

Observational Study of Humidified High-Flow Nasal Cannula Compared with Nasal Continuous Positive Airway Pressure

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Objectives To conduct an in vitro evaluation of a humidified high-flow nasal cannula (HFNC) system at different flows, cannula sizes, and air leaks and also an in vivo analysis of mean end-expiratory esophageal pressure (EEEP) from nasal continuous positive airway pressure at 6 cm H₂O (NCPAP+6) versus HFNC.

Study design In the in vitro study, we measured HFNC system pressure and flow, with varying degrees of leak and with and without the use of a pressure-limiting valve. In the in vivo study, we measured EEEP in 15 newborns on NCPAP+6 and then on HFNC at 6 L/minute, with flow decreased by 1 L/minute every 30 minutes. Heart rate, respiratory rate, fraction of inspired oxygen, arterial oxygen saturation, respiratory distress syndrome score, and EEEP were recorded for each intervention. Data analysis was done using repeated-measures analysis of variance and linear regression.

Results In the in vitro study, in the absence of leaks, the pressures were limited by the pressure-limiting valve only at flows \geq 2 L/minute. With leaks of 30% and 50%, delivered pressures were always $<$ 3 cm H₂O. In the in vivo study, respiratory rate increased from baseline (NCPAP+6) as flow decreased ($P < .02$). Inpatient and interpatient coefficients of variation were always high.

Conclusions A pressure-limiting valve is necessary in a HFNC system. Although mean EEEP levels were similar in NCPAP+6 and HFNC, tachypnea developed as flow diminished. This system apparently cannot predict EEEP, because of interpatient and inpatient variation. (*J Pediatr* 2009;154:177-82)

Despite the use of exogenous surfactant replacement and antenatal steroid therapy, respiratory distress syndrome (RDS) remains a leading cause of morbidity and mortality in preterm infants. RDS is the result of a series of complex, interrelated events, including atelectasis, ventilation-perfusion mismatch, and lung inflammation/injury.¹ The cascade of events that typifies RDS and its long-term counterpart, chronic lung disease, is rooted in the intrinsic deficits of the preterm lung and is exacerbated by mechanical ventilation, a mainstay of therapy.

The use of noninvasive ventilatory strategies in the treatment of RDS may minimize lung inflammation and injury associated with mechanical ventilation.² Avoidance of intubation and increased use of nasal continuous positive airway pressure (NCPAP) has proven to be an effective strategy for treating RDS.³⁻⁵ This approach also has been associated with a decreased incidence of chronic lung disease.³ In the recently published COIN trial, Morley et al⁵ reported that early use of NCPAP in preterm infants decreased the risk of death and also the need for oxygen therapy at 28 days of life. They also found that early NCPAP is associated with less surfactant use and less mechanical ventilation exposure.⁵

NCPAP has some common clinical limitations, however. First, the administration of NCPAP entails inherent mechanical difficulties in appropriately maintaining the nasal prong apparatus within the small neonatal nose. Second, the nasal prongs used to deliver NCPAP can cause trauma to the septum. Finally, some preterm infants do not tolerate the NCPAP apparatus, which must be tightly affixed to the nose and face. The humidified high-flow nasal cannula (HFNC) system has been introduced to neonatal respiratory care as a way to provide positive distending pressure to a neonate with respiratory distress. HFNC therapy aims to maximize patient tolerance by using heated, humidified gas flow

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EEEP	End-expiratory esophageal pressure	NICU	Neonatal intensive care unit
FiO ₂	Fraction of inspired oxygen	RDS	Respiratory distress syndrome
HFNC	High-flow nasal cannula	SaO ₂	Arterial oxygen saturation
NCPAP	Nasal continuous positive airway pressure	SEM	Standard error of mean

(≥ 1 L/minute)⁶ through a standard neonatal nasal cannula. HFNC provides positive distending pressure and has been reported to provide respiratory support comparable to that of NCPAP.⁷

Sreenan et al⁸ found HFNC to be as effective as NCPAP in the management of apnea of prematurity and also demonstrated that the positive distending pressure provided by HFNC varied with patient weight. Spence et al⁹ found significant intrapharyngeal pressure delivery with HFNC at flows ≥ 3 L/minute. The optimum HFNC gas flow to use in any given patient hinges on several factors. Some important questions should first be addressed:

1. Is the chosen HFNC system safe; that is, is the delivered pressure within a range generally used for treatment?
2. How much positive distending pressure does a particular flow level provide?
3. Are delivered pressures related to patient or cannula size?

In an attempt to address these questions, we evaluated a commercially available HFNC system (Fisher & Paykel RT329; Salter Labs, Arvin, California) both in vitro and in vivo.

METHODS

In Vitro Study

Using a calibrated gas flow analyzer (Fluke Biomedical, Everett, Washington), pressure and gas flow values were analyzed in triplicate at 5 different points within the HFNC system: at the gas flow source, immediately before the pressure-limiting valve, immediately after the pressure-limiting valve, at the end of the HFNC circuit tubing, and at the distal end of the nasal cannula (Figure 1). available at www.jpeds.com). Both the preterm and neonatal cannulas (Fisher & Paykel BC series, 2.4 mm prong diameter; Salter Labs) were analyzed, because these are the sizes used most often in our neonatal intensive care unit (NICU). Initial gas flow input varied from 1 to 6 L/minute. Measurements were obtained at the various points with the system set up according to the manufacturer's instructions with humidified air at 37°C and with the pressure-limiting valve in place, set at 45 cm H₂O pressure. The same measurements were repeated with the pressure-limiting valve removed from the system. With the pressure-limiting valve in place, measurements were taken after the introduction of 30% and 50% leaks distal to the nasal cannula. A T-piece with an inline stopcock (same internal diameter as the nasal cannula) was connected distal to the cannula, with the stopcock positioned to allow a fixed 30% or 50% leak of gas flow for each measurement (Figure 1).

In Vivo Study

In this observational, internal crossover study using the patient as his or her own control, patient eligibility was based on the following inclusion criteria: receiving NCPAP ventilatory support at ≥ 72 hours of age and requiring a fraction of inspired oxygen (FiO₂) of 21%-50% on NCPAP. Exclusion

criteria included FiO₂ > 50%; presence of pneumothorax or pleural effusion; anatomic abnormalities of the airway, lungs, or esophagus; and cyanotic congenital heart defect. Baseline historical data were obtained from the patient's hospital chart. This study was registered at www.clinicaltrials.gov (#NCT00356668). Approval for this human research was obtained from the Children's Hospitals and Clinics of Minnesota's Institutional Review Board.

After written informed consent was obtained from the parent or legal guardian, the patient's positive end-expiratory pressure on NCPAP was adjusted to 6 cm H₂O (NCPAP+6) using the Dräger Babylog 8000 system (Dräger America, Telford, Pennsylvania). Hudson short binasal prongs (Hudson Respiratory Care, Temecula, California) were used for all patients. Many different devices can be used to provide NCPAP in the NICU, but we used ventilator-derived NCPAP for all patients to minimize variation. The patient was placed in the supine position with the mouth closed throughout the data collection period. After the patient was on NCPAP+6 for 30 minutes, baseline FiO₂, arterial oxygen saturation by pulse oximetry (SaO₂), and RDS score were documented. During the study, SaO₂ goals were maintained in accordance with our NICU's protocol based on gestational age. The patient was maintained in the usual thermoneutral environment throughout the study. Feedings were given according to the patient's preset feeding plan as prescribed by the NICU care team before the start of the study.

During NCPAP+6 therapy, a saline-filled catheter (8 Fr Argyle; Sherwood Medical, St Louis, Missouri) was placed in the patient's mouth and into the distal esophagus. The catheter was attached to a differential pressure transducer (Abbott Critical Care 46085-60; Abbott Laboratories, Abbott Park, Illinois) to measure the esophageal pressure as an indication of positive distending pressure in the airways. The catheter was measured and positioned using a standard nomogram for initial placement into the stomach; positioning was verified by auscultation. The catheter was then withdrawn into the distal esophagus and positioned to achieve a waveform that was free of cardiac artifact and remained negative during inspiration.⁷ An occlusion test, in which the ratio of esophageal pressure to airway opening pressure equaled 1, was performed to validate correct positioning.¹⁰ After a 25-minute equilibration period, a 5-minute continuous esophageal pressure tracing (SpaceLabs Inc, Redmond, Washington) was recorded. Heart rate, respiratory rate, FiO₂, and SaO₂ were recorded each minute during the 5-minute recording period. RDS score, including scoring of respiratory rate, air entry, cyanosis, retractions, and audible grunting, was recorded each minute during the 5-minute recording period.¹¹ EEEP was measured from 100 selected breaths that were consecutive and demonstrated no movement or cardiac artifact.

The infant was then placed on humidified HFNC at 6 L/minute of gas flow (Fisher & Paykel RT329 System; Salter Labs). A standardized neonatal HFNC was used in all patients (Fisher & Paykel BC2435; Salter Labs). After 25

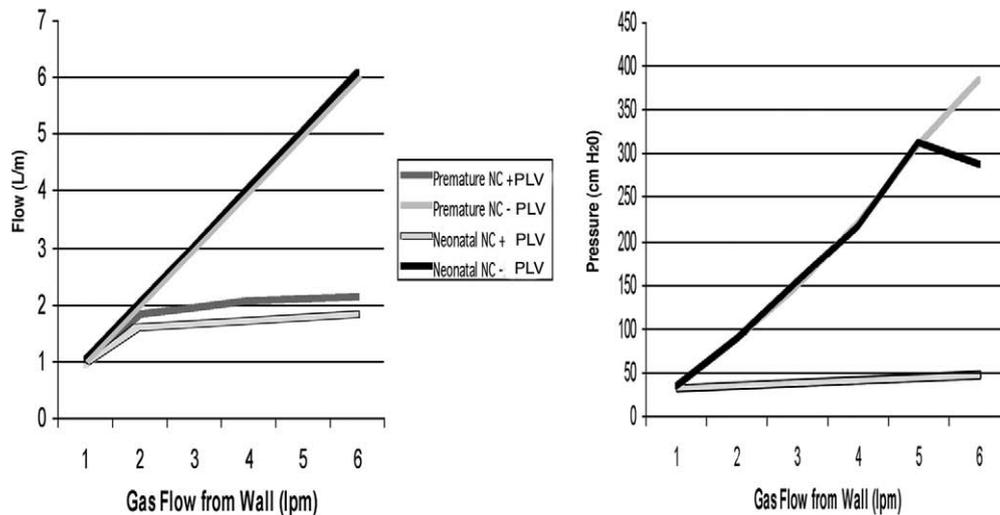


Figure 3. Analysis of gas flow and pressure delivery at the distal end of the nasal cannula with increasing gas flow input. NC, nasal cannula; PLV, pressure-limiting valve.

minutes on these settings, esophageal pressure was recorded continuously for 5 minutes. Similarly, heart rate, respiratory rate, FiO_2 , SaO_2 , and RDS score were recorded each minute during the 5-minute recording period. The liter flow was then decreased in 1-L increments to a minimum of 1 L/minute with 25 minutes at each new setting, followed by continuous recording of esophageal pressure and physiological data collection as described previously. The study came to an end when data had been obtained on 1 L/minute or when the patient demonstrated signs of intolerance, including persistent tachypnea, an increase of $> 50\%$ in apnea and bradycardia spells compared with 1 hour prestudy baseline, or hypoxia with an increase in supplemental $\text{FiO}_2 > 0.3$ compared with prestudy baseline FiO_2 on NCPAP. The esophageal pressure catheter was removed when the study was completed.

Data were analyzed using commercial statistical software (Statview; SAS Institute, Cary, North Carolina and Graphpad Prism 5.0a; Hearne Scientific Software, Chicago, Illinois). In vitro and in vivo data were analyzed using repeated-measures analysis of variance. Mean values of EEEP and physiological data were used for analysis. P values $< .05$ were considered statistically significant.

RESULTS

In Vitro Study

With the HFNC system completely intact with the pressure-limiting valve in place and set at 45 cm H_2O , as gas flow was increased, delivered flow was preserved throughout the system, and pressures ranged from 35.7 cm H_2O at 1 L/minute to 45.8 cm H_2O at 6 L/minute, apparently limited by the pressure-limiting valve (Figure 2; available at www.jpeds.com). Delivered flow and pressure were attenuated distal to the nasal cannula at gas flows ≥ 2 L/minute. Distal to the neonatal nasal cannula, gas flow delivery ranged from 0.99 L/minute at 1 L/minute to 1.82 L/minute at 6 L/minute, and pressure delivery ranged from 32 cm H_2O at 1 L/minute to

44.6 cm H_2O at 6 L/minute (Figure 3). The data obtained when using the preterm nasal cannula were very similar (Figure 3).

Removal of the pressure-limiting valve allowed for preservation and delivery of the initial gas flow amounts as well as excessive pressure delivery distal to the nasal cannula, as evidenced by the pressures at 5 L/minute and 6 L/minute actually dropping secondary to the HFNC apparatus breaking apart as the tubing disengaged from the insertion site on the humidifier (Figure 3).

With the HFNC system intact and the pressure-limiting valve in place, introduction of 30% and 50% leaks in gas flow distal to the neonatal nasal cannula dramatically decreased the pressure delivery at all gas flow amounts tested. With a 30% flow leak, pressure delivery ranged from 0.63 cm H_2O at 1 L/minute to 2.03 cm H_2O at 6 L/minute. With a 50% flow leak, pressure delivery ranged from 0.1 cm H_2O at 1 L/minute to 0.5 cm H_2O at 6 L/minute (Figure 4).

In Vivo Study

The study group comprised 15 patients with a mean (\pm standard deviation) age 5 ± 1.9 days, birth weight 1324 ± 424 g, and gestational age of 29.5 ± 1.9 weeks at birth. All 15 patients had a primary diagnosis of RDS of prematurity. Eight of the 15 patients received exogenous surfactant replacement before study initiation, with the final dose given 2-10 days before study initiation. Nine of the 15 patients were receiving caffeine citrate therapy at the time of study initiation. None of the patients had documented concerns for increased intra-abdominal pressure or an abnormal intra-abdominal process, such as necrotizing enterocolitis, gastroschisis, omphalocele, or intra-abdominal masses. Three patients developed apnea and increased oxygen needs at 1 L/minute; EEEP data were not recorded for this flow rate on those patients.

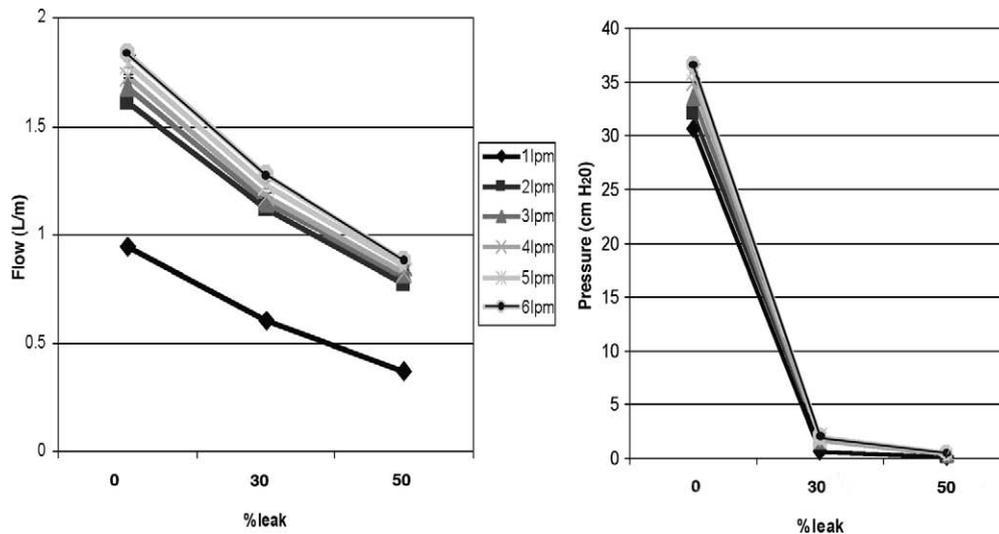


Figure 4. Gas flow and pressure measurements after introduction of 30% and 50% leak distal to the neonatal nasal cannula. NC, nasal cannula.

Table I. Physiological measurements obtained during measurements made during the different treatments

	Heart rate, beats/minute	Respiratory rate, breaths/minute	F _i O ₂	SaO ₂ , %	EEEP, cm H ₂ O
NCPAP+6	152 (16)	49 (12)	0.22 (0.04)	96 (2.6)	3.4 (5.3)
6 L/minute	150 (14)	50 (11)	0.23 (0.04)	96 (2.8)	3.0 (6.2)
5 L/minute	146 (13)	49 (10)	0.23 (0.04)	96 (3.7)	2.0 (6.3)
4 L/minute	146 (10)	53 (12)	0.22 (0.03)	96 (2.3)	1.9 (4.4)
3 L/minute	147 (14)	56 (16)	0.22 (0.04)	94 (4.4)	0.6 (5.2)
2 L/minute	148 (13)	60 (14)*	0.24 (0.06)	95 (3.0)	0.6 (4.2)
1 L/minute	147 (17)	66 (23)*	0.25 (0.06)	94 (3.4)	0.2 (3.8)

Values are reported as mean ± standard deviation.

*P < .02.

In all 15 patients, heart rate, F_iO₂, SaO₂, and RDS score did not differ between NCPAP and all gas flow levels on HFNC. Respiratory rate increased significantly as flows decreased on HFNC ($P < .02$; Table I). When all EEEP values obtained during the 5-minute recording periods at each measurement level were averaged, EEEP values increased with increasing flows ($P < .01$; $r^2 = 0.92$; Figure 5). When EEEP at NCPAP+6 was compared with EEEP at each flow level, values were similar ($P = .08$; repeated-measures analysis of variance). Both interpatient and inpatient coefficients of variation were very high, ranging from 51% to 180% inpatient and from 161% to 1885% interpatient for EEEP on NCPAP and at all flows on HFNC (Table II; available at www.jpeds.com).

DISCUSSION

Despite very limited information on their performance, HFNC systems are being increasingly used for noninvasive neonatal respiratory support. We investigated pressure delivery for one such system both in vitro and in vivo in this observational study of humidified HFNC compared with NCPAP. The main findings in vitro were the demonstrated

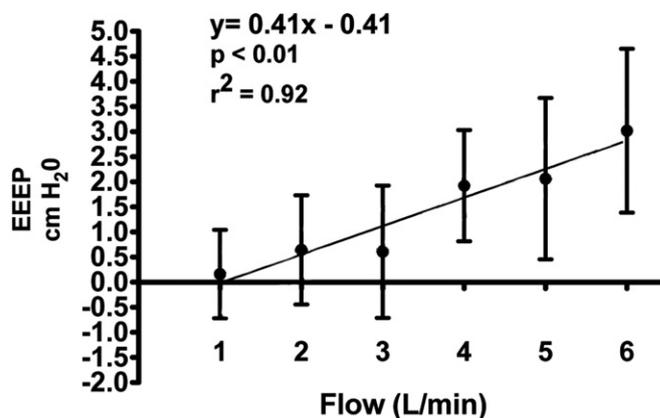


Figure 5. EEEP (mean ± standard error of the mean) at different tested flow rates plotted with a regression of the data.

need for a pressure-limiting valve to control potential excessive pressure delivery, along with a dramatic reduction in the delivered pressures in the face of a 30%-50% flow leak distal to the nasal cannula. In vivo, the patients demonstrated increasing tachypnea with decreasing HFNC gas flow. The

coefficient of variation was generally >100% for EEEP on NCPAP and at all HFNC gas flows. In addition, EEEP values increased with increasing HFNC gas flow.

Although numerous NICUs are currently using an HFNC system, to date there have been few studies regarding its use in this population. The type of study (prospective vs retrospective), type of HFNC delivery system, and amount of gas flow evaluated varies among these studies, which can be problematic when attempting to generalize their findings.^{8,12,13} Similarly, the small data set reveals conflicting results; for example, Campbell et al¹⁴ found higher rates of extubation failure in infants treated with HFNC compared with NCPAP, whereas Shoemaker et al¹⁵ found increased failure of early NCPAP compared with early HFNC in their retrospective study.

The present study evaluated the effects of the pressure-limiting valve on HFNC pressure delivery. This is important information, because gas flow through an HFNC differs from that in conventional NCPAP. In an HFNC, gas flow is directed straight to the patient, and when no pressure-limiting valve is in place, the only potential pressure-limiting controls are the patient's nose or mouth.

Difficulties exist in interpretation and widespread application of the findings in many HFNC studies. First, the studies were performed before the pressure-limiting valve became a standard component of HFNC systems. Second, the valve "pop-off" pressure may vary among manufacturers. Finally, some HFNC systems are "homemade" and have no pressure-limiting valve in place.^{7-9,14-17} Few studies have directly compared, in a controlled manner, the delivered positive distending pressure and physiological outcomes when applying NCPAP versus HFNC in the same study population. Saslow et al⁷ compared the VapoTherm HFNC (VapoTherm, Stevensville, Maryland) at 3, 4, and 5 L/minute versus NCPAP and found no significant changes in the work of breathing and only minimal changes in esophageal pressures. Sreenan et al⁸ compared NCPAP with a noncommercial HFNC system and found significant positive distending pressure at gas flows >2.5 L/minute and varying pressure delivery with patient weight. Kubicka et al,¹⁶ using both VapoTherm and Fisher & Paykel HFNC devices, recently described predictable oral cavity pressures comparable to that with NCPAP in infants weighing <1500 g and receiving HFNC of 4L/minute with their mouths closed; however, the NCPAP values were not obtained from the actual study cohort, and each infant studied was on a set gas flow amount that did not vary. The remaining studies that have evaluated NCPAP and HFNC data lacked data for both interventions within the entire study population.

Although the body of literature on in vivo HFNC is growing, for multiple reasons, applying the data to the neonatal population as a whole is difficult. As mentioned earlier, few studies have directly compared NCPAP and varying levels of HFNC within the same population. Other sources of variability include the type of HFNC used (commercially available systems vs homemade systems) and whether or not

the system has an intrinsic pressure-limiting valve. The internal diameter of the nasal prongs, which has varied among studies, also has an effect on gas flow and pressure delivery. Finally, methods for assessing positive distending pressure within the lungs have varied. Those studies that have attempted to quantify positive distending pressure have involved differences between extrathoracic (ie, oral cavity, nasopharyngeal) and intrathoracic (ie, esophageal) pressure measurements and their suitability as surrogates for pulmonary distending pressure.^{18,19}

The present study attempted to reconcile as many of these issues as possible. Our entire study population received and had data collected on both NCPAP and HFNC. A standard nasal cannula (2.4 mm outer diameter) was used in all patients and fit adequately in terms of septal distance and nares size. The mouth was closed during the entire data collection period.²⁰ The Fisher & Paykel system was used as commercially marketed with a pressure-limiting valve set at 45 cm H₂O pressure. EEEPs were scored after a lengthy equilibration time (25 minutes) and from numerous waveforms (100 data points). Limitations of our study include the small sample size, inability to control for differences in patient pathology, and inability to quantify leaks around the nasal cannulas. Because this was an observational study, the sample size was obtained based on a reasonable time frame for study completion. Although the primary pulmonary diagnosis for each patient was RDS of prematurity, there was no way to control for other diagnoses that could be contributing to or exacerbating a patient's respiratory status.

Future studies of this technique could add to these current data. In addition to EEEP measurements, simultaneous oropharyngeal measurements could be obtained to evaluate the relationship of values from these 2 locations, potentially allowing for a more practical pressure monitoring system than the cumbersome esophageal pressure measurement technique. A more reliable, yet relatively noninvasive method of directly measuring intrapulmonary pressures would be ideal. The use of pressure-directed rather than flow-directed HFNC may make the technique easier to manage and use reliably. Of course, it would be very useful to compare different HFNC systems with each other to further investigate whether pressure and flow delivery are HFNC system-specific or whether similar results are produced from commercially manufactured HFNC devices.

In summary, having a pressure-limiting valve within a HFNC system appears to be necessary to limit the potential for inadvertent delivery of very high distending pressures to the preterm lung. With the Fisher & Paykel HFNC system, it appears impossible to predict EEEP for a given flow level, likely due to variable leaks around the nose and mouth and variations in underlying pathology. Our data do not demonstrate a predictable relationship between patient size and pressure delivery resulting from a given HFNC gas flow. Although mean EEEP levels did not differ between NCPAP and HFNC at 1-6 L/minute, massive interpatient and inpatient variation existed. Further evaluation of HFNC

with large, randomized clinical trials is needed before HFNC can be considered a standard component of noninvasive mechanical support of preterm infants.

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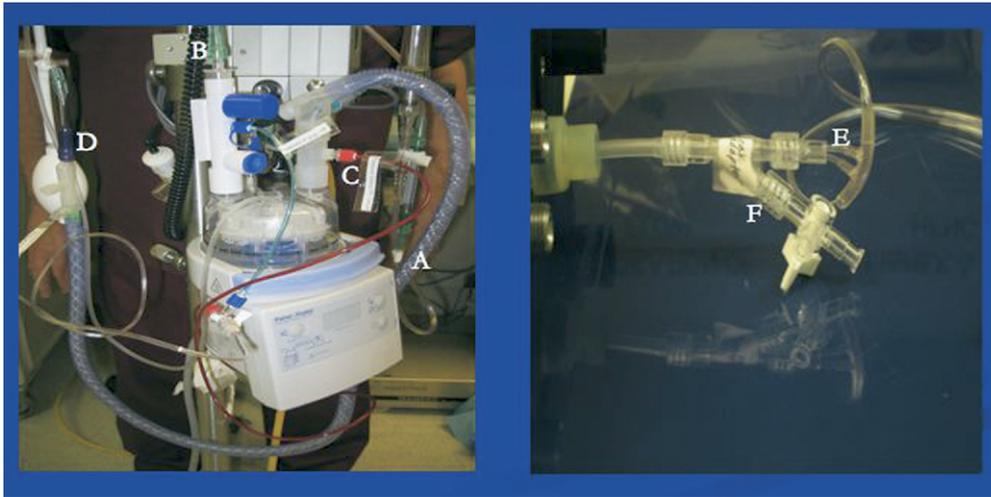


Figure 1. Fisher & Paykel high-flow nasal cannula system and points of pressure and flow measurements. A, at the gas flow source; B, before the pressure-limiting valve; C, after the pressure-limiting valve; D, end of the HFNC circuit tubing; E, at the distal end of the cannula; F, stopcock system used to create the variable air leak.

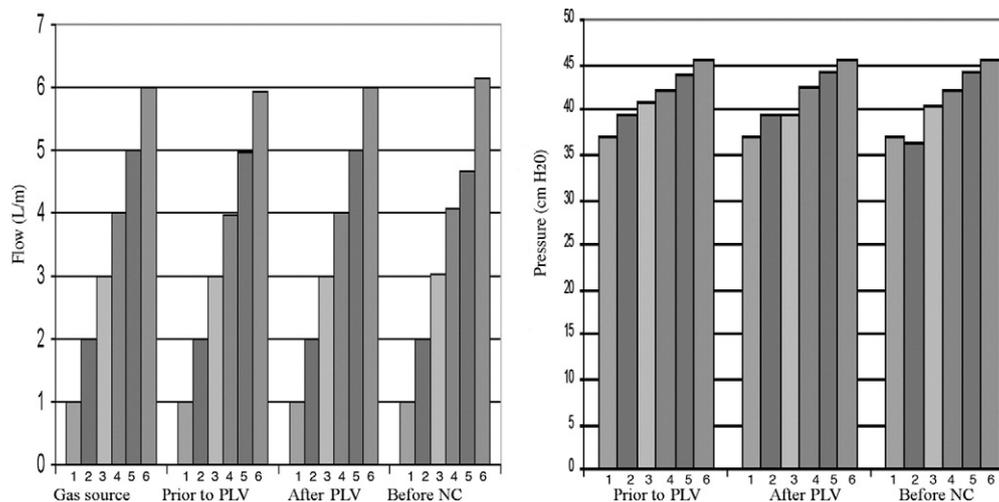


Figure 2. Gas flow and pressure delivery within the RT329 HFNC system at increasing amounts of gas flow. PLV, pressure-limiting valve; NC, nasal cannula; y-axis, measured flow and pressure; x-axis, site of measurement, set flow rate.

Table II. Mean interpatient and inpatient coefficients of variation (%) for EEEP

	NCPAP+6	6 L/minute	5 L/minute	4 L/minute	3 L/minute	2 L/minute	1 L/minute
Interpatient	161	209	302	223	841	654	1 885
Inpatient	122	117	180	143	51	147	99

Coefficient of variation = (Standard deviation/mean) × 100.