**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 ($\Delta P_{es}$) and respiratory rate were measured on high-flow humidified nasal cannula at 2, 5, and 8 L/min. $\Delta P_{es}$ and respiratory rate were multiplied to generate the Pressure,Rate Product, a well-established objective measure of effort of breathing. Baseline $P_{es}$, 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$_2$O·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 $P_{es}$ 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
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 non-intubated patients (14). Pes measurements were recorded while on CPAP mode of ventilation of 4–5 cm H2O 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. FIO2 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 FIO2 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 H2O·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 $\Delta$Pes 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 $\Delta$Pes was lower on CPAP (median, 9.9 cm H$_2$O; IQR, 3.6–15 compared with standard NC (median, 11.8; IQR, 7.3–20; $p < 0.0001$), HFNC 2 L/min (median, 12.9; IQR, 6.3–18; $p < 0.0001$), 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, 25–46; $p = 0.001$), 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 ($p = 0.07$).

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$_2$O ± 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; $p = 0.09$) 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

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

$^a$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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous Positive Airway Pressure at 4–5 cm H$_2$O Measured for Intubated Children ($n = 18$)</th>
<th>Standard Nasal Cannula at 2 L/min ($n = 20$)</th>
<th>HFNC 2 L/min ($n = 24$)</th>
<th>HFNC 5 L/min ($n = 25$)</th>
<th>HFNC 8 L/min ($n = 24$)</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure · rate product (cm H$_2$O·min)$^a$</td>
<td>334 (159–390)</td>
<td>454 (249–620)</td>
<td>421 (233–621)</td>
<td>341 (232–475)</td>
<td>329 (195–402)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Change in pleural pressure (cm H$_2$O)$^a$</td>
<td>9.9 (3.6–15.0)</td>
<td>11.8 (73–20.0)</td>
<td>12.9 (6.3–18.0)</td>
<td>14.0 (6.0–18.3)</td>
<td>12.2 (6.4–17.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean respiratory rate (breaths/min)$^b$</td>
<td>35 (25–54)</td>
<td>32 (26–54)</td>
<td>34 (27–55)</td>
<td>29 (25–46)</td>
<td>29 (22–40)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Pleural pressure at end exhalation (cm H$_2$O)$^b$</td>
<td>5.8 (± 4.8)</td>
<td>4.5 (± 4.2)</td>
<td>4.8 (± 4.3)</td>
<td>5.5 (± 5.0)</td>
<td>5.4 (± 4.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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.
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 H2O increase in positive pressure on HFNC = 0.007) or HFNC 2 LPM (p < 0.0001). PRP was lower on HFNC 5 LPM compared with HFNC 2 LPM (p = 0.01).

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

**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.
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 2L/min, there was no difference in effort of breathing on CPAP compared with HFNC 5L/min or HFNC 8L/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 5L/min. Future studies should be designed to evaluate the support provided by CPAP compared with HFNC at flows more than or equal to 5L/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 8L/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


