Empirical Probability of Positive Response to PEEP Changes and Mechanical Ventilation Factors Associated With Improved Oxygenation During Pediatric Ventilation

Craig D Smallwood, Brian K Walsh, John H Arnold, and Andrew Gouldstone

BACKGROUND: PEEP is titrated to improve oxygenation during mechanical ventilation. It is clinically desirable to identify factors that are associated with a clinical improvement or deterioration following a PEEP change. However, these factors have not been adequately described in the literature. Therefore, we aimed to quantify the empirical probability of PEEP changes having a positive effect upon oxygenation, compliance of the respiratory system (C_{RS}), and the ratio of dead space to tidal volume (V_D/V_T). Further, clinical factors associated with positive response during pediatric mechanical ventilation are described. METHODS: Mechanically ventilated pediatric subjects in the ICU were eligible for inclusion in the study. During PEEP increases ($PEEP_{increase}$), a responder was defined as having an improved S_{pO_2}/F_{IO_2} ratio; non-responders demonstrated a worsening S_{pO_2}/F_{IO_2} ratio in the following hour. When PEEP was decreased ($PEEP_{decrease}$), a responder was anyone who maintained or increased the S_{pO_2}/F_{IO_2} ratio; non-responders demonstrated a worsening S_{pO_2}/F_{IO_2} ratio. Features from continuous mechanical ventilation variables were extracted, and differences between responders and non-responders were identified. RESULTS: 286 PEEP change cases were eligible for analysis in 76 subjects. For $PEEP_{increase}$ cases, the empirical probability of positive response was 56%, 67%, and 54% for oxygenation, C_{RS}, and V_D/V_T, respectively. The median S_{pO_2}/F_{IO_2} increase was 13. For $PEEP_{decrease}$, the empirical probability of response was 46%, 53%, and 46% for oxygenation, C_{RS}, and V_D/V_T, respectively. $PEEP_{increase}$ responders had higher F_{IO_2} requirements (70.8 vs 52.5%, $P < .001$), mean airway pressure (14.0 vs 12.9 cm H_2O, $P = .03$), and oxygen saturation index (9.9 vs 7.5, $P = .002$) versus non-responders. For $PEEP_{decrease}$, V_D/V_T was lower in responders (0.46 vs 0.50, $P = .031$). CONCLUSIONS: In children requiring mechanical ventilation, the responder rate was modest for both $PEEP_{increase}$ and $PEEP_{decrease}$ cases. These data suggest that PEEP titration often does not have the desired clinical effect, and predicting which patients will manifest a positive response is complex, requiring more sophisticated means of assessing individual subjects. *Key words: mechanical ventilation; positive end-respiratory pressure; oxygenation; dead-space ventilation; pediatrics*. [Respir Care 2019;64(10):1193–1198. © 2019 Daedalus Enterprises]

Introduction

In mechanically ventilated children with hypoxic respiratory failure, PEEP titration is typically implemented to improve oxygenation through the reversal of atelectasis and prevention of further alveolar collapse. However, PEEP can ameliorate or exacerbate lung injury.[1] PEEP changes are frequently made at the bedside, but little guidance exists in the pediatric literature to predict who is likely to respond to an intervention. The physiologic rationale for increasing PEEP in most cases is to improve functional

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residual capacity and to reduce the physiologic ratio of dead space to tidal volume (V_D/V_T), shunt fraction, and ventilation/perfusion mismatch.[2-4] Although the use of moderate to high levels of PEEP has been shown to be safe

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in the pediatric population,[5-8] widespread and consistent application has not been recommended.[9,10] Oxygenation is an important clinical target in pediatric subjects because it is associated with lower mortality during severe illness, such as ARDS.[11,12] Despite the importance of oxygenation, there is a paucity of investigations reporting the proportion of PEEP changes that are associated with a positive response, and investigations targeting PEEP management are needed.[13] Therefore, we sought to quantify the proportion of PEEP changes that had a positive effect on oxygenation in children receiving mechanical ventilation and to identify factors that could be readily obtained at the bedside that are associated with response.

QUICK LOOK

Current knowledge

PEEP is typically titrated to improve oxygenation during mechanical ventilation, but can be adjusted to impact compliance and hemodynamics. PEEP can ameliorate or exacerbate lung injury.

What this paper contributes to our knowledge

In children requiring mechanical ventilation, improvements in oxygenation were observed only in 56% and 46% of PEEP increases and decreases, respectively. These data suggest that PEEP titration often does not have the desired clinical effect, particularly during ventilator weaning.

Methods

Subjects were enrolled in the study if they were admitted to the pediatric ICU, age was < 18 y, they received mechanical ventilation for > 24 h, continuous mechanical ventilation data were recorded during that time period, and they exhibitted hypoxic respiratory failure defined as an oxygen saturation index ≥ 5.[9]

All subjects were mechanically ventilated (Servo-i, Getinge AB-Maquet, Gothenburg, Sweden) and connected to a bedside physiologic monitor (IntelliVue MP90, Philips Healthcare, Andover, Massachusetts). A medical device-interfacing module (IntelliBridge EC10, Philips Healthcare) was used to connect the mechanical ventilator and monitor to a research server. Data were recorded at a frequency of 0.2 Hz for the duration of invasive mechanical ventilation in the ICU. Demographic and outcome data were abstracted from the medical record for each subject, and the diagnosis was recorded according to the ICD-9 and ICD-10 codes and binned to either primary respiratory, surgical procedure, neurologic, sepsis, or other.[14] The modified Bohr V_D/V_T was calculated according to established methods.[15,16] Usual ventilator management included lung-protective strategies where appropriate (permissive hypercapnia, tidal volumes ~5–8 mL/kg), titration of PEEP according to the S_{pO_2} and F_{IO_2} requirement, and maintenance of endotracheal tube leak to be < 10%.

Both the physiologic monitor and mechanical ventilator offer built-in preprocessing inclusive of artifact detection. However, these signals can still be corrupted by noise and artifact.[17] A band-pass filter was applied to physiologic data to filter out data that were beyond the physiologic range according to established methods.[18]

For all included subjects, an instance where PEEP was manipulated was identified to assess response to PEEP and extract data from the required time period. These PEEP cases were defined as a 2-h period: 1 h preceding and 1 h following a change in PEEP. This time frame has been reported as the time required to achieve equilibration of pulmonary compliance and oxygenation following modest changes in PEEP level in mechanically ventilated children.[19] A quality function was built to ensure that only clean cases were analyzed. A clean PEEP case was defined as one in which no ventilator changes were made (other than PEEP and F_{IO_2}); the PEEP change was sustained for > 1 h.

For cases in which the PEEP was increased, a responder was defined as an individual who exhibited any improvement in oxygenation by S_{pO_2}/F_{IO_2} ratio, dynamic compliance of the respiratory system (C_{RS}), or V_D/V_T; $[x_{post} - x_{pre}] > 0$ (where $x = [S_{pO_2}/F_{IO_2}$ ratio, C_{RS}, $V_D/V_T]$). For cases in which PEEP was decreased, a responder was defined as an individual in whom S_{pO_2}/F_{IO_2} ratio, C_{RS}, or V_D/V_T was maintained; $[x_{post} - x_{pre}]$ (where $x = [S_{pO_2}/F_{IO_2}$, C_{RS}, $V_D/V_T]) \geq 0$.

The D'Agostino and Pearson omnibus test was applied to test the normality of the data. Because the data were not normally distributed, continuous variables are presented as median values with interquartile ranges (IQR). Subjects had multiple cases where PEEP was increased or decreased. To account for this, generalized estimating equations were utilized to compare continuous demographic and respiratory features and categorical features between responders

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Table 1. Description of the Study Population

Parameter	Value
Age, y	1.9 (0.9–6.6)
Sex, *n* female (%)	38 (50)
Weight, kg	10.3 (7.1–20.0)
Height, cm	80 (65–109)
Ventilation duration, d	5.7 (3.4–14.4)
ICU length of stay, d	11.0 (5.7–20.9)
Hospital length of stay, d	22.0 (7.5–108.1)
Primary diagnosis, *n* (%)	
Respiratory	25 (33)
Surgical	18 (24)
Sepsis	6 (8)
Neurologic	5 (7)
Other	22 (29)

Continuous values are expressed as median (interquartile range) unless otherwise indicated.

and non-responders (by S_{pO_2}/F_{IO_2} ratio). Data aggregation, cleaning, and analyses were conducted using MATLAB (V9.1.0.441655, Mathworks, Natick, Massachusetts). Statistical analyses were performed using SPSS v. 23 (SPSS, Chicago, Illinois). The study protocol was approved by the institutional review board.

Results

In total, 76 subjects demonstrated PEEP change cases that were included in the analysis. A description of the population is shown in Table 1. A total of 286 PEEP cases were analyzed (ie, 166 increases and 120 decreases). The PEEP was increased by 1, 2 and $\geq$ 3 cm H_2O in 58%, 26%, and 16% of the cases, respectively. The PEEP was decreased by 1, 2 and 3 cm H_2O in 80%, 17%, and 3% of the cases, respectively. In the $PEEP_{increase}$ cases, the empirical probability of positive response was 56%, 67%, and 54% for S_{pO_2}/F_{IO_2} ratio, C_{RS}, and V_D/V_T, respectively. For $PEEP_{decrease}$, the empirical probability of acceptable response was 46%, 53%, and 46% for oxygenation, mechanics, and V_D/V_T, respectively.

There were statistically significant differences in ventilation parameters in the hour preceding the PEEP change in the $PEEP_{increase}$ group; responders had higher F_{IO_2} (70.8% vs 52.5%, $P < .001$), higher mean airway pressure (14.0 vs 12.9 cm H_2O, $P = .03$), and increased oxygen saturation index (9.9 vs 7.5, $P = .002$) in the hour preceding the PEEP change compared to non-responders (Table 2).

For $PEEP_{increase}$ group, the median (IQR) change in S_{pO_2}/F_{IO_2} ratio was 13 (5-30) and −19 (−40 to −7) for responders and non-responders, respectively. For decreases in PEEP, the responder rate was 47%, and V_D/V_T was lower in responders compared to non-responders (0.46 vs 0.50, $P = .031$) (Table 3). For the $PEEP_{decrease}$ group, the median (IQR) change in S_{pO_2}/F_{IO_2} ratio was 8 (3-21) and −8 (−16 to −3) for responders and non-responders, respectively. There were no differences in age, weight, height, or sex between responders and non-responders for either the $PEEP_{increase}$ group or the $PEEP_{decrease}$ group.

Discussion

Quantifying the proportion of PEEP changes having a positive or acceptable effect on oxygenation in children is important. Our data show that, when increasing PEEP as a part of routine care, oxygenation was improved in just over half (56%) of the cases. Responders demonstrated worse lung injury relative to non-responders with significantly greater F_{IO_2} requirements, mean airway pressure, and oxygen saturation index in the hour preceding the change. On the other hand, just under half (47%) of cases demonstrated acceptable oxygenation following a decrease in PEEP. There were no differences in the demographic or ventilator features between $PEEP_{decrease}$ responders and non-responders.

Most pediatric experimental and clinical investigations including PEEP titration have been done in combination with a recruitment maneuver.[6,20-22] Few studies in the pediatric literature have assessed the titration of PEEP without a recruitment maneuver. In the adult literature, end-expiratory transpulmonary pressure,[23] dynamic compliance,[24] dead space,[25] electrical impedance tomography, computed tomography,[26] and ultrasonography[27] have been proposed as methods to individualize or assess PEEP titration. In a cohort of adult subjects with ARDS, Pintado et al[28] assessed the utility of an individualized approach to setting PEEP based on best pulmonary compliance. The authors did not report the success of individual PEEP changes but did note that, in the compliance-guided group, the P_{aO_2}/F_{IO_2} ratio was 146 compared to 133 in the control group. However, this finding was not statistically significant and represented only a trend. In our study, we sought to quantify the number of PEEP changes that would be classified as responders or non-responders. Further, mechanically ventilated children have been noted to have distinct pathophysiologic characteristics during lung injury compared to adults; children have increased chest wall compliance, preserve the function of surfactant during lung injury, and have immune response that are different from those of adult subjects.[29-31] Head-to-head comparison with adult studies must be done with this in mind.

Weaning from mechanical ventilation includes stepped reduction in ventilator support (including PEEP) and comprises up to 40% of the total duration of ventilation.[32] In children, efforts to introduce protocols for ventilator weaning have demonstrated mixed results.[33-35] Inappropriate application of PEEP can result in alveolar over distention, increased work of breathing, worsening ventilation-perfusion matching, as well as effects on the circulatory system

Table 2. Comparison Between PEEP Responders and Non-Responders Following a PEEP Increase

Clinical Parameter	Responders*	Non-Responders	*P*
C_{dyn}, mL/kg/cm H_2O	0.42 (0.25–0.53)	0.44 (0.29–0.50)	.60
PEEP, cm H_2O	8 (6–10)	7 (5–8)	.44
S_{pO_2}, %	95 (93–97)	94 (93–96)	.45
P_{peak}, cm H_2O	24 (22–28)	23 (20–26)	.21
F_{IO_2}, %	71 (55–86)	52 (46–65)	< .001
V_T, mL/kg	6.0 (5.0–7.2)	6.7 (5.3–7.2)	.43
Breathing frequency, breaths/min	28 (24–36)	27 (24–32)	.37
$\bar{P}_{aw}$, cm H_2O	14.0 (11.9–16.5)	13.0 (10.8–14.8)	.03
Oxygen saturation index	9.9 (7.4–14.8)	7.5 (5.7–8.4)	.002
V_D/V_T	0.47 (0.42–0.52)	0.44 (0.40–0.51)	.52
ΔPEEP, *n* (%)	1 (1–2)	1 (1–2)	.73
1 cm H_2O	59 (63)	37 (51)	
2 cm H_2O	19 (20)	24 (26)	
3 cm H_2O	14 (15)	11 (15)	
4 cm H_2O	2 (2)	0 (0)	

Continuous values are expressed as median (interquartile range) unless otherwise indicated.
* Responders were defined as those demonstrating oxygenation improvement in the first hour following the PEEP change relative to the preceding hour.
C_{dyn} = dynamic respiratory system compliance
P_{peak} = peak airway pressure
V_T = tidal volume
$\bar{P}_{aw}$ = mean airway pressure
V_D = dead space volume

Table 3. Comparison Between PEEP Responders and Non-Responders Following a PEEP Decrease

Clinical Parameter	Responders*	Non-Responders	*P*
C_{dyn}, mL/kg/cm H_2O	0.45 (0.38–0.60)	0.48 (0.32–0.54)	.41
PEEP, cm H_2O	8 (7–10)	8 (7–11)	.68
S_{pO_2}, %	96 (95–97)	96 (93–97)	.73
P_{peak}, cm H_2O	24 (22–26)	25 (21–27)	.93
F_{IO_2}, %	54 (50–64)	52 (47–73)	.59
V_T, mL/kg	6.8 (6.0–7.7)	6.1 (5.6–7.3)	.23
Breathing frequency, breaths/min	27 (23–32)	30 (25–38)	.22
$\bar{P}_{aw}$, cm H_2O	13.7 (11.9–15.7)	13.4 (12.0–16.6)	.94
Oxygen saturation index	7.4 (6.2–11.6)	7.5 (6.4–11.3)	.81
V_D/V_T	0.46 (0.42–0.53)	0.50 (0.44–0.63)	.03
ΔPEEP, *n* (%)	1 (1–1)	1 (1–1)	
−3 cm H_2O	2 (4)	1 (2)	
−2 cm H_2O	9 (16)	12 (19)	
−1 cm H_2O	45 (80)	51 (80)	

Continuous values are expressed as median (interquartile range) unless otherwise indicated.
* Responders were defined as those demonstrating oxygenation improvement in the first hour following the PEEP change relative to the preceding hour.
C_{dyn} = dynamic respiratory system compliance
P_{peak} = peak airway pressure
V_T = tidal volume
$\bar{P}_{aw}$ = mean airway pressure
V_D = dead space volume

and distribution of blood flow within the lung itself.[36-38] These factors could delay weaning and prolong duration of mechanical ventilation. The fact that we were only able to identify a single factor associated with a positive weaning response supports these reports. The use of V_D/V_T has been shown to be associated with the discontinuation of pediatric mechanical ventilation.[39] However, the prognostic value of using V_D/V_T has not be adequately demonstrated and therefore embedding these findings into clinical practice remains difficult.

There are important limitations to our study that should also be considered. The study was conducted retrospectively, and therefore the PEEP increases and decreases were not strictly controlled. Indeed, in cases where oxygenation is acceptable but chest wall compliance is poor, PEEP is increased to reduce the work of breathing. However, because this study was designed to assess the prevalence of responders and non-responders to current practice (usual care), a protocol could not be designed to ascribe specific conditions for PEEP titration. Furthermore, the prevalence of obesity-induced reductions in chest wall compliance are rare in children, especially because the cohort age, height, and weight were reasonable. The definitions for positive response to PEEP increases and decreases may not be acceptable for all patients and conditions. For instance, a stricter definition for positive response would only reduce the proportion of responders. Subjects enrolled in this study demonstrated a mix of demographics and underlying conditions; therefore, application of the findings to specific diseases may not be appropriate without further study. However, the cohort largely reflects a mix of conditions and severity of illness that is typically seen in large academic pediatric ICU environment.

Conclusions

In children requiring mechanical ventilation with hypoxic respiratory failure, the empirical probability of a positive response was not much better than the flip of a coin, ranging from 46% to 67%). These data suggest that PEEP titration is a difficult clinical problem and that improved methods for responder identification are needed. Factors associated with a positive response include the baseline PEEP level, higher peak inspiratory pressure, higher F_{IO_2}, higher mean airway pressure, and increased oxygen saturation index. A reduced V_D/V_T was associated with successfully decreasing PEEP. These data provide baseline performance data for PEEP titration and may provide valuable information for future methods needed to aid clinicians in identifying subjects likely to benefit from or tolerate a change in PEEP.

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