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High-Flow Nasal Cannula: Impact on Oxygenation and Ventilation in an Acute Lung Model

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SUMMARY

Introduction—High-flow nasal cannula therapy (HFNC) has been shown to be more effective than continuous positive airway pressure (CPAP) in reducing intubations and ventilator days. HFNC likely provides mechanisms to support respiratory efficiency beyond application of distending pressure. We reason that HFNC washout of nasopharyngeal dead space impacts CO_2 removal along with oxygenation. The aim of this study was to demonstrate the flow dependence of CO_2 reduction and improved oxygenation during HFNC and the dependence on leak around the nasal prongs.

Materials and Methods—Neonatal piglets (n=13; 2-6kg) were injured with IV oleic acid and supported with HFNC at 2 through 8 L/minute. High and low leak around the nasal prongs was accomplished by using single and double prong cannulae, respectively. Measurement of hemodynamic, respiratory and blood gas parameters were made at each setting following 10 minutes for physiologic equilibration. Tracheal pressures were recorded by transmural catheters.

Results—With HFNC, CO_2 trended downward in a flow dependent manner independent of leak. Oxygenation and tracheal pressures increased in a flow dependent manner with the greatest effect during double prong. At 8L/minute, tracheal pressures did not exceed 6±1 cmH_2O.

Conclusions—HFNC improves gas exchange in a flow dependent manner; double prong had greater impact on O_2; single prong had greater impact on CO_2 elimination.

Keywords

high-flow nasal cannula; animal model; gas exchange; dead space; lung mechanics

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INTRODUCTION

Continuous positive airway pressure (CPAP) is often a preferred intervention over mechanical ventilation with neonatal respiratory distress syndrome in that oxygenation is improved and lung volume is recruited while supporting spontaneous ventilatory efforts.[1,2] Some essential clinical criteria to remain on CPAP are effective spontaneous respiratory effort and CO_2 elimination. Hypercapnia, or apnea that may be secondary to hypercapnia, are cited as some of the more common reasons for progressing to more invasive forms of ventilatory support. Therefore, it is thought that if CO_2 retention during CPAP can be reduced or eliminated, many infants can be spared potential lung injury and subsequent chronic lung disease induced by mechanical ventilation.

High-flow nasal cannula (HFNC) (>2 liters per minute, (lpm)) has been proposed by some physicians as an alternative to CPAP in maintaining infants without the need for intubation and mechanical ventilation.[3] The use of HFNC in place of conventional methods has been controversial and as yet not well documented in the literature as being more effective than CPAP. Given the paucity of translational research investigating the mechanism of action of HFNC, we sought to investigate this mechanism further. We hypothesized that the mechanism of gas exchange with HFNC is associated with the washout of nasopharyngeal anatomical dead space in addition to the potential impact of positive airway pressure generation.

In a recent study, we used tracheal gas insufflation (TGI) with CPAP in lung injured piglets using a specially designed endotracheal tube to allow for insufflation of fresh gas flow (No. 6501.30; Vygon, Ecouen, France).[4] The results showed asignificant reduction in CO_2 retention associated with prosthetic dead space washout in spontaneously breathing piglets with oleic acid induced lung injury. Such a therapy, in non-intubated patients, may increase the number of infants that can be sustained without intubation or mechanical ventilation and these infants may be weaned sooner.

Given our TGI results, we reasoned that the beneficial clinical responses to HFNC may be related to the high-flow rates effectively flushing the nasopharyngeal cavity of expiratory gas. Thus, we proposed that the HFNC may provide a practical means to wash out nasopharyngeal dead space during spontaneous breathing without the need for intubation. The present study was designed to demonstrate this washout effect and the flow dependence of CO_2 elimination and oxygenation during HFNC. In addition, the study was conducted to demonstrate the independent effects of airway pressure under different leak conditions. We also hypothesized that HFNC therapy would affect CO_2 retention in a flow dependent manner without markedly increasing intra-tracheal pressure and improve respiratory parameters compared to a control group of animals treated with mask CPAP (minimal leak).

MATERIALS AND METHODS

Animal Preparation

Thirteen spontaneously breathing newborn piglets (15-20 days old, weight 2-6 kg) were instrumented, placed on mask CPAP of 5 cmH_2O and injured by intravenous administration of oleic acid. All thirteen piglets were treated with CPAP (minimal leak), single prong (SP) HFNC with a high degree of leak around the nasal prongs (HI LEAK), and double prong (DP) HFNC with a low degree of leak around the nasal prongs (LOW LEAK). The three treatment conditions were administered in a randomized, repeated measure, crossover design described below. Following experimentation, animals were sacrificed with pentobarbital (50 mg/kg) and saturated potassium chloride (2 mEq). At baseline, injury and at each treatment condition (following 10 minutes for physiologic equilibration) measurements were made of

arterial blood chemistry, pulmonary function and intra-tracheal pressure. All procedures for the animal protocol in this study were approved by the Life Science Center Animal Care and Use Committee at Nemours Children's Clinic - Wilmington of The Nemours Foundation.

Instrumentation and Injury Protocol

The piglets were anesthetized with an anesthetic solution (ketamine: 23 mg/kg; azepromazine: 0.58 mg/kg; and xylazine: 0.8 mg/kg [KAX]) given as two 1 ml/kg intramuscular injections separated by 10 minutes. The skin and soft tissues were locally infiltrated with 0.5% lidocaine HCl (4 mg/kg) and instrumented with 5.0 F catheters placed in the jugular vein and carotid artery. Additionally, a 5.0 F fluid filled catheter was placed directly into the mid trachea approximately 2 cm below the cricoid ring at a perpendicular orientation for measurements of dynamic tracheal pressure. The tracheal catheter insertion site was sealed with surgical glue to eliminate leak around the catheter. Subsequent anesthesia was maintained with an intravenous infusion of KAX at 0.4 ml/kg/hr, along with diazepam every two hours and additional KAX every one half an hour. Maintenance fluid was provided by a continuous infusion of 5% dextrose solution at a rate of 6 ml/kg/hr. Arterial blood pressure was monitored by attaching the arterial catheter to a standard pressure transducer via bedside patient monitor (Model M1175A, Hewlett Packard). ECG electrodes were placed for monitoring. Throughout the protocol the animal's rectal temperature was monitored and maintained at 37-38°C on a radiant warmer bed (Resuscitaire®; Hill-Rom Air-Shields, Hatboro, PA).

Following instrumentation, baseline measurements were made and then lung injury was initiated. Oleic acid (0.08 ml/kg; Sigma) was emulsified in 0.5 ml/kg blood and infused into the central venous line in four equal doses with ample time to allow stabilization between doses. The injury model has been previously described[4] and the oleic acid dose was refined in a pilot study to achieve a 50% reduction in PaO_2 and respiratory compliance while preserving spontaneous respiration.

Treatment Protocol

Following the injury procedure and a 30 minute stabilization period, all thirteen animals were exposed to HI LEAK, LOW LEAK and CPAP (minimal leak) in randomly assigned order. For each treatment scenario, flow rate (HFNC) or pressure (CPAP) was increased incrementally by 2 (lpm or cmH_2O) from least to greatest magnitude and then incrementally back to the least; the two sets of data for each increment were then averaged to filter out the residual effects of the previous level of treatment. To be consistent with current neonatal clinical practice, HFNC flow rates ranged from 2 to 8 lpm and CPAP pressures used ranged from 2 to 6 cmH_2O flow was held constant at 8 l/min. Inspired oxygen fraction was always held at 1.0 for consistency and so that PaO_2 reflects the a/A ratio.

HFNC therapy was administered using a Vapotherm 2000i (Vapotherm, Inc, Stevensville, MD) with a pediatric nasal cannula. Given the small diameter of the piglet nares relative to the human, the pediatric cannula fully occluded both nares of the piglet, thus representing the LOW LEAK condition. To achieve the HIGH LEAK condition where only half the area of the nares was obstructed (as per manufacturer's recommendation), one of the prongs of a pediatric cannula was removed and the hole sealed, such that one nare of the piglet was occluded with the cannula prong and the other nare was open to exhaust.

CPAP was administered by a VIP Bird infant ventilator (Bird Products Corp., Palm Springs, CA) set to the CPAP mode. The ventilator circuit was attached to the piglet using a semi-cone shaped face mask lined with silicone that conformed to the piglet's head shape to minimize the addition of prosthetic dead space. Furthermore, the base of the face mask

(around the piglets head) allowed for minimal gas leak to allow washout of any remaining prosthetic dead space from the mask. Under all conditions, the ventilator was able to generate the prescribed levels of CPAP as indicated by ventilator circuit and pig tracheal pressure measures.

Pulmonary Function Assessment

Arterial blood gases and chemistry were measured by a standard patient blood analyzer (Stat Profile®, Nova Biomedical, Waltham, MA). Blood gas parameters measured included pH, $PaCO_2$, PaO_2, hemoglobin, hematocrit, HCO_3, and base excess values. The blood gas measurements were obtained 10 minutes after each change in respiratory support to ensure adequate physiologic equilibration given that the respiratory system compensates for changes in acid-base status within this time period.[5] Respiratory parameters were assessed by inductive plethysmography (SomnoStar PT, SensorMedics, Yorba Linda, CA), including relative tidal volume, respiratory rate and thoracoabdominal synchrony. In all animals, relative tidal volumes, respiratory rates and minute ventilations were determined prior to lung injury during manual bagging (via mask CPAP) with low (2-4 ml/kg) and high (6-8 ml/kg) tidal volume strategies in order to establish relative calibration standards for inductive plethysmography.

Data Analysis

Data was analyzed using linear regression or analysis of variance (ANOVA) to assess differences associated with type and/or magnitude of therapy. Post-hoc analyses were done, where appropriate, using Bonferroni comparisons. Significance was accepted with p values < 0.05.

RESULTS

Thirteen piglets were utilized for the study and demonstrated a stable injury; age 13 ± 8 days and weight 6.0 ± 0.2 kg. The injury was associated with a substantial increase in $PaCO_2$ (37.3 mmHg ± 6.6 vs 49.1 mmHg ± 6.1; $p < 0.01$) despite the transition from room air to FiO2 of 1.0 and an increase in A-a gradient (23.3 +/− 12.1 vs 254.3 +/− 88.9; $p < 0.01$). These findings are demonstrated in Figure 1.

Tracheal Pressure

As shown in Figure 2, it was possible to record direct temporal changes in tracheal pressure at each specific therapeutic intervention. A data acquisition recorder (DASH 8Xe) was used for the tracheal measurements. As such, these traces provided evaluation of pressure response to increments in CPAP or flow during HFNC perturbations. Based on summarized data shown in Figure 3A and 3B, there was a direct linear relationship between each prescribed CPAP setting and tracheal pressure (slope=0.6;r^2=0.99;p=0.02). Similarly, a direct linear relationship existed between flow rate and tracheal pressure under the LOW LEAK condition (slope=0.21;r^2=0.82; p =0.04). Under the HIGH LEAK condition, the linear relationship between flow and resultant tracheal pressure showed a significant rise in tracheal pressure between 2 and 8 lpm of flow (r^2=0.81;p= 0.04). Overall, mean tracheal pressures were higher during the low leak condition compared to high leak flow conditions.

Pulmonary and Physiologic Parameters

No differences were seen in respiratory rate and relative tidal volume across therapies or orders of magnitude (i.e., incremental pressures (CPAP) or flow rates (HFNC). The relative minute ventilation values determined through integration of rates and relative tidal volumes (inductive plethysmography) also showed no differences as demonstrated in Table 1.

Physiologic parameters were measured for all piglets under every condition. Measurements included rectal temperature, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, respiratory rate and SaO_2 values. The means and standard deviations for each parameter under all conditions are depicted in Table 2. There was no significance found for any of these values.

Ventilation Indices

Figure 4 shows the effects of incremental increases in CPAP and HFNC therapies on $PaCO_2$. With initiation of CPAP (2 cmH_2O), arterial carbon dioxide tension ($PaCO_2$) decreased from the basal injury level ($p<0.05$); however, no further decease in $PaCO_2$ was seen with the incremental increases in CPAP pressure. With HFNC, in the LOW LEAK condition a significant relationship was found between flow rate and partial pressure of carbon dioxide (slope=-0.73; $r^2 = 0.92$;$p<0.01$) where $PaCO_2$ decreased with incremental increases in flow rate in a sigmoidal fashion. In the HIGH LEAK condition, $PaCO_2$ was restored to baseline levels immediately (2 lpm of flow) and therefore did not decrease further with incremental increases in flow rate.

Oxygenation

Oxygenation versus CPAP/flow rate data is shown in Figure 5. With CPAP administration, arterial oxygen tension (PaO_2) rose to over 400 mmHg but did not change with incremental increases in CPAP pressure. However, PaO_2 showed a flow dependent increase for both LOW LEAK and HIGH LEAK conditions. In the LOW LEAK condition, PaO_2 responded in a significant linear relationship with throughout the range of flow rates 2-8 lpm (slope=30.6; $r^2 = 0.85$;$p = 0.03$), and there was a 400 mmHg plateau from 8-10 lpm. Under the HIGH LEAK condition, PaO_2 rapidly increased from 2 to 6 lpm before reaching a 400 mmHg plateau above 6 lpm.

DISCUSSION

This study demonstrated two important findings. First, with HFNC tracheal pressures were comparable to CPAP pressures at the same flow range. Second, washout of nasopharyngeal dead space is associated with improved gas exchange using HFNC and may allow patients to breathe more comfortably as represented clinically.[6] As our results demonstrate, tracheal pressures in the neonatal piglets were no greater than with traditional CPAP ventilation and pressures. This is consistent with HFNC clinical studies that report lower esophageal pressures compared to CPAP at 6 cmH_2O.[7-11]

With respect to gas exchange, the impact of increasing flow on ventilation and oxygenation occurred independent of tracheal pressure generation alone. With increasing CPAP pressure in this injured lung model, neither $PaCO_2$ nor PaO_2 demonstrated progressive change. However, with HFNC under both leak conditions $PaCO_2$ and PaO_2 improved in a somewhat flow dependent manner reflected by saturation curves, ($PaCO_2$ decreased with increasing flow until saturation and PaO_2 increased with increasing flow until saturation). These saturation relationships are consistent with nasopharyngeal dead space washout (like) as demonstrated in the literature from tracheal gas insufflation.

Tracheal gas insufflation is a means of flushing prosthetic dead space using a catheter inserted into an endotracheal tube, or a specially designed endotracheal tube for gas insufflation.[6,12-15] With this technique, insufflation of fresh gas is fed through the catheter at low flows (typically 0.5-1.0 lpm). This method supplies fresh gas during inspiration, and also flushes the prosthetic tube dead space between the catheter tip and the oral/nasal openings during expiration and the end expiratory pause. By flushing prosthetic dead space

during the expiratory phase of the respiratory cycle, the subsequent inspiratory breath contains more fresh gas and less residual end-expiratory gas. Therefore, alveolar gas fractions are moved toward fresh gas values; i.e., less carbon dioxide and more oxygen, thereby improving respiratory efficiency.[16-18] However, the limitation of tracheal gas insufflation is that it requires intubation.[4]

With gas insufflation, at any given liter flow the volume of dead space to be flushed is determined by the time allotted by end-expiration and the expiratory pause.[6,12-15] Therefore, greater gas flows will flush more dead space until a flow rate is reached that can flush all of the available anatomical/prosthetic dead space in the allotted time; beyond this liter flow, increased flow rates accomplish no further effect, generating a saturation cure for alveolar and thus arterial gas composition.

In the current study, tracheal pressures with HFNC rose in a linear fashion and did not exceed 6 cm H_2O up to flows of 8 lpm, while both ventilation and oxygenation responses reached saturation near 6-8 lpm flow. Therefore, we determined that nasopharyngeal dead space washout was a more predominant factor in determining gas exchange response to incremental flow as compared to incremental pressure increases. As compared to CPAP and LOW LEAK, the partial pressure of carbon dioxide was lower for flow rates (< 6 lpm) in the high leak condition. We attribute this phenomenon to a better washout of the nasopharyngeal cavity with HIGH LEAK, making a high leak situation more desirable since effective gas exchange can be achieved at a lower tracheal pressure.

Although several recent articles have reported estimates of tracheal pressure, positive end distending pressure and continuous positive airway pressure generated during the use of high frequency nasal cannula therapy, these studies are confounded by several measurement limitations. The results to date have been collected by means of nasal pharyngeal pressure monitoring, oral cavity pressure monitoring or esophageal pressure monitoring. Although these methods are all minimally invasive; they provide only an estimation of actual airway pressure. The major complication with these forms of measurement are the following: inaccurate pressure assessment due to catheter placement or catheter design, catheter orientation with respect to the gas flow, frequency response of the measurement system, as well as variable gas leak from the oral cavity. In our study, we used precise, accurate, and responsive dynamic tracheal pressure monitoring/recording via a fluid filled catheter surgically placed mid trachea with a perpendicular orientation (with respect to gas flow). Using this technique, as described, we did not find significantly elevated tracheal pressures over the flow ranges tested. This is the first time this method has been used to directly measure tracheal pressures during high flow nasal cannula therapy.[3, 7, 19-21]

Taking into account the possibility of other physiologic adjustments in minute ventilation impacting alveolar and therefore blood gas compositions, we measured relative minute ventilation using inductive plethysmography. No changes in this relative minute ventilation were noted, indicating that changes in blood gas values were directly associated with the change in therapy paradigm. In addition, since therapeutic interventions were randomized during the study, there were no alterations in lung injury or alveolar dead space, which could have accounted for changes in gas exchange. Taken together, these data support the conclusion that HFNC may augment carbon dioxide elimination by means of nasopharyngeal dead space washout.

As in all animal model studies, a limitation to this study is the translation of data to clinical application. The anatomy of a piglet, especially the nasopharyngeal anatomy is very different from a human. In this regard, we believe that the cavernous human nasopharynx, as opposed to the elongated pig nasopharynx would flush more easily without as much pressure

development. Nonetheless, we contend that the anatomy is similar enough to study physiologic mechanisms, and the piglet as model for treatment of lung injury has been well established.[4,22]

The current data suggest that HFNC therapy may be used as a first line option over traditional CPAP support. This study shows that HFNC provides improved levels of arterial CO_2, whereas CPAP does not, independent of changes in minute ventilation. Therefore, HFNC can be viewed as a truly non-invasive means of ventilatory support. In addition, by way of nasopharyngeal dead space elimination, HFNC can serve as a means of oxygenation support independent of, or in addition to, supplemental oxygen administration. Clinical studies are now warranted to refine flow needs in the human scenario to optimize these effects demonstrated in this preclinical model.

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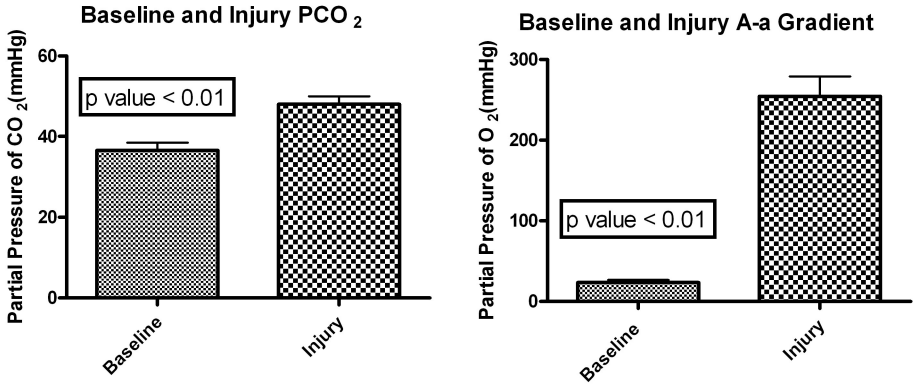

Figure 1. Baseline and Injury

Gas exchange alterations following oleic acid injury. Left panel; change in arterial PCO_2, baseline vs. injury. Right panel; change in A-a gradient baseline vs. injury. N=13; $p < 0.01$

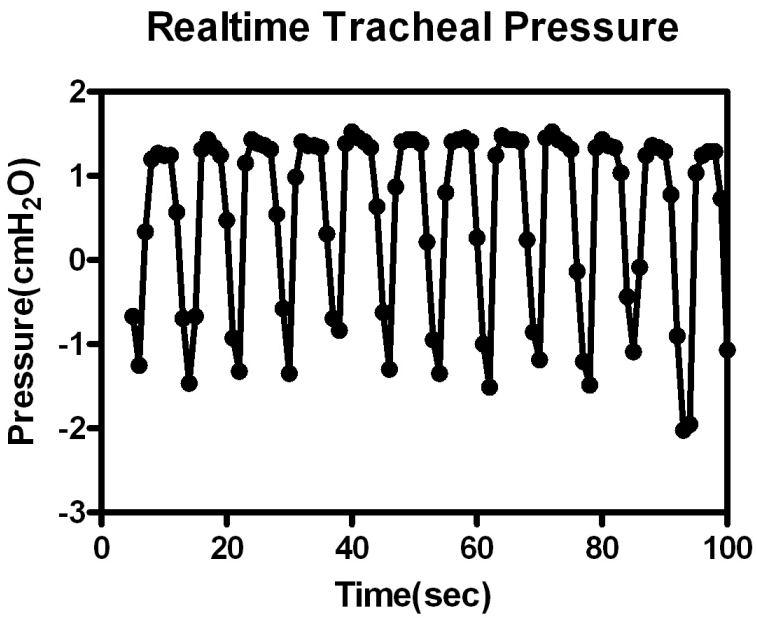

Figure 2. Real-time Tracheal Pressures

Typical tracing of real time tracheal pressure as recorded using a water-filled catheter at SP 2 lpm.

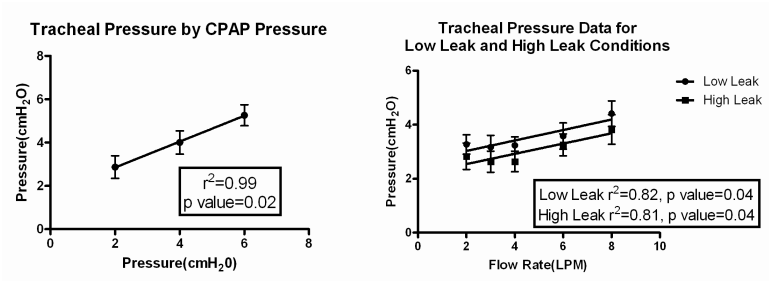

Figure 3. Tracheal Pressures

Summarized data for tracheal pressures during CPAP; r^2=0.99;p=0.02 (left panel). Tracheal pressures for high (r^2=0.81;p=0.04) and low leak conditions (r^2=0.82;p=0.04) (right panel).

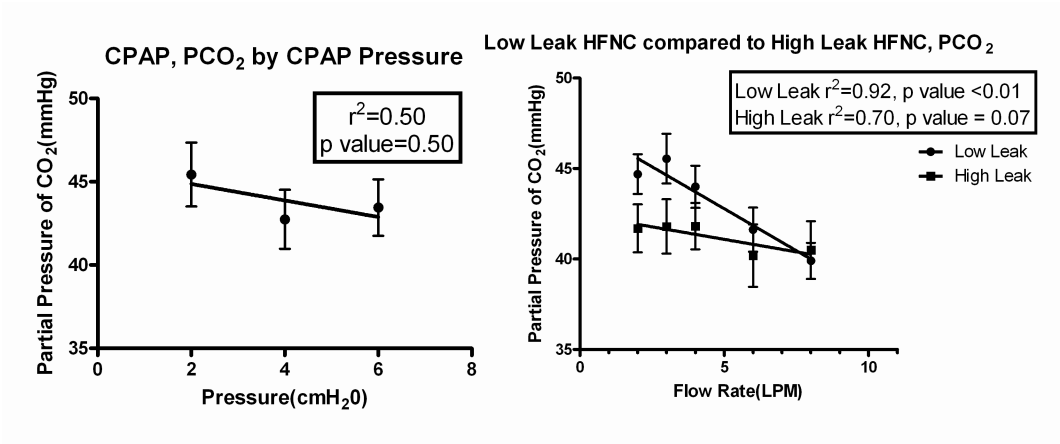

Figure 4. Partial Pressure Carbon Dioxide

Effects of incremental increases in CPAP on PCO r^2 2 =0.5;p=0.5(left panel). Effects of incremental increases in HFNC flow rate on PCO (low 2 2 leak r =0.92;p<0.01; low leak r^2=0.7;p=0.07) (right panel).

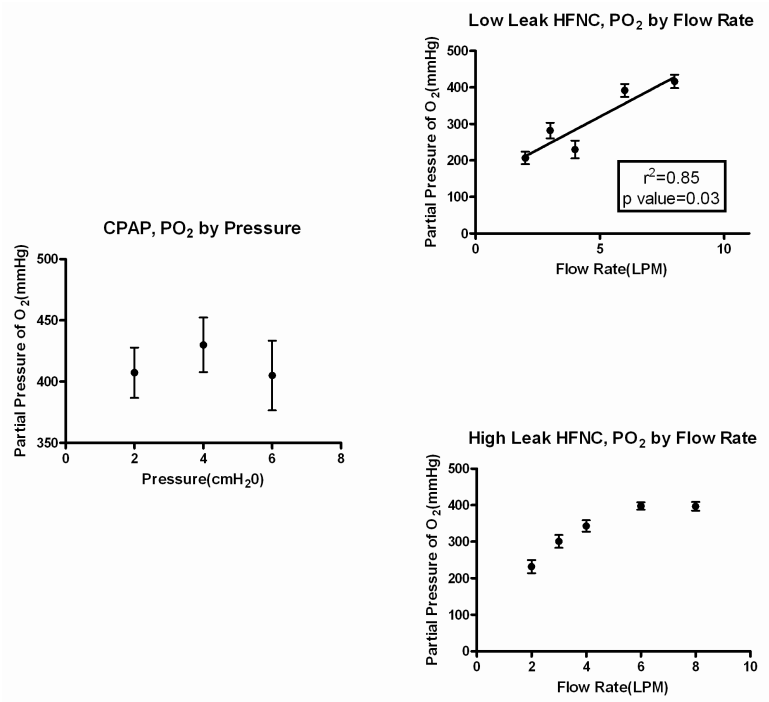

Figure 5. Partial Pressure Oxygen

Effects of incremental increases in CPAP on PO_2 (left panel). Effects of incremental increases in HFNC flow rate on O_2 in low leak condition (r^2=0.85;p=0.03) (top right panel). Effects of incremental increases in HFNC flow rate on O_2 in high leak condition (bottom right panel).

Table 1

Minute Ventilation Values (AU) as a Function Flow

CPAP			Single Prong				Double Prong			
2 cmH_2O 8 l/min	4 cm H_2O 8 l/min	6 cm H_2O 8 l/min	2 l/min	4 l/min	6 l/min	8 l/min	2 l/min	4 l/min	6 l/min	8 l/min
28416 ± 16979	24923 ±21774	29117 ±18453	30752 ±20644	26464 ±19453	26184 ±22237	27210 ±27210	26709 ±18505	26340 ±22168	28895 ±23593	27080 ±19216

Note: Minute ventilation data is presented in arbitrary units (AU) as determined by respiratory inductive plethysmography (RIP) measurements. Data represent mean ± SD.

Table 2

Physiologic Parameters as a function of CPAP, SP, and DP across experimental conditions.

	CPAP				Single Prong (SP)				Double Prong (DP)			
	Baseline 5 cmH_2O 8 l/min	**Injury 5 cmH_2O 8 l/min**	**2 cmH_2O 8 l/min**	**4 cmH_2O 8 l/min**	**2 l/min**	**4 l/min**	**6 l/min**	**8 l/min**	**2 l/min**	**4 l/min**	**6 l/min**	**8 l/min**
Temperature (°C)	37.3 +0.9	37.6 +0.7	37.8 ±0.7	37.8 ±0.7	37.9 +0.7	37.8 +0.7	38 +0.6	38 +0.7	37.8 +0.7	37.8 +0.7	37.9 +0.7	38 +0.7
Systolic Blood Pressure	88.2 +13.6	96.2 +13.3	101.3 ±14.3	99.3 ±13.3	103.8 +13.9	104.2 +15.7	101.1 +15.3	100.3 +13	104.1 +13.9	103.1 +16	98.3 +17.5	98.2 +17
Diastolic Blood Pressure	55.4 +6.7	65.4 +6.9	68.2 ±10.9	66.6 ±11.5	68.2 +11.8	71 +10.9	69.9 +12	68.1 +12.2	69.9 +9.9	69.8 +10.8	69.9 +11.5	68.5 +10.8
Mean Arterial Blood Pressure	68.3 +8.5	79.3 +9.2	83.8 ±11.3	81.5 ±11.8	83 +11.2	85.6 +11.9	84.2 +12.3	82.6 +12	85.7 +10.3	84.8 +11.9	82.5 +13.6	82.2 +12.9
Heart Rate	165.1 +32.3	132.8 +15.1	138.8 ±32.3	138.4 ±25.1	141 +29.6	134.2 +29.8	128.2 +21.1	135.7 +33.2	142.5 +32.1	136.5 +29.9	137.1 +33.1	129.7 +33
Respiratory Rate	48.8 +17.1	49.5 +14.4	50.2 ±16.7	43.4 ±12.2	54.1 +20.8	56 +19.6	51.8 +14.4	48.5 +15.7	52.9 +19.5	51.2 +18.7	51.7 +15	53 +11.8
SaO_2	95.1 +3.9	96.3 +3.7	97.6 ±2.2	98 ±1.7	94.3 +9.5	98.1 +1.4	97.1 +3	96.6 +4.4	95.6 +3.9	96.7 +2.8	96.2 +2.6	96.3 +3.4

Note: All data are presented as mean ± SD and no parameters were found to be significant as a function of condition or flow.