

ORIGINAL ARTICLE

Pharyngeal pressure with high-flow nasal cannulae in premature infants

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Objective: The aim of this study was to measure pharyngeal pressures in preterm infants receiving high-flow nasal cannulae.

Study Design: A total of 18 infants were studied (median gestational age 34 weeks, weight 1.619 kg). A catheter-tip pressure transducer was introduced into the nasopharynx. Flow was sequentially increased to a maximum of 8 l min⁻¹ and decreased to a minimum of 2 l min⁻¹.

Result: There was a strong association between pharyngeal pressure and both flow rate and infant weight ($P < 0.001$, $r^2 = 0.61$), but not mouth closure. This relationship could be expressed as pharyngeal pressure (cm H₂O) = 0.7 + 1.1 F (F = flow per kg in l min⁻¹ kg⁻¹).

Conclusion: High-flow nasal cannulae at flow rates of 2 to 8 l min⁻¹ can lead to clinically significant elevations in pharyngeal pressure in preterm infants. Flow rate and weight but not mouth closure are important determinants of the pressure transmitted.

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Introduction

High-flow nasal cannulae (HFNC) are a novel means of respiratory support in preterm infants. This refers to the delivery of humidified, heated and blended oxygen/air at flow rates of greater than 1 l min⁻¹ via nasal cannulae.¹ Preliminary studies suggested that such flow rates in preterm infants could provide positive end-expiratory pressure.^{2,3} As a consequence of this, and because of its apparent ease of use and reduced nasal trauma, HFNC has gained considerable clinical support,⁴ and has been used as an

alternative to nasal continuous positive airway pressure (CPAP).^{3–9} However to date, relatively little has been published on its efficacy or safety.

When infants receive conventional nasal CPAP, it is possible to measure and regulate the pressure applied to the pharynx from the circuit. Expiratory or blow-off valves ensure that the delivered pressure does not exceed the prescribed level. In comparison, the calibre of tubing delivering the gas via HFNC is significantly smaller, and consequently the resistance to flow and pressure in the circuit is much higher.¹⁰ In HFNC the pressure delivered to the airway cannot be determined directly from the pressure in the circuit. There has been concern about the possibility of lung overdistension and trauma from unmeasured and variable pressure transmitted to the pharynx with HFNC.¹¹ It is unclear what flow rates of HFNC are safe to use, what rates are likely to be effective and what factors might affect the transmission of pressure to infants.

The aim of this study was to measure pharyngeal pressure in preterm infants receiving HFNC at flow rates of 2 to 8 l min⁻¹.

Methods

Study population

This study was carried out in a convenience sample of stable infants receiving HFNC for treatment of respiratory distress syndrome, chronic lung disease or apnoea of prematurity at the Mercy Hospital for Women. The institutional ethics committee approved the study. Written informed parental consent was obtained in all cases.

Measurement of pharyngeal pressure

Pharyngeal pressures were measured using a 0.21 cm diameter catheter with a single solid-state catheter-tip pressure transducer (CTO-1, Gaeltec, Dunvegan, Scotland). Signals were amplified and digitized at 200 Hz by a preamplifier (Neomedix Systems, Sydney, Australia) and recorded on a Macintosh computer (Apple, Cupertino, CA, USA) using Uromac software (Neomedix). The catheter was calibrated before and after each series of measurements using a water manometer.

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High-flow system

Short, narrow-calibre, tapered nasal cannulae (Fisher and Paykel Healthcare, Auckland, New Zealand) were connected to a standard humidifier base (MR850, Fisher and Paykel) and circuit without pressure-limiting valve (Oxygen Therapy System RT 329, Fisher and Paykel). Cannulae were chosen to fit into the infant's nostrils comfortably without occluding them ('neonatal cannula' outer diameter 0.14 cm, 'infant cannula' outer diameter 0.19 cm, 'paediatric cannula' outer diameter 0.27 cm). The gas administered via the high-flow system was a blended mixture of oxygen and air, titrated to achieve acceptable oxygen saturation. Flow rates typically used in clinical care were 2 to 8 l min⁻¹.

Study protocol

If infants had an indwelling nasogastric tube this was removed prior to the study and replaced at its completion. The pressure-transducer catheter was introduced into either nostril to a distance 1 cm less than the measured distance from tip of nose to tragus. This distance ensured positioning in the nasopharynx, with minimal irritation to the infant. Correct positioning was ensured by observation of a stable respiratory waveform. When the infant was settled, the flow was changed in increments of 1 l min⁻¹. Flow was sequentially increased from the infant's starting rate up to a maximum of 8 l min⁻¹ and then decreased to a minimum of 2 l min⁻¹ before returning to the starting point.

Mouth position

At each level of flow pressures were recorded with and without active mouth closure. Pressure was recorded initially with the mouth in the resting position (designated 'passive', involving no active measures to close the mouth), and then with the mouth actively closed. Active mouth closure was obtained by gently placing one finger under the chin of the infant.¹²

Measurements

For each measurement episode, stable recording of at least 20 s was observed before changing parameters. Mean pharyngeal pressure of the longest period of stable recording was calculated using Uromac software. Heart rate and oxygen saturation were recorded continuously during the study.

Statistical analysis

Continuous variables were summarized with median and range or interquartile range (25th to 75th centile). The association of pharyngeal pressure with each of flow, weight and mouth closure was assessed using multiple linear regression while robust standard errors were used to account for correlation between measurements taken from the same infant. Since regression residuals were found to increase with flow rate, an alternative prediction model with constant variance was also sought (Appendix A). All statistical analyses were performed using Stata version 9.2. (StataCorp., College Station, TX, USA)

Results

A total of 18 infants were studied. They had a median gestational age at birth of 27.1 (range 24.5 to 34.3) weeks, and a birth weight of 0.944 kg (0.534 to 1.868). Ten of the infants were female. At the time of the study, their median corrected gestational age was 33.6 weeks (range 29.1 to 53) and weight was 1.619 kg (0.816 to 4.400). The infants' median inspired oxygen concentration at the start of the study was 0.21 (interquartile range 0.21 to 0.3), and flow rate was 4 l min⁻¹ (2 to 5). The study was well tolerated without complication, though several infants experienced transient apnoea at low flow rates. 'Neonatal' cannulae were used in 13 of 18 infants. 'Infant' cannulae were used in two infants (weight 1.398 and 1.858 kg). 'Paediatric' cannulae were used in the remaining three infants (all >2.6 kg).

Pharyngeal pressures stabilized quickly after changes in flow rate. A sample pharyngeal pressure recording is illustrated in Figure 1. Pharyngeal pressures were less than or equal to 10 cm water at all flow rates except in two infants. One infant (0.816 kg) had a mean pharyngeal pressure of 12 cm water at a flow rate of 8 l min⁻¹ with mouth in the passive position. A second infant (1.674 kg) had a pharyngeal pressure of 11.9 cm water when receiving HFNC at 8 l min⁻¹, but only with his/her mouth actively closed.

Pharyngeal pressure increased with increasing flow in the infants studied (Figure 2). There was strong evidence for a linear association between pressure and flow that was unaltered by adjustment for infant weight and mouth closure ($P < 0.001$ for both adjusted and unadjusted analyses, $r^2 = 0.61$). Average pressure increased by 0.8 cm H₂O for each 1 l min⁻¹ increase in flow (95% confidence interval 0.63 to 0.97).

Infant weight was also associated with pressure ($P = 0.001$), with average pressure decreasing by 1.4 cm H₂O (95% confidence interval -2.2 to -0.67) for each 1 kg increase in weight. There was no evidence for an association between mouth closure and pressure ($P = 0.16$; Figure 2).

The relationship between pharyngeal pressure, flow and weight could be expressed as pharyngeal pressure (cm H₂O) = 2.6 + 0.8 F - 1.4 wt (F = flow in l min⁻¹, wt = weight in kg). This relationship could also be expressed in terms of flow per kg (Figure 3).

The alternative prediction model produced similar expected results for pharyngeal pressure to the standard regression equation (Appendix A).

Discussion

In this sample of preterm infants receiving oxygen/air via nasal cannulae at flow rates of 2 to 8 l min⁻¹, pharyngeal pressure increased linearly with flow delivered and decreased linearly with infant weight. We derived two models for predicting pharyngeal

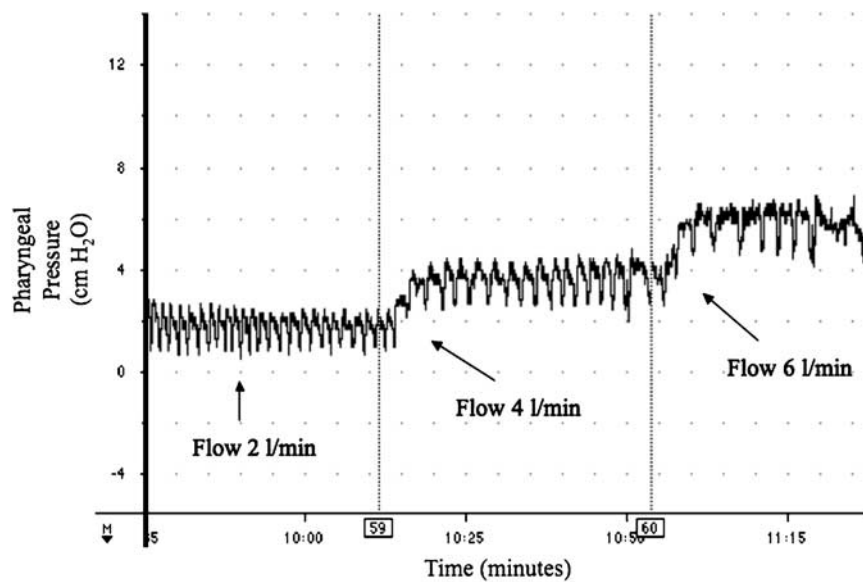


Figure 1 Measured pharyngeal pressure at variable flow rate in one infant. Compressed recording in one infant (1.398 kg) over 2 min. The rhythmical fluctuations in pharyngeal pressure are related to infant breathing. During this recording flow was increased from 2 to 4 to 6 l min⁻¹.

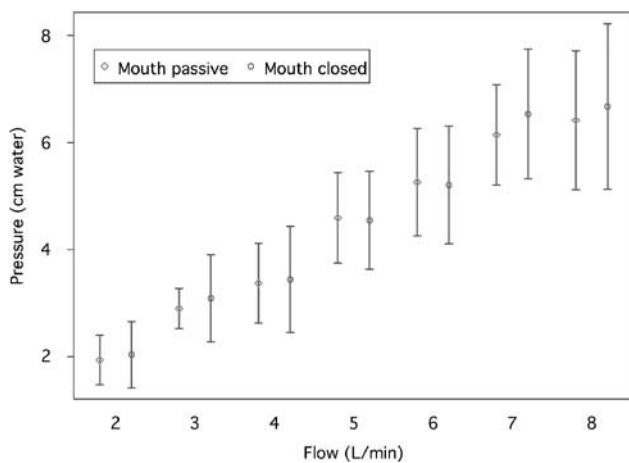


Figure 2 Mean pharyngeal pressure (with 95% confidence intervals) recorded at flow rates 2 to 8 l min⁻¹.

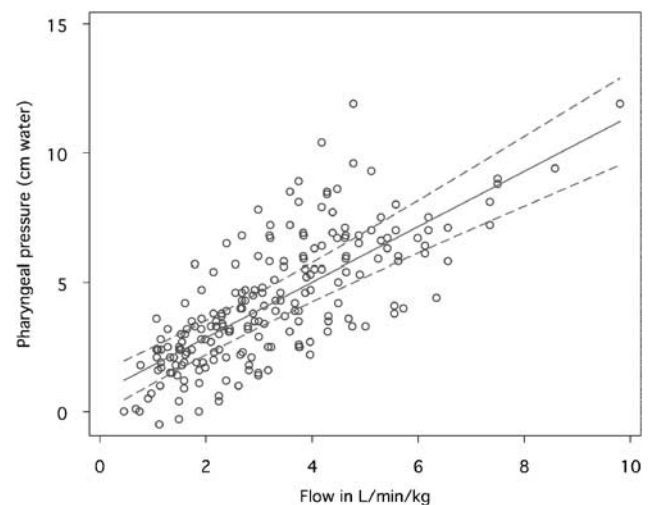


Figure 3 Pharyngeal pressure vs flow per kg. Linear regression with 95% confidence interval. Predicted pressure (cm water) = 0.7 + 1.1 × F (F = flow per weight in l min⁻¹ kg⁻¹).

pressure in infants of a given weight and at a given flow rate (see above). There was some variability between infants in the measured pharyngeal pressure, particularly at higher flow rates.

Previous studies have measured oesophageal pressure and demonstrated increases in proportion to flow rate when flows of more than 1 l min⁻¹ were delivered to infants.^{2,3} However, there is some difference between the pressures obtained during this study and those previously measured (Table 1). Locke *et al.*² measured changes in oesophageal pressure from baseline in preterm infants. They showed large increases in oesophageal pressure at comparatively low flow rates (1 to 2 l min⁻¹), but only in a subset of infants in whom larger diameter cannulae were used.³ They did

not assess the relationship between infant weight and oesophageal pressure. Sreenan *et al.*³ titrated the flow rate of nasal cannulae to achieve the same oesophageal pressure as that measured during nasal CPAP set at 6 cm H₂O. In that study the mean change from baseline in oesophageal pressure was 4.5 cm H₂O, and the flow rate required was estimated as (0.92 + 0.68 wt).³

Considerably lower pressures were measured in a more recent study in 18 preterm infants, where flow rates of 3 to 5 l min⁻¹ led to oesophageal pressures of less than 2 cm H₂O.⁹ Interestingly in the same study, the oesophageal pressure in infants receiving nasal CPAP set at 6 cm H₂O was only 1.8 cm H₂O.⁹

Table 1 Pharyngeal or oesophageal pressures (cm H₂O) in preterm infants receiving HFNC: predicted or measured values for a 1.5 kg infant

	n	Site of pressure measurement and timing	Cannula diameter (cm)	Flow (l min ⁻¹)		
				2	4	6
Locke ^{2a}	7	Oesophageal (end-expiratory)	0.3	9.8	NA	NA
Sreenan ^{3b}	40	Oesophageal (end-expiratory)	NA	4.5	NA	NA
Saslow ^{9c}	18	Oesophageal (end-expiratory)	0.25	NA	1.6	NA
This study ^d	18	Pharyngeal (mean)	0.14	2.1	3.7	5.3

Abbreviation: NA, Not available.

^aMeasured values (mean weight 1.594 kg). Measurements were obtained from 0.5–2.1 min⁻¹.

^bPredicted value of pharyngeal pressure for a 1.5 kg infant at a flow of 1.9 l min⁻¹. Cannula size not recorded.

^cMeasured values (mean weight 1.542 kg). Measurements were obtained from 3–5 l min⁻¹. In the discussion the authors mention that the cannula area was 5.07 mm², which would correspond to a cannula diameter of 0.25 cm.

^dPredicted values for a 1.5 kg infant using the standard regression equation.

Two potential explanations for the differences in results in this study compared to earlier studies include measurement technique and cannula size relative to the size of the nares.

Measurement technique

We recorded mean pharyngeal pressure rather than end-expiratory oesophageal pressure, and used a pressure-tip transducer rather than an air-filled balloon.

While end-expiratory pressures are higher than mean pressures, the difference in our study was not usually more than 0.5 to 1 cm H₂O. Mean pressures are easier to reliably measure over long recording periods.

Traditionally oesophageal pressures have been used to estimate pleural pressure in infants undergoing assessment of respiratory mechanics.¹³ Air- or fluid-filled catheters have been used, however accurate results require significant skill, and technical problems can affect the validity of measurements.¹³ In comparison, catheters with pressure transducers at the tip correlate well with balloon catheter systems,^{14,15} are well tolerated by acutely ill patients¹⁴ and appear to be accurate and reliable in infants.¹³ They have excellent linearity, and minimal hysteresis.¹⁶ In adults, catheter-tip pressure transducers have largely superseded open catheter techniques in studies of sleep or deglutition.¹⁷

There are very few studies reporting oesophageal pressures in infants receiving nasal CPAP. As an alternative, some authors have measured pressure in the upper airway since it provides a useful measure of how much pressure has been transmitted from the CPAP delivery system.¹² Pedersen *et al.*¹⁸ measured both oropharyngeal and oesophageal pressures in infants receiving CPAP via a Benviste device. Pharyngeal but not oesophageal pressures were proportional to the flow rate administered.¹⁸ Recently De Paoli *et al.*¹² measured mean pharyngeal pressure using an air-perfused catheter in 11 preterm infants receiving nasal CPAP. They were clearly able to demonstrate changes in pharyngeal pressure with changes in the set CPAP.¹²

With nasal CPAP or with mechanical ventilation in infants, oesophageal pressures are lower than those measured in the upper airway or ventilator circuit,^{18,19} consistent with an anticipated downstream reduction in pressure. Nevertheless, transmitted pressures in this study were consistently lower than those reported by Sreenan and Locke in the oesophagus. Measurement technique does not appear to explain this discrepancy.

Cannula size

In the study by Locke *et al.*,² there was no measurable increase in oesophageal pressure in six infants in whom 0.2 cm diameter cannulae were used. High-transmitted pressures were only obtained with 0.3 cm cannulae.² Why would this make a difference to pressure transmission? From Poiseuille's law, the pressure change across a circuit will be proportional to flow multiplied by the resistance. Locke *et al.*² documented that the mean nares diameter in the infants studied was 0.4 cm, implying that the gap between the cannula and nostril would be 0.05 cm on each side with the larger cannulae. It seems plausible that the difference between the smaller and larger cannulae was due to the substantial reduction in leak around the cannulae with the larger size and consequent increase in total airway resistance. Sreenan *et al.*³ did not document the size of cannulae used.

In our study, the majority of infants used cannulae with an outer diameter of 0.14 cm, but larger cannulae were used in the five largest infants. In those infants lower mean pressures were recorded, consistent with the hypothesis that the significance of cannula size is not the absolute size, but its size relative to the nares of the infant.

In summary, cannula size may explain the lower pressures measured in this study and in that by Saslow *et al.*⁹ The earlier studies appear to have overestimated the pressures generated by HFNC. This would potentially explain the higher reintubation rate in infants randomized to HFNC in a recently published pilot study.⁸ That study randomized 40 infants to HFNC or CPAP following

extubation using flow rates according to the formula generated by Sreenan *et al.*³ The mean flow rate used was 1.6 l min^{-1} , which our study would predict delivered a pharyngeal pressure of only $2.5 \text{ cm H}_2\text{O}$.

Mouth position

An additional factor affecting pressure transmission may be mouth opening. De Paoli *et al.*¹² demonstrated significant differences in pharyngeal pressure in infants receiving nasal CPAP when the mouth was in a passive position compared to when it was closed. Pharyngeal pressure increased by $1.1 \text{ cm H}_2\text{O}$ with mouth closure across a range of CPAP pressures.¹² This effect is presumably due to reduction/elimination of mouth leak (and consequence significant increase in pharyngeal resistance). In contrast our study would suggest that for HFNC mouth position has little effect on pharyngeal pressure. One explanation for the lack of effect of mouth closure with HFNC is that the mouth leak compared to nasal leak is relatively less important. With HFNC there is a large and audible leak of gas flow around the cannulae, whereas with nasal CPAP minimum leak at the nose is ensured by selecting the largest prongs that will fit snugly in the nostrils without causing blanching of the surrounding tissue.

Limitations

There are some limitations to the conclusions that can be drawn from this study. The short duration of recording provides an indication of transmitted pressure, though intermittent higher or lower pressures might be seen with longer study. While catheter-tip pressure transducers provide reliable measures of changes in respiratory pressures, they can be susceptible to baseline drift, and hence absolute measurements may be less accurate.¹⁴ We calibrated catheters before and after each study period to exclude significant drift. The catheters were placed in the nasopharynx to minimize disturbance of infants, and to reduce artefacts from tongue movement or swallowing. However, the position of the catheters may have influenced nasal resistance,¹² and consequently artificially elevated the pressures measured. In the majority of infants the 0.21 cm catheter replaced a 0.17 cm diameter nasogastric feeding tube, and hence this effect is likely to be small. Pleural pressures cannot be directly inferred from measurements of pharyngeal pressure, and the amount of respiratory support that corresponds to a given pharyngeal pressure is not clear. However, pharyngeal pressure measurements provide a guide to the pressures transmitted to the upper airway from HFNC that can be compared with those delivered by conventional CPAP. It should also be noted that results from this study cannot be extrapolated to flow rates greater than 8 l min^{-1} , and infants $<1 \text{ kg}$ or $>4 \text{ kg}$.

Nevertheless, this study confirms that preterm infants receiving HFNC at flow rates of 2 to 8 l min^{-1} can receive transmitted pharyngeal pressures that are similar to those observed in infants on nasal CPAP. Safety concerns in relation to HFNC have revolved

around questions of whether the pressures transmitted might lead to barotrauma.¹¹ This study was not designed to answer that question. It is somewhat reassuring that the pressures generated in the nasopharynx were within the range of commonly used CPAP pressures, however in two infants at flow rates of 8 l min^{-1} the mean pressure measured was greater than $10 \text{ cm H}_2\text{O}$.

Consequently it may be prudent to limit flows used in small preterm infants, particularly those less than 1 kg . Modifications to the high-flow nasal cannula circuit since our study was undertaken include the introduction of a pressure-limiting valve. This valve effectively limits the flow that can be delivered via the smaller cannulae (a maximum of 6 l min^{-1} via the 0.14 cm cannulae, and 7 l min^{-1} via the 0.19 cm cannulae). It might also mitigate any transient elevations in pharyngeal pressure associated with infants (especially larger infants) forcibly expiring against the constant nasal cannula flow.

This study provides the basis for a better understanding of the variables that affect pharyngeal pressure transmission in HFNC, and may help guide appropriate levels of flow to use in infants of different sizes. However, the safety and efficacy of this mode of respiratory support need to be determined in large clinical trials before its widespread adoption into clinical care.

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Disclosure/Conflict of Interest

The authors do not have any duality of interests.

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Appendix A

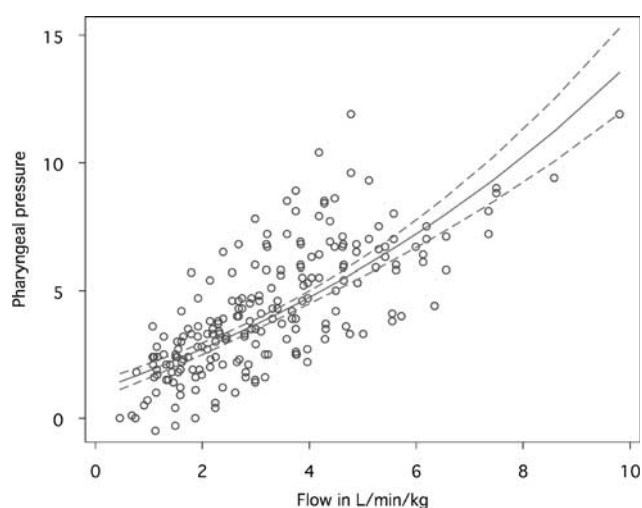


Figure 4 Pharyngeal pressure vs flow per kg. Log-transformed linear regression with 95% confidence interval.

Alternative prediction model

Since regression residuals were found to increase with flow rate, a zero-skewness logarithmic transformation was applied to the outcome to provide an alternative prediction model with constant variance (Figure 4).

$$\text{Predicted pharyngeal pressure (cm water)} = e^{(2.1947 + 0.075303F - 0.14711 \text{ wt})} - 6.2436.$$

Results using this model were similar to those obtained using the untransformed regression equation.