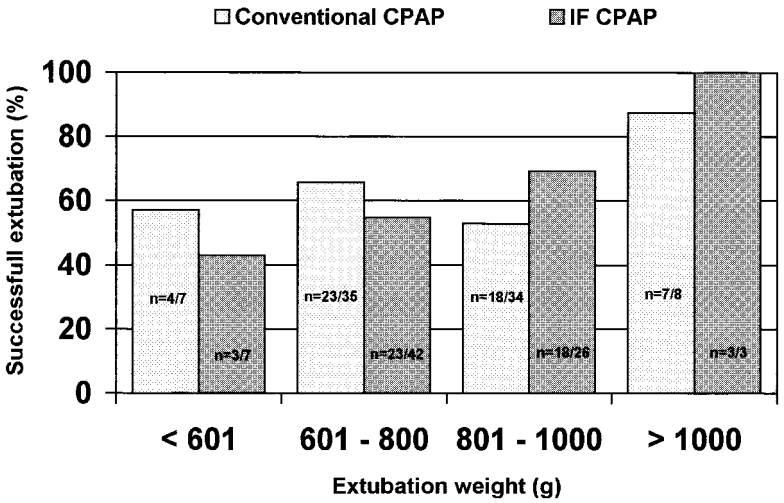

Fig 4. Successful extubation as a function of extubation weight.

TABLE 4. Ventilatory Settings and Blood Gas Parameters 1 Hour Before First Extubation Attempt

Ventilatory Settings and Blood Gas Parameters	Conventional CPAP† (n = 84)	IF CPAP‡ (n = 74)
F_{IO_2} (mean ± SD)	0.33 ± 0.11	0.33 ± 0.10
MAP		
CMV (mean ± SD)	4.5 ± 1.2	4.6 ± 1.5
HFOV* (mean ± SD)	7.5 ± 2	7 ± 1.5
Blood pH (mean ± SD)	7.36 ± 0.06	7.34 ± 0.06
Blood P_{CO_2} (mean ± SD)	46.6 ± 11.9	47.2 ± 11.8

MAP indicates mean airway pressure; CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation.
* Excludes 1 infant in each group extubated from high-frequency jet ventilation.

differences between the 2 CPAP groups with respect to blood gas parameters or ventilator settings in the hour before first extubation attempt. Eleven (13%) infants in the conventional CPAP group and 13 (17%) infants in the IF CPAP group were extubated directly from high-frequency ventilation. One infant in each group was extubated from the Bunnell Life Pulse high-frequency jet ventilator; the other infants were extubated directly from the SensorMedics 3100A high-frequency oscillatory ventilator.

There were no statistical differences between the groups with respect to the outcomes of death, survival without BPD, or total number of days on CPAP (including initial and subsequent extubation attempts) as shown in Table 5. However, infants who were randomized to IF CPAP had fewer days on supplemental O_2 (P = .03), and their length of hospitalization was shorter (P = .017).

The reasons for extubation failure are depicted in Fig 5. As shown, the most common reason for extubation failure was apnea and bradycardia, occurring in almost 60% of the infants who required reintubation. Nearly equal numbers of infants required reintubation because of inadequate oxygenation and inadequate ventilation on NCPAP (approximately 15% in each category).

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TABLE 5. Secondary Outcomes of Death Survival Without BPD, Days on CPAP, and Days on Supplemental Oxygen

Secondary Outcome	Conventional CPAP (n = 84)	IF CPAP (n = 78)	P Value
Death (n [%])	3 (4%)	8 (10%)	.12
Survival without BPD (n [%])	31 (37%)	30 (38%)	.87
Days on CPAP			
Mean ± SD	10.17 ± 8.53	8.74 ± 8.04	.27
Range	0.06–37.79	0–36.32	
Supplemental O_2 (d)			
Mean ± SD	77.2 ± 35.1	65.7 ± 31.4	.03
Range	0.5–224	3–147	
Length of stay (d)			
Mean ± SD	86.3 ± 37.34	73.7 ± 28.7	.017
Range	16–269	13–147	

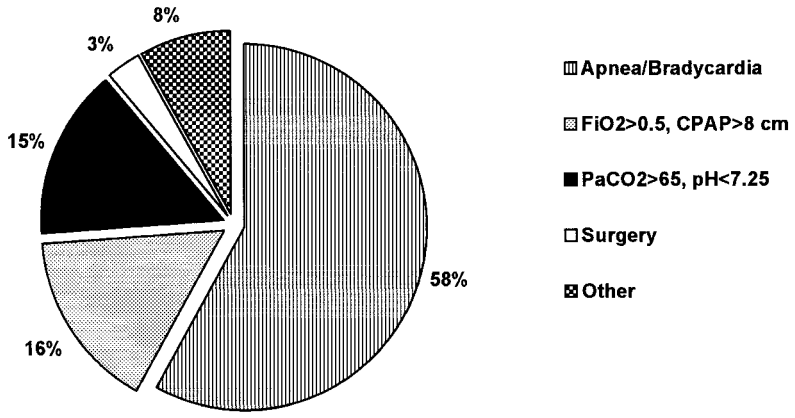

Fig 5. Reasons for extubation failure.

DISCUSSION

This prospective, randomized, controlled trial is the largest published study to examine extubation outcomes in infants with BW ≤1000 g. This is also the first published randomized, controlled trial to compare IF CPAP with conventional CPAP to facilitate successful extubation of ELBW infants. In this study, we showed that infants who were extubated to IF CPAP were as likely but no more likely to be extubated successfully than infants who were placed on conventional CPAP using nasal prongs and a pressure/time-limited ventilator (61.5% vs 61.9%, respectively). Similar to our retrospective analysis and similar to the data available in the literature,[3,5,20] the failure rate at the time of first extubation attempt for infants with a BW ≤1000 g was approximately 40%.

The study patients were well matched in terms of BW, gestational age, and sex, as well as severity of illness (using Clinical Risk Index for Babies score as a surrogate marker) as shown in Table 2. Although the infants in the conventional CPAP group had a higher mean weight at extubation (828 ± 195 g vs 781 ± 135 g in the IF CPAP group) and were older at the time of initial extubation attempt (16.4 ± 18.8 days vs 12.9 ± 13.2 days in the IF CPAP group), these differences did not reach statistical significance. We did not find any statistical difference in the rate of successful extubation between the 2 CPAP groups among 3 BW subcategories: ≤600 g, 601 to 800 g, and 801 to 1000 g (Fig 3). Among the infants who weighed ≤600 g at the time of first extubation attempt, 50% (7 of 14 infants) were extubated successfully, a percentage that was similar to the 60% success rate (82 of 137 infants) among those who weighed 601 to 1000 g (P = .77). Infants with extubation weight >1000 g had >90% likelihood of successful extubation (Fig 4). The ventilator settings and blood gas parameters 1 hour before the first extubation attempt were nearly identical in both groups (Table 4).

The number of surviving ELBW infants who require prolonged mechanical ventilation has increased in the past decade.[24] Efforts to limit the duration of intermittent positive pressure ventilation led to attempts at early weaning of ventilatory support to decrease morbidity and mortality. Early extubation of ELBW infants is fraught with difficulties because of upper airway instability, relatively poor respiratory drive, compliant chest wall, alveolar atelectasis and residual lung damage. CPAP, applied by various means and devices,[3,7,25] is frequently used to wean infants from mechanical ventilation. Many studies have shown that NCPAP is more beneficial than oxyhood[2,4,9,25–28] by preventing atelectasis, decreasing the frequency of apnea/bradycardia episodes, and improving lung function. However, the use of endotracheal CPAP before extubation proved to be more deleterious than extubation directly to NCPAP,[27,29,30] particularly among the smallest infants.

Several published studies have investigated the efficacy of weaning infants from mechanical ventilation to nasal intermittent positive pressure ventilation (NIPPV) compared with NCPAP. Most studies that evaluated NIPPV had a small sample size.[6,20] Ryan et al,[31] when studying the advantages of

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NIPPV over NCPAP, showed no benefit of NIPPV in the treatment of apnea of prematurity. However, the study endpoint encompassed only a short time period of 6 hours after extubation. Lin et al[6] found decreased apnea in infants who were on NIPPV during a 4-hour observation period.

Recently, in a prospective randomized study, Khalaf et al[5] found synchronized NIPPV to be more effective than NCPAP in weaning infants with respiratory distress syndrome from mechanical ventilation. The extubation success rate in the synchronized NIPPV group was 94% at 72 hours postextubation. Despite a higher mean gestational age and mean weight at extubation in the Khalaf et al study, the rate of successful extubation at 72 hours in the NCPAP group was identical (60%) to our findings at 7 days. Although the results are encouraging, larger prospective studies are needed to evaluate the safety and efficacy of this technique in ELBW infants.[32] Future studies should include additional endpoints such as survival without BPD, length of hospital stay, incidence of complications such as gastrointestinal perforation and nosocomial infections, and long-term survival and developmental outcomes.

Despite no difference in our primary outcome of successful initial extubation attempt or in the total number of days on NCPAP, infants in the IF CPAP group had fewer total days on supplemental O_2 and shorter lengths of hospitalization. If future studies confirm this association, then there may be a cost advantage to the use of IF CPAP.

Extubation failure remains a common clinical problem among ELBW infants. In our study, apnea/bradycardia was the most common reason for extubation failure in both CPAP groups. In our combined cohort, 58% of ELBW infants who failed extubation did so because of apnea and bradycardia episodes. This finding is consistent with that of another reported study.[33] Methods for preventing apnea and bradycardia have been the subject of a number of studies. The use of prophylactic methylxanthines for extubation in ELBW infants has been shown to reduce the frequency and/or severity of apnea/bradycardia in larger preterm infants[34,35] but does not eliminate the problem entirely, and questions about safety remain unresolved.[36] Several studies have shown that NIPPV can be an effective therapeutic tool for decreasing apnea of prematurity.

CONCLUSIONS

We found no difference in the rate of extubation failure between the IF CPAP and conventional CPAP groups. Innovative approaches to the postextubation treatment of these infants are needed. Novel interventions that reduce the frequency of apnea and bradycardia are likely to reduce extubation failure among this population of vulnerable infants.

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THE ANTISEPSIS SCAMS

"Listerine had first been marketed in the late 19th century as a proprietary promoted to physicians and was named after Sir Joseph Lister, antiseptic surgery's pioneer. Touted as 'the best antiseptic for both internal and external use,' it was recommended for treating gonorrhea and for 'filling the cavity, during ovariotomy.' In 1921, the ebullient Gerald Lambert, son of the founder, decided to vend his product direct to the public in a massive way. Within a few years, the company's sales had spurted phenomenally, and net earnings had multiplied 40-fold. Much of Listerine's success must be credited to 'halitosis.' This coined word frightened the continent, not because bad breath was a fatal malady but because it was a social disaster. Listerine advertising raised worrisome doubts in each reader's mind with telling slogans like 'even your best friends won't tell you,' and 'often a bridesmaid but never a bride.'"

Young JH. *The Medical Messiahs*. Princeton, NJ: Princeton University Press; 1967

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A Randomized, Controlled Trial Comparing Two Different Continuous Positive Airway Pressure Systems for the Successful Extubation of Extremely Low Birth Weight Infants

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