Effort of Breathing in Children Receiving High-Flow Nasal Cannula

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Objective: High-flow humidified nasal cannula is often used to provide noninvasive respiratory support in children. The effect of high-flow humidified nasal cannula on effort of breathing in children has not been objectively studied, and the mechanism by which respiratory support is provided remains unclear. This study uses an objective measure of effort of breathing (Pressure. Rate Product) to evaluate high-flow humidified nasal cannula in critically ill children.

Design: Prospective cohort study.

Setting: Quaternary care free-standing academic children's hospital.

Patients: ICU patients younger than 18 years receiving high-flow humidified nasal cannula or whom the medical team planned to extubate to high-flow humidified nasal cannula within 72 hours of enrollment.

Interventions: An esophageal pressure monitoring catheter was placed to measure pleural pressures via a Bicore CP-100 pulmonary mechanics monitor. Change in pleural pressure (ΔPes) and respiratory rate were measured on high-flow humidified nasal cannula at 2, 5, and 8 L/min. ΔPes and respiratory rate were multiplied to generate the Pressure.Rate Product, a well-established objective measure of effort of breathing. Baseline Pes, defined as pleural pressure at end exhalation during tidal breathing, reflected the positive pressure generated on each level of respiratory support.

Measurements and Main Results: Twenty-five patients had measurements on high-flow humidified nasal cannula. Median age was 6.5 months (interquartile range, 1.3–15.5 mo). Median Pressure,Rate Product was lower on high-flow humidified nasal cannula 8 L/min (median, 329 cm H_2O·min; interquartile range, 195–402) compared with high-flow humidified nasal cannula 5 L/min (median, 341; interquartile range, 232–475; $p = 0.007$) or high-flow humidified nasal cannula 2 L/min (median, 421; interquartile range, 233–621; $p < 0.0001$) and was lower on high-flow humidified nasal cannula 5 L/min compared with high-flow humidified nasal cannula 2 L/min ($p = 0.01$). Baseline Pes was higher on high-flow humidified nasal cannula 8 L/min than on high-flow humidified nasal cannula 2 L/min ($p = 0.03$).

Conclusions: Increasing flow rates of high-flow humidified nasal cannula decreased effort of breathing in children, with the most significant impact seen from high-flow humidified nasal cannula 2 to 8 L/min. There are likely multiple mechanisms for this clinical effect, including generation of positive pressure and washout of airway dead space. (*Pediatr Crit Care Med* 2014; 15:1–6)

Key Words: noninvasive ventilation; positive pressure ventilation; respiratory distress; respiratory effort; respiratory support; work of breathing

High-flow humidified nasal cannula (HFNC) is a commonly used mode of noninvasive respiratory support in infants and children (1). This unique oxygen delivery system warms and humidifies air before it passes into the nasal cavity, enabling flows up to 30 L/min to be comfortably delivered in pediatric patients. HFNC is often preferred over other methods of noninvasive respiratory support because it is better tolerated by patients and has a compact delivery system allowing more room for patient care (2, 3). Despite its widespread use, little is known about the effect of HFNC on effort of breathing in the pediatric population or the mechanism by which HFNC may provide respiratory support (4).

Use of an objective measure of effort of breathing can help answer these questions for pediatric patients. Previous pediatric studies have used clinical scoring systems to suggest improved effort of breathing on HFNC (5, 6). However, validity of clinical scoring systems may be affected by observer bias and poor interrater reliability, making it difficult to draw meaningful conclusions from these studies (7). Nonpediatric

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studies that use more objective measures of respiratory effort report no improvement in effort of breathing on HFNC compared with standard nasal cannula (NC) or nasal continuous positive airway pressure (CPAP) (8, 9). Pressure.Rate Product (PRP), calculated by multiplying the change in pleural pressure and respiratory rate (RR), provides a more objective measure of effort of breathing than clinical respiratory scores and has been well established in children and adults (10–13). Placement of an esophageal pressure (Pes) monitoring catheter enables direct measurement of Pes as a surrogate for pleural pressure in this calculation.

This study evaluates the effect of HFNC on effort of breathing, as determined by PRP. We hypothesized that effort of breathing would significantly decrease as flow rate of HFNC increased in critically ill children.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board at Children's Hospital Los Angeles. Children admitted to the PICU or cardiothoracic ICU (CTICU) from May 2010 to November 2011 were screened for enrollment. Children younger than 18 years who were receiving HFNC or whom the medical team planned to extubate to HFNC within 72 hours of enrollment were included. Children with recent facial, oropharyngeal, or esophageal surgery or trauma and children with bilateral choanal obstruction were excluded, as bedside placement of Pes monitoring catheters was not possible for these patients. Patients with missing data on both CPAP and HFNC were also excluded. Direct measurement of Pes was performed using an Pes monitoring catheter (Viasys, Yorba Linda, CA) and a Bicore CP-100 pulmonary mechanics monitor (CareFusion, Yorba Linda, CA).

Study Design

We conducted a prospective cohort study to evaluate effort of breathing, as determined by PRP, at increasing flow rates of HFNC in critically ill children. After informed consent was obtained, an Pes monitoring catheter appropriate for the patient's age and height was placed. A Bicore CP-100 pulmonary mechanics monitor was attached to the esophageal catheter to record pressure measurements. Correct placement in the lower one third of the esophagus was confirmed by occlusion test, showing simultaneously measured negative deflections in esophageal and airway pressure on intubated patients and by Pes waveforms and chest radiograph on nonintubated patients (14). Pes measurements were recorded while on CPAP mode of ventilation of 4–5 cm H_2O for intubated patients. Patients were then extubated to HFNC at flow rates ranging from 2 to 8 L/min as determined by the primary medical team. HFNC was then adjusted to 2, 5, and 8 L/min in random order, and measurements were recorded at each rate of flow. F_{IO_2} was kept constant for all patients during CPAP and HFNC measurements. Pes and RR measurements were also recorded on a standard NC gas flow circuit, attached to wall oxygen and humidification per hospital protocol and delivered at a constant rate of 2 L/min with F_{IO_2} of 1. Nasal prongs were left in place when switching from HFNC to standard NC gas flow to minimize patient agitation and discomfort. The distal end of the tubing connected to the nasal prongs was disconnected from the HFNC circuit and reconnected to the standard NC gas flow circuit. This was done after measurements on HFNC were complete to minimize the number of times the HFNC circuit was disconnected. Pes measurements were collected for a minimum of 2 minutes during periods of quiet breathing on each level of respiratory support. Additional data elements, including heart rate, RR, peripheral oxygen saturation, activity level, and nursing interventions, were recorded.

Change in pleural pressure (ΔPes) was calculated based on Pes waveform analysis as the difference between average peak and trough Pes measurements during tidal breathing. Average RR was determined and used to calculate the PRP (ΔPes × RR) for each patient on each level of respiratory support. Baseline Pes was defined as the peak Pes during normal tidal exhalation. Baseline Pes measurements reflect the positive pressure generated on each level of respiratory support.

Statistical Analysis

Descriptive statistics were performed for all PRP, ΔPes, RR, and Baseline Pes data. Square root transformation was used for analysis of nonparametric data. Repeated-measures analysis of variance was used to compare data across all levels of respiratory support. Post hoc correction for multiple comparisons was performed using a Bonferroni correction for unequal group sizes. All data were analyzed using Stata Statistical Software: Release 12 (StataCorp, College Station, TX).

RESULTS

Demographic data for the 25 children enrolled in the study are presented in **Table 1**. Study patients had a median age of 6.5 months (interquartile range [IQR], 1.3–15.5) and median weight of 6.4 kg (IQR, 4.0–8.5). The most common reason for ICU admission was pre- or postsurgical procedure (13, 52%). Nine patients (36%) had a primary diagnosis of complex congenital heart disease, and 20 patients (80%) were intubated at time of study enrollment.

ΔPes and RR measurements were collected on HFNC for 25 patients, CPAP for 18 patients, and standard NC for 20 patients. CPAP measurements were excluded for one patient in whom postextubation upper airway obstruction limited comparison of CPAP and HFNC measurements. One patient had missing data on HFNC 2 L/min due to displacement of the esophageal catheter, and one patient had missing data on HFNC 8 L/min due to technical issues with the Bicore machine.

PRP, ΔPes, and RR were analyzed for all 25 patients (**Table 2**). Median PRP was significantly lower on HFNC 8 L/min (median, 329 cm H_2O·min; IQR, 195–402) compared with HFNC 5 L/min (median, 341; IQR, 232–475; $p = 0.007$) or HFNC 2 L/min (median, 421; IQR, 233–621; $p < 0.0001$) and was lower on

HFNC 5 L/min compared with HFNC 2 L/min ($p = 0.01$) (**Fig. 1**). Median PRP was lower on CPAP (median, 334; IQR, 159–390) compared with standard NC ($p < 0.0001$) and HFNC 2 L/min ($p = 0.003$) but not compared with HFNC 5 L/min or HFNC 8 L/min (all $p > 0.05$).

There was a trend toward lower median ΔPes on HFNC 8 L/min compared with standard NC ($p = 0.05$) but not compared with HFNC 2 L/min or HFNC 5 L/min (all $p > 0.05$). Median ΔPes was lower on CPAP (median, 9.9 cm H_2O; IQR, 3.6–15) compared with standard NC (median, 11.8; IQR, 7.3–20.0; $p < 0.0001$), HFNC 2 L/min (median, 12.9; IQR, 6.3–18.0; $p < 0.0001$), or HFNC 5 L/min (median, 14.0; IQR, 6.0–18.3; $p = 0.002$) but not compared with HFNC 8 L/min (median, 12.2; IQR, 6.4–17.3; $p = 0.07$).

Median RR was significantly lower on HFNC 8 L/min (median, 29 breaths/min; IQR, 22–40) compared with CPAP (median, 35; IQR, 25–54; $p = 0.001$), standard NC (median, 32; IQR, 26–54; $p < 0.0001$), or HFNC 2 L/min (median, 34; IQR, 27–54; $p < 0.0001$) but not compared with HFNC 5 L/min (median, 29; IQR, 25–46; $p = 0.12$). Median RR was lower on HFNC 5 L/min than on HFNC 2 L/min ($p = 0.042$).

Baseline Pes was analyzed for the 18 patients with CPAP data as a measure of the positive pressure generated on each level of respiratory support (**Fig. 2**). Baseline Pes was higher on CPAP (mean ± SD) (5.7 cm H_2O ± 4.8) compared with standard NC (3.9 ± 4.3; $p = 0.03$), HFNC 2 L/min (3.8 ± 3.9; $p = 0.002$), or HFNC 5 L/min (4.1 ± 4.5; $p = 0.009$) but not compared with HFNC 8 L/min (4.5 ± 4.3; $p = 0.13$). When all 25 patients with HFNC measurements were included in this analysis, we found that Baseline Pes was higher on HFNC 8 L/min compared with HFNC 2 L/min ($p = 0.03$). However, there was no difference in Baseline Pes on HFNC 8 L/min compared with HFNC 5 L/min ($p > 0.05$) or on HFNC 5 L/min compared with HFNC 2 L/min ($p > 0.05$).

None of the children had clinically notable adverse events including pneumothorax or pneumomediastinum. One patient was reintubated within 24 hours due to upper airway obstruction.

TABLE 1. Demographic Characteristics of the Study Population

Demographic Variable	
Total number of patients	25
Age (mo)[a]	6.5 (1.3–15.5)
Weight (kg)[a]	6.4 (4.0–8.5)
Gender (male)	12 (48%)
Location of admission	
PICU	16 (64%)
Cardiothoracic ICU	9 (36%)
ICU admit category	
Procedure[b]	13 (52%)
Respiratory distress	9 (36%)
Neurologic compromise	1 (4%)
Metabolic derangement	2 (8%)
Comorbidities	
Complex congenital heart disease[c]	9 (36%)
Chronic lung disease	8 (32%)
Intubation history	
Intubated at study enrollment	20 (80%)
Days intubated prior to study enrollment[a]	7 (4–13)

[a]Median with interquartile range.
[b]Immediately pre- or postoperative.
[c]Not including simple atrial or ventricular septal defects.

TABLE 2. Effort of Breathing at Each Level of Respiratory Support

Variable	Continuous Positive Airway Pressure at 4–5 cm H_2O Measured for Intubated Children ($n = 18$)	Standard Nasal Cannula at 2 L/min ($n = 20$)	HFNC 2 L/min ($n = 24$)	HFNC 5 L/min ($n = 25$)	HFNC 8 L/min ($n = 24$)	p[a]
Pressure · rate product (cm H_2O·min)[b]	334 (159–390)	454 (249–620)	421 (233–621)	341 (232–475)	329 (195–402)	0.0003
Change in pleural pressure (cm H_2O)[b]	9.9 (3.6–15.0)	11.8 (7.3–20.0)	12.9 (6.3–18.0)	14.0 (6.0–18.3)	12.2 (6.4–17.3)	0.0002
Mean respiratory rate (breaths/min)[b]	35 (25–54)	32 (26–54)	34 (27–55)	29 (25–46)	29 (22–40)	0.0004
Pleural pressure at end exhalation (cm H_2O)[c]	5.8 (± 4.8)	4.5 (± 4.2)	4.8 (± 4.3)	5.5 (± 5.0)	5.4 (± 4.7)	0.01

HFNC = high flow nasal cannula.
[a]p value given for repeated measures analysis of variance (ANOVA). Square root transformation performed for Pressure.Rate Product, change in pleural pressure, and respiratory rate data for ANOVA analysis.
[b]Median with interquartile range.
[c]Mean ± SD.
Data presented for all 25 children enrolled in the study.

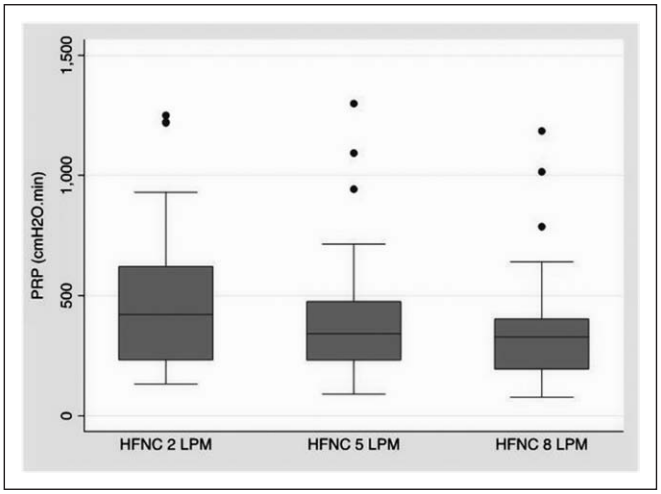

Figure 1. Pressure.Rate Product (PRP) (cm H_2O · min) for all 25 children enrolled in the study. One child had missing data on high-flow humidified nasal cannula (HFNC) 2 L/min (LPM), and one child had missing data on HFNC 8 LPM. *Boxes* represent median with upper quartile and lower quartile range, and *whiskers* show nonoutlier maximum and minimum values. *Dots* represent outliers more than 1.5 times of upper quartile. PRP data transformed for repeated-measures analysis of variance. Bonferroni corrected *p* values are given below. PRP was lower on HFNC 8 LPM compared with HFNC 5 LPM ($p = 0.007$) or HFNC 2 LPM ($p < 0.0001$). PRP was lower on HFNC 5 LPM compared with HFNC 2 LPM ($p = 0.01$).

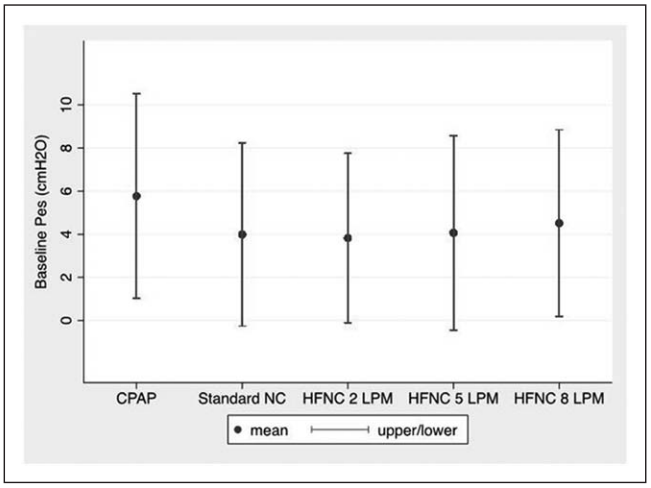

Figure 2. Baseline Pes (cm H_2O), pleural pressure at end exhalation during normal tidal breathing, for the 18 children with continuous positive airway pressure (CPAP) data presented as mean ± SD. Baseline Pes reflects the positive pressure generated on each level of respiratory support. Data analyzed using repeated-measures analysis of variance with Bonferroni correction for multiple comparisons. Bonferroni corrected *p* values are given below. Baseline Pes was higher on CPAP 4–5 cm H_2O (5.7 ± 4.8) than on standard nasal cannula (NC) (3.9 ± 4.3; $p = 0.03$), on high-flow humidified nasal cannula (HFNC) 2 L/min (LPM) (3.8 ± 3.9; $p = 0.002$), and on HFNC 5 LPM (4.1 ± 4.5; $p = 0.009$). There was no difference in Baseline Pes on CPAP compared with HFNC 8 LPM (4.5 ± 4.3; $p = 0.13$). We additionally compared Baseline Pes for all 25 patients with measurements on HFNC. For these 25 patients, Baseline Pes was higher on HFNC 8 LPM compared with HFNC 2 LPM ($p = 0.03$). There was no difference in Baseline Pes on HFNC 8 LPM compared with HFNC 5 LPM ($p > 0.05$) or on HFNC 5 LPM compared with HFNC 2 LPM ($p > 0.05$).

DISCUSSION

This is the first pediatric study to demonstrate objectively a decrease in a measure of effort of breathing with increased flow rates of HFNC. We found that effort of breathing, as determined by PRP, decreased by approximately 25% when flow rate of HFNC was increased from 2 to 8 L/min. Previous adult and neonatal studies that objectively measured effort of breathing showed no improvement on HFNC (3, 15). However, pediatric studies demonstrated that HFNC decreased effort of breathing based on improved clinical respiratory scores (3, 6, 16). Use of subjective clinical scoring systems, inconsistent or low gas flow rates, and lack of control groups make it difficult to draw meaningful conclusions from these studies. Our study addresses these limitations by using an objective measure of effort of breathing to compare measurements in children receiving similar clinically relevant flow rates of HFNC.

There are a number of different mechanisms by which HFNC may decrease effort of breathing. Previous studies suggest that HFNC generates positive pressure, which may improve effort of breathing through alteration in upper airway resistance or improved lung recruitment (17, 18). To evaluate if positive pressure was being generated, we compared Baseline Pes, defined as the pleural pressure generated at end exhalation during tidal breathing, on each level of respiratory support (**Table 2**; **Fig. 2**). We expected that Baseline Pes would be lowest on standard NC and would become more positive, approaching CPAP values, if positive pressure was being generated by HFNC. We found that Baseline Pes increased when flow rate of HFNC increased from 2 to 8 L/min, indicating pressure was becoming more positive at this higher flow rate. Our results suggest that generation of positive pressure is one of the mechanisms by which HFNC exerts its clinical effect. However, it is unlikely that a 1 cm H_2O increase in positive pressure on HFNC 8 L/min compared with HFNC 2 L/min would fully explain the 25% decrease in effort of breathing noted in our study cohort. In addition, many of our young patients spent much of the time with their mouths open, leading to transient benefits of positive pressure while on HFNC (19).

HFNC may also have improved effort of breathing by washing out airway dead space. In children less than 10 kg, the peak inspiratory flow rate of 500 mL/kg/min is exceeded at HFNC rates more than or equal to 5 L/min and anatomic dead space is significantly reduced (20). A reduction in proportional dead space volume improves the efficiency of breathing allowing children to decrease their RR (21, 22). Although we did not measure arterial carbon dioxide levels in this study, we did find a decrease in RR with increased flow rates of HFNC suggesting more effective ventilation. In addition, the effect of nasopharyngeal dead space washout is likely to be more pronounced in our study population, with a median age of 6.5 months, as proportional airway dead space is higher than in older children (23).

A recent study suggests different mechanisms for HFNC during sleep and wakefulness states (21). Healthy adult patients had increased tidal volumes and decreased RRs in response to HFNC while awake. However, tidal volumes decreased while asleep resulting in a significant decrease in minute ventilation. Although it would be challenging to time effort of breathing measurements with the sleep-wake cycle in our young study cohort, future studies that include older more cooperative

children may be better able to evaluate mechanistic changes during sleep and wakefulness in a pediatric population.

We studied HFNC in children with a wide range of acute and chronic illness admitted to the PICU or CTICU. Our study population had a high prevalence of congenital heart disease, varying degrees of chronic lung disease, and a variety of reasons for increased effort of breathing. Twenty percent of our study patients were placed on HFNC outside of the immediate extubation period for respiratory distress related to pneumonia, bronchiolitis obliterans, respiratory syncytial virus bronchiolitis, or cardiac insufficiency. Although previous studies focus on the use of HFNC in children with bronchiolitis or for postextubation respiratory support, our results suggest that HFNC may be effective in more heterogeneous pediatric patient populations outside of the immediate extubation period (16, 24). Evaluation in a larger study cohort would enable comparison of HFNC in a heterogeneous population with that in specific patient subgroups. Although our study was not powered for subgroup analysis, future studies may be able to better quantify these effects.

Our group has shown in previous studies that effort of breathing increases marginally after extubation (11). Although the effort of breathing was lower for intubated children on CPAP compared with extubated children on standard NC or HFNC 2 L/min, there was no difference in effort of breathing on CPAP compared with HFNC 5 L/min or HFNC 8 L/min. As this study was not powered for CPAP comparison, it is possible that we were unable to detect a true difference in effort of breathing on CPAP versus HFNC more than or equal to 5 L/min. Future studies should be designed to evaluate the support provided by CPAP compared with HFNC at flows more than or equal to 5 L/min in young children.

Our study has some important limitations. Missing data decreased our power to detect a difference in effort of breathing at various levels of support within the entire study cohort. In addition, only 23 patients had complete data on all three flow rates of HFNC, and it is possible that missing data from the other two patients could have biased our results. Only two patients in our study were older than 2 years, and none were less than 34 weeks corrected gestational age at study enrollment. Weight and age may affect the fit of the NC and the flow rates required to generate positive pressure or washout dead space. Therefore, our results may not be generalizable to older patients or premature infants. Finally, this study was designed only to evaluate the physiologic effects of HFNC. The relevance of these findings to short- and long-term clinical outcomes requires further investigation.

Despite a lack of robust physiologic or outcome data in pediatric patients, HFNC has become a widely used mode of noninvasive respiratory support. We demonstrated a quantifiable improvement in effort of breathing in response to increased flow rates of HFNC in a relatively heterogeneous cohort of critically ill children. Our findings support the use of HFNC for children with increased effort of breathing due to a variety of etiologies. Well-designed prospective randomized controlled trials are needed to compare the effectiveness of HFNC with that of more established methods of noninvasive respiratory support.

CONCLUSIONS

We conclude that HFNC has a clear impact on effort of breathing with a median 25% reduction in effort of breathing as flow rate increases from 2 to 8 L/min. The mechanisms of benefit are likely multifactorial and may include generation of positive pressure and washout of airway dead space. Additional studies are needed to evaluate the effect of HFNC on clinical outcomes in a heterogeneous group of children with respiratory insufficiency.

REFERENCES

1. Shoemaker MT, Pierce MR, Yoder BA, et al: High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: A retrospective study. *J Perinatol* 2007; 27:85–91
2. Sreenan C, Lemke RP, Hudson-Mason A, et al: High-flow nasal cannulae in the management of apnea of prematurity: A comparison with conventional nasal continuous positive airway pressure. *Pediatrics* 2001; 107:1081–1083
3. Lampland AL, Plumm B, Meyers PA, et al: Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. *J Pediatr* 2009; 154:177–182
4. Ojha S, Gridley E, Dorling J: Use of heated humidified high-flow nasal cannula oxygen in neonates: A UK wide survey. *Acta Paediatr* 2013; 102:249–253
5. Roca O, Riera J, Torres F, et al: High-flow oxygen therapy in acute respiratory failure. *Respir Care* 2010; 55:408–413
6. Woodhead DD, Lambert DK, Clark JM, et al: Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: A prospective, randomized, masked, crossover trial. *J Perinatol* 2006; 26:481–485
7. Wang EE, Law BJ, Stephens D, et al: Study of interobserver reliability in clinical assessment of RSV lower respiratory illness: A Pediatric Investigators Collaborative Network for Infections in Canada (PICNIC) study. *Pediatr Pulmonol* 1996; 22:23–27
8. Saslow JG, Aghai ZH, Nakhla TA, et al: Work of breathing using high-flow nasal cannula in preterm infants. *J Perinatol* 2006; 26:476–480
9. Chatila W, Nugent T, Vance G, et al: The effects of high-flow vs low-flow oxygen on exercise in advanced obstructive airways disease. *Chest* 2004; 126:1108–1115
10. Klein M, Reynolds LG: Relief of sleep-related oropharyngeal airway obstruction by continuous insufflation of the pharynx. *Lancet* 1986; 1:935–939
11. Willis BC, Graham AS, Yoon E, et al: Pressure-rate products and phase angles in children on minimal support ventilation and after extubation. *Intensive Care Med* 2005; 31:1700–1705
12. Graham AS, Chandrashekharaiah G, Citak A, et al: Positive end-expiratory pressure and pressure support in peripheral airways obstruction: Work of breathing in intubated children. *Intensive Care Med* 2007; 33:120–127
13. Collett PW, Perry C, Engel LA: Pressure-time product, flow, and oxygen cost of resistive breathing in humans. *J Appl Physiol* 1985; 58:1263–1272
14. Beardsmore CS, Helms P, Stocks J, et al: Improved esophageal balloon technique for use in infants. *J Appl Physiol* 1980; 49:735–742
15. Corley A, Caruana LR, Barnett AG, et al: Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. *Br J Anaesth* 2011; 107:998–1004
16. Spentzas T, Minarik M, Patters AB, et al: Children with respiratory distress treated with high-flow nasal cannula. *J Intensive Care Med* 2009; 24:323–328
17. Sivieri EM, Gerdes JS, Abbasi S: Effect of HFNC flow rate, cannula size, and nares diameter on generated airway pressures: An in vitro study. *Pediatr Pulmonol* 2013; 48:506–514

18. Kubicka ZJ, Limauro J, Darnall RA: Heated, humidified high-flow nasal cannula therapy: Yet another way to deliver continuous positive airway pressure? *Pediatrics* 2008; 121:82–88
19. Hasan RA, Habib RH: Effects of flow rate and airleak at the nares and mouth opening on positive distending pressure delivery using commercially available high-flow nasal cannula systems: A lung model study. *Pediatr Crit Care Med* 2011; 12:e29–e33
20. Argent AC, Newth CJ, Klein M: The mechanics of breathing in children with acute severe croup. *Intensive Care Med* 2008; 34:324–332
21. Mündel T, Feng S, Tatkov S, et al: Mechanisms of nasal high flow on ventilation during wakefulness and sleep. *J Appl Physiol* 2013; 114:1058–1065
22. Frizzola M, Miller TL, Rodriguez ME, et al: High-flow nasal cannula: Impact on oxygenation and ventilation in an acute lung injury model. *Pediatr Pulmonol* 2011; 46:67–74
23. Numa AH, Newth CJ: Anatomic dead space in infants and children. *J Appl Physiol* 1996; 80:1485–1489
24. McKiernan C, Chua LC, Visintainer PF, et al: High flow nasal cannulae therapy in infants with bronchiolitis. *J Pediatr* 2010; 156:634–638