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Neonatal Nasal High Flow: Clinical paper summaries

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Research in high flow therapy: mechanisms of action

AIM:

To review proposed mechanisms for the efficacy of nasal high flow (NHF) therapy.

DETAILS:

NHF oxygen therapy is being increasingly utilized in a variety of patients with different diseases. The precise mechanisms by which NHF oxygen therapy alters gas exchange and influences the respiratory system have not been fully elucidated. However, available data suggest that there are five contributors to the effectiveness of NHF oxygen therapy.

Washout of nasopharyngeal deadspace: The most common reasons for needing to switch to invasive ventilation are hypercapnia and apnoea secondary to hypercapnia. Therefore, if deadspace in the nasopharyngeal cavity (and overall deadspace) is reduced, alveolar ventilation will be a greater fraction of minute ventilation. NHF oxygen therapy has been shown to have an immediate effect on ventilation rates and to improve oxygenation, indicating that deadspace is reduced. In addition, the results of animal studies of tracheal gas insufflation (TGI) support the notion that deadspace washout is a lung protective strategy for acute lung injury.

Reduced work of breathing (WOB): The nasopharyngeal surface area, distensibility of the nasopharynx and gas volume all contribute resistance to gas flow. NHF oxygen therapy provides nasopharyngeal gas flows that are equal to, or greater than, a patient's peak inspiratory flow thereby decreasing resistance which in turn translates into a reduction in resistive WOB. The effects of NHF oxygen therapy on expiration are not as well understood. However, it is speculated that expiratory efforts may be assisted secondary to a potential Coanda effect.

Improved mechanics: Even short periods inspiring gas at ambient temperature and humidity can significantly decrease pulmonary compliance and conductance during mechanical ventilation in infants. Improved respiratory compliance has been documented in infants receiving NHF oxygen therapy for respiratory support. These results indicate that, by reducing distending pressure and therefore also functional residual volume, adequate conditioning of inspired gases during NHF oxygen therapy affects physiological responses in the lung.

Reduced metabolic cost of gas conditioning: There is an energy cost associated with conditioning of inspired gases by the upper airway. This cost is higher when gas is cooler and drier. Furthermore, the increase in minute ventilation that often accompanies lung pathologies means that the volume of gas requiring conditioning is greater. Use of a NHF oxygen therapy system that warms and humidifies inspired gas presumably reduces the energy required for gas conditioning.

Provision of distending pressure: Ventilatory mechanics can be improved by providing distending pressure to the lungs which then improves lung compliance and gas exchange. There is the potential for continuous positive airway pressure (CPAP) to be generated during NHF oxygen therapy. This is dependent on the leak rate which is in turn highly dependent on the relationship between the size of nasal prongs and the nose, and requires the mouth to be closed. One clinical study in infants receiving NHF oxygen therapy showed that pharyngeal pressure was correlated with flow and inversely correlated with infant size.

CONCLUSION:

Delivery of warmed and humidified gases using NHF oxygen therapy is a viable treatment option, which is comfortable for the patient and minimizes deterioration of nasopharyngeal structures.

KEY POINTS:

- The five proposed mechanisms for the efficacy of NHF oxygen therapy are: washout of nasopharyngeal deadspace; reduced WOB, improved mechanics; reduced metabolic cost of gas conditioning; and provision of distending pressure.
- HFT can be regarded as a viable device for gas conditioning.
- Numerous studies have established the safety and efficacy of NHF in acute care.
- There are some studies which demonstrated the application of NHF beyond conventional oxygen therapy.

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High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence

AIM:

To review evidence for the use of high-flow nasal cannula (HFNC) oxygen therapy in preterm infants based on data drawn from 19 studies identified by literature searching.

DETAILS:

HFNC delivers humidified gas via nasal prongs, which are available in a variety of sizes. The use of HFNC oxygen therapy in preterm infants is increasing in popularity. Indications where HFNC is being used include: primary support for respiratory distress syndrome (RDS), treatment of apnoea of prematurity (AOP), and weaning from nasal continuous positive airway pressure (nCPAP). HFNC may offer some advantages over nCPAP in terms of ease of application and better facial access.

Pressure generation: Pressures generated by HFNC appear to be less than or similar to those usually delivered with nCPAP. The pressures will vary depending on the presence of mouth leak, and also in the presence of nasal obstruction. Results from studies predicting pressure during HFNC oxygen therapy vary and should be interpreted with caution due to the number of methodological limitations and design differences.

Respiratory mechanics: Beneficial effects of HFNC include the generation of distending pressure, and reduced thoraco-abdominal asynchrony and respiratory effort. Heating and humidification of inspired gases is important for achieving these benefits. Comparisons between HFNC and nCPAP have demonstrated comparable effectiveness of the two strategies.

Prevention of extubation failure: HFNC has been suggested as an alternative to nCPAP for prevention of extubation failure in the neonatal intensive care unit. However, there has been little published evidence to support this to date. HFNC did not perform well compared with nCPAP in one study[1], but the flow rates used were much lower than those currently used in clinical practice. Another study reported an advantage for HFNC over nCPAP[2], while a different trial showed that extubation failure was similar with the two devices[3]. Larger, prospective randomized, controlled clinical trials are currently underway which will potentially provide more reliable and useful data.

Treating RDS or AOP: Data from small trials suggest that HFNC has beneficial effects when used to treat RDS or AOP[4-7]. In the only comparative clinical trial, there was no difference in intubation rate, duration of hospitalization and the combined outcome of death or bronchopulmonary dysplasia in infants treated with HFNC or nCPAP [unpublished data].

Weaning from nCPAP: Available data are conflicting. One study showed similar outcomes with continuation of nCPAP or changing to HFNC while another reported clinically important increases in days on oxygen and duration of respiratory support in patients switched to HFNC oxygen therapy compared with continued on nCPAP.

Safety: With the exception of early issues with bacterial contamination of the Vapotherm HFNC device, which have since been addressed, few important adverse outcomes have been reported during HFNC oxygen therapy. Nasal trauma appears to be reduced compared with nCPAP when HFNC is used.

However, the safety of HFNC in preterm infants has yet to be clearly defined and further data from larger, randomized studies are required.

Recommendations: Evidence for the feasibility of HFNC oxygen therapy as an alternative treatment for preterm infants is growing, although no long-term data are currently available. However, surveys show widespread use of HFNC in this population. It is recommended that only heated, humidified HFNC systems be used to prevent drying of the airway mucosa and maintain secretion quality. Flow rates should be ≥2 L/min and prongs should be selected so that the nares are not completely occluded. An appropriate balance between efficacy and safety can be achieved by using a starting flow rate of 4-6 L/min.

CONCLUSION:

Further research is needed to clearly define whether HFNC oxygen therapy is effective and safe compared with nCPAP. NCPAP is the current standard of care for non-invasive respiratory support. The results of on-going studies investigating the use of HFNC as post-extubation support and for the treatment of RDS are required before any recommendation can be made about the widespread use of HFNC to treat preterm infants.

KEY POINTS:

- Evidence for the feasibility of HFNC oxygen therapy as an alternative respiratory support treatment for preterm infants is growing.
- Heated, humidified HFNC systems with flow rates ≥2 L/min should be used.
- Widespread use of HFNC oxygen therapy to treat preterm infants cannot yet be recommended due to lack of data.

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A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants

AIM:

To determine whether heated humidified (HH) high-flow nasal cannula (HFNC) oxygen therapy increases the rate of successful extubation in premature infants following endotracheal positive pressure ventilation, compared with conventional nasal continuous airway pressure (nCPAP) oxygen therapy.

METHOD:

In this prospective study, conducted at the Mercy Hospital for Women in Melbourne, Australia, premature infants (born at <32 weeks' gestational age) who required endotracheal intubation and positive pressure ventilation and were considered ready for extubation were randomized to HH HFNC (Vapotherm) or nCPAP (Hudson Respiratory Care) oxygen therapy; patients were also stratified by gestational age (<28 weeks vs. 28–31.6 weeks).

In the HFNC group, nasal cannulae with a 1.5mm external diameter were used and patients were extubated to a flow rate of 8 L/min; flow rate was weaned to a minimum of 4 L/min. nCPAP was delivered via bi-nasal prongs with an external diameter of 3.7–4.6 mm and a positive end-expiratory pressure (PEEP) of 8 cm H_2O or 7 cm H_2O for FiO_2 values of >0.3 and <0.3, respectively; PEEP was weaned to a minimum of 5 cm H_2O. Oxygen saturation targets for both groups were 85–92%. The assigned respiratory support was continued until it was no longer required or patients were switched to non-humidified low-flow sub-nasal oxygen ≤0.2 L/min.

The primary outcome measure was extubation failure within 7 days, defined as one or more of the following: apnea (respiratory pause >20 sec), >6 episodes in 6 hours or an episode requiring intermittent positive pressure ventilation; acidosis (pH <7.25 and PCO_2 >66 mmHg); sustained increase in FiO_2 of >15% from extubation. Patients were re-intubated at the treating physician's discretion. Secondary outcome measures included nasal trauma, the duration of respiratory support, supplemental oxygen requirement, and bronchopulmonary dysplasia. Nasal trauma was assessed using the sum of thrice-daily nasal trauma score recordings during the 7 days after extubation; nasal trauma at the internal and external nares, philtrum and septum were rated from 0 (normal) to 3 (skin tear).

RESULTS:

Between 1 January 2009 and 31 July 2009 a total of 132 infants were randomized to either HFNC (n=67) or nCPAP (n=65). The baseline characteristics of the HFNC and nCPAP groups were similar with the exception of sex; although there were more male infants in the nCPAP group (63% vs. 49% for HFNC); no relationship was seen between sex and the primary outcome.

HFNC and nCPAP oxygen therapy were associated with similar extubation failure rates at 7 days (see table). Stratification of patients by gestational age (<28 weeks vs. ≥28 weeks) also showed no significant difference between HFNC and nCPAP therapy in extubation failure rates at 7 days; overall extubation failure rates were higher among infants born at <28 weeks' gestational age than those born at 28–32 weeks (44% vs. 15%; p<0.001). HFNC oxygen therapy was associated with significantly reduced nasal trauma compared with nCPAP. Furthermore, at 7 days after extubation, 20% of the infants randomized to nCPAP switched to HFNC oxygen therapy due to nasal trauma.
No significant differences were seen in bronchopulmonary dysplasia rates or the durations of supplemental oxygen and respiratory support (see table).

VARIABLE	HFNC (N=67)	nCPAP (N=65)	P-VALUE
Extubation failure at 7 days (primary outcome), % pts.	22	34	NS
Apnoea, % pts.	21	26	NS
Acidosis, % pts.	0	5	NS
FiO_2 increase >15%, % pts.	10	18	NS
Nasal trauma score first week, mean (SD)	3.1 (7.2)	11.8 (10.7)	<0.001
BPD at 36 weeks' gestation, % pts.	36	43	NS
Respiratory support, mean completed weeks (SD)	33.5 (2.88)	34.3 (3.51)	NS
Supplemental oxygen, mean completed weeks (SD)	36.9 (2.54)	38.0 (3.26)	0.06

BPD, bronchopulmonary dysplasia; HFNC, high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; NS, not significant; pts., patients; FiO_2, fraction of inspired oxygen; SD, standard deviation

DISCUSSION:

HFNC and NCPAP oxygen therapy were associated with similar rates of extubation failure at 7 days in this study. The extubation failure rate with nCPAP oxygen therapy in this study was lower than expected based on historical controls at the same institution (34% vs. 50% in 2004–2006); this difference may be due to the change in the standard nCPAP delivery device used from a single nasopharyngeal prong to bi-nasal prongs in late 2005.

Nasal trauma was significantly reduced with HFNC versus nCPAP oxygen therapy. Although damage to the nasal mucosa caused by the bi-nasal prongs used in nCPAP is usually mild and resolves after cessation of treatment, in some cases disfigurement and long-term functional effects may occur. Nasal trauma may also be associated with an increased risk of nosocomial sepsis; however, further study is required before conclusions can be drawn. Larger randomized controlled trials of HFNC oxygen therapy in preterm infants are warranted, particularly those born at <28 weeks' gestational age as this subgroup has a higher rate of extubation failure.

CONCLUSION:

HFNC and nCPAP oxygen therapy are associated with similar rates of extubation failure at 7 days in premature infants, although nasal trauma is reduced with the use of HFNC.

KEY POINTS:

- HFNC oxygen therapy is associated with a similar rate of extubation failure at 7 days to nCPAP oxygen therapy in premature infants undergoing extubation.
- HFNC oxygen therapy significantly reduces nasal trauma compared with NCPAP therapy.

High-flow nasal cannulae in very preterm infants after extubation

AIM:

To compare the efficacy and safety of high-flow nasal cannula (HFNC) and nasal continuous positive airway pressure (nCPAP) for the noninvasive respiratory support of very preterm infants following extubation.

METHOD:

During this multicenter, randomized, noninferiority trial, very preterm infants (gestational age of <32 weeks) from three Australian neonatal intensive care units were randomly assigned to treatment with HFNC or nCPAP following extubation. Infants in the HFNC group were treated with the Optiflow device comprising the MR850 humidifier and binasal infant cannulae (Fisher & Paykel Healthcare) at flow rates of 5–6 L/min; infants who failed HFNC were treated with nCPAP. In the nCPAP group, binasal midline prongs (Fisher & Paykel Healthcare) or subnasal prongs (Hudson RCI) were used with an initial pressure of 7cm of water; infants who failed treatment in this group were reintubated. A mechanical ventilator or an underwater "bubble" system was used to generate nCPAP.

Treatment failure within 7 days (168 hours) of extubation was the primary endpoint. The prespecified secondary endpoints included: reintubation during the 7-day primary endpoint period; requirement for supplemental oxygen at a gestational age of 36 weeks; pneumothorax following study entry; total number of days of any respiratory support following study entry; duration of oxygen supplementation following study entry; and length of hospital admission. Furthermore, the incidence, cause, and need for a change of treatment as a result of nasal trauma were documented. A pneumothorax occurring during the randomized treatment period and death before hospital discharge were listed as predefined serious adverse events.

RESULTS:

A total of 303 very preterm infants were included in the study. HFNC was noninferior to nCPAP with regard to the primary endpoint (risk difference 8.4 percentage points; 95% confidence interval [CI] -1.9, 18.7; see table). There were no significant differences between HFNC and nCPAP groups in terms of the reasons for treatment failure. Of the infants in the HFNC group who reached failure criteria, 48% were successfully treated with nCPAP without reintubation. There was no significant difference between the HFNC and nCPAP groups for the secondary endpoint of reintubation within 7 days of extubation (risk difference -7.4 percentage points; 95% CI -16.6, 1.8; p=0.12). Furthermore, no significant differences were seen between the two treatment groups for other secondary endpoints and serious adverse events. HFNC was associated with significantly lower rates of nasal trauma and the need for a change in therapy due to nasal trauma. Similarly, the rate of nasal trauma as a result of randomized treatment was significantly lower in the HFNC group, compared with the nCPAP group.

VARIABLE	HFNC (N=152)	nCPAP (N=151)	P-VALUE
Primary endpoint (% infants)			
Treatment failure within 7 days of extubation	34.2	25.8	NS
Secondary endpoints			
Reintubation within 7 days of extubation (% infants)	17.8	25.2	NS
Oxygen supplementation at gestational age of 36 weeks (% infants)	30.9	34.4	NS
Pneumothorax following study entry (% infants)	0.7	2.6	NS
Duration of respiratory support following study entry (median number of days [IQR])	34 (7–55)	38 (11–57)	NS
Duration of oxygen therapy following study entry (median number of days [IQR])	38 (0–78)	49 (8–83)	NS
Median number of days in any hospital (IQR)	79 (63–105)	84 (65–106)	NS
Nasal trauma (% infants)			
Any documented	39.5	54.3	0.01
Leading to change of treatment	5.3	17.9	0.001
Caused by randomized treatment	19.1	53.0	<0.001
Serious adverse events (% infants)			
Pneumothorax during randomized treatment	0.0	0.7	NS
Death before discharge	3.3	4.0	NS

nCPAP, nasal continuous positive airway pressure; HFNC, high-flow nasal cannula; IQR, interquartile range; NS, not significant.

CONCLUSION:

The results of this study show that the efficacy and safety of respiratory support with HFNC and nCPAP are similar in very preterm infants following extubation. However, these findings are restricted to infants post extubation, and the results should not be extrapolated to the use of HFNC as a primary respiratory treatment following birth. Randomized controlled studies are needed to determine the effectiveness of HFNC as a primary respiratory support strategy.

KEY POINTS:

- The results of this study show that HFNC is similarly effective to nCPAP in very preterm infants following extubation
- The findings of this study indicate that the use of HFNC as respiratory support should be restricted to infants who have undergone extubation.
- Additional randomized controlled trials are required to determine the effectiveness of HFNC as respiratory support in a primary setting from birth.

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Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates

AIM:

To determine the safety and efficacy of heated humidified high flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) when used as non-invasive respiratory support in neonates with respiratory dysfunction.

METHOD:

This was a randomized, controlled, unblinded, multicenter trial. Infants included were between 28 and 42 weeks gestational age, had a birth weight ≥1000g, and there was an intention to manage them with non-invasive respiratory support either from birth (initiated within the first 24 hours of life), or at any age following a period of mechanical ventilation. Infants were randomized to heated humidified HFNC or nCPAP, and stratified according to birth weight (1000-1999g and ≥2000g) and age at randomization (≤7 days vs. >7 days).

No specific device was mandated for the study; heated humidified HFNC was provided using the Comfort Flo (Hudson RCI™), Fisher & Paykel Healthcare and Vapotherm devices, whilst nCPAP was provided via interfaces including bubble and Infant Flow nCPAP System (CareFusion). Initial flow rate for heated humidified HFNC was determined according to current infant weight: 1000-1999g infants received 3 L/min, 2000-2999g infants received 4 L/min, and ≥3000g infants received 5 L/min. Within each weight category, flow rate could be increased by ≤3 L/min above the initial flow rate. The starting pressure for nCPAP was 5-6 cm H_2O or a pressure equivalent to the positive end-expiratory pressure level on ventilator support. Pressure could be increased to a maximum of 8 cm H_2O. nCPAP could be discontinued when the heated humidified HFNC flow rate was <2 L/min or nCPAP was 4-5 cm H_2O and the infant remained stable. Oxygenation and ventilation targets were 85-98% for oxygen saturation (SpO_2), and 40-65 mmHg for partial pressure of carbon dioxide (PCO_2).

The primary outcome of the study was failure of study support mode (defined as the need for intubation within the first 72 hours of treatment). Secondary endpoints included rates of bronchopulmonary dysplasia (BPD), total ventilator days, days on supplemental oxygen, and a need for delayed intubation.

RESULTS:

Between December 2007 and April 2012, 432 infants were enrolled in the study and randomized to either heated humidified HFNC (n=212) or nCPAP (n=220). Demographic characteristics between groups were similar. More than 90% of infants were <7 days of age at randomization, and the most common diagnosis was respiratory distress syndrome.

There was no significant difference between groups in the primary outcome of failure of support within 72 hours (see table), and the reasons for early failure and intubation were similar between groups (increasing respiratory distress: 83% in both heated humidified HFNC and nCPAP groups [p=0.951]; increased fraction of inspired oxygen [FiO_2]: 39% and 50% in the heated humidified HFNC and nCPAP groups [p=0.539]; and severe apnea: 22% and 11% in the heated humidified HFNC and nCPAP groups [p=0.438]). Infants managed with nCPAP had fewer days of any positive pressure support, and a shorter duration of study mode support compared to infants managed with heated humidified HFNC (see table). At 7 days post-study entry, significantly more infants receiving heated humidified HFNC than nCPAP remained on the treatment. There were no differences in the other endpoints measured. Adverse events were similar between groups, and rates of failure were also similar between different devices used.

VARIABLE	HEATED HUMIDIFIED HFNC	nCPAP	P-VALUE
Early respiratory failure, % pts	11	8	NS
Need for reintubation, % pts	15	11	NS
Remaining on therapy 7 days post-study entry, % pts	23	9	<0.001
BPD, % pts	20	16	NS
Home O_2, % pts	19	18	NS
Median days on positive pressure support	6	4	<0.001
Median days on study mode	4	2	<0.001
Median days on supplemental O_2	10	8	NS

BPD, bronchopulmonary dysplasia, HFNC, high flow nasal cannula; nCPAP, nasal continuous positive airway pressure; NS, not significant; O_2, oxygen; pts, patients.

CONCLUSION:

The results of this study show that there was no difference in early support failure rates or several respiratory outcomes in infants with respiratory dysfunction treated with HFNC or nCPAP. HFNC appears to have a similar efficacy and safety profile to nCPAP when used to treat infants with respiratory dysfunction. The same results were found whether heated humidified HFNC was used as initial therapy or post-extubation. Patients receiving HFNC were treated significantly longer than patients receiving nCPAP, but there was no evident reason for this difference found when caregivers were asked to assess patient comfort, device humidification or ease of use. Despite the difference in length of treatment between groups, there were no long-term effects in the heated humidified HFNC group versus the nCPAP group based on the results of the other endpoints examined.

KEY POINTS:

- Heated humidified HFNC appears to have a similar efficacy and safety profile to nCPAP when used in infants with a gestational age ≥28 weeks and respiratory dysfunction, irrespective of whether heated humidified HFNC was used as initial therapy or after extubation.
- Patients receiving heated humidified HFNC were treated significantly longer than patients receiving nCPAP, but no reason for this difference was found.
- Despite this difference, there were no long-term effects in the heated humidified HFNC group versus the nCPAP group based on the results of the other endpoints examined.

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A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS

AIM:

To compare endotracheal intubation requirement in preterm infants with respiratory distress syndrome (RDS) treated with nasal high flow (NHF) oxygen therapy or noninvasive positive pressure ventilation (NIPPV).

METHOD:

In this single-center, prospective, randomized, controlled, pilot study, preterm infants (gestational age <35 weeks, weight >1000 g) with RDS were randomized to treatment with NHF oxygen therapy (Vapotherm® device, Precision Flow™ or 2000i; Vapotherm, Inc.) via Vapotherm nasal prongs at flow rates of 1–5 L/min or NIPPV (SLE 2000 or 5000; Specialized Laboratory Equipment Ltd) via nasal prongs (INCA; Ackrad Labs); synchronized mode was chosen, at 12–30 breaths/min, with inspiratory time 0.3 sec, positive end-expiratory pressure (PEEP) 6 cmH_2O, and peak inspiratory pressure (PIP) of 14–22 cmH_2O. The fraction of inspired oxygen (FiO_2) was set to maintain oxygen saturation on pulse oximetry (SpO_2) at 88–92% in both modes of NRS. Surfactant was administered as a rescue therapy. The primary outcome was the proportion of infants who failed noninvasive respiratory support (NRS) and needed endotracheal intubation or were switched to another form of NRS. Secondary outcomes included clinical features such as respiratory status, duration of ventilation and neonatal outcomes. Safety was assessed by recording nasal trauma, air leak, gastrointestinal perforation, and discomfort.

RESULTS:

Seventy-six of the 293 eligible patients were enrolled in the study (38 in each treatment group). NRS failure rates are shown in the table. Duration of NRS was independently associated with the mode of NRS (p=0.005) and patent ductus arteriosus (p<0.001). There were no significant differences between the NHF and NIPPV treatment groups with respect to blood pressure, heart rate, respiratory rate and oxygenation in the 6 hours prior to mechanical ventilation (MV) in patients with NRS failure. However, $PaCO_2$ was significantly higher (p=0.01) and pH significantly lower (p=0.04) prior to the need for MV in infants treated with NHF versus NIPPV.

Clinical outcomes, including rates of bronchopulmonary dysplasia, intra-ventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis and sepsis were comparable between the NHF and NIPPV groups. Time to full feeds and length of stay were also comparable between treatment groups. No nasal trauma was recorded, and air leak was only reported in 2 patients receiving NHF.

	NIPPV (N=38)	NHF oxygen therapy (n=38)
Failed NRS, n (%)	13 (34.2)	12 (31.6)
Time to stop NRS, days	2.0 (0.3–6.5)	4.0 (1.0–15.0)[a]
Endotracheal ventilation, n (%)	13 (34.2)	11 (28.9)
Time to mechanical ventilation, h	47.0 (2.5–152.0)	27.0 (2.0–54.0)

Data are presented as median (range), or number of patients (%). NRS, noninvasive respiratory support.
[a]p=0.006 vs NIPPV.

CONCLUSION:

Initial treatment with NHF oxygen therapy may be as effective as NIPPV for preventing the requirement for intubation and MV in preterm infants with RDS, with a similar rate of complications. Data from randomized, controlled trials are required before NHF can be recommended as the primary form of NRS for premature infants with RDS.

KEY POINTS:

- NHF oxygen therapy may be as effective as NIPPV for the first-line treatment of RDS in premature infants.
- Complication rates are similar after treatment of preterm infants with RDS using NHF oxygen therapy or NIPPV.
- Additional research is required before NHF can be recommended as the primary form of noninvasive respiratory support for premature infants with RDS.

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Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants

AIM:

To assess nurses' perceptions of nasal high flow (NHF) oxygen therapy compared with nasal continuous positive airway pressure (nCPAP) as post-extubation respiratory support for very preterm infants.

METHOD:

Nurses who administered NHF oxygen therapy or nCPAP as part of a randomized clinical trial were surveyed using a standardized questionnaire. During the study, NHF was delivered using the Optiflow system and binasal prongs (Fisher & Paykel Healthcare) and nCPAP was given via a humidified 'bubbler' system (Fisher & Paykel Healthcare) or a mechanical ventilator, using Hudson binasal prongs (Teleflex Medical); the trial results were not available at the time the survey was administered. Nurses were asked how likely it was that NHF would prevent the need for reintubation compared with CPAP in 4 different infant groups. There were six response options, ranging from 'much less likely to work than nCPAP' to 'will always work'. Other questions included which of the two noninvasive respiratory support methods the nurse would rather use and which type of noninvasive respiratory support was the loudest. Nurses were also asked to rate their level of agreement with five different statements about NHF versus nCPAP as 'strongly agree', 'somewhat agree', 'strongly agree' and 'don't know'.

RESULTS:

A total of 99/144 (69%) eligible nurses completed the survey. Agreement with different statements about NHF versus nCPAP is shown in the table. The majority of nurses (55.6%) thought that NHF was much less likely to work than nCPAP for an infant of 24 weeks' gestation weighing 500 g, and 22% of respondents thought that NHF would never work in this patient group. In infants of 28 or 30 weeks' gestation weighing 1.2 or 1.5 kg, respectively, the proportion of nurses who thought that NHF would have equivalent efficacy to nCPAP was 44% and 57%, respectively. For the oldest group of infants (30 weeks' gestation), 15.1%, 9.7% and 7.5% of nurses, respectively, thought that NHF was a little more likely to work, much more likely to work, or will work. nCPAP was the preferred mode of noninvasive respiratory support for a 24-week infant in 92.1% of nurses and for a 26-week infant in 79.3%, whereas NHF oxygen therapy was preferred by 76.9% of nurses for a 28-week infant and by 92.5% of nurses for a 30-week infant. The proportion of nurses rating that mode as the loudest was 69.1% for bubble nCPAP, 20.6% for ventilatory nCPAP and 2.1% for NHF oxygen therapy (3.1% thought there was no difference and 5.2% didn't know).

	PERCEPTION OF NHF OXYGEN THERAPY VS nCPAP			
% RESPONDENTS	STRONGLY AGREE	SOMEWHAT AGREE	STRONGLY DISAGREE	DON'T KNOW
Easier to set up and use	43.4	49.5	6.1	1.0
More comfortable for infants	80.8	14.1	5.1	0
Causes less nasal trauma	65.7	25.3	6.1	3.0
Parents prefer it	54.5	28.3	2.0	15.2
Infants tolerate feeds better	7.1	36.7	7.1	48.5

CONCLUSION:

Nurses using NHF oxygen therapy were aware of varying efficacy across different gestational ages, consistent with the findings of the clinical trial during which data were collected, and have a preference for NHF over nCPAP in preterm infants ≥28 weeks' gestation.

KEY POINTS:

- Nurses are able to accurately define which groups of preterm infants in which to use NHF oxygen therapy rather than nCPAP.
- Nurses prefer NHF oxygen therapy over nCPAP for noninvasive respiratory support in preterm infants of ≥28 weeks' gestation.
- The majority of nurses think that NHF oxygen therapy is easier to use, more comfortable, causes less nasal trauma, and is preferred by parents as noninvasive respiratory support in very preterm infants compared with nCPAP.

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Effect of HFNC flow rate, cannula size, and nares diameter on generated airway pressure: an in vitro study

AIM:

To investigate the effect of high flow nasal cannula (HFNC) flow rate settings on delivered airway pressure with different nasal prong-to-nares diameters in an active neonatal lung model.

METHOD:

HFNC oxygen therapy [RT329; Fisher & Paykel] was supplied to a test lung set to simulate normal to moderately affected lungs of a 1-3kg infant. Fixed flow rates of 0, 1, 2, 3, 4, 5 and 6 L/min were tested. Two different sizes of nasal cannulae were used [Fisher & Paykel], a neonatal cannula (outer prong diameter 3mm) and an infant cannula (outer prong diameter 3.7mm). Each cannula was tested using 7 different simulated nare openings (internal diameter 3-7mm). Resulting ratios of prongs to nares were 0.43-1.06, with corresponding nares occlusion of 18.4-100.0%. Full or partial mouth closure was simulated by closing a Teflon stopcock (5mm orifice situated midway between the nares/prongs and the test lung) by 100% or 50%, respectively.

RESULTS:

Overall, when the mouth-leak valve was set to the open position there was an increase in airway pressure as both the prong-to-nares diameter ratio and HFNC flow rate increased, and cannula flow was almost exactly the same as HFNC flow from 0-5 L/min. Under the same conditions, when there was full nasal occlusion the maximum airway pressure was <1.7 cm H_2O at the highest flow rate tested (6 L/min). Airway pressures were higher in the mouth closed versus mouth open condition, but remained <10 cm H_2O even at 6 L/min. When the mouth-leak valve was closed and the prong-to-nares ratio was >0.9 (equivalent to 85-100% occlusion of the nares), airway pressures quickly reached those that would trigger the pressure-release valve at flow rates of <2 L/min.

DISCUSSION:

There is a trend towards utilisation of alternatives to endotracheal ventilation to provide respiratory support in premature infants. The aim is to reduce the incidence of chronic lung disease in these children. Noninvasive ventilation options include nasal continuous positive airway pressure, nasal intermittent positive-pressure ventilation and HFNC oxygen therapy. Use of a heated and humidified HFNC system is the only one of these which does not require close fitting of nasal prongs within the nares. Adequate but not excessive positive pressure support requires a balance between prong size of the nares and the flow rates of the gas. Selection of the correct nasal prong-to-nares ratio helps to ensure delivery of the appropriate level of pressure support.

CONCLUSION:

The data generated in this in vitro study indicate that an appropriate nasal prong-to-nares ratio and an integrated pressure-release valve are important for safe and effective delivery of HFNC oxygen therapy in preterm infants.

KEY POINTS:

- For HFNC to be safe and effective in preterm infants, selection of an appropriate nasal prongs-to-nare ratio is important.
- An integrated pressure-release valve is an important component of a safe and effective HFNC system for use in preterm infants.

Fisher & Paykel Healthcare has provided funding for the study.

Pharyngeal pressure with high-flow nasal cannulae in premature infants

AIM:

To measure pharyngeal pressure in premature infants receiving high-flow nasal cannula (HFNC) therapy at flow rates of 2-8 L/min.

METHOD:

Eighteen infants (10 female; median corrected gestational age 33.6 weeks; median weight 1.619 kg) who were receiving HFNC for the treatment of respiratory distress syndrome, chronic lung disease or apnoea of prematurity were included in the study. Pharyngeal pressures were measured using a 0.21 cm diameter catheter with a single solid-state catheter-tip pressure transducer (CTO-1; Gaeltec). The catheter was inserted into one nostril to a distance 1 cm less than the measured distance from tip of nose to tragus, to ensure positioning in the nasopharynx. Flow rate was increased sequentially in increments of 1L/min to a maximum of 8 L/min, then decreased to a minimum of 2 L/min. Stable recording of >20 seconds was observed before changing parameters. Mean pharyngeal pressure over the longest period of stable recording was calculated. Short, narrow-calibre, tapered nasal cannulae (Fisher & Paykel Healthcare) were connected to a standard humidifier base (MR850; Fisher & Paykel Healthcare) and circuit without a pressure-limiting valve (Oxygen Therapy System RT329; Fisher & Paykel Healthcare). Pressures were recorded with the mouth in the resting position (passive) and with the mouth actively closed (by gently placing a finger under the infant's chin). Cannulae were chosen to comfortable fit into the patient's nostrils without occluding them. Neonatal cannulae (outer diameter 0.14cm) were used in 13 infants, infant cannulae (0.19 cm) were used in 2 infants, and paediatric cannulae (0.27 cm) were used in the remaining 3 patients.

RESULTS:

There was a significant linear relationship between pharyngeal pressure and flow rate ($p < 0.001$), that was not affected by adjustment for infant weight or mouth closure. The average increase in pressure for each 1 L/min increase in flow was 0.8 cm H_2O. There was also a significant association between infant weight and pressure ($p = 0.001$), with average pressure decreasing by 1.4 cm H_2O for each 1 kg increase in body weight. No association between mouth closure and pharyngeal pressure was observed. The relationship between pharyngeal pressure, flow and bodyweight could be expressed as: 2.6 + 0.8 F – 1.4 wt (where F is flow in L/min and wt is bodyweight in kg).

DISCUSSION:

The pressures recorded in this study are lower than those reported previously. Both cannula diameter and measurement technique may have contributed to the differences. HFNC is an alternative to nasal continuous positive airway pressure (NCPAP). Changes in pharyngeal pressure relative to flow rate have also been documented with NCPAP, with mouth closure increasing pharyngeal pressure by 1.1 cm H_2O. In contrast, mouth closure had no effect on pharyngeal pressure during HFNC in this study. One of the safety concerns with HFNC is that the pressures transmitted may lead to barotrauma. While this trial was not designed to answer that question, the ranges of pressures generated during HFNC were within the range of commonly used NCPAP pressures. However, pressures of >10 cm H_2O were documented in 2 infants during HFNC therapy. Therefore, it may be prudent to limit the flows used during HFNC therapy in preterm infants, particularly those with a bodyweight of less than 1 kg.

CONCLUSION:

This study increases understanding of the pressures generated during HFNC therapy in preterm infants, and the variables affecting these pressures. The results may help guide appropriate flow levels for use in infants of different bodyweights.

KEY POINTS:

- No studies have previously examined pressures generated during the use of HFNC in premature infants.
- There was a significant relationship between flow rate and pharyngeal pressure.
- There was a significant inverse relationship between body weight and pharyngeal pressure.
- In the majority of patients, pressures generated during HFNC were similar to those commonly used for NCPAP.
- Generation of pressures >10 cm H_2O In 2 patients indicate that it may be prudent to limit flows used during HFNC therapy, particularly in premature infants with a bodyweight of <1 kg.

Work of breathing using high-flow nasal cannula in preterm infants

AIM:

To investigate the work of breathing (WOB) in preterm infants treated with a high-flow nasal cannula (HFNC) or nasal continuous positive airway pressure (nCPAP).

METHOD:

Eighteen preterm infants (birth weight <2.0 kg) received respiratory support with HFNC and nCPAP in a random order. The indication for respiratory support was mild respiratory distress syndrome, chronic lung disease and/or apnoea of prematurity. Respiratory support was given via Inca nasal prongs (Ackrad Laboratories). HFNC therapy was given at rates of 3, 4 and 5 L/min, and CPAP (Infant Bird Ventilator, Viasys Healthcare) was given at 6cm H_2O. Data were collected over the last 30 seconds of each 5-minute treatment period. Respiratory inductance plethysmography was used to record chest wall and abdominal movements, oesophageal pressure was measured using an oesophageal cathether to approximate pleural pressures.

RESULTS:

There were no significant differences between nCPAP and the 3 different levels of HFNC with respect to WOB, tidal volume, respiratory rate and phase angle. Compliance was significantly higher with HFNC 5 L/min compared with NCPAP ($p = 0.03$). End-distending pressures during HFNC did not vary significantly versus nCPAP except for HFNC 5 L/min ($p < 0.05$). Mean end distending pressures were below 2 cmH_2O from baseline readings in all cases.

DISCUSSION:

HFNC therapy has been used as an alternative to nCPAP, assuming comparable respiratory support; however, very few data exist. Data from this study showed no significant difference between HFNC and nCPAP in terms of WOB. There has been some concern about overdistension and potential harm from pneumothoraces with HFNC therapy. However, in this study, increases in end-distending pressures were small.

CONCLUSION:

HFNC therapy provides similar respiratory support to nCPAP at 6cm H_2O in preterm neonates requiring mild respiratory support. However, additional data on the effects of HFNC therapy, specifically outcomes data, length of hospital stay, and rates of chronic lung disease, infection and pneumothorax, are required.

KEY POINTS:

- The HFNC used in this study (Vapotherm®) is being used to wean from and in some cases an alternative to nCPAP, especially in mild respiratory dysfunction.
- The positive end distending pressures generated in infants during HFNC is comparable to that of nCPAP. This is unsurprising as the flows used in standard nCPAP and those used in HFNC are similar in this study.
- There were no significant differences between nCPAP and HFNC in all other measured respiratory factors (WOB, Vt, RR and phase angle).
- Because end distending pressure can be delivered via nasal cannula, some form of pressure relief is always recommended.

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Respiratory mechanics during NCPAP and HHHFNC at equal distending pressures

AIM:

To compare the effects of nasal high flow (NHF) oxygen therapy and nasal continuous positive airway pressure (nCPAP) at the same level of retropharyngeal pressure (P_{rp}) on lung function and mechanics in preterm infants with respiratory distress syndrome (RDS).

METHOD:

Preterm infants of 28 to <33 weeks' gestational age and postnatal age <96 hours who were receiving either nCPAP (SiPAP; Viasys Healthcare) or NHF (Precision Flow; Vapotherm) for mild-to-moderate RDS were eligible for inclusion in this randomized, crossover trial. Each infant was treated with nCPAP and NHF oxygen therapy in a random order. nCPAP pressures of 2, 4, and 6 cmH_2O and NHF flows of 2, 4 and 6 L/min were tested for 15 minutes each, also in random order. Mouth leak was avoided by manual closure of the mouth during data collection. Continuous recording was performed for oxygen saturation (SpO_2), heart rate, transcutaneous partial pressure of oxygen ($PtcO_2$) and carbon dioxide ($PtcCO_2$), lung volume, esophageal pressure (P_{es}) and P_{rp}. P_{es} and P_{rp} were measured by catheters inserted into the esophagus and pharynx, respectively.

RESULTS:

Twenty infants were enrolled between December 2011 and June 2012. Pressures generated during treatment with different levels of NHF and nCPAP were similar (see table). Although the respiratory rate and percentage contribution of the rib cage to tidal volume were slightly lower, and the Inspiratory Asynchrony Indices (IAI) slightly higher with NHF versus nCPAP, there were no statistically significant differences between the two ventilation methods with respect to breathing parameters, gas exchange and respiratory mechanics. Increasing P_{rp} from 2 to 4 cmH_2O during both NHF and nCPAP was associated with similar significant reductions in respiratory rate and slight increases in tidal volume and $PtcO_2$. Overall inspiratory resistive work of breathing did not differ significantly during administration of NHF and nCPAP, despite significantly higher values for the upper respiratory component during NHF versus nCPAP. Both forms of noninvasive ventilation were well tolerated at all pressures/flows tested..

	P_{RP} 2 cmH_2O		P_{RP} 4 cmH_2O	
	STRONGLY AGREE	SOMEWHAT AGREE	STRONGLY DISAGREE	DON'T KNOW
P_{rp} at end expiration, cmH_2O	2.1 (1.9, 2.4)	1.9 (1.7, 2.2)	3.8 (3.3, 4.2)	3.8 (3.6, 4.1)
Change in P_{rp}, cmH_2O	1.3 (1.1, 2.4)	1.7 (1.2, 2.4)	1.2 (1.1, 2.0)	2.0 (1.5, 3.1)
Change in P_L, cmH_2O	4.1 (3.2, 5.9)	4.2 (3.4, 5.4)	3.3 (2.7, 5.3)	4.3 (3.3, 6.5)

Values are median (interquartile range).

nCPAP, nasal continuous positive airway pressure; NHF, nasal high flow oxygen therapy; P_L, transpulmonary pressure; P_{rp}, retropharyngeal pressure

CONCLUSION:

Although the mechanisms of pressure generation are different, application of similar end-expiratory pressures via NHF oxygen therapy and nCPAP is associated with similar changes in breathing pattern, gas exchange, lung mechanics and work of breathing in preterm infants with mild-to-moderate RDS.

KEY POINTS:

- The effects of NHF oxygen therapy and nasal CPAP on breathing pattern, gas exchange, lung mechanics and work of breathing are similar when treatment is delivered at similar end-expiratory pressures.

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Definitions

Airway resistance	A measure of the impedance to ventilation caused by the movement of gas through the airways. This measurement is calculated as the change in pressure along a tube divided by flow.
Apnea of prematurity (AOP)	A phenomenon that occurs in premature babies when the part of the central nervous system that controls breathing is not yet mature enough to allow continuous breathing. This results in large bursts of breath followed by periods of shallow or stopped breathing.
Barotrauma	Trauma caused by rapid or extreme changes in air pressure.
Broncopulmonary Dysplasia (BPD) or Chronic Lung Disease	Most common sequelae of prolonged mechanical ventilation characterized by chronic respiratory failure. Several factors contribute to the chronic lung damage such as prematurity with incomplete lung development, pulmonary barotraumas, oxygen toxicity, pulmonary edema, inflammatory reaction and airway obstruction.
Body Temperature and Pressure Saturation (BTPS)	Body temperature, atmospheric pressure and saturated with water vapor. Equivalent to core temperature saturated with water vapor (37 °C, 44mg/L).
Bubble continuous positive airway pressure (BCPAP)	Continuous positive airway pressure therapy delivered via a bubble generator.
Coanda effect	A term originating from the field of aeronautical engineering. The Coanda effect is an entrainment effect whereby high-speed fluid from a nozzle entrains fluid from the body that it enters. An obstruction to this action by a wall/barrier causes a low-pressure area on one side of the jet, causing a deflection in flow, redirecting flow to the barrier.
Continuous positive airway pressure (CPAP)	A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilatory circuit.
Core temperature	Considered to be the optimal level of humidity for delivery to patients whose upper airway has been bypassed by an endotracheal or tracheotomy tube. Also known as BTPS (37 °C, 44mg/L).
Dead space	Volume in the airway path that is common to both the inspiratory and expiratory passages. Volume of gas that does not participate in gas exchange. It is ventilated but NOT perfused by the pulmonary circulation: • Alveolar dead space: Volume of gas ventilating unperfused alveoli that has no blood perfusion (shunt or pulmonary embolism). • Anatomic dead space: Volume of gas within the conducting zone of the lungs and upper airway. (Amount of volume that does not enter the alveoli.) • Mechanical dead space: Expired air that is re-breathed through connecting tubing. • Physiological dead space: Anatomic and alveolar dead space.
End distending pressure	Pressure in the lungs at the end of expiration.
Endotracheal tube (ETT)	A tube inserted through the mouth or nose into the trachea to maintain an unobstructed airway.
Extubation	Withdrawing an endotracheal tube (ETT) from a patient's airway.
Fraction of inspired oxygen (FiO_2)	The proportion of oxygen in the air that is inspired.
Full-term	An infant born between 37 and 40 weeks gestation.
Functional residual volume	The volume in the lungs at the end-expiratory position.
Gestational age	Period of time between conception and birth.

Heated humidifier (HH)	A humidifier device that heats and humidifies the inspiratory flow of gas that is delivered to the patient.
Hypercapnia	The presence of an abnormally high level of carbon dioxide in the circulating blood.
ICU	Intensive Care Unit.
Inspiratory Time (T_i)	The time over which the tidal volume is delivered or inspiratory pressure is maintained.
Intubation	The insertion of an ETT or tracheostomy tube into the trachea.
Low birth weight (LBW)	Birth weight less than 2500g.
Lung compliance	The ability of the lungs to stretch during a change in volume relative to an applied chamber pressure.
Mechanical ventilation (MV)	The use of an invasive artificial airway to mechanically assist or replace spontaneous breathing, when patients cannot do so on their own.
Minute ventilation (VE)	The volume of gas that moves in and out of the lungs in one minute; it is calculated by multiplying the exhaled tidal volume by the respiratory rate.
Nasal delivery of continuous positive airway pressure (nCPAP)	A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit.
Nasal high flow (NHF) therapy	A technique to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through nasal cannulae. Also known as High Flow Nasal Cannula (HFNC).
Nasal oxygen cannula	A small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient, which is used to deliver oxygen at a concentration higher than that in ambient air.
Nasal trauma	Trauma to the nasal skin and septum caused by pressure from binasal prongs.
Neonate	Premature infants or sick newborns less than 30 days old. These babies are usually found in the NICU of the hospitals.
NICU	Neonatal Intensive Care Unit.
Noninferiority trial	A trial that is designed to determine whether the effect of a new treatment is not worse than a standard treatment.
Noninvasive positive pressure ventilation (NIPPV)	The delivery of positive pressure ventilatory support without the need for an invasive artificial airway.
Noninvasive ventilation (NIV)	The delivery of ventilatory support without the need for an invasive artificial airway.
Nosocomial infections	Infections acquired in the hospital inpatient environment, not resulting from the reasons for which the patient was admitted.
Over distension	An injury caused by over inflation of the lung.
Oxygen saturation (SpO_2)	Oxygen saturation as measured by pulse oximetry.
Partial pressure of carbon dioxide ($PaCO_2$)	The part of total blood gas pressure exerted by carbon dioxide gas; a measure of how much carbon dioxide is dissolved in the blood and how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The part of total blood gas pressure exerted by oxygen gas; a measure of how much oxygen is dissolved in the blood and how well oxygen is able to move from the airspace of the lungs into the blood.
Pediatric	Referring to children up to 21 years of age; usually found in the PICU.

Phase angle	The degree of difference between the rib cage and abdominal movement during breathing. A measurement often used to indicate respiratory distress.
Physiological dead space	Anatomic and alveolar dead space.
PICU	Pediatric Intensive Care Unit.
Pleural pressure	The pressure surrounding the lung, within the pleural space.
Pneumothoraces	Condition in which air escapes from the lungs into the chest cavity and compresses the lungs.
Pneumothorax	Air or gas in the pleural space.
Positive end-expiratory pressure (PEEP)	It is a pressure above atmospheric pressure in the airway throughout the expiratory phase of positive pressure ventilation. PEEP is used during mechanical ventilation to improve oxygenation.
Positive end-inspiratory pressure (PIP)	The highest pressure applied to the lungs during inspiration.
Positive pressure ventilation (PPV)	Administration of oxygen under pressure during mechanical ventilation.
Preterm	An infant born before 37 weeks gestation regardless of their weight. Usually the preterm infant are found in the NICU of the hospital on some form of respiratory support. They can be further divided into: • Moderate to late preterm: 32 to <37 weeks gestation • Very preterm: 28 to <32 weeks gestation • Extremely preterm: <28 weeks gestation.
Relative humidity (RH)	The maximum amount of water a gas can hold at a given temperature.
Respiratory distress syndrome (RDS)	A lung disease of the newborn, most frequently occurring in premature infants, that is caused by abnormally high alveolar surface tension as a result of a deficiency in lung surfactant; also called hyaline membrane disease.
Respiratory Inductance Plethysmography	A way of measuring respiratory parameters using electrical bands placed around the chest.
Respiratory rate	The amount of breaths over a specified time period.
Surfactant	A substance produced in the lungs that tends to reduce the surface tension of the fluid in the lungs and helps make the small air sacs in the lung (alveoli) more stable.
Tidal volume (V_T)	Volume of air inspired or expired with each normal breath. The amount of gas delivered to a patient in one breath.
Tracheal gas insufflation (TGI)	An adjunctive ventilatory technique that delivers fresh gas into the trachea either continuously or only during a specific segment of the respiratory cycle.
Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$)	Partial pressure of carbon dioxide in blood measured through the skin using a small electrochemical sensor.
Transcutaneous partial pressure of oxygen ($PtcO_2$)	Partial pressure of oxygen in blood measured through the skin using a small electrochemical sensor.
Very low birth weight (VLBW)	Infants with birth weight less than 1500g.
Work of breathing (WOB)	The force required to expand the lung against its elastic properties.

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