Clinical Research on High Flow Nasal Cannula Therapy
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Washout of Nasopharyngeal Dead Space


Frizzola and colleagues demonstrate that by way of purging anatomical dead space in a piglet model, High Flow Therapy (HFT) results in a ventilation effect that is not matched by CPAP therapy. The study shows that the impact HFT has on blood gas parameters is a function of flow, and not inadvertent pressure development. Moreover, these data demonstrate that cannulae which do not obstruct the nares, as compared to more obstructive cannulae, produce the optimal effect on blood O2 and CO2 at significantly lower flow rates and subsequently lower resulting end-distending pressure development. In simpler terms, the more of the nares that are exposed the greater the degree of flush. Therefore, this validation research for the mechanisms behind the efficacy of HFT provides evidence that HFT should be applied with minimally occlusive nasal prongs, and flow parameters set to optimize anatomical flush, and not administered in a way to promote pressure development.


Dysart et al summarizes the mechanisms of action behind the efficacy of HFT via nasal cannula. The mechanisms discussed include washout of nasopharyngeal dead space, reduction of inspiratory resistance in the nasopharynx, improvement in airway and lung mechanics, mild distending pressure and a reduction in energy expenditure associated with inspiratory gas conditioning.


Calvano et al describe how they used High Flow Therapy (HFT; Vapotherm 2000i) to comfort and provide high oxygen fractions to an end-stage multi-lobar pneumonia patient who would not tolerate a mask to receive her prescribed non-invasive ventilation (this patient could not be intubated as per a DNR order). The paper describes how HFT improved not only oxygenation, but also work of breathing, comfort and nutrition.


Chatila et al showed that adult patients with airflow restriction were able to exercise longer (p < 0.05) on high flow oxygen therapy (HFT; 20 l/min) than on conventional low flow oxygen (< 6 l/min) despite matched FIO2. In addition to the overall longer performance, during HFT patients demonstrated lower dyspnea scores (p < 0.03), improved breathing patterns (RR, RR/Vt; p < 0.05), and lower arterial pressure (p < 0.05) and better oxygenation (p < 0.001). This study supports Vapotherm’s proposed mechanisms of action with respect to improving both oxygen and CO2 composition of alveolar gas by way of dead space elimination. The patients oxygenation indices were reported as significantly improved, plus the improvement in exercise time while demonstrating a lower breathing rate would indicate an effect on CO2 (CO2 was not different despite differences in work). Furthermore, the patients’ Ti/Ttotal was lower (p < 0.05) on HFT which may be indicative of reduced airway resistance.


Numa and Newth demonstrate that extrathoracic dead space volumes in infants are typically 2.5 to 3 fold greater, expressed as volume per unit of body weight, compared to adults. A review of literature shows that adult extrathoracic dead space volume (i.e., anatomic reservoir) is on average 0.8 ml/kg of body weight. In the neonatal / pediatric population, extrathoracic dead space volumes show a significant, inverse relationship with age. Herein, neonates have an extrathoracic dead space volume of around 3 ml/kg, which decreases with age to below 1.5 ml/kg after 2 years of age. Only by six years of age did some of the children studies have an extrathoracic dead space volume similar in relative size to adults.


Nakos et al shows that flushing anatomical dead space of the upper airway in humans during spontaneous breathing improves respiratory work indices while reducing blood carbon dioxide.

Dewan and Bell describe the effectiveness of high flow nasal cannula in maintaining oxygenation and work tolerance. This paper shows that high flow oxygen delivery by nasal cannula is more effective at maintaining blood oxygen saturation and work performance than low flow oxygen cannula. Furthermore, the data indicate that high flow nasal cannula therapy is similar in efficacy to transtracheal catheters, which are intended to attenuate the effects of anatomical dead space on breathing efficiency. This paper therefore supports the proposed mechanism of action for high flow nasal cannula related to dead space washout.


Price and colleagues generically discuss use and tolerance of Vapotherm HFT on various patient populations as a means of delivering humidified supplemental breathing gases. The authors describe some of the perceived mechanisms of action including mild distending pressure and the impact of humidification on mobilizing secretions. Additionally, the authors analyzed data from 72 patients and showed that use of HFT reduced respiratory rate and increased arterial oxygen saturation, while a patient survey revealed that 90% of the patients were satisfied with the therapy.


Shepard and Burger evaluated the variations in nasopharyngeal flow resistance between inspiratory and expiratory phases of the breathing cycle. This study demonstrates that in normal subjects, inspiratory resistance through the nasopharynx is greater than expiratory resistance as a result of the distensibility of nasopharyngeal tissues. This information supports the concept that HFT via nasal cannula can reduce inspiratory work of breathing by reducing resistance normally associated with the encroachment of nasal tissues secondary to a negative nasopharyngeal pressure.


Rea and colleagues investigated the long-term use of heated-humidified, high flow nasal cannula (HFNC) for humidification therapy in 108 COPD patients randomized to receive their typical care or HFNC for 12 months. Patients on HFNC had significantly fewer exacerbation days (18.2 versus 33.5 days; p = 0.045), increased time to first exacerbation (median 52 versus 27 days; p = 0.0495), and reduced exacerbation frequency (2.97/patient/year versus 3.63/patient/year; p = 0.067) compared with typical care. Additionally, patients on HFNC had improvement in quality of life scores and lung function compared with typical care.


Solomita and colleagues describe the shortcomings of heated wire circuit technologies for maintaining humidification during delivery of conditioned breathing gases. Although the emphasis behind this bench protocol is with regard to mechanical ventilation, the study demonstrates that heated wire circuit systems do not accurately maintain humidity of the conditioned gases. The study data show that while heated wire circuits can affect the temperature of the gas at the patient end, these systems allow for substantial water vapor loss within the patient circuit.


Hasani and colleagues evaluated the impact of delivering humidified respiratory gas by nasal cannula on mucociliary clearance by assessing retention of labeled tracer particles. They demonstrate that just three hours a day of humidification therapy in patients with bronchiectasis significantly improved clearance. The authors speculate that humidified respiratory gas treatment can be useful in patients with respiratory diseases that hinder the mucociliary transport process.

Wang et al identify that the ideal oxygen percentage for use in resuscitation in newborns is between room air (21%) and 100%. Therefore there is a need for oxygen blending in the delivery room.


Woodhead et al performed a crossover design study showing that when using optimal warming and humidification for nasal gas flows above 1 l/min (i.e., Vapotherm technology), nasal mucosa appeared more normal (p < 0.001) and patients had less pronounced indices of labored respiratory effort (p < 0.05). Additionally, some patients failed on conventional high flow cannula therapy and needed to be rescued to Vapotherm or reintubation; no infants failed on Vapotherm. These findings support Vapotherm’s proposed mechanisms that optimal warming and humidification not only preserves nasal tissue architecture but also have a positive impact on pulmonary mechanics, thus enhancing ease of breathing.


Waugh and Granger describe the ability of the Vapotherm technology to accurately condition breathing gases. This report is an independent bench analysis that demonstrates Vapotherm technology delivers gas to the patient interface that is saturated with water vapor and at precisely controlled temperature at flows up to 40 lpm.


Dr. Rankin reviews the factors that determine optimal humidification for respiratory gases. This paper examines the relationship between water content of the inspired gas and mucosal function to determine that the optimal conditioning for inspired gas is 37ºC and 100% relative humidity.

Changes in airway resistance induced by nasal inhalation cold dry, dry, or moist air in normal individuals. Fontanari, P, et al. Journal of Applied Physiology October 1, 1996 vol. 81 no. 4 1739-1743

Fontanari et al evaluated the impact of gas conditioning on airway resistance in normal participants through the impact on the receptors in the nasal mucosa. This paper shows breathing warm, humid gas versus cool, dry gas results in a significant improvement in airway resistance. Furthermore, these authors demonstrate that the resistance change is due to stimulation of receptors in the nose because this response is eliminated when mouth breathing or when receptors in the nose are blocked. The results of this study support the proposition that HFT via nasal cannula should be done with optimal temperature and humidification to reduce resistive work of breathing.


Williams and colleagues review the impact of respiratory gas temperature and humidification on airway mucosal cell function. This report reviews peer-reviewed manuscripts and other valuable information sources to construct a model for optimal gas conditioning and show the effects, both acute and chronic, of inadequate gas conditioning. This paper emphasizes the importance of precise respiratory gas warming and absolute humidification to protect airway cell function during respiratory support efforts.


Greenspan et al show that without warming and humidification of breathing gas, there is a statistically significant and clinically relevant adverse effect on dynamic compliance, airway conductance and elastic work of breathing. The implication is that better warming and humidification (to body temperature and saturated with water vapor) of respiratory gases alone can have a substantial impact on respiratory mechanics.

Holleman-Duray et al describe how the use of high flow therapy (HFT; Vapotherm 2000i) supports infants post extubation. The patient data, compared to historical control where CPAP was used prior to their adoption of HFT, resulted in extubation from higher ventilator rates (p < 0.01) and fewer days on ventilators (p < 0.05). These data support Vapotherm's proposed mechanisms of action for HFT with respect to CO2 elimination and improved alveolar oxygen concentrations. In addition, this study showed that incidence of ventilator-associated pneumonia was reduced (p < 0.05), and infants were discharged with greater weights (p < 0.05) despite similar lengths of stay and time to full feeds. The decrease in pneumonia is likely associated with reduction in ventilator time, while the greater discharge weights may be indicative of a reduced respiratory work effort (caloric consumption).

Effects of flow on airway pressure during nasal high-flow oxygen therapy. Parke, RL, et al. Respiratory Care, Volume 56, Number 8, August 2011 , pp. 1151-1155(5)

Parke and colleagues evaluated pressure build in the nasopharynx using the Fisher & Paykel nasal high flow system set at 30, 40 and 50 LPM of flow. These authors found average pressures to be dependent on flow rate and whether the mouth was open or closed. Average pharyngeal pressures were between 1.9 and 3.3 cmH2O with the mouth closed and between 1.0 and 1.7 cmH2O with the mouth open. These data agree with the other published reports that mild pressure does develop, and although it is considered to be a mechanism of action for HFT, is not of great enough magnitude to be concerning.


Spentzas and colleagues demonstrated a improvement in comfort and oxygenation, while reducing ARDS score in pediatric patients receiving HFT. The authors show that mild pressure develops in the nasopharynx (4 +/- 2 cmH2O) and they propose that this may be a mechanism of action for the efficacy of the therapy. This hypothesis is supported with chest x-rays that showed improved aeration or no change in 40 or the 46 patients.


Urbano and colleagues used a pediatric manikin bench model to evaluate HFT against high flow nasal mask or oronasal interface; this manikin model is a much better portrayal of actual airway geometry compared to other bench studies on HFT. Pressures were measured in the airway as well as the device circuit while delivering flows up to 20 L/min. The data confirm that the nasal cannula does not generate significant, or in this case measureable, airway pressure when applied without holding the mouth closed to block up oral pathway for gas flow. However, compared to the mask applications, circuit pressure is increased 30 to 100 fold when the same high flows are administered through the cannula. Thus, although a HFT device must be able to tolerate the high pressures associated with nasal cannula delivery, HFT does not create a marked CPAP effect. In this regard, the authors concluded that the effects seen with HFT must be related to other mechanisms.


Despite the negative conclusion that is based on the false belief that pressure needs to be more substantial, the data show that the patients are quite stable on High Flow Therapy despite lower pressure.


Volsko and colleagues used a bench model of the nasopharynx attached to a lung simulator to test the hypothesis that airway pressures generated by HFNC at flows between 2-6Lpm are minimal and clinically unimportant. These authors utilized a lung simulator and attached a capped 22mm adaptor which had holes drilled, using a standardized CPAP sizing template, to simulate the nares of a patient with a closed mouth. The range of expiratory pressures generated by all cannula sizes were 0.04 cmH20 to 1.3 cmH20. The data confirmed that insignificant pressures were generated at these flow rates in a correctly sized cannula, not occluding 50% of the nares.

Saslow et al evaluate the use of high flow therapy (HFT; Vapotherm 2000i) with respect to breathing effort and airway pressure development. The most intriguing findings in this paper are that HFT up to 5 l/min does not produce more airway pressure than CPAP set to 6 cmH2O. In fact, these authors demonstrate that at 5 l/min airway pressure is significantly less than with a CPAP of 6. Although complex, this finding may have an explanation based on the concepts of gas flow properties where greater flow currents in the nasopharyngeal cavity may actually unload pressure forces to the airways.


Locke and colleagues evaluated the use of conventional low flow oxygen cannula on development of airway distending pressure and influence on breathing pattern in neonates. These authors demonstrated that when they used a smaller of two cannulae (2 mm outer diameter) no distending pressure developed and breathing pattern was unaltered, but when they used a larger cannula (3 mm outer diameter) pressure developed and thoracoabdominal synchrony improved proportional to flow. These data have been important in identifying the influence of cannula fit to the development of pressure with nasal cannula use.

Comparisons to Alternative Therapies


Parke and colleagues evaluated high flow oxygen therapy between a high flow nasal cannula and a high flow oxygen mask in patients with mild hypoxemic respiratory failure. The high flow cannula resulted in significantly greater therapeutic success than a high flow mask (p = 0.006). Additionally, fewer patients progressed to NIV (10% with cannula versus 30% with mask; p = 0.10), and the nasal cannula group had fewer desaturations (P = 0.009). Seventy-one percent face mask group had at least one desaturation, compared to 42% in the nasal cannula group (P = 0.16). This paper demonstrates the impact on oxygen and CO2 associated with purging the anatomical dead space as opposed to a mask therapy that does not purge the nasopharynx.


Roca and colleagues show evaluated high flow oxygen therapy between a high flow nasal cannula and an oxygen mask in a crossover study design (each patient evaluated both methods). With a sample of twenty adult patients (mean age of 57 years) the high flow cannula resulted in significantly improved in patient tolerability indices including dyspnea (p = 0.001), dry mouth (p < 0.001) and comfort (p < 0.001). Physiologically, the high flow cannula increased arterial oxygen pressure (p < 0.01) and reduced respiratory rate (p < 0.001) without changing PaCO2, compared to the face mask delivery of oxygen. Note: accompanying editorial by Jeffrey Anderson on page 485 of the same issue. The editorial that accompanies this paper provides additional discussion as to the multiple mechanisms of action for high flow nasal cannula.


Miller and Dowd compared the efficacy of the Vapotherm system compared to the Fisher and Paykel system with regard to extubation success. Importantly, this was a pilot study of 40 patients and was therefore not powered to make any conclusions. The authors indicate from the variance data that the study would need 300 patients to make a statistical determination. Despite the lack of power, they showed that the extubation failure rate at 72 hrs was 18% for Fisher & Paykel, while only 9% for Vapotherm. Extubation failure rates for the period up to 7 days was 30% for Fisher & Paykel, and only 27% for Vapotherm. Note that the authors also did a price comparison, and that these data were based on the 2000i unit that was in use at the time. The price comparison data is more favorable for Vapotherm with the newer generation components.

Collins and colleagues compared the efficacy of Vapotherm HFT to CPAP therapy postextubation in 132 infants less than 32 weeks gestation. If extubated to CPAP infants were started at 7-8 cmH2O, if extubated to HFT flow rate was started at 8 L/min. There were no statistical differences in the rate of extubation failure or bronchopulmonary dysplasia between groups or in any gestational age stratification. Although BPD rates were not different, there was a trend for shorter duration of supplemental oxygen use in the HFT infants (p < 0.06). The absolute percentage of infants meeting the criteria for failed extubation was less for Vapotherm HFT (22%) than for CPAP (34%). Additionally, HFT resulted in significantly less nasal trauma (p < 0.001), and in fact 12 (20%) of the infants assigned to CPAP were rescued with HFT because of nasal trauma. This prospective randomized controlled trial of Vapotherm HFT vs CPAP demonstrates that HFT is more effective than CPAP in preterm infants, both greater and less than 28 weeks gestation. This conclusion is based on the trend for less extubation failure, coupled with the significant reduction in costly iatrogenic complications associated with the CPAP nasal interface.


For the conditions represented in this population of infants 28 weeks gestational age, HHHFNC appears to have similar clinical efficacy and safety to nCPAP as a mode of noninvasive respiratory support. This finding was evident whether HHHFNC was used as the initial mode of support or when primarily applied at the time of extubation.


Although the result for primary outcome was close to the margin of noninferiority, the efficacy of high-flow nasal cannulae was similar to that of CPAP as respiratory support for very preterm infants after extubation.


Wolfson and colleagues investigated the precise changes in airway mechanics associated with heliox breathing in neonates. They confirmed that in spontaneous breathing infants there was a marked reduction in pulmonary resistance associated with heliox breathing that resulted in a significant reduction in resistive work of breathing with no changes in minute ventilation. These authors discus how this reduced efforts and energy expenditure reduces the risk of respiratory muscle fatigue, and subsequently the need for mechanical ventilation.


Singhaus and colleagues investigated the safety and efficacy associated with growth and development while breathing heliox. Four-day-old rabbit pups were randomized to be raised in air or heliox (21% O2; 79% He) for two weeks. All pups thrived in both environments, achieving expected developmental milestones. There were no physiologically significant group differences in weight, growth factors, tissue weight, blood chemistry or muscle enzyme activity.


Nawab and colleagues investigated the use of helium-oxygen gas (heliox) as a ventilation medium on lung inflammation indices. These authors showed a dramatic reduction in pulmonary pro-inflammatory mediators when using heliox versus a nitrogen-oxygen mixture, resulting in an improvement in lung morphology. These data indicate that heliox improved the distribution of inspired gas, thereby recruiting more gas exchange units, improving gas exchange efficiency, reducing ventilatory and oxygen requirements, and thereby attenuating lung inflammation.

HFT is designed as flow rates that exceed patient inspiratory demand at various minute volumes. Historically, high flow therapy has been used with face masks, where the high flows flush the mask volume to facilitate high inspiratory oxygen fractions. While effective in supporting oxygenation, mask therapy can be limited by factors including ability to eat/drink and communicate, as well as feelings of claustrophobia, leading to poor patient compliance.


Pressure in the patient circuit is necessary to drive high flows through a nasal cannula, but this circuit pressure is isolated from the patient’s nasopharynx. In individual patients, nasopharyngeal pressure during HFT is dependent on factors which include flow rate, patient’s size, and the relationship between the cannula prong size and the internal diameter of the nares. However, pressure generation has been evaluated in a number of recent papers and shown to be moderate.


HFT is defined as nasal cannula gas flows which exceed a patient’s spontaneous inspiratory flow rate while purging nasopharyngeal dead space during exhalation. Moreover, this technique requires heated-humidification systems that can adequately condition breathing gases to preserve airway mucosa thus making this therapy tolerable, and in fact comfortable. HFT results in a number of fundamental physiologic interactions that result in improved respiratory efficiency that support patients with respiratory distress. HFT has been used for more than ten years and has been shown safe and effective. Efficacy has been shown to supersede that of conventional front line therapies and have advantages over non invasive pressure support therapies.


HFT is a unique noninvasive respiratory support modality in the NICU. It is based on the concepts of dead space elimination for breathing efficiency and the delivery of ideally conditioned respiratory gases to an already fragile lung. A misconception that stifles the adaptation of HFT is that it is an uncontrolled form of CPAP. The mechanistic literature, however, does not support this presumption and a significant amount of clinical data suggests that pressure is not a concern when HFT is applied correctly. Importantly, the neonatal community would benefit from the uniform adaptation of a definition that is based on research and guides the cannula design aspects and flow requirement. These studies suggest that cannula fit should not occlude more than 50% of the nares and that flows should be between 3 and 8 L/min.


The delivery of heliox with the Vapotherm Precision Flow Heliox device has a distinct advantage over other methods of noninvasive heliox delivery. By providing a nasal cannula gas flow that exceeds a patient’s spontaneous inspiratory flow rate, the patient inhales the precise gas mixture provided by the cannula without the entrainment of room air. Also with this approach, the nasopharyngeal region of the patient’s upper airway becomes an internal reservoir of the intended gas mixture, making blended medical gas delivery more precise and efficient. Therefore, when providing heliox via HFT the effects of helium balance gas on respiratory resistance is not hampered by the dilution of the helium gas by entrainment of room air, and the desired therapeutic affect can be achieved using the minimally invasive cannula patient interface.