ORIGINAL ARTICLE

Extended Continuous Positive Airway Pressure in Preterm Infants Increases Lung Growth at 6 Months

A Randomized Controlled Trial

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Abstract

Rationale: Extended continuous positive airway pressure (eCPAP) in the neonatal ICU (NICU) for stable preterm infants increases lung volumes. Its effect on lung growth after discharge is unknown.

Objectives: To assess whether 2 weeks of eCPAP in stable preterm infants is associated with increased alveolar volume (V_A) at 6 months corrected age.

Methods: This randomized controlled trial was conducted at Oregon Health & Science University. Outpatient assessors were unaware of treatment assignment. One hundred infants were randomized to eCPAP versus CPAP discontinuation (dCPAP) to room air.

Measurements and Main Results: The primary outcome was V_A by the single breath hold technique at 6 months corrected age. Secondary outcomes included D_{LCO} and forced expiratory flows (FEFs). FRC was measured in the NICU. Infants randomized to eCPAP ($n = 54$) versus dCPAP ($n = 46$) had the following measurements shown as adjusted mean (SE): V_A (500.2 [24.9] vs. 418.1 [23.4] ml; adjusted mean difference, 82.1 [95% confidence interval (CI), 8.3–155.9]; $P = 0.033$); D_{LCO} (3.4 [0.2] vs. 2.8 [0.1] ml/min/mm Hg; adjusted mean difference, 0.6 [95% CI, 0.1–1.1]; $P = 0.018$); measurement of FEF at 50% of the expired volume (500.6 [18.2] vs. 437.9 [17.9] ml/s; adjusted mean difference, 62.7 [95% CI, 4.5–121.0]; $P = 0.039$); FEF between 25% and 75% of expired volume (452.0 [17.4] vs. 394.4 [17.4] ml/s; adjusted mean difference, 57.5 [95% CI, 1.3–113.8]; $P = 0.046$).

Conclusions: Infants randomized to eCPAP versus dCPAP had significantly increased V_A at 6 months corrected age. D_{LCO} and FEFs were also increased. Extending CPAP in stable preterm infants in the NICU may be a nonpharmacologic and safe therapy to promote lung growth.

Clinical trial registered with www.clinicaltrials.gov (NCT04295564).

Keywords: nasal continuous positive airway pressure; preterm infants; alveolar volume; lung diffusion capacity; airway function

Preterm birth affects 10% of births in the United States and is the most common cause of altered lung development, with potential lifelong respiratory consequences (1, 2).

After neonatal ICU (NICU) discharge, infants born preterm have an increased risk for wheezing, asthma, and respiratory illness hospitalizations compared with full-term infants (1, 2). When assessed during infancy, infants born preterm have impaired airway and lung parenchymal function when studied using forced expiratory flow (FEF)

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

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At a Glance Commentary

Scientific Knowledge on the Subject: The early application of nasal continuous positive airway pressure (CPAP) is the standard of care for the acute management of preterm infants with respiratory distress. However, the optimal duration of CPAP in stable preterm infants is unknown, and mechanical stretch from CPAP may stimulate lung growth and development, which is impaired in preterm infants.

What This Study Adds to the Field: This study demonstrates that extending the duration of nasal bubble CPAP in stable preterm infants can stimulate both their lung and blood vessel growth, as shown by physiologic lung testing at about 6 months of corrected age. Extending CPAP in stable preterm infants in the neonatal ICU may be a nonpharmacologic and safe therapy to promote lung growth and function.

maneuvers and D_{LCO} (3, 4). Reduced airway function during infancy is associated with increased respiratory morbidity that persists into adulthood in longitudinal cohorts (5, 6). Lower lung function early in life often tracks and remains low into adulthood, potentially being an important determinant of chronic obstructive pulmonary disease (2, 7, 8). These findings suggest that improving early life lung function, such as following preterm birth, may improve the lifelong trajectory of lung function and may minimize respiratory morbidity in adulthood, including chronic obstructive pulmonary disease.

The early application of nasal continuous positive airway pressure (CPAP) after preterm delivery is the standard of care for acute management of preterm infants with respiratory distress (9). CPAP can acutely increase FRC and improve gas exchange, thus avoiding invasive mechanical ventilation and minimizing lung injury and the development of bronchopulmonary dysplasia (BPD) (10–12). We and others have demonstrated in young animals that chronic CPAP increases lung volume (13, 14). In a pilot randomized controlled trial (RCT) in convalescing stable preterm human infants, we demonstrated that 2 weeks of extended CPAP (eCPAP) compared with discontinuation of CPAP (dCPAP) to room air resulted in larger lung volumes in the NICU (15). Although CPAP may minimize lung injury in the NICU, chronic mechanical stretch of the lung with CPAP may also stimulate lung growth and development, which might persist after NICU treatment. Therefore, we hypothesized that eCPAP compared with dCPAP in the NICU stimulates lung growth and development, which would be present in infants evaluated as outpatients after NICU discharge. Our primary outcome was assessment of alveolar volume (V_A) at 6 months corrected age, and our secondary outcomes included assessment of D_{LCO} and FEFs. FRC was also measured in the NICU. Some of the results of these studies have been previously reported in the form of abstracts (16, 17).

Methods

Study Design and Oversight

This was an investigator-initiated, single-center RCT conducted at the Oregon Health & Science University (OHSU) level IV NICU, with the primary outcome of lung function testing at about 6 months corrected age performed in the research infant pulmonary function laboratory at OHSU. The protocol (*see* online supplement) was approved by the OHSU Institutional Review Board, and informed consent was obtained for all participants. An independent Data and Safety Monitoring Board reviewed the study every 6 months for safety.

Participants

Infants were screened for inclusion if they were >24 and ≤32 weeks of gestational age (GA) at birth and had required CPAP for ≥24 hours for clinical care, either for initial respiratory support or status post extubation (15). Infants were randomized to 2 weeks of eCPAP or dCPAP after consent was obtained and they met CPAP respiratory stability criteria (15, 18, 19) for ≥12 hours at <35 weeks postmenstrual age (PMA). The 2-week treatment period was chosen, as this was the treatment interval used in our pilot RCT, which had demonstrated increased lung volumes in the NICU in stable preterm infants randomized to eCPAP (15). Exclusion criteria at the time of consent are outlined in Figure 1.

Allocation and Masking

Allocation was performed at the data center via REDCap using a permuted block randomization stratified by delivery GA (<29 and ≥29 wk). Qualifying twin pairs were allocated to the same treatment arm (the first twin randomized and the second assigned) (20). Blinding the treatment allocation was not feasible in the NICU, as it was not ethical or logistically possible to continue infants randomized to dCPAP to remain with Hudson prongs in place without treatment administration. However, REDCap blinds the clinical team to the randomization schema, and all assessors of the infants' outcomes from discharge through 12 months of age were blind to treatment allocation in the NICU. This included the pediatric pulmonologist (K.D.M.) supervising the outpatient lung function measurements and personnel administering the respiratory questionnaires. Importantly, the statistician (J.E.S.) analyzed all outcomes blinded to the infant's treatment allocation.

Interventions

The OHSU NICU has a long history of exclusive bubble CPAP use and follows institutional guidelines regarding all aspects of its administration and discontinuation (15). Briefly, CPAP is administered as bubble CPAP, with distending pressure delivered via a bubble delivery system (Infant Bubble CPAP system; Fisher and Paykel) through appropriately sized Hudson nasal prongs (Teleflex) with chinstrap applied (21), and an 8 F orogastric tube to vent the infant's stomach. The nares are assessed every 3–4 hours for redness or inadvertent pressure and prongs repositioned as needed. As previously published, at OHSU, preterm infants are maintained on CPAP until "CPAP respiratory stability criteria" (15, 19) are met for ≥12 hours, at which time CPAP is discontinued and the infant is placed on room air. The published CPAP respiratory stability criteria followed at OHSU and for this study are: CPAP of 5 cm H_2O, no oxygen requirement, respiratory rate < 70 breaths/min, retraction score of ≤1, fewer than three self-resolving apneas (<20 s) and/or bradycardia (<100 bpm) and/or desaturations (pulse oximeter oxygen saturation [Sp_{O_2}] < 86%) per hour for the last 6 hours, average Sp_{O_2} > 86% for at least 90% of the time over the past 24 hours, not being treated for patent ductus arteriosus

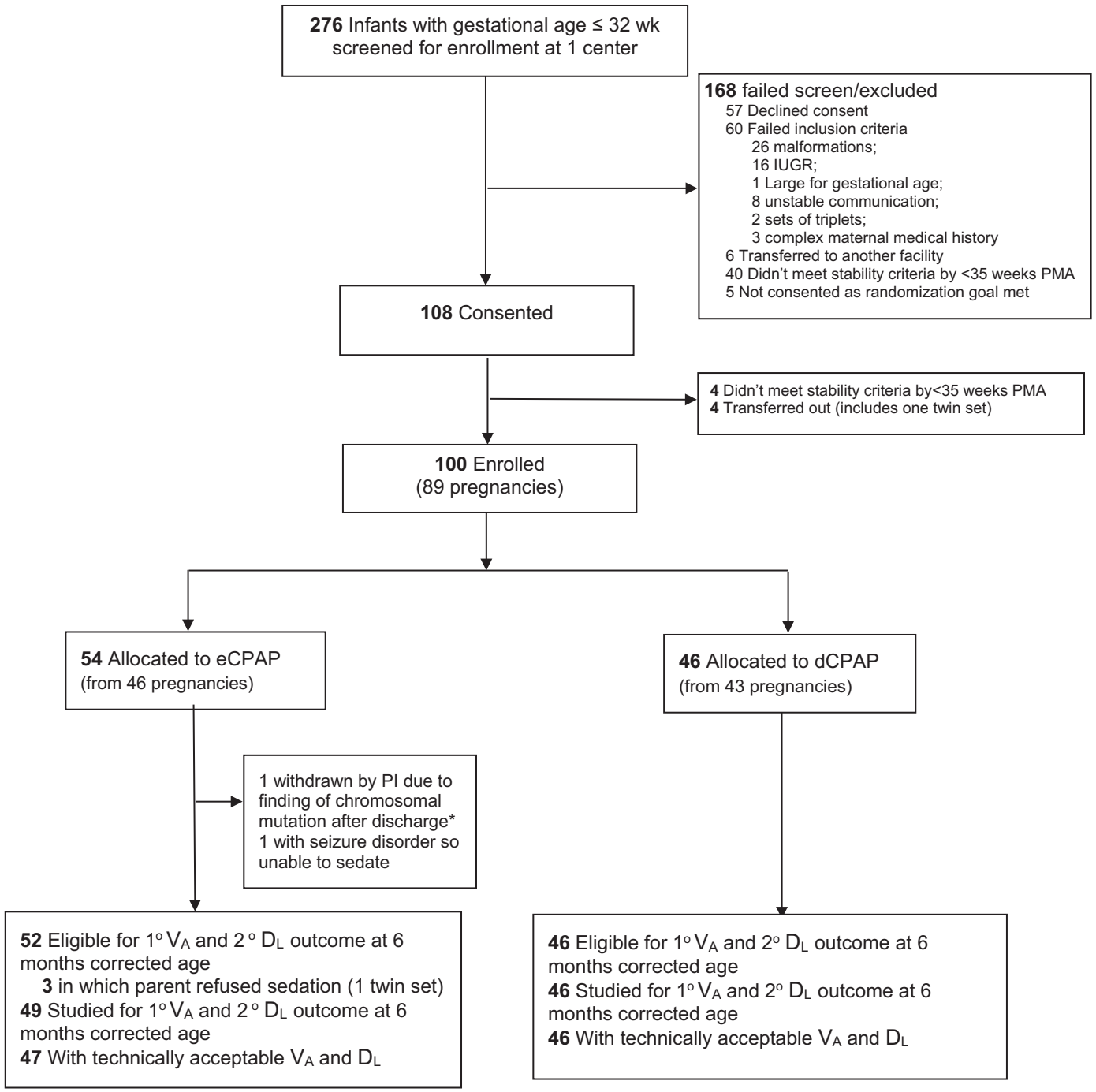

Figure 1. CONSORT diagram for infants in the extended continuous positive airway pressure (eCPAP) study. Screening, enrollment, randomization, and follow-up of infants randomized to eCPAP compared with dCPAP through outpatient testing. For twin pairs allocated in the study, the first twin was randomized and the second twin was assigned to the same treatment arm when CPAP respiratory stability criteria were met. *Withdrawn by the principal investigator after discharge from the neonatal ICU because of diagnosis of a rare ARID1B chromosomal mutation after discharge. dCPAP = discontinuation of continuous positive airway pressure; IUGR = intrauterine growth restriction; PI = principal investigator; PMA = postmenstrual age; V_A = alveolar volume.

or sepsis, and tolerating time off CPAP during routine care (up to 15 min).

After consent was obtained and CPAP respiratory stability criteria were met, a nonsedated measurement of FRC was done in the NICU. Allocation to eCPAP or dCPAP was then performed via REDCap. The infant's clinical status was monitored daily by research staff, and study data were collected during the treatment period through hospital discharge. Treatment failure was predefined as remaining on the assigned

treatment allocation for <9 of the 14 days. Infants allocated to dCPAP were placed back on CPAP if they exhibited specific signs of respiratory distress as previously published (15), and those allocated to eCPAP were taken off CPAP if significant nasal septal breakdown or abdominal distention occurred (15). In both scenarios, the infant was returned to their allocated treatment arm if stabilization occurred within 5 days (15) (*see* Table E1 in the online supplement). FRC was repeated at the end of the 2-week treatment period in the NICU. Because FRC cannot be measured with the infant on CPAP, infants on eCPAP were taken off CPAP at the end of 2 weeks of treatment, and FRC was immediately measured.

Measurements and Outcomes

V_A, D_{LCO}, and FEFs at outpatient testing. Infants were studied after sedation with oral chloral hydrate at 50–100 mg/kg (22). Testing was supervised by a pediatric pulmonologist (K.D.M.) blinded to treatment allocation in the NICU, performed by three experienced respiratory therapists, and reviewed for acceptability, reproducibility, and completeness by blinded, trained, licensed respiratory therapists (C.T. or J.B.). All testing was done ⩾3 weeks after a respiratory illness, if one had occurred.

Measurements of V_A and D_{LCO} were obtained using an induced respiratory pause technique at an elevated lung volume (30 cm H_2O) that we developed and previously described (4, 23, 24). During passive expiration after the 4-second induced respiratory pause for gas exchange, carbon monoxide (CO) and helium (He) concentrations were used to calculate V_A and D_{LCO}. The measurements were corrected to body temperature and pressure saturated conditions. Results were expressed as averages of two to three measurements within 10%, adjusting for hemoglobin.

FEF measurements in triplicate were obtained using the raised-volume rapid thoracic compression technique that we developed and previously described (22, 25, 26).

FRC in the NICU. FRC measurements were obtained with the nitrogen washout technique as previously described, using the infant pulmonary function cart (SensorMedics 2600; SensorMedics Inc.) at the infant's bedside in the NICU, at least 30 minutes after a feed and by standard acceptance criteria (27–29).

Respiratory questionnaires/occurrence of wheeze (exploratory outcome). A standardized respiratory questionnaire was administered monthly though 12 months corrected age (26, 30). Wheeze was defined as a positive response from the primary caretaker to any of the following: parental report of wheeze, healthcare provider diagnosis of wheeze, wheezy bronchitis or asthma, or any bronchodilator or steroid use (Table E2). As defined *a priori*, only patients with one or more respiratory questionnaires completed at ⩾4 months corrected age were included in the respiratory clinical outcomes analyses.

Safety monitoring. All subjects were monitored for adverse events that occurred after consent according to standard definition by electronic medical record review and physical examination (including vital sign monitoring during sedation at the outpatient tests).

Sample size calculation. The primary outcome was V_A at outpatient testing in former preterm infants allocated to eCPAP versus dCPAP in the NICU. We hypothesized a 12% higher V_A at 6 months corrected age in the eCPAP versus dCPAP participants (31). Using an analysis of covariance model and assuming a mean V_A of 642 ml (SD, 189) based on data of the overall mean and SD from the control and CPAP groups from Assaf and colleagues (31), and using the covariates of sex and height at the time of testing, which have an estimated coefficient of determination of 0.63 with the response of V_A, a sample size of 34 infants per group was needed at outpatient testing to yield 80% power for detecting a 12% difference (effect size = 0.42) in V_A in the eCPAP versus dCPAP group at $\alpha = 0.05$. We chose a 12% difference as meaningful because we have shown that preterm infants who develop BPD have impaired parenchymal development, with V_A and D_{LCO} values 10–15% lower than full-term infants (4). To achieve our desired sample size at 6 months of age, we estimated the need to allocate 100 infants in the NICU. This projection accounted for a conservative 10% cohort loss during the NICU stay and an additional 15% loss from NICU discharge to follow-up. These losses were anticipated because of the fragility of the preterm population, the requirement for sedation during follow-up lung function testing, and the need to wait at least 3 weeks after any respiratory infection before performing outpatient testing.

Statistical Analyses

All analyses were based on intention to treat and performed by a statistician (J.E.S.) blinded to the infants' treatment assignment. Postrandomization maternal and infant demographic and clinical characteristics were compared using the Student's *t* tests for continuous variables (or Wilcoxon tests for nonnormal distributed data) and chi-square tests for categorical variables (Fisher's exact test when >20% of cells had expected cell counts <5).

Generalized linear mixed models (GLMMs) were used to compare the primary outcome of V_A between the eCPAP and dCPAP groups to adjust for GA at delivery (stratification variable). GLMM, a generalized form of ANOVA, was used to allow for the random effect of twin sets in alignment with the power analyses. Because lung function measures are highly dependent on infant length and sex, we adjusted for length at testing and sex (as covariates) in the GLMMs. The secondary outcomes of D_{LCO}, FEFs (specifically FEF_{50} [measurement of FEF at 50% of the expired volume]), and FRC were analyzed with the same general approaches described for the primary outcome of V_A. Logistic regression models, using similar GLMM approaches, were used to compare the occurrence of wheeze between the two groups, adjusting for GA at delivery. These GLMMs were also used when analyzing FRC data between two time points (treatment allocation and 14-d follow-up at the end of treatment).

Multiple imputation was used to derive imputed values for the missing data on the main outcomes, using the demographic characteristics and 10,000 imputations. The main analyses were then modeled again, with the missing values replaced by the imputed values.

All the outcomes were also analyzed with the same general approach using a per-protocol analysis in which only infants who received the treatment intervention as allocated for ⩾9 of the 14 treatment days were included. All analytic assumptions were verified. All analyses were conducted using the SAS 9.4 (SAS Institute).

Results

Study Patients

The study was registered at ClinicalTrials.gov (NCT04295564), and recruitment occurred from January 2020 through January 2023.

A total of 276 infants ⩽32 weeks GA at birth who required ⩾24 hours of CPAP for clinical care were screened for eligibility. There were 168 infants who failed screening, with 57 declining participation (Figure 1). A total of 100 infants (from 89 pregnancies) were enrolled in the study, with 54 infants (from 46 pregnancies) allocated to eCPAP and 46 (from 43 pregnancies) to dCPAP. V_A (primary outcome) and $D_{L_{CO}}$ measurements were obtained in 93 of 98 eligible infants (95% of eligible) at about 6 months corrected age (Figure 1). There were no participant withdrawals of consent and no loss to follow-up. Seven infants in the eCPAP arm did not complete V_A testing for the following reasons: one diagnosed with ARID1B mutation diagnosed after discharge and discontinued from study by the principal investigator, one with seizure disorder so could not be sedated, three mothers (one with a set of twins) refused sedation for the outpatient test, and one infant with a technically unacceptable test.

The baseline characteristics of the mothers and infants are shown in Table 1. The lowest GA was 25.7 weeks in the eCPAP and 24.7 weeks in the dCPAP group. About 25% of infants in both groups were <29 weeks GA at birth. Both groups of infants were allocated into the study at 32.4 weeks PMA, with comparable weights and lengths. Treatment failure was greater in the dCPAP than the eCPAP group (22% vs. 3.7%; $P < 0.05$). Both groups had comparable FRC measurements at allocation, but the infants in the eCPAP group had a significantly higher FRC at the end of the 2 weeks of treatment (adjusted P value <0.01) (Table 1 and Figure 2). There was no significant difference between the eCPAP and dCPAP groups regarding the time to first feed or full feeds, occurrence of BPD as defined by Jobe and Bancalari (32) (7.4% vs. 6.5%), or discharge PMA between the groups.

V_A (Primary Outcome) and $D_{L_{CO}}$ (Secondary Outcome)

Measurements of V_A and $D_{L_{CO}}$ (done with same testing maneuver) were completed in 95% of the eligible participants. The eCPAP group had seven twin pairs, versus three in the dCPAP group ($P < 0.05$). Both groups were tested at about 6 months corrected age and had comparable weights and lengths at the time of testing (Table 1). Infants in the eCPAP versus dCPAP group had significantly higher adjusted mean (SE) measurements of V_A (500.2 [24.9] vs. 418.1 [23.4] ml; adjusted mean difference, 82.1 [95% confidence interval (CI), 8.3–155.9]; $P = 0.033$) and $D_{L_{CO}}$ (3.4 [0.2] vs. 2.8 [0.1] ml/min/mm Hg; adjusted mean difference, 0.6 [95% CI, 0.1–1.1]; $P = 0.018$) at outpatient testing (Table 2 and Figures 3A and 3B). The multiple imputed data showed similar results with similar significance.

Other Secondary Outcomes

Measurements of FEFs were obtained in 76 infants. The infants in the eCPAP versus dCPAP group demonstrated significantly higher adjusted mean (SE) measurements of: FEF_{50} (500.6 [18.2] vs. 437.9 [17.9] ml/s; adjusted mean difference, 62.7 [95% CI, 4.5–121.0]; $P = 0.039$) and FEF between 25% and 75% of expired volume (452.0 [17.4] vs. 394.4 [17.4] ml/s; adjusted mean difference, 57.5 [95% CI 1.3–113.8]; $P = 0.046$) (Table 2 and Figure 3C).

Per-Protocol Analyses

The findings of significantly improved V_A, $D_{L_{CO}}$, and FEFs in the eCPAP versus dCPAP groups were also demonstrated in the per-protocol populations (Table E3).

Respiratory Questionnaires/Occurrence of Wheeze (Exploratory Outcome)

Monthly standardized respiratory questionnaires were obtained in all 99 eligible infants (one infant had been withdrawn by the principal investigator because of the diagnosis of a rare ARID1B mutation after discharge), with a median number of 12 respiratory questionnaires in both groups. The occurrence of wheeze was 23 (43.4%) out of 53 in the eCPAP and 26 (56.5%) out of 46 in the dCPAP group ($P = 0.20$).

Safety Monitoring

There were two serious adverse events in the study: one vocal cord paralysis in the dCPAP and one episode of sepsis requiring intubation in the eCPAP group. Both serious adverse events were unrelated to the study. There was an imbalance in infants with reported adverse events that were possibly or probably related to the intervention: neonatal apnea ($n = 5$), neonatal respiratory insufficiency ($n = 4$), and neonatal tachypnea ($n = 2$), all in the dCPAP group. In the eCPAP group, there were three infants with mild nasal mucosal erythema; however, none of the infants in the eCPAP group had nasal breakdown or feeding intolerance requiring CPAP discontinuation. Ten infants (22%) in the dCPAP arm had to be placed back on CPAP because of symptoms of increased respiratory distress, as per predefined criteria (Table E1).

Discussion

The current RCT confirmed our hypothesis that eCPAP treatment of stable preterm infants in the NICU stimulated lung growth that persisted after NICU discharge. Our primary pulmonary physiologic outcome of mean V_A was significantly greater in eCPAP than in dCPAP, which is consistent with the significantly increased FRC demonstrated in the NICU at the end of the 2-week treatment period. In addition to a persistently greater lung volume, our findings of our secondary pulmonary physiologic outcomes of a greater $D_{L_{CO}}$ and greater FEFs in the eCPAP compared with dCPAP subjects are also consistent with our hypothesis that eCPAP stimulated lung growth. Last, our clinical outcome, the occurrence of wheeze, was 43.4% in the eCPAP and 56.5% in the dCPAP arm but did not reach statistical significance, likely because of small sample size. Overall, our findings are consistent with our hypothesis that eCPAP stimulates lung growth after preterm birth and potentially can improve the trajectory of lung function and minimize the lifetime respiratory morbidity in infants born preterm.

Early CPAP administration rather than invasive intubation and mechanical ventilation after preterm delivery is the standard of care to support the preterm lung and decrease BPD (9). Historically, neonatologists have attempted to quickly wean clinically stable preterm infants off CPAP to minimize potential adverse events, such as nasal septal breakdown, feeding intolerance, or impaired family bonding (33). In this RCT, there were no cases of treatment failure in the eCPAP arm due to nasal septal breakdown or feeding intolerance, and both groups achieved full oral feeds and hospital discharge at a similar PMA. Significantly more infants in the dCPAP group failed their treatment allocation, requiring placement back on CPAP because of meeting predefined criteria for increased respiratory distress, compared with the treatment failure rate in the eCPAP arm. However, the percentage of infants who required resumption of CPAP was lower than reported in other CPAP discontinuation trials (19, 34, 35).

Previous *in vivo* studies in young animals have demonstrated that CPAP application of 5 cm H_2O for 1–2 weeks

Table 1. Maternal and Infant Characteristics

Characteristic	eCPAP	dCPAP
Maternal ($n = 89$)	$n = 46$	$n = 43$
Age, yr, mean (SD)	30.9 (5.8)	31.5 (6.3)
Gravida, median (25th–75th percentile)	2 (1–3)	2 (1–3)
Maternal race		
American Indian or Alaska Native	2 (4.3)	1 (2.3)
Asian	2 (4.3)	2 (4.7)
Black or African American	1 (2.2)	4 (9.3)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)
White	37 (80.4)	34 (79.1)
Unknown or not reported	2 (4.3)	1 (2.3)
Multiracial	2 (4.3)	1 (2.3)
Maternal ethnicity		
Not Hispanic or Latino	38 (82.6)	35 (81.4)
Hispanic or Latino	8 (17.4)	8 (18.6)
Public insurance	17 (37.0)	22 (51.2)
High school education or less	13 (28.3)	16 (37.2)
Prenatal care	46 (100)	43 (100)
Twin pairs	8 (17.4)	3 (7.0)
Maternal history of asthma	11 (23.9)	7 (16.3)
Ever-smoker	16 (34.8)	16 (37.2)
Smoked during this pregnancy	3 (6.5)	5 (11.6)
Preeclampsia	15 (32.6)	17 (39.5)
Antenatal steroid treatment	39 (84.8)	36 (83.7)
Cesarean delivery	31 (67.4)	29 (67.4)
Born at study hospital	41 (89.1)	40 (93.0)
Gestational age at birth, wk, mean (SD)	30.2 (1.8)	30.2 (2.0)
Gestational age < 29 wk	12 (26.1)	12 (27.9)
Enrolled infants ($n = 100$)	$n = 54$	$n = 46$
Female	19 (35.2)	24 (52.2)
Birth weight, g, mean (SD)	1,420 (328)	1,434 (359)
Treated with surfactant	14 (25.9)	17 (37.0)
Treated with mechanical ventilation in NICU for >1 h	19 (41.3)	20 (37)
Postmenstrual age at treatment allocation, wk, mean (SD)	32.4 (0.9)	32.4 (0.8)
Weight at treatment allocation, g, mean (SD)	1,579 (258)	1,582 (243)
Length at treatment allocation, cm, mean (SD)	41.4 (1.8)	41.1 (2.0)
On caffeine during 2-wk treatment period	44 (81)	40 (87)
Failed allocated treatment arm*	2 (3.7)	10 (22)†
FRC at treatment allocation, ml, mean (SE)‡	41.0 (1.5)	44.5 (1.4)
FRC at the end of 2 wk of treatment allocation, ml, mean (SE)§	57.5 (1.7)	50.1 (1.6)†
Characteristics for infants who completed V_A and D_{LCO} testing	$n = 47$	$n = 46$
Female	16 (34.0)	24 (52.2)
Birth weight, g, mean (SD)	1,422 (305)	1,434 (359)
White race	37 (78.7)	33 (71.7)
Ethnicity, not Hispanic or Latino	34 (72.3)	37 (80.4)
Gestational age at delivery <29 wk	12 (25.5)	13 (28.3)
Infants from twin pairs	14 (29.8)	6 (13.0)‖
Postmenstrual age at treatment allocation, wk, mean (SD)	32.4 (0.8)	32.4 (0.8)
Corrected age at outpatient test, mo, mean (SD)	7.3 (1.5)	7.0 (1.3)
Height at outpatient test, cm, mean (SD)	67.5 (2.8)	67.2 (3.1)
Weight at outpatient test, kg, mean (SD)	8.0 (1.0)	7.8 (1.0)

Definition of abbreviations: dCPAP = discontinuation of continuous positive airway pressure; eCPAP = extended continuous positive airway pressure; NICU = neonatal ICU; V_A = alveolar volume.
Data are given as *n* (%) unless otherwise noted.
*Treatment failure defined *a priori* as remaining on assigned treatment allocation for <9 days of 14-day treatment period.
†$P < 0.01$ between groups for FRC at the end of the 2-week treatment period by multivariable mixed linear models to account for the correlation between twin pairs and to adjust for gestational age at birth (stratification variable), sex, and length at allocation to treatment.
‡Completed in 52 and 46 infants.
§Completed in 51 and 45 infants. FRC data are presented as adjusted mean (SE).
‖$P < 0.05$.

increased lung volume compared with sham treatment (14). Assessment of pulmonary pressure–volume curves and lung histology suggested that the larger lungs were structurally normal and not emphysematous. The results of these studies suggested that CPAP increased lung growth and development; however, these studies were limited to animals born term, and CPAP was applied to young animals not in the neonatal period. Our previous cross-sectional evaluation of human infants born preterm

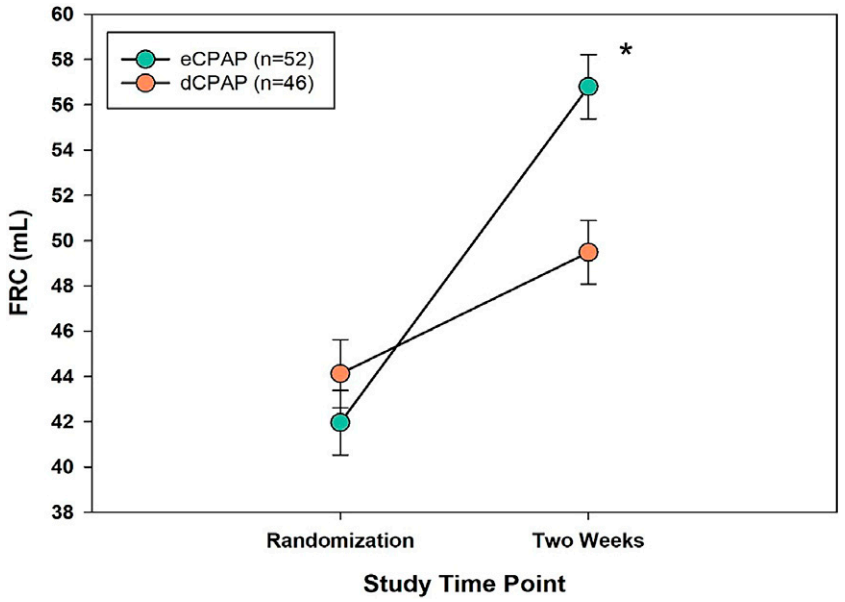

Figure 2. FRC measurements in the neonatal ICU. Data are shown as mean ± SE. *P* values for the difference in FRC at allocation and at the end of the 2-week treatment period are based on generalized multivariable linear mixed models to account for the covariance structure with twin sets and to adjust for gestational age at birth (allocation stratification variable), sex, and length at allocation to treatment arm. *$P < 0.01$ for comparison at 2 weeks. dCPAP = discontinuation of continuous positive airway pressure; eCPAP = extended continuous positive airway pressure.

and treated with CPAP in the NICU found higher V_A and higher $D_{L_{CO}}$ when evaluated as infants after NICU discharge (31). These findings suggested that CPAP treatment in the NICU improved lung growth and development. More recently, using a nonhuman primate model of preterm birth, we found that CPAP of 5 cm H_2O compared with sham treatment for 9 days was associated with an increased alveolar number (36). Cumulatively, prior *in vivo* studies of animal models and humans support our current RCT that eCPAP stimulates lung growth and development in preterm human infants.

Strengths and Limitations

A major strength of our study includes its RCT design, with very high cohort retention, completion of blinded outpatient lung function testing, and a high completion rate of monthly respiratory questionnaires. In addition, our NICU has consistent application and weaning criteria of CPAP for preterm infants, and there were no parent-initiated subject withdrawals.

Our current study also confirmed our previous finding in our pilot trial that 2 weeks of eCPAP in the NICU in stable preterm infants increased FRC compared with dCPAP, which was discontinued based on respiratory stability criteria (15). We also used an innovative assessment of V_A and $D_{L_{CO}}$, which we have previously described (4, 23, 24, 31). These outcomes enabled us to compare lung growth and development for the treatment groups as infants after NICU discharge. The measurement of FEFs using raised-volume rapid thoracic compression (22, 25, 26) also provided an important assessment of improved airway function in the eCPAP group.

There are several limitations of our study. It was a single-center RCT, which may limit generalizability to other NICUs. We used innovative measures of lung function after NICU discharge; however, our testing required mild sedation, and this methodology is not commercially available. Our study did not include preterm infants with the most severe respiratory disease, as they did not meet the CPAP respiratory stability criteria before 35 weeks PMA. Therefore, our results may not be applicable to those preterm infants with more severe respiratory disease. Last, our clinical outcome of wheeze was obtained by parental report rather than assessment by medical personnel, which may have affected the accuracy of the wheeze outcome. However, as both treatment groups were evaluated monthly with the same standardized respiratory questionnaire by personnel blinded to treatment allocation, we do not believe this approach altered the potential clinical benefit of eCPAP treatment. Pragmatic multicenter

Table 2. Outpatient Lung Function Analyses of Alveolar Volume, $D_{L_{CO}}$, and Forced Expiratory Flows

	eCPAP [*Adjusted Mean (SE)*] (*n* = 47)	dCPAP [*Adjusted Mean (SE)*] (*n* = 46)	Adjusted Mean Difference (95% CI) (eCPAP–dCPAP)*	% Change (eCPAP–dCPAP)	Adjusted *P* Value*
Alveolar volume, ml	500.2 (24.9)	418.1 (23.4)	82.1 (8.3 to 155.9)	19.6	0.0334
$D_{L_{CO}}$ ml/min/mm Hg	3.4 (0.2)	2.8 (0.1)	0.6 (0.1 to 1.1)	21.4	0.0179
FEF_{50}, ml/s†	500.6 (18.2)	437.9 (17.9)	62.7 (4.5 to 121.0)	14.3	0.0387
$FEF_{25–75}$, ml/s†	452.0 (17.4)	394.4 (17.4)	57.5 (1.3 to 113.8)	14.6	0.0464
FEF_{75}, ml/s†	249.5 (13.0)	210.5 (13.0)	39.0 (−3.1 to 81.0)	18.5	0.0638
FVC, ml†	325.8 (11.7)	312.8 (11.3)	12.9 (−24.2 to 50.1)	4.2%	0.4273

Definition of abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; dCPAP = discontinuation of CPAP; eCPAP = extended CPAP; FEF = forced expiratory flow; FEF_{50} = FEF at 50% of the expired volume; $FEF_{25–75}$ = FEF between 25% and 75% of expired volume; FEF_{75} = FEF at 75% of the expired volume.

**P* values and 95% CIs for the difference between the treatment groups based on multivariable mixed linear models to account for the correlation between twin pairs and to adjust for gestational age at birth (stratification variable), sex, and length at outpatient testing.

†FEFs completed in 38 infants in eCPAP group and 38 infants in dCPAP group.

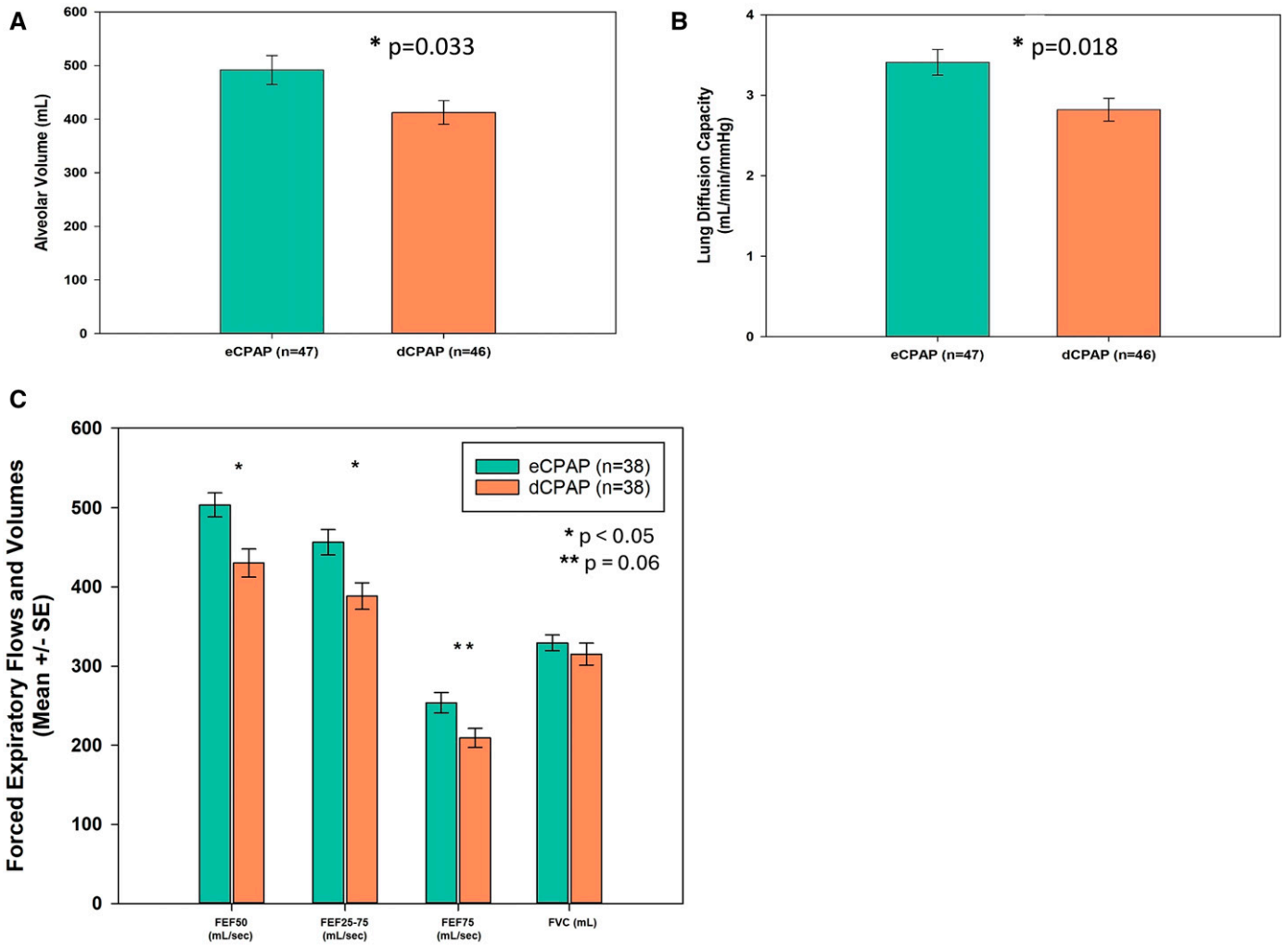

Figure 3. Alveolar volume, D_{LCO}, and forced expiratory flows (FEFs) in infants at outpatient testing. (*A* and *B*) Data are shown as mean ± SE. *P* values for the difference in alveolar volume ($P = 0.033$) and D_{LCO} ($P = 0.018$) between the treatment groups are based on generalized multivariable linear mixed models to account for the correlation between twin pairs and to adjust for gestational age at birth (stratification variable), sex, and length at outpatient testing. Both measurements are obtained from the same lung function maneuver. (*C*) FEFs in 38 infants assigned to eCPAP and 38 infants assigned to dCPAP. *P* values for the difference in FEFs between the treatment groups are based on generalized multivariable linear mixed models to account for the correlation between twin pairs and to adjust for gestational age at birth (stratification variable), sex, and length at outpatient testing. dCPAP = discontinuation of continuous positive airway pressure; eCPAP = extended continuous positive airway pressure; $FEF_{25–75}$ = FEF between 25% and 75% of the expired volume; FEF_{50} = FEF at 50% of the expired volume; FEF_{75} = FEF at 75% of the expired volume.

trials are essential to enhance the diversity of randomized infants; include larger populations of very low birth weight infants at high risk for BPD who are most likely to benefit from this simple, safe, and cost-effective intervention; and provide sufficient power to assess clinical respiratory and neurodevelopmental outcomes.

Conclusions

Among stable preterm infants using CPAP in the NICU, an extended 2 weeks of CPAP significantly increased their alveolar volume, lung diffusion capacity, and FEFs when assessed after NICU discharge at about 6 months corrected age. Our findings suggest that extending CPAP in stable preterm infants in the NICU may be a nonpharmacologic and safe therapeutic strategy to promote lung growth and development after preterm birth. Future studies need to evaluate the optimal duration and magnitude of CPAP in the context of promoting lung growth and development. In addition, longitudinal follow-up is required to determine whether extended CPAP in the NICU can improve lung function trajectory and long-term respiratory health after preterm birth. ■

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