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ORIGINAL ARTICLES

Variation in Positive End-Expiratory Pressure Levels for Mechanically Ventilated Extremely Low Birth Weight Infants

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Objective To test the hypothesis that significant positive end-expiratory pressure (PEEP) level variation exists between neonatal centers.

Study design We performed a secondary analysis cohort study of the Nasal Intermittent Positive-Pressure Ventilation trial. Our study population was extremely low birth weight infants requiring mechanical ventilation within 28 days of life. The exposure was neonatal center; 34 international centers participated in the trial. Subjects from centers with fewer than 5 eligible cases were excluded. The main outcome was the maximal PEEP level used during the first course of mechanical ventilation. Infant characteristics judged a priori to directly influence clinical PEEP level selection and all characteristics associated with PEEP at $P < .05$ in bivariable analyses were included with and without center in multivariable linear regression models. Variation in PEEP level use between centers following adjustment for infant characteristics was assessed.

Results A total of 278 extremely low birth weight infants from 17 centers were included. Maximal PEEP ranged from 3 to 9 cm H_2O, mean = 5.7 (SD = 0.9). Significant variation between centers remained despite adjustment for infant characteristics ($P < .0001$). Further, center alone explained a greater proportion of the PEEP level variation than all infant characteristics combined.

Conclusions Marked variation in PEEP levels for extremely low birth weight infants exists between neonatal centers. Research providing evidence-based guidance for this important aspect of respiratory care in preterm infants at high risk of lung injury is needed. *(J Pediatr 2017;■■:■■-■■).*

Trial Registration ClinicalTrials.gov NCT00433212

Positive end-expiratory pressure (PEEP) is a key component of mechanical ventilation. PEEP provides a continuous distending pressure throughout the respiratory cycle, limiting airway collapse and maintaining lung volumes.[1,2] However, both insufficient and excessive PEEP levels may cause harm, impairing gas exchange directly and through injury-mediated inflammation. Insufficient PEEP causes lung injury through atelectrauma, and excessive levels facilitate over distension and volutrauma.[3,4] Expert opinion suggests selection of an "optimal" PEEP level that supports gas exchange while minimizing lung injury requires an individualized approach. This should reflect an individual infant's underlying disease severity, rather than selection of a standard single level for all infants.[3,5-7]

Minimizing lung injury during invasive mechanical ventilation remains an important target for reducing bronchopulmonary dysplasia (BPD) in preterm infants. Although the preferential use of noninvasive respiratory support over mechanical ventilation is an appropriate and increasingly applied evidence-based strategy, 46%-83% of very preterm infants at highest risk of BPD fail noninvasive support and nonetheless require mechanical ventilation.[8-10]

Evidence-based guidance for PEEP level selection in preterm infants is lacking; even descriptive data of typical practice is sparse.[11] This lack of data may contribute to practice variation between neonatal centers. We are aware of a single recent study describing PEEP level practice in neonates, a cross-sectional survey of ventilation practice in a European cohort.[12] This study observed PEEP levels <5 cm

AIC	Akaike information criterion
BPD	Bronchopulmonary dysplasia
ELBW	Extremely low birth weight
FiO_2	Fraction of inspired oxygen
NIPPV	Nasal Intermittent Positive-Pressure Ventilation
PEEP	Positive end-expiratory pressure

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H_2O applied more commonly than values ≥5 cm H_2O. The objective of the present study was to test the hypothesis that significant PEEP level variation exists between centers participating in an international clinical trial despite adjustment for infant characteristics reflective of differences in disease severity.

Methods

We performed a secondary cohort study using prospectively collected data from the international, multicenter Nasal Intermittent Positive-Pressure Ventilation (NIPPV) trial (ClinicalTrials.gov: NCT00433212), conducted between 2007 and 2011.[13] The NIPPV trial enrolled 1009 extremely low birth weight (ELBW) infants (birth weight <1000 g) of gestational age <30 weeks who were eligible for noninvasive support within 28 days of life. Infants were excluded from NIPPV enrollment if they were expected to die, had congenital anomalies, required surgery, or had a neuromuscular disease. Respiratory status variables, including ventilator variables such as PEEP level, were collected longitudinally 3 times daily for the first week after enrollment and daily thereafter. For the current study, we examined PEEP level data from the initial course of invasive mechanical ventilation. To ensure use of accurate, prospectively collected PEEP level and covariate data, we only included subjects requiring intubation and conventional mechanical ventilation for the first time after study enrollment. Cases of endotracheal intubation for administration of surfactant only were excluded by identifying cases in which a single instance of mechanical ventilation variables were available. This secondary study protocol using deidentified data was designated nonhuman subjects research by the institutional review board of the Children's Hospital of Philadelphia.

The primary exposure of interest was the neonatal center enrolling the subject. The NIPPV trial was conducted in 34 international, academic neonatal intensive care centers. With knowledge of the distribution of participating centers, we also defined 5 global regions for a geographic comparison of PEEP level use: Canada, the US, the British Isles, continental Europe, and the Middle East/Asia. We excluded centers and corresponding subjects contributing fewer than 5 eligible cases.

The main outcome was the maximal PEEP level (cm H_2O) used during the first postenrollment course of conventional mechanical ventilation within 28 days of age. We excluded PEEP level values beyond 28 days of age to focus on the management of early respiratory failure rather than of evolving or established BPD. PEEP level data from infants initially undergoing mechanical ventilation with high-frequency modalities were included if they were subsequently transitioned to conventional mechanical ventilation within 28 days of life. For these infants, PEEP data reflects the subsequent period of conventional mechanical ventilation; mean airway pressure levels applied during high-frequency modalities were not considered. As secondary outcomes, we also assessed initial, minimal, and mean PEEP levels for each subject. As maximal PEEP levels may reflect outlier values selected during exceptional circumstances during an infant's course, analogous results for mean PEEP levels are also presented for key analyses.

We identified infant characteristics that have a plausible association with respiratory disease severity and could, therefore, influence PEEP level selection as covariates to adjust for differences in case-mix between centers. We classified infant characteristics as either baseline or clinical characteristics. Baseline characteristics were those established at birth, and clinical characteristics described the infant's postnatal course. Baseline characteristics considered for adjustment were maternal race, infant sex, receipt of antenatal corticosteroids, maternal chorioamnionitis, cesarean delivery, gestational age, and birth weight. We selected 4 clinical characteristics directly influencing PEEP level selection for a priori mandatory inclusion in the multivariable model used for adjustment: highest fraction of inspired oxygen (FiO_2) prior to or during maximal PEEP level use, need for inotropic support prior to or during maximal PEEP level use, history of air leak syndrome at trial enrollment and history of pulmonary hemorrhage at trial enrollment. Additional clinical characteristics considered for adjustment were 1- and 5-minute Apgar scores, Score for Neonatal Acute Physiology-II[14] at 12 hours of life, receipt of ibuprofen or indomethacin prophylaxis, highest recorded blood gas carbon dioxide prior to or during maximal PEEP level use (mm Hg), duration of intubation in days prior to maximal PEEP level use, use of high-frequency ventilation, and several medications reflective of respiratory disease severity during the course of mechanical ventilation: surfactant, ibuprofen/indomethacin, caffeine, postnatal corticosteroids, and diuretics.

Statistical Analyses

Cohort characteristics were summarized with standard descriptive statistics. Preliminary analyses examined all covariates for potential collinearity. We considered continuous variables with a correlation coefficient of greater than 0.9 and categorical variables with a contingency table diagonal cell count less than 10% of the total sample to be sufficiently collinear for removal from subsequent analyses. No variable pairs met these criteria. We then performed bivariable analyses between all covariates and maximal PEEP level. All covariates associated with maximal PEEP at $P < .05$ were included together with the a priori characteristics in a multivariable linear regression model using robust sandwich variance estimates. This was then repeated adding center to the model as an explanatory variable, using center-specific indicator variables to allow mean maximal PEEP to vary by center. A Wald test provided a global test of difference in PEEP level among centers adjusting for infant characteristics. Graphical displays of PEEP level by center or global region adjusting for infant characteristics were produced by plotting estimated marginal means following multivariable analyses. Model fit for PEEP level selection was compared for all infant characteristics without center, only center, and both together as explanatory variables using R-squared values and Akaike information criterion (AIC).[15] AIC is a measure of the relative quality of fit between models that penalizes the addition of explanatory variables; a decrease in AIC following the addition of variables to a model reflects improved fit despite this penalty. We used AIC to verify that any observed increase in R-square following inclusion of center was

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not simply a reflection of the additional model parameters. Analogous methods were applied to initial, minimal, and mean PEEP levels in secondary analyses. In an additional planned comparison, we compared maximal and mean PEEP levels between global regions adjusting for infant characteristics. In exploratory analyses, we used Spearman correlation coefficient to compare a center's mean maximal PEEP level and the following outcomes: highest FiO_2 during the initial mechanical ventilation course, duration of intubation, proportion of infants with death or BPD, and proportion of infants developing an air leak syndrome postenrollment. All analyses were performed with STATA v 14 (StataCorp, College Station, Texas).

Results

A total of 1009 ELBW infants were enrolled in the NIPPV trial across 34 international centers. Parents of 2 infants withdrew consent. Five hundred five infants received mechanical ventilation prior to enrollment. Of the remaining 502, 303 (60.4%) underwent conventional mechanical ventilation within 28 days of life, of which 25 were enrolled at centers providing fewer than 5 eligible subjects. The final study cohort was composed of 278 infants from 17 centers. Study cohort characteristics are displayed in **Table I**. The median gestational age was 26 weeks, with a median birth weight of 812 g. The median duration of invasive mechanical ventilation support was 2 days. No eligible subjects had a documented pulmonary hemorrhage prior to enrollment, excluding this covariate from subsequent analyses.

The primary outcome of maximal PEEP ranged from 3 to 9 cm H_2O, mean = 5.7 (SD = 0.9). Corresponding values for secondary PEEP level outcomes were initial PEEP: 2-7 cm H_2O, 5.2 (0.7); minimal PEEP: 2-7 cm H_2O, 5.0 (0.7), and mean PEEP: 2.5-7.5 cm H_2O, 5.3 (0.7). **Figure 1** displays the unadjusted observed maximal PEEP levels used in subjects across centers, with larger circles reflecting a greater frequency of observations at the corresponding PEEP level. Maximal PEEP levels between 5 and 7 cm H_2O were most common; 5 of 17 centers (29%) used maximal levels below this range on at least 1 occasion, and 4 of 17 centers (24%) used maximal levels above this range on at least one occasion. Outlying centers tended to cluster as low or high PEEP using centers, with a single center ("N") selecting levels both below and above the 5-7 cm H_2O range.

In multivariable analysis adjusting for infant characteristics and neonatal center, significant associations between infant characteristics and higher maximal PEEP were only observed for longer duration of intubation, use of high frequency ventilation, and receipt of inotropic support (**Table II**; available at www.jpeds.com). Maximal PEEP level variation between centers was significant despite adjustment for infant characteristics (Wald global test of difference among centers, $P < .0001$; **Figure 2**, A). The multivariable model containing all infant characteristics but excluding center had a coefficient of determination (R^2) of 0.16 with an AIC of 715, reflecting that infant characteristics were weakly associated with PEEP level and poorly explained the observed variation.

Table I. Cohort infant characteristics

Variables	(n = 278)
Baseline	
Maternal race, no. (%)*	
White	154 (57)
Black	60 (22)
Asian	34 (13)
Other	23 (8)
Sex, no. (%)	
Female	132 (47)
Male	146 (53)
Received antenatal corticosteroids, no. (%)	256 (92)
Maternal chorioamnionitis diagnosed, no. (%)	48 (17)
Cesarean delivery, no. (%)	190 (69)
Gestational age, median [IQR], wk	26 [25-27]
Birth weight, median [IQR], g	812 [712-905]
Clinical	
One-min Apgar score, median [IQR]	6 [4-7]
Five-min Apgar score, median [IQR]	8 [7-9]
SNAP-II score at 12 h of life, mean (SD)	33.9 (9.9)
History of air leak syndrome at enrollment, no. (%)	3 (1.1)
History of pulmonary hemorrhage at enrollment, no. (%)	0 (0)
Received ibuprofen or indomethacin prophylaxis, no. (%)	43 (15)
Highest recorded FiO_2, median [IQR]†	0.45 [0.32-0.63]
Highest recorded carbon dioxide, median [IQR], mm Hg†	64 [50-77]
Any use of high frequency ventilation, no. (%)	113 (41)
Duration of intubation, median [IQR], d†	2 [0-7]
Therapies received during mechanical ventilation course, no. (%)‡	
Surfactant	60 (22)
Ibuprofen or indomethacin	98 (35)
Caffeine	262 (94)
Inotrope†	37 (13)
Postnatal corticosteroids	33 (12)
Diuretics	64 (23)

SNAP-II, Score for Neonatal Acute Physiology-II.
*$n = 271$; represents greatest degree of missing data for covariates.
†Variable restricted to period of mechanical ventilation occurring prior to observing maximal PEEP.
‡Therapies received during initial postenrollment course of mechanical ventilation restricted to first 28 days of life, unless otherwise specified.

Figure 3 (available at www.jpeds.com) displays predicted mean maximal PEEP levels for each center as a function of infant characteristics, showing minimal variation in the expected PEEP at each center. This further emphasizes that the observed variation was not a reflection of differences in infant characteristics between centers. Addition of center to the multivariable model improved explanatory power substantially (R^2 0.45; AIC 630). Of note, a model with center alone excluding all infant characteristics explained a greater proportion of the PEEP level variation ($R^2 = 0.29$) than the multivariable model without center but including all infant characteristics.

Analogous findings were seen for the secondary outcomes of initial, minimal, and mean PEEP levels. For each, significant PEEP level variation between centers remained despite adjustment for infant characteristics. This is displayed for mean PEEP level in **Figure 2**, B. Also for each, center alone explained a greater proportion of the PEEP level variation than all infant characteristics together. Associations between infant characteristics and secondary PEEP level outcomes as well as a summary table of results analogous to those reported above for maximal PEEP are provided in online-only materials (**Tables III-VI**; available at www.jpeds.com).

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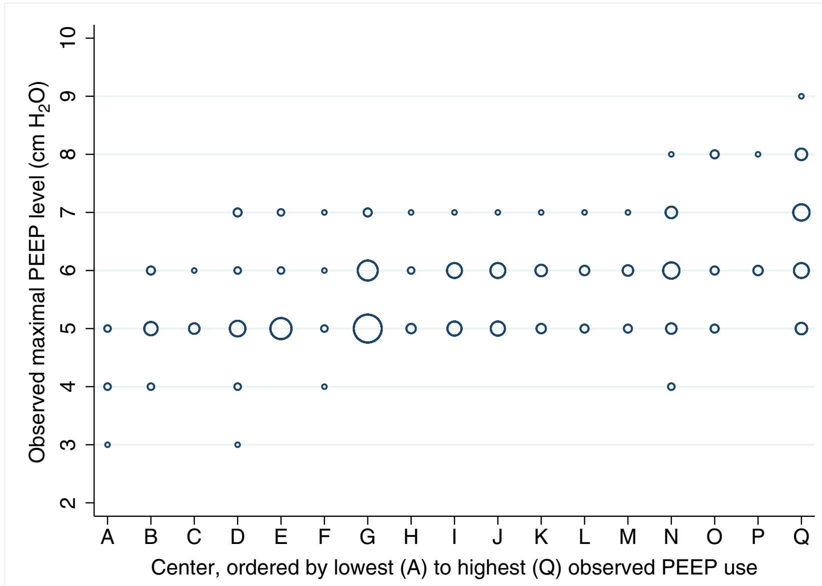

Figure 1. Observed maximal PEEP levels across neonatal centers. Plot depicts unadjusted frequency distribution at each center, ordered from lowest (A) to highest (Q) observed PEEP use. Frequency of subjects at each PEEP level depicted by circle size; larger circles represent a greater number of subjects.

The study cohort had the following global distribution of subjects: US 128 (46%), British Isles 62 (22%), Canada 44 (16%), Middle East 24 (8.6%), and Continental Europe 20 (7.2%). In multivariable analysis evaluating global region as an independent variable and adjusting for infant characteristics, there was significant maximal PEEP level variation among regions (Wald global test of difference among regions, $P < .0001$, Figure 4, A). Canadian centers used higher maximal PEEP

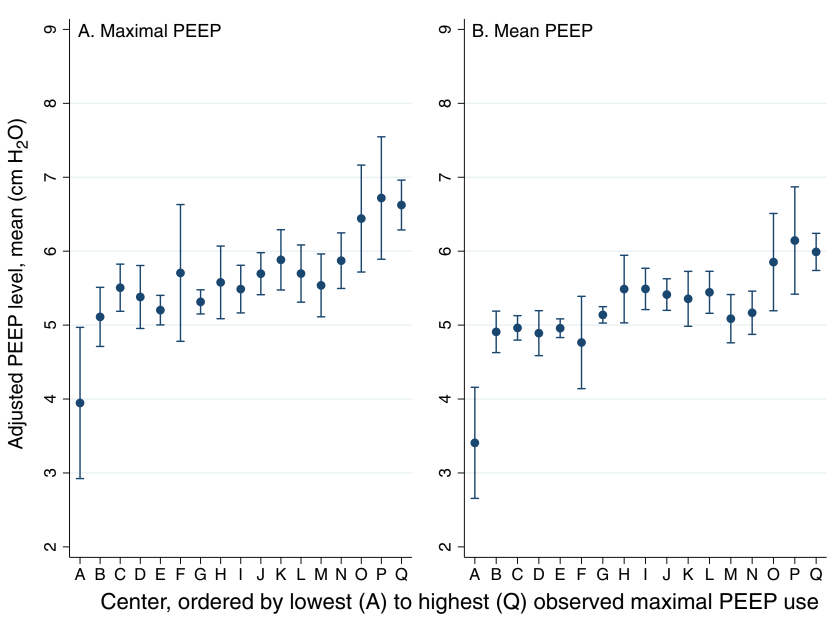

Figure 2. Adjusted PEEP levels across neonatal centers after accounting for differences in infant characteristics. Plots depict estimated marginal means and 95% CIs for each center, ordered from lowest (A) to highest (Q) unadjusted maximal PEEP use. Estimated marginal means obtained through adjustment for all infant characteristics included in multivariable analysis. Results are displayed for **A,** maximal and **B,** mean PEEP levels.

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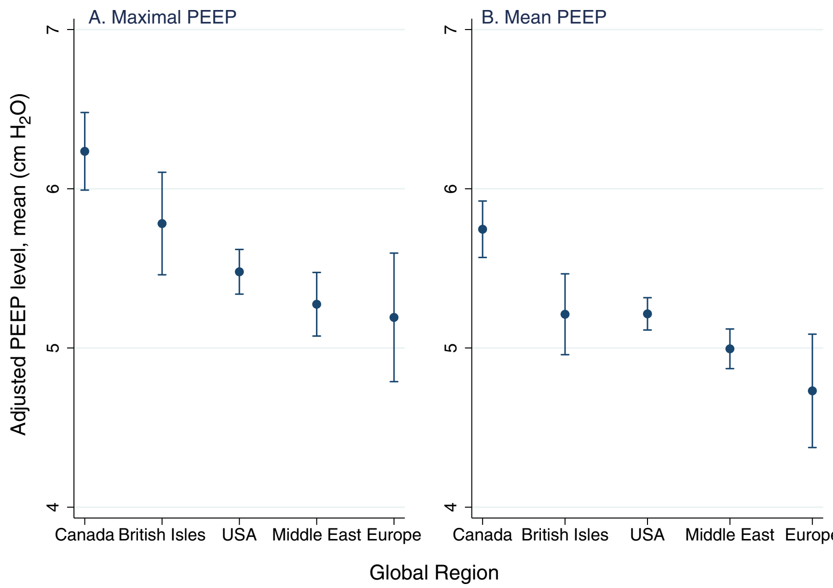

Figure 4. Adjusted PEEP levels across global region after accounting for differences in infant characteristics. Plots depict estimated marginal means and 95% CIs for each global region. Estimated marginal means obtained through adjustment for all infant characteristics in multivariable analysis. Results are displayed for **A,** maximal and **B,** mean PEEP levels.

(adjusted mean = 6.2 cm H_2O, 95% CI = 6.0, 6.5) than all other regions (British Isles 5.8 cm H_2O [5.5, 6.1], United States 5.5 [5.3, 5.6], Middle East 5.3 [5.1, 5.5], continental Europe 5.2 [4.8, 5.6]), and centers in the British Isles used higher maximal PEEP levels than centers in the Middle East and continental Europe. Using an analogous approach, there was also significant mean PEEP level variation among regions (Wald global test of difference among regions, $P < .0001$, **Figure 4**, B). Canadian centers also used higher mean PEEP (adjusted mean = 5.7 cm H_2O, 95% CI = 5.6, 5.9) than all other regions (British Isles 5.2 cm H_2O [5.0, 5.5], US 5.2 [5.1, 5.3], Middle East 5.0 [4.9, 5.1], continental Europe 4.7 [4.4, 5.1]) and centers in the British Isles used higher maximal PEEP levels than centers in continental Europe and centers in the US used higher levels than centers in the Middle East and continental Europe.

We estimated the correlation between each center's mean maximal PEEP level and respiratory outcomes of interest. A moderate positive correlation was observed between higher PEEP use and both longer duration of intubation (rho = 0.4) and greater death or BPD (rho = 0.44), a weak positive correlation between higher center PEEP use and higher delivered FiO_2 (rho = 0.29) and essentially no correlation between higher center PEEP and more air leak syndromes (rho = 0.01). All estimated correlations were not statistically significant in this sample of 17 centers.

Discussion

This study examined whether significant PEEP level variation exists between centers after adjusting for differences in infant characteristics. We found significant between-center variation, such that center alone explained more of the PEEP level variation than all relevant infant characteristics combined. This explanatory power was not simply because of the additional model parameters included, as we observed a sizeable decrease in AIC. These results were found for the main outcome of maximal PEEP level and were consistent for the secondary outcomes of initial, minimal, and mean PEEP level. In contrast to expert opinion that PEEP should be individualized to match an infant's disease severity,[3,5-7] our results suggest that PEEP level selection is currently driven more so by neonatal center than an infant's physiologic needs. Although the observed maximal PEEP level range of 3-9 cm H_2O may not seem excessive in absolute terms, it represents a 3-fold relative difference between the low and high ends of the range. The possibility of meaningful changes in lung function and injury resulting from PEEP levels differences within this range is plausible.[16,17] We observed significant global regional differences, with Canadian centers on average using the highest PEEP levels and continental European centers using the lowest levels. Our finding of lowest PEEP level use in continental Europe is consistent with a 2007-2008 cross-sectional survey from this region that reports a mean random PEEP level of 4.5 cm H_2O. These PEEP levels are lower than any of the regional values observed in this broader international cohort.[12]

We note some limitations in our study. First, there may exist residual confounding. We considered 22 separate infant characteristics, including granular data directly reflective of gas exchange, as covariates in explaining PEEP level selection. However, there may exist infant characteristics associated with PEEP level selection that were not included in our analysis. For example, our data did not capture the degree of expansion observed on chest radiography or an infant's work of breathing;

both may influence clinical PEEP level selection.[18] Second, our findings may not generalize to all ELBW infants requiring mechanical ventilation. We restricted inclusion to infants failing noninvasive support and requiring initial mechanical ventilation after study enrollment to ensure use of accurate, prospectively collected PEEP level and covariate data. We, therefore, excluded infants requiring early mechanical ventilation support, such as those intubated as part of neonatal resuscitation. Further, all infants were born at tertiary care academic neonatal centers. Inferences about global regional differences are made from a restricted sample of centers from each region. Of note, several regions contained both low and high PEEP-using centers.

We assessed only crude correlations between center mean maximal PEEP levels and selected clinically relevant respiratory outcomes of interest because we felt the risk of confounding bias in the association between PEEP level selection and these outcomes was high, particularly in light of the observed global regional differences. Broad differences in population demographics and co-interventions across regions not amenable to adjustment with our data set likely influence these respiratory outcomes. Although positive correlations between higher PEEP and higher FiO_2 requirements, duration of intubation and rates of death or BPD compel further study, we are not able to address this question currently.

Data guiding evidence-based PEEP level selection in preterm infants is lacking. The most recent Cochrane systematic review includes 12 subjects from a single study reporting short-term physiologic outcomes and concludes insufficient evidence for practice recommendation.[11] In contrast, a systematic review of PEEP level selection in adults with acute respiratory distress syndrome includes 7 randomized controlled trials enrolling 2565 patients.[19] This highlights both the relevance of appropriate PEEP level selection in preventing lung injury and the relative paucity of data in preterm infants.

Even descriptive data for PEEP level selection in preterm infants is sparse. We are only aware of the previously mentioned European cross-sectional survey of neonatal ventilation practice reported by Van Kaam et al in 2010.[12] In contrast to our study, this report includes neonates of all birth weights and gestational ages rather than focusing on preterm infants at highest risk of ventilator-induced lung injury and BPD.

In summary, we report significant between-center variation in the selection of PEEP levels for ELBW infants despite adjustment for infant characteristics. We speculate this reflects a lack of data on PEEP level practice in the neonatal literature. Research providing evidence-based guidance for this important aspect of respiratory care in vulnerable preterm infants is needed. ■

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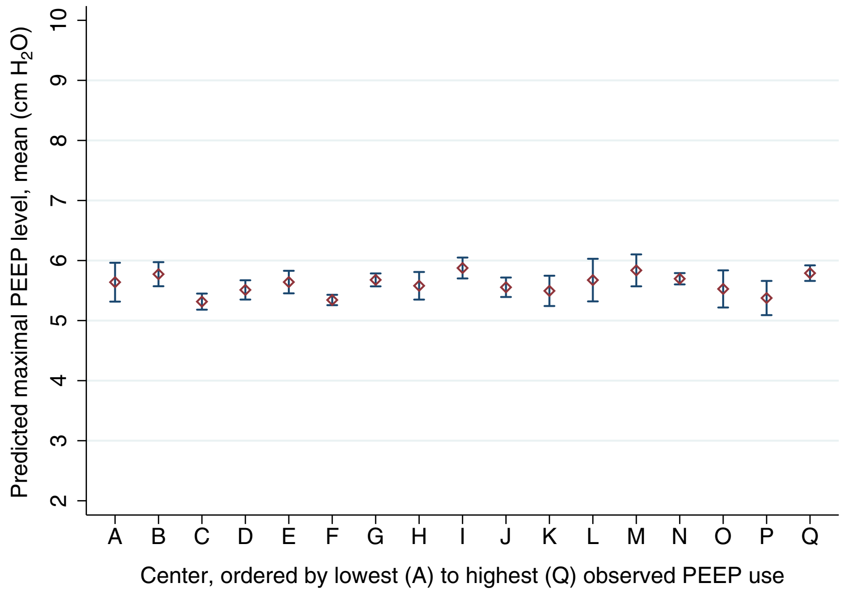

Figure 3. Predicted maximal PEEP levels across neonatal centers as a function of infant characteristics. Plot depicts mean and 95% CIs for each center, ordered from lowest (A) to highest (Q) unadjusted PEEP use. Predicted values for each subject determined by all infant characteristics included in multivariable analysis. This emphasizes that observed variation in PEEP level use across centers is not a reflection of differences in infant characteristics between centers.

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Table II. Infant characteristics: associations with maximal PEEP level used

Variables	Unadjusted bivariable associations* Estimated mean difference (95% CI) in maximal PEEP (cm H_2O)	Adjusted multivariable associations, including center† Estimated mean difference (95% CI) in maximal PEEP (cm H_2O)
Baseline characteristics		
Maternal race		
White (reference)	-	
Black	0.04 (–0.22, 0.30)	
Asian	–0.21 (–0.58, 0.15)	
Other	0.26 (–0.12, 0.63)	
Sex		
Female (reference)	-	
Male	0.16 (–0.06, 0.38)	
Received antenatal corticosteroids	0.22 (–0.17, 0.61)	
Maternal chorioamnionitis diagnosed	–0.14 (–0.46, 0.18)	
Cesarean delivery	–0.07 (–0.31, 0.16)	
Gestational age, per each wk	–0.03 (–0.10, 0.05)	
Birth weight, per each 100 g	–0.05 (–0.13, 0.03)	
Clinical characteristics		
One-min Apgar score, per each point	**–0.05 (–0.10, –0.01)**	–0.02 (–0.06, 0.03)
Five-min Apgar score, per each point	–0.02 (–0.07, 0.04)	
SNAP-II score at 12 h of life, per each 10 points	–0.09 (–0.20, 0.03)	
History of air leak syndrome at enrollment‡	0.01 (–1.93, 1.95)	–0.01 (–1.71, 1.73)
Received ibuprofen or indomethacin prophylaxis	**0.38 (0.04, 0.72)**	0.00 (–0.37, 0.37)
Highest recorded FiO_2, per each 10%‡,§	**0.10 (0.05, 0.15)**	0.03 (–0.01, 0.07)
Highest recorded carbon dioxide, per each 10 mm Hg§	**0.09 (0.04, 0.15)**	–0.03 (–0.09, 0.03)
Any use of high frequency ventilation	**0.35 (0.13, 0.57)**	**0.25 (0.05, 0.45)**
Duration of intubation, per 10 d	**0.34 (0.18, 0.50)**	**0.20 (0.02, 0.38)**
If therapy received during mechanical ventilation course:		
Surfactant	0.10 (–0.17, 0.37)	
Ibuprofen or indomethacin	**0.37 (0.14, 0.60)**	0.22 (–0.02, 0.47)
Caffeine	–0.36 (–0.77, 0.04)	
Inotrope‡,§	**0.64 (0.29, 0.99)**	**0.54 (0.21, 0.86)**
Postnatal corticosteroids	**0.46 (0.08, 0.83)**	–0.18 (–0.52, 0.17)
Diuretics	**0.52 (0.24, 0.81)**	0.21 (–0.08, 0.49)

Bold values highlight variables meeting statistical significance in their respective models.
*Bivariable associations with maximal PEEP level performed for all baseline and clinical characteristics.
†Multivariable analysis included all variables identified a priori as clinically influencing PEEP level selection and all additional variables associated at the 0.05 level with PEEP in bivariable analysis.
‡Included in multivariable model through a priori identification as clinically influencing PEEP level use.
§Variable temporally restricted to period of mechanical ventilation occurring prior to or during maximal PEEP.

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Table III. Infant characteristics: associations with minimal PEEP level used

Variables	Unadjusted bivariable associations* Estimated mean difference (95% CI) in minimal PEEP (cm H_2O)	Adjusted multivariable associations, including center† Estimated mean difference (95% CI) in minimal PEEP (cm H_2O)
Baseline characteristics		
Maternal race		
White (reference)	-	
Black	0.03 (–0.18, 0.23)	
Asian	–0.04 (–0.24, 0.16)	
Other	0.09 (–0.17, 0.35)	
Sex		
Female (reference)		
Male	**0.21 (0.04, 0.38)**	**0.17 (0.02, 0.36)**
Received antenatal corticosteroids	–0.18 (–0.49, 0.12)	
Maternal chorioamnionitis diagnosed	–0.24 (–0.50, 0.02)	
Cesarean delivery	–0.01 (–0.20, 0.18)	
Gestational age, per each wk	0.02 (–0.03, 0.08)	
Birth weight, per each 100 g	0.01 (–0.05, 0.08)	
Clinical characteristics		
One-min Apgar score, per each point	–0.01 (–0.04, 0.03)	
Five-min Apgar score, per each point	0.04 (–0.01, 0.08)	
SNAP-II score at 12 h of life, per each 10 points	–0.00 (–0.01, 0.00)	
History of air leak syndrome at enrollment‡	–0.30 (–0.85, 0.24)	0.17 (–0.55, 0.90)
Received ibuprofen or indomethacin prophylaxis	0.20 (–0.03, 0.43)	
Highest recorded FiO_2, per each 10%‡,§	0.02 (–0.01, 0.06)	0.02 (–0.02, 0.06)
Highest recorded carbon dioxide, per each 10 mm Hg§	0.02 (–0.02, 0.06)	
Any use of high frequency ventilation	–0.01 (–0.18, 0.17)	
Duration of intubation, per each 10 d	–0.03 (–0.15, 0.09)	
If therapy received during mechanical ventilation course:		
Surfactant	–0.09 (–0.27, 0.10)	
Ibuprofen or indomethacin	–0.08 (–0.24, 0.09)	
Caffeine	**–0.30 (–0.59, –0.01)**	–0.11 (–0.43, 0.21)
Inotrope‡,§	–0.14 (–0.36, 0.09)	0.06 (–0.19, 0.31)
Postnatal corticosteroids	**–0.34 (–0.59, –0.09)**	**–0.42 (–0.68, –0.16)**
Diuretics	0.16 (–0.05, 0.37)	

Bold values highlight variables meeting statistical significance in their respective models.
*Bivariable associations with minimal PEEP level performed for all baseline and clinical characteristics.
†Multivariable analysis included all variables identified a priori as clinically influencing PEEP level selection and all additional variables associated at the 0.05 level with PEEP in bivariable analysis.
‡Included in multivariable model through a priori identification as clinically influencing PEEP level use.
§Variable temporally restricted to period of mechanical ventilation occurring prior to or during minimal PEEP.

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Table IV. Infant characteristics: associations with initial PEEP level used

Variables	Unadjusted bivariable associations* Estimated mean difference (95% CI) in initial PEEP (cm H_2O)	Adjusted multivariable associations, including center† Estimated mean difference (95% CI) in initial PEEP (cm H_2O)
Baseline characteristics		
Maternal race		
White (reference)	-	
Black	–0.04 (–0.23, 0.15)	
Asian	–0.17 (–0.39, 0.05)	
Other	–0.09 (–0.33, 0.15)	
Sex		
Female (reference)		
Male	**0.17 (0.00, 0.34)**	0.10 (–0.04, 0.24)
Received antenatal corticosteroids	0.04 (–0.27, 0.36)	
Maternal chorioamnionitis diagnosed	–0.21 (–0.46, 0.03)	
Cesarean delivery	0.07 (–0.12, 0.26)	
Gestational age, per each wk	–0.00 (–0.06, 0.05)	
Birth weight, per each 100 g	0.01 (–0.05, 0.07)	
Clinical characteristics		
One-min Apgar score, per each point	–0.03 (–0.07, 0.01)	
Five-min Apgar score, per each point	0.00 (–0.05, 0.05)	
SNAP-II score at 12 h of life, per each 10 points	–0.00 (–0.01, 0.01)	
History of air leak syndrome at enrollment‡	**–0.55 (–1.10, –0.01)**	–0.57 (–1.19, 0.05)
Received ibuprofen or indomethacin prophylaxis	**0.29 (0.07, 0.51)**	–0.05 (–0.30, 0.21)
FiO_2 at initial PEEP level selection, per each 10%‡	**0.08 (0.03, 0.13)**	**0.05 (0.00, 0.09)**
First recorded carbon dioxide after initial PEEP level selection, per each 10 mm Hg	**0.08 (0.01, 0.14)**	0.06 (–0.01, 0.12)
Any use of high frequency ventilation	0.03 (–0.14, 0.21)	
If therapy received during mechanical ventilation course:		
Surfactant	0.02 (–0.16, 0.20)	
Ibuprofen or indomethacin	–0.04 (–0.21, 0.13)	
Caffeine	–0.23 (–0.59, 0.13)	
Inotrope during initial PEEP level selection‡	–0.03 (–0.36, 0.29)	0.14 (–0.15, 0.43)
Postnatal corticosteroids	–0.15 (–0.39, 0.10)	
Diuretics	0.16 (–0.03, 0.35)	

Bold values highlight variables meeting statistical significance in their respective models.
*Bivariable associations with initial PEEP level performed for all baseline and clinical characteristics.
†Multivariable analysis included all variables identified a priori as clinically influencing PEEP level selection and all additional variables associated at the 0.05 level with PEEP in bivariable analysis.
‡Included in multivariable model through a priori identification as clinically influencing PEEP level use.

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Table V. Infant characteristics: associations with mean PEEP level used

Variables	Unadjusted bivariable associations* Estimated mean difference (95% CI) in mean PEEP (cm H_2O)	Adjusted multivariable associations, including center† Estimated mean difference (95% CI) in mean PEEP (cm H_2O)
Baseline characteristics		
Maternal race		
White (reference)	-	
Black	0.04 (–0.15, 0.23)	
Asian	–0.10 (–0.36, 0.16)	
Other	0.14 (–0.13, 0.42)	
Infant sex		
Female (reference)		
Male	0.14 (–0.02, 0.31)	
Received antenatal corticosteroids	0.06 (–0.26, 0.38)	
Maternal chorioamnionitis diagnosed	–0.20 (–0.46, 0.06)	
Cesarean delivery	0.05 (–0.13, 0.22)	
Gestational age, per each wk	–0.02 (–0.07, 0.04)	
Birth weight, per each 100 g	–0.02 (–0.08, 0.03)	
Clinical characteristics		
One-min Apgar score, per each point	–0.02 (–0.06, 0.01)	
Five-min Apgar score, per each point	0.01 (–0.03, 0.05)	
SNAP-II score at 12 h of life, per each 10 points	–0.01 (–0.01, 0.00)	
History of air leak syndrome at enrollment‡	–0.18 (–1.26, 0.90)	0.11 (–0.99, 1.20)
Received ibuprofen or indomethacin prophylaxis	**0.27 (0.03, 0.50)**	–0.14 (–0.41, 0.14)
Highest recorded FiO_2, per each 10%‡	**0.04 (0.01, 0.08)**	0.02 (–0.02, 0.05)
Highest recorded carbon dioxide, per each 10 mm Hg	**0.04 (0.01, 0.08)**	0.02 (–0.03, 0.07)
Any use of high frequency ventilation	0.13 (–0.04, 0.30)	
Duration of intubation, per 10 d	**0.13 (0.03, 0.23)**	0.02 (–0.10, 0.14)
If therapy received during mechanical ventilation course:		
Surfactant	0.07 (–0.11, 0.26)	
Ibuprofen or indomethacin	0.13 (–0.03, 0.29)	
Caffeine	–0.26 (–0.53, 0.00)	
Inotrope‡	0.17 (–0.06, 0.40)	0.15 (–0.07, 0.38)
Postnatal corticosteroids	0.02 (–0.24, 0.28)	
Diuretics	0.16 (–0.05, 0.37)	

Bold values highlight variables meeting statistical significance in their respective models.
*Bivariable associations with mean PEEP level performed for all baseline and clinical characteristics.
†Multivariable analysis included all variables identified a priori as clinically influencing PEEP level selection and all additional variables associated at the 0.05 level with PEEP in bivariable analysis.
‡Included in multivariable model through a priori identification as clinically influencing PEEP level use.

Table VI. Neonatal center explains a significant proportion of the minimal, initial and mean PEEP level variation observed in ELBW infants

PEEP level	Neonatal center, Wald-test for global group difference in adjusted multivariable analysis	Multivariable model with infant characteristics and center		Multivariable model with infant characteristics*		Model with center only	
		R^2	AIC	R^2	AIC	R^2	AIC
Minimal	$P < .0001$	0.33	538	0.08	595	0.29	542
Initial	$P < .0001$	0.38	521	0.11	598	0.33	532
Mean	$P < .0001$	0.40	485	0.06	579	0.34	499

R^2, coefficient of determination.
*Multivariable model included all variables identified a priori as clinically influencing PEEP level selection and all additional variables associated at the 0.05 level with each respective PEEP level outcome in bivariable analyses.

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