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REVIEW

Research in high flow therapy: Mechanisms of action

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Summary
Recently, heater/humidifier devices that use novel methods to condition breathing gases from an external source have been introduced. The addition of sufficient warmth and high levels of humidification to breathing gas has allowed for higher flow rates from nasal cannula devices to be applied to patients (i.e., high flow therapy). This article provides a review of the proposed mechanisms behind the efficacy of high flow therapy via nasal cannula, which include washout of nasopharyngeal dead space, attenuation of the inspiratory resistance associated with the nasopharynx, improvement in conductance and pulmonary compliance, mild distending pressure and reduction in energy expenditure for gas conditioning.

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Introduction

Relative to progress and complexities of modern mechanical ventilators, advancement in technology to efficiently warm and humidify respiratory source gases has been lagging. Recently, devices that use a variety of different methods to condition breathing gases from an external source, have been introduced for use in patients across all ages and in clinical or home settings. Heretofore, insufficient humidification has limited use of high supplemental gas flow rates delivered through the nose. The addition of sufficient warmth and high levels of humidification to the breathing gas has allowed for higher flow rates from nasal cannula (NC) devices to be applied to patients. Patients ranging in ages from preterm newborns to adults are now receiving flow rates ranging from 2 to 40 L/min to support breathing through a variety of conditions. In newborns, high flow devices are being used in the preterm population with respiratory distress syndrome as well as a mode for oxygen delivery in full term newborns with hypoxic respiratory failure. In the pediatric age range, high flow devices are finding use in typical situations that might have otherwise required intubation or CPAP. Disease processes from infectious causes of pulmonary dysfunction such as viral bronchiolitis or bacterial pneumonia to reactive airway disease are being treated now high flow cannula devices. In adults, these devices are used in a variety of clinical settings where increased flow rates are believed to benefit the patient in the context of their respiratory disease. These adult disease processes range from pulmonary edema to chronic obstructive pulmonary disease (COPD) to acute respiratory distress syndrome (ARDS) post-extubation. This article provides a review of the proposed mechanisms behind such devices.

Mechanisms of action for high flow therapy (HFT)

The use of high flow therapy (HFT) devices in clinical settings is rapidly growing. These devices are being applied to patients across age groups in a variety of disease conditions. The mechanisms through which HFT devices affect the respiratory system and alter gas exchange are still under investigation but a growing body of evidence is supporting the mechanisms of action for HFT to be five-fold.

1) HFT provides for washout of nasopharyngeal dead space, which contributes to establishing improved fraction of alveolar gases with respect to carbon dioxide as well as oxygen.[1]
2) The distensibility of the nasopharynx provides significant resistance on inspiratory relative to expiratory efforts.[2] HFT provides adequate flow rates to match inspiratory flow and thus markedly attenuates the inspiratory resistance associated with the nasopharynx, and thus eliminates related work of breathing.
3) The provision of adequately warmed and humidified gas to the conducting airways improves conductance and pulmonary compliance compared to dry, cooler gas.[3]
4) The provision of adequately warmed and humidified gas through the nasal pharynx reduces the metabolic work associated with gas conditioning.
5) High flow through the nasopharynx can be titrated to provide positive distending pressure for lung recruitment.[4]

Washout of nasopharyngeal dead space

A principle mechanism of action for HFT may be through flushing the dead space of the nasopharyngeal cavity, thereby reducing overall dead space and resulting in alveolar ventilation as a greater fraction of minute ventilation. Thus, there is an improvement in the efficiency of respiratory efforts. The essential clinical criteria to remain on non-invasive respiratory support modes are effective spontaneous respiratory effort and CO_2 elimination. Hypercapnia, or apnea that may be secondary to hypercapnia, are the most common reasons for progressing to more invasive forms of ventilatory support. Therefore, if CO_2 retention during conventional non-invasive ventilation (such as continuous positive airway pressure [CPAP]) can be reduced or eliminated, many patients can be spared invasive mechanical ventilation and the associated potential lung injury and subsequent chronic lung and airway diseases.

A reasonable comparison for this dead space washout mechanism is to tracheal gas insufflation (TGI). Dead space washout by way of TGI has been demonstrated with numerous studies to enhance minute ventilation by promoting CO_2 elimination.[5–9] By reducing prosthetic dead space, TGI facilitates pulmonary gas exchange and reduces the ventilator pressure and volume requirements.[10,11] Studies in juvenile animal models of acute lung injury have demonstrated that TGI using a novel endotracheal tube design reduces physiological dead space during mechanical ventilation. Both pressure and volume requirements to support gas exchange were lower than with conventional mechanical ventilation (CMV). Importantly, corresponding biomarkers of lung structure were improved and those of lung and systemic inflammation were attenuated as compared to CMV with lower peak inspiratory pressures.[12,13] These studies support that dead space washout offers potential as a lung protective strategy for acute

injury in the developing lung and may be a useful clinical adjunct to respiratory management.

Subsequent to the mechanical ventilation studies, Nakos and colleagues investigated the use of TGI in spontaneously breathing patients and demonstrated reductions in $PaCO_2$, tidal volume, minute ventilation and dead space.[14] These results were demonstrated in adults with COPD that were weaned from mechanical ventilation. This approach has also been evaluated in early development. In this regard, TGI was used with CPAP in intubated animals using a specially designed endotracheal tube to allow for insufflation gas flow (No. 6501.30; Vygon, Ecouen, France).[15] The results were robust with respect to the reduction in CO_2 retention by spontaneously breathing piglets with oleic acid induced mild respiratory distress. However, the impact of this study was limited because the piglets needed to be intubated to accomplish TGI with the Vygon endotracheal tube. Application of such a therapy would, in theory, dramatically increase the number of infants that can be sustained without mechanical ventilation, or weaned sooner.

Data from published clinical studies support the theory that HFT eliminates dead space because of the immediate impact on ventilation rates. A study by Dewan and Bell investigated exercise tolerance in COPD patients receiving respiratory support by transtracheal catheters (TTC), and compared low and high flows through nasal cannulae to low and high flow through the TTCs.[1] TTCs are catheters placed in the patient's trachea for the direct purpose of increasing respiratory efficiency by TGI dead space washout. Dewan and Bell showed that exercise tolerance was greater for high flow than low flow regardless of method of administration ($p < 0.01$), but high flow via nasal cannula was just as effective for dead space washout as with TTC. These data confirm that dead space washout is a primary mechanism of action during HFT.

A neonatal trial of an early extubation protocol done Holleman-Duray et al. showed that infants extubated to HFT, compared to other non-invasive support modes, from significantly greater ventilator rates (33 ± 8 vs 28 ± 8 breaths/min; $p < 0.05$).[16] In another example, a published case report on a pediatric burn patient showed that respiratory rate decreased immediately following initiation of Vapotherm HFT (63–38 breaths/min), with a secondary sustained decrease in heart rate (175–144 beats/min) after a short period.[17]

Dead space removal also has an impact on oxygenation. Data from Chatila and colleagues demonstrated in exercising adult chronic obstructive pulmonary disease (COPD) patients that HFT compared to conventional low flow through nasal prongs enhanced oxygenation.[18] During matched workloads and with matched inspiratory oxygen fraction, exercising patients maintained greater arterial oxygen tension ($p < 0.001$) despite a reduction in respiratory rate ($p < 0.05$) while using HFNC. While using HFT these patients were able to exercise longer (10 ± 2 vs 8 ± 4 min; $p < 0.05$), and these patients also maintained arterial CO_2 and pH while breathing less frequently with no change in tidal volumes.

A few studies published as abstracts reinforce the nasopharyngeal washout effect by evaluating oxygen concentration of the airways and lungs. The use of a bench model showed that airway oxygen fractions were greater with the use of HFT via nasal cannula versus non-rebreathing masks.[19,20] Additionally, a study in normal human subjects showed that nasopharyngeal oxygen concentrations were greater with higher flow rates, and greater if the patients has an open mouth.[21]

Reduction of inspiratory resistance (work of breathing) by providing adequate flow

The design of the nasopharynx facilitates humidification and warming of inspired gas by contact with the large surface area. By definition, this large wet surface area and nasopharyngeal gas volume can account for an appreciable resistance to gas flow. In addition, after analyzing nasal and oral flow-volume loops, Shepard and Burger showed that the nasopharynx has a distensibility that contributes to variable resistance.[2] When inspiratory gas is drawn across this large surface area, retraction of the nasopharyngeal boundaries results in a significant increase in inspiratory resistance compared to expiratory resistance. CPAP has been shown to reduce this supraglottic resistance up to 60% by mechanically splinting the airways.[22] However, HFT most likely minimizes the inspiratory resistance associated with the nasopharynx by providing nasopharyngeal gas flows that match or exceed a patient's peak inspiratory flow. This change in resistance translates to a decrease in resistive work of breathing.

Saslow and colleagues published data from neonates indicating that work of breathing with HFT between 3 and 5 L/min was equivalent to that with nasal CPAP set to 6 cm H_2O.[23] This reported equivalency was shown despite a significantly lower esophageal pressure (1.32 ± 0.77 vs 1.76 ± 1.46 cm H_2O; $p < 0.05$); thus, there is a mechanism of action other than distending pressure effecting work of breathing with HFT.

The effects of high nasal gas flows on expiration are less understood; however, comparison to other devices supports some hypotheses on what happens during the expiratory phase. The Infant Flow CPAP driver incorporates the Coanda effect in switching flow during expiration, such that the patient experiences an entrainment effect of expiratory gas during expiration.[24,25] In this regard, one might speculate that during HFT, inspiratory flow is split such that a portion of gas flow enters the trachea and a smaller portion exits the mouth. During expiration, it is possible that the exiting gas from the trachea separates gas flow from the back wall of the nasopharynx by disrupting the boundary layer, thus assisting expiration out the mouth similar to the infant flow device. Thus, the Coanda effect would be experienced by the patient in the nasopharyngeal region during expiration and potentially assisting expiratory efforts.

Improved mechanics by supplying adequately warmed and humidified gas

Studies from the 1990's demonstrated the negative effects of using non-warmed, non-humidified gas to support respiration. Dr. Greenspan and colleagues demonstrated that just five minutes of respiration with ambient gas, not

warmed or humidified, in ventilated infants resulted in a significant decrease in both pulmonary compliance and conductance.[3] Furthermore, Fontanari and colleagues showed that receptors in the nasal mucosa respond to cold and dry gas to elicit a protective bronchoconstrictor response in both normal subjects[26] and asthmatics.[27] On and colleagues showed this cool, dry air induced bronchoconstriction response to be associated with muscarinic receptors in the nasal mucosa.[28]

In non-intubated infants receiving respiratory support by nasal cannula, Saslow and colleagues showed greater respiratory compliance in infants with 5 L/min of HFT conditioned gas compared to 6 cm H_2O of conventional CPAP using a standard humidification unit (1.03 ± 0.47 vs 0.83 ± 0.49 ml/cm H_2O/kg).[23] These compliance data were despite a significantly lower esophageal pressure in the HFT treated infants (1.32 ± 0.77 vs 1.76 ± 1.46 cm H_2O; $p < 0.05$). Because HFT resulted in less distending pressure, and therefore less functional residual volume, these data support the proposition that adequacy of conditioning for breathing gas does impact the physiologic response of the organ tissues. These study findings agree with those of Dr. Greenspan and colleagues with respect to compliance; however, regarding airway conductance, this parameter was not measured in the Saslow study.

Reduction in the metabolic cost of gas conditioning

Under normal physiologic functioning of the respiratory tract, the nasal air passages warm inspiratory air from ambient to 37 °C and humidify the incoming air to 100% relative humidity (RH).[29–31] Whereas many of the factors involved in this process are unclear or not easily definable, we believe that it can be ascertained that there is some significant energy cost to the process of gas conditioning.

By definition, gas that is at 100% RH holds as much water as possible before water droplets begin to spontaneously form. Furthermore, Dalton's law dictates that as gas gets warmer it hold more water vapor per unit volume at any percent RH. Thus, as gas is conditioned by the nasal mucosa, heat energy is required not only to warm the air, but also vaporize water into the air. This process of water vaporization requires a significant amount of heat energy in the same way that sweating cools our bodies on a warm day.[32] However, the times when gas conditioning presents the greatest thermal challenge are when the ambient air is cooler and drier, thus body heat is typically not in reserve. In this regard, the nasal mucosal tissues likely need to produce this heat for warming and water vaporization.

The most simplistic formula for the energy requirement of gas conditioning is represented as:

$$E_{total}/L = E_g \cdot (37 - T_{amb}) + E_{vap} \cdot (44\,mg - AH_{amb})$$

Here, E_{total}/L is the total energy required per liter of inspired gas, E_g is the energy required to raise 1 L of gas 1 °C (roughly 1.2 J), and E_{vap} is the energy required to raise 1 mg of water from 37 to 100 °C plus the latent heat of vaporization for 1 mg of water (.263 + 2.260 J, respectively). T_{amb} represents the ambient gas temperature, which is subtracted from body temperature (37 °C). AH_{amb} represents the absolute humidity of ambient gas per liter, and that is subtracted from the absolute humidity of gas at body temperature and saturated (44 mg H_2O/L).

As a typical example, consider inspiring ambient air that is room temperature (21 °C) and 50% RH (containing 9 mg water/L). Each liter of air will need to be raised 16 °C and have 35 mg of water vaporized into it, requiring 107.5 J (26 Calories) per liter of inspired gas. Therefore, an adult with a typical 500 ml tidal volume and a respiratory rate of 12 breaths/min may require approximately 156 calories/min for conditioning gas. Also, note that there must be some metabolic cost of generating mucus and moving the water.

It is assumed that the nasal airways are very efficient at capturing heat and moisture from expired gas to be recycled on subsequent inspirations.[29–31] Nonetheless, without 100% efficiency there is presumable some energetic cost to conditioning inspired air. Furthermore, with lung pathologies there is a rise in minute ventilation resulting in greater gas volumes to be conditioned, and current non-invasive therapies can supply gas flows to the nasal passages that supersede minute volumes inspired to the lungs. In this regard, utilizing HFT with a device that completely warms and humidifies inspiratory gas likely impacts oxygen need and CO_2 production by reducing this energy requirement. This presumption is supported by the clinical data indicating improved weight gain in infants on Vapotherm compared to those on conventional CPAP support.[16]

Provision of distending pressure

The form of non-invasive respiratory support most common in the neonatal intensive care setting is continuous positive airway pressure (CPAP).[33] It is believed that providing distending pressure to the lungs results in improved ventilatory mechanics by optimizing lung compliance and assists with gas exchange by maintaining patency of alveoli.[34–36] Whereas HFT is not necessarily intended to provide CPAP, if gas flow and nasal prong dimensions are set appropriately for patient size distending pressure can be accomplished.

Nasal cannula size is a critical factor in determining CPAP generation as it relates to air leak around the cannula prongs. Dr. Locke and colleagues showed that using 2.0 cm OD nasal prongs with conventional oxygen therapy (>2 L/min) does not generate significant esophageal pressures or impact breathing patterns; however, using a larger 3.0 cm OD cannulae in the same infants produced a correlation between gas flow and esophageal pressure ($r = 0.92$), reaching a mean pressure of 9.8 cm H_2O at 2.0 L/min of flow.[37] Therefore, distending pressure provided by nasal cannula and respiratory gas flow is dependent on leak rate, determined by the nasopharyngeal anatomy as well as the relationship between nasal prong size and nares of the nose. In fact, a recent bench study by Kahn and colleagues showed that even bubble CPAP results in appreciable overshoots of pharyngeal pressure when the nasal prong size relative to the nares allows for too little leak, and too much leak essentially negates generation of intended pharyngeal pressure.[38]

Typically, CPAP generated by nasal cannula in the NICU setting is done with approximately 1–3 L/min of flow with adequate nasal prong size (relative to the nare internal dimensions) and a closed mouth to create up to 8 cm H_2O of pharyngeal pressure.[39] When flow and resistance components are managed accordingly, bench data presented by

Limauro and colleagues indicated that HFT nasal cannulae do not likely deliver a clinically relevant level of CPAP unless an infant's mouth is closed and the leak around the nares minimized.[40] In a follow-up clinical study, these authors showed that oral pressures in 16 infants receiving HFT were only clinically significant in the smallest infants and when the mouth was closed.[41] Spence and colleagues demonstrated that HFT can be used effectively to provide CPAP ($<$5 cm H_2O in this study).[4] However, these researches held the mouth closed with a strap on these infants and did not report the nasal cannulae or nostril nare dimensions.

Wilkinson and colleagues recently showed that HFT in infants can result in clinically relevant increases in pharyngeal pressures, and that the pharyngeal pressure is directly related to flow, but inversely related to infant size.[42] This study provides evidence to support the fundamental relationship between pressure and flow where pressure is directly proportional to flow and resistance ($P \sim F \times R$). Therefore, as the infants get smaller in size, the pressure resulting from any flow rate increased as a result of the resistance provided by the smaller anatomy. In this regard, major limitations of the study were that nasal prong size (effecting leak around the prongs) was not decreased with decreasing infant size to normalize the resistance, and flow rates were not optimized. With respect to the later point, it is likely that the smaller infants did not require as much flow as the larger infants to effect dead space washout and support inspiratory efforts.

Summary

HFT through nasal cannula is now a viable option because of devices that completely warm and humidify inspiratory gases to body temperature and 100% saturation. Properly conditioned gas provides for patient comfort and minimizes deterioration of nasopharyngeal structures. The mechanisms of actions of HFT are five-fold: HFT 1) flushes dead space of the nasopharyngeal cavity allowing for better ventilation as well as oxygenation, 2) provides a flow adequate to support inspiration therefore reducing inspiratory work of breathing, 3) improves lung and airway mechanics by eliminating the effects of drying/cooling, 4) reduces or eliminates the metabolic cost of gas conditioning, and 5) can be used to provide end distending pressure. Numerous studies have shown the safety and efficacy of nasal cannula HFT in the acute care setting, and a number of studies have demonstrated potential for HFT in terms of efficacy beyond conventional oxygenation support.

Conflict of interest statement

Kevin Dysart and Thomas Shaffer have received research funding from Vapotherm, Inc. Thomas Miller is an employee of Vapotherm, Inc.

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