The Relationship between High Flow Nasal Cannula Flow Rate and Effort of Breathing in Children

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Objective To use an objective metric of effort of breathing to determine optimal high flow nasal cannula (HFNC) flow rates in children <3 years of age.

Study design Single-center prospective trial in a 24-bed pediatric intensive care unit of children <3 years of age on HFNC. We measured the percent change in pressure·rate product (PRP) (an objective measure of effort of breathing) as a function of weight-indexed flow rates of 0.5, 1.0, 1.5, and 2.0 L/kg/minute. For a subgroup of patients, 2 different HFNC delivery systems (Fisher & Paykel [Auckland, New Zealand] and Vapotherm [Exeter, New Hampshire]) were compared.

Results Twenty-one patients (49 titration episodes) were studied. The most common diagnoses were bronchiolitis and pneumonia. Overall, there was a significant difference in the percent change in PRP from baseline (of 0.5 L/kg/minute) with increasing flow rates for the entire cohort ($P < .001$) with largest change at 2.0 L/kg/min (–21%). Subgroup analyses showed no significant difference in percent change in PRP from baseline when comparing the 2 different HFNC delivery systems ($P = .12$). Patients ≤8 kg experienced a larger percent change in PRP as HFNC flow rates were increased ($P = .001$) than patients >8 kg.

Conclusions The optimal HFNC flow rate to reduce effort of breathing in infants and young children is approximately 1.5-2.0 L/kg/minute with more benefit seen in children ≤8 kg. *(J Pediatr 2017;189:66-71).*

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High flow nasal cannula (HFNC) oxygen delivery is a commonly used method of noninvasive respiratory support for critically ill children.[1] Recent randomized controlled trial data highlight that HFNC may be superior to "regular" nasal cannula in preventing treatment failure or the need for intensive care for children with moderate bronchiolitis.[2] Several retrospective studies have agreed with this finding on intensive care utilization and shown that HFNC is associated with lower rates of intubation and mechanical ventilation.[3-5]

Emerging literature also demonstrates that HFNC can improve respiratory mechanics. In preterm infants, HFNC has been shown to reduce thoracoabdominal asynchrony,[6] improve gas exchange,[7] and lower effort of breathing.[6] In term infants, Pham et al[8] showed that there was a significant decrease in effort of breathing (as measured by pressure·rate product [PRP]) in infants with bronchiolitis supported with 2 L/kg/minute of HFNC compared with those with no respiratory support, but they did not evaluate any intermediate levels of support. Previous studies have also described a dose-dependent relationship between increasing levels of HFNC and decreasing objective metrics of effort of breathing in neonatal[9] and pediatric[10] literature, but these prior studies have measured effort of breathing at absolute flow rates, not evaluating potentially significant differences in optimal flow rates for patients of varied ages (eg, between a 1-month-old and 3-year-old child).

Building on this previous work, we hypothesized that there is a relationship between HFNC flow rate and patient effort of breathing and that this relationship may be affected by the type of HFNC delivery system used and patient weight.

Methods

We performed a single-center prospective trial in the 24-bed multidisciplinary medical-surgical pediatric intensive care unit at Children's Hospital Los Angeles (CHLA) from September 2014 to June 2016. This study was approved by the CHLA

CHLA	Children's Hospital Los Angeles	PA	Phase angle
FP	Fisher & Paykel	PRP	Pressure·rate product
HFNC	High flow nasal cannula	RIP	Respiratory inductance plethysmography
IBW	Ideal body weight	VT	Vapotherm

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Vapotherm, Inc. provided a limited number of high flow nasal cannula delivery systems for use in this study but this company did not have any role in (1) study design, (2) collection, analysis, and interpretation of data, (3) the writing of the report, or (4) the decision to submit the paper for publication. The authors declare no conflicts of interest.

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institutional review board, and informed consent was obtained. All patients ≤3 years of age admitted to the CHLA pediatric intensive care unit and placed on HFNC by the clinical team were eligible. We excluded patients if they had a corrected gestational age less than 37 weeks or contraindications to either esophageal pressure probe placement (eg, nasopharyngeal or esophageal anomalies) or respiratory inductance plethysmography (RIP) bands (eg, abdominal wall defects such as omphalocele).

Measurements were performed using a pair of RIP bands (Nox Medical, Reykjavik, Iceland) and an esophageal pressure probe (CareFusion, Avea, SmartCath, Houten, The Netherlands). The RIP bands and esophageal pressure probe were connected to the BiCore II instrument (CareFusion), which provided interface between these sensors and a laptop computer. We recorded and analyzed data on a laptop computer using Polybench software (Applied Biosignals GmbH, Weener, Germany) and performed postprocessing of the measurements using Vivosense software package (Vivonetics, San Diego, California).

Measurements were obtained at flow rates of 0.5, 1.0, 1.5, and 2.0 L/kg/minute up to a maximum flow rate of 30 L/minute on 2 different HFNC delivery systems: Fisher & Paykel (FP [Auckland, New Zealand]) and Vapotherm (VT [Exeter, New Hampshire]). The respiratory pattern was allowed to stabilize at each flow rate for an average of 2 minutes before measurement began. Flow levels were trialed in a random order, each for a 5-minute period. Measurements were collected during quiet tidal breathing and periods of artifact, such as crying or coughing, were removed from analysis using the postprocessing software (Vivosense). With one exception, patients were first studied on the FP HFNC delivery system and then (when available) transitioned to the VT HFNC delivery system. Patients were left on the VT HFNC delivery system for the remainder of their measurements until weaned off HFNC. Each subject had up to 2 daily measurements at each of the stated flow rates as long as they remained on HFNC (up to a maximum of 5 days).

Using esophageal manometry, we calculated the PRP: the product of the peak-to-trough change in esophageal pressure (cmH_2O) and the respiratory rate (breaths per minute) (**Figure 1**; available at www.jpeds.com). This has been previously validated as a metric of patient effort of breathing[11-14] where larger absolute values signify greater effort of breathing. From RIP, we calculated the phase angle (PA). PA is a measure of thoracoabdominal asynchrony and is a nonspecific surrogate metric for effort of breathing.[15]

For each 5-minute titration episode, we calculated the median PRP and PA, which were used for analysis. After each set of measurements, we informed the clinical team of the flow rate that resulted in the lowest effort of breathing.

Statistical Analyses

The primary outcome was percent change in PRP from baseline, to account for within subject variability and repeated measurements per patient. Because we hypothesized that the effects of HFNC flow rates may be dependent on patient size, we further stratified our cohort into subgroups of ≤8 kg and >8 kg. Secondary outcomes included absolute PRP value and PA. Baseline demographic characteristics of each patient were noted including patient diagnosis, age, race, sex, and weight.

Analysis was performed in Statistica v 12 (Statsoft, Tulsa, Oklahoma), and continuous data were presented as median with IQR given that they were not always normally distributed. Differences in the primary outcome of percent change in PRP from baseline were evaluated using Wilcoxon signed-rank test. Secondary outcomes were analyzed using Friedman or Kruskal-Wallis ANOVA for non-normal distribution with multiple comparisons analysis based on a Bonferroni adjustment. Based on previous data from our group,[10] a difference in PRP of approximately 100 cmH_2O*breaths/minute was considered clinically significant. Using this effect size, with an alpha of 0.05 and desired power of 0.8, our goal sample size was calculated at 20 patients.

Results

A total of 54 patients meeting inclusion criteria were approached, and 21 patients were consented and studied for a total of 49 titration episodes. Demographic and clinical characteristics were recorded (**Table**) and patients screened and studied are described in a CONSORT diagram (**Figure 2**; available at www.jpeds.com). The most common reason consent was refused was related to placement of the esophageal catheter.

Analyzing all titration episodes on all types of HFNC delivery systems, the median absolute PRP decreased as weight-indexed flow rates increased ($P < .001$) (**Figure 3**; available at www.jpeds.com). The median PA did not exhibit a change with increasing flow rates ($P = .91$) (**Figure 4**; available at www.jpeds.com). When analyzing the primary outcome of percent change in PRP from baseline, there was a dose-dependent relationship between increasing flow rates and greater percent change in PRP from baseline with the largest reduction seen at 2.0 L/kg/minute ($P < .001$) (**Figure 5**). Flow rates between 1.5 and 2.0 L/kg/minute resulted in similar percent change in PRP from baseline (−20% and −21%, respectively). Multiple comparisons analysis showed that flow

Table. Patient demographics (n = 21): median (IQR or percent)

Median age (mo)	6 (2, 12)
Median weight (kg)	6.5 (5, 9)
Median weight compared with IBW (kg)	−0.5 (−1.7, 0.6)
Ethnicity/race: n (%)	
African American	2 (10)
Hispanic	15 (71)
Not specified	4 (19)
Respiratory illness: n (%)	
Bronchiolitis	13 (62)
Pneumonia	3 (14)
Other	5 (24)
Patients intubated: n (%)	2 (10)
Median HFNC duration (d)	2 (1-4)
Median PICU LOS (d)	4 (2-6)
Median hospital LOS (d)	7.5 (5.8-14.3)

LOS, length of stay; *PICU*, pediatric intensive care unit.