High Flow Therapy and Specialty Gases:

Heliox Ventilation and the Development of Precision Flow® Heliox

Thomas L Miller, PhD

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About Vapotherm

Vapotherm, Inc. is the innovator of humidified high flow nasal cannula therapy (HFT) and manufactures devices for acute and chronic respiratory care.
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Executive Summary

The purpose of this white paper is to discuss the application of specialty medical gases using high flow nasal cannula therapy (HFT®), with specific emphasis on helium-oxygen gas mixtures (heliox). Basic principles of HFT are introduced to explain how breathing gases can be delivered to the lung and airways in precise mixtures through an open system, and done more efficiently compared to closed circuitry models for ventilator assistance. Furthermore, a discussion of heliox with HFT expands on how these concepts work in concert to noninvasively reduce a patient's work of breathing.

Vapotherm pioneered the concept of HFT with the introduction of technologies that were able to surmount prior obstacles to complete respiratory gas conditioning. By delivering adequately conditioned breathing gases to a patient with a nasal cannula interface, flow rates can now be used which surpass conventional limitations of a nasal cannula (typically 6 L/min in an adult) to reach flow rates that meet or exceed a patient's inspiratory flow rate. The achievement of HFT unlocked a number of mechanisms of action for nasal gas insufflation that results in a multifactorial therapeutic effect.

Over the last decade, HFT has been used extensively and has been well studied. A large number of clinical studies have demonstrated the ability of HFT to enhance oxygenation, ventilation and reduce dyspnea in adult patients with various pulmonary pathologies. HFT has been shown to aid patients with acute respiratory failure, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and asthma among others.

An extensive body of literature on ventilation with heliox shows that there is a marked reduction in respiratory resistance when gas is undiluted by room air and the helium balance gas represents at least 50-60% of the mixture. In this regard, the delivery of heliox with Vapotherm HFT devices has a distinct advantage over other methods of noninvasive specialty gas 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 any entrainment of room air needed to meet a balance of an inspiratory demand. Also with this approach, the nasopharyngeal region of the patient's upper airway becomes an internal reservoir of the intended gas mixture. This makes gas delivery more efficient in that it is not diluted by a bolus of trapped expiratory gas and more precise in that it is not affected by variable flow from a delivery system that reacts to spontaneous patient flow. Therefore, when providing heliox via HFT, the intended effect of the specialty gas mixture is not hampered by dilution of the metered gas, and the desired therapeutic affect can be achieved using a minimally invasive cannula patient interface.

"This white paper focuses on the impact of HFT delivery of heliox, however the concepts pertaining to precise and efficient delivery of specialty gases apply to other gases that are currently in use or being explored for mechanical and/or anti-inflammatory effects."

Introduction to the Precision Flow® Heliox and Vapotherm's Specialty Gas Program

Vapotherm's technology and device platforms are well suited for the precise delivery of specialty medical gases. In some instances, such as with inhaled nitric oxide, a modified patient disposable cartridge set allows injection and monitoring of a medical gas that requires a unique delivery system. In other circumstances such as heliox ventilation, the blending capabilities of the specialty gas have been integrated into the existing device platform. The Precision Flow® Heliox device represents advancement in functionality by extending breathing gas conditioning in addition to precise blending and flow control capability for heliox. The Vapotherm platform allows for the delivery of breathing gases at or near body temperature and saturated with water vapor. This approach allows breathing gases to be delivered via nasal cannula, as opposed to a conventional face mask, at flow rates that meet or exceed a patient's inspiratory demand.

High flow respiratory gas delivery with nasal cannula results in an advantageous physiologic impact. This impact is based on fundamental mechanisms associated with purging nasopharyngeal dead space and exposing the lung and airways to ideally warmed and humidified respiratory gases. This white paper focuses on the impact of HFT delivery of heliox, however the concepts pertaining to precise and efficient delivery of specialty gases apply to other gases that are currently in use or being explored for mechanical and/or anti-inflammatory effects.[1] Heliox use as a respiratory gas is based on the premise that the lower density of helium compared to nitrogen results in a significant reduction of flow resistance in the patient's airway resulting in reduced work of breathing. Together, a high-flow nasal cannula with heliox makes heliox delivery possible without a face-occluding mask and also makes heliox gas delivery more efficient by means described in the following section.

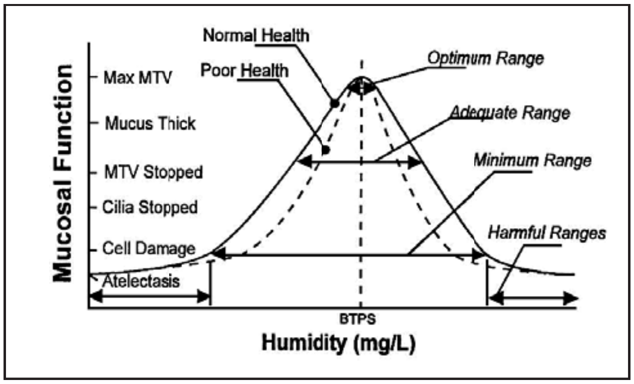
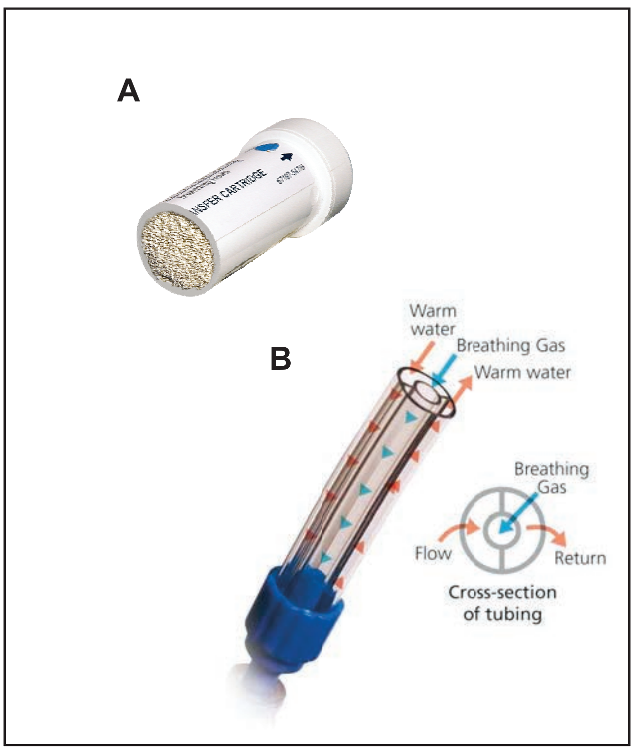


Figure 1 (above). *This figure from Williams et al[3] shows that mucosal function is dramatically impacted by absolute humidity, which is a function of both relative humidity and temperature. Here BTPS represents body conditions where gas contains 44 mg·L-1 of water vapor. MTV = mucus transport velocity.*

Figure 2. *Technologies such as the Vapotherm® Vapor Transfer Cartridge (A) have improved the task of gas conditioning. The large surface area of the hollow tube filled with vapor-permeable fibers allows the respiratory gas passing through to be instantly warmed to a precise temperature and humidified to saturation. Vapotherm's water-jacketed patient delivery tube (B) maintains the conditioning state of the patient gas in the center lumen with a dynamic insulation system. In this tube design, water circulated out and back into the outer jacket is at the temperature the gas is intended to be.*



Fundamentals of High Flow Therapy (HFT)

The Vapotherm platform utilizes innovative membrane humidification technology to efficiently condition gas to body temperature and saturated with water vapor, as well as an innovative water-jacketed delivery tube design to maintain energy state of the conditioned gas as it is conducted to the patient. These technologies allow for an array of mechanisms by which nasal cannula gas flow that is in excess of a patient's inspiratory flow rate can improve respiratory efficiency and work of breathing. This section represents a synopsis of the literature on this experience, which provides the background for understanding the role of HFT in the noninvasive delivery of specialty medical gases.

Humidification of Breathing Gases

The nasal mucosa is designed to warm and humidify breathing gas prior to entering the conducting airways and the lungs.[2] This is accomplished by a large surface area to interact with inspiratory gas. Exposing the nasopharyngeal tissues to a continuous flow of gas that is greater than a normal minute ventilation rate and which is also unsaturated with water vapor and below body temperature can overload these tissues. This operational overload results in significant dysfunction, drying and damage of the nasal mucosa[3-6] that furthermore contributes to compounding conditions such as staphylococcal sepsis[7] and perhaps contributing to lung inflammation.[8] Additionally, even at low flows, conventional nasal cannula therapy is uncomfortable and raises numerous patient complaints, particularly related to dry nose and mouth.[9]

To support respiratory therapies, efforts have been made to create systems that saturate and adequately warm respiratory gases. Ideally, inspiratory gas should be warmed to body temperature (37ºC) and humidified to 100% relative humidity (Figure 1).[10, 11] Typically, low flow nasal cannula therapy less than 4 L/min is not thought to require humidification.[12] However, for flows greater than 6 L/min the American Society for Testing and Materials requires humidification systems to produce inspiratory gas with at least 60% relative humidity at ambient temperatures.[13] However, in our modern definition of HFT, whereby cannula gas is constantly bathing the nasal mucosal tissues, it is recommended that gases are conditioned to mimic body conditions more precisely. The Vapotherm family of devices that use vapor transfer membranes with a water jacketed delivery tube system have been shown to produce 99.9% relative humidity, with the passage of water into the breathing gas in a vapor phase (Figure 2).[13] Humidification with vapor versus aerosolized water is the least likely to cause airway and lung injury by latent heat loss and deposition of water droplets.[11]

In a bench study, Drs. Waugh and Granger evaluated the capability of two HFT gas conditioning systems to meet American Association of Respiratory Care (AARC) standards and manufacturers' claims.[13] This data showed that the Salter Labs high-flow cannula system (Salter Labs, Arvin, CA) produced inspiratory gas that was at ambient temperature and between 72% and 79% relative humidity at up to 15 L/min of flow. The Vapotherm system, however, produced inspiratory gas at body temperature (37ºC) and 99.9 ± 0.0% relative humidity. Compared to manufacturer's claims, these test results were significantly less for the Salter Labs device at 5 and 10 L/min of flow ($p < 0.01$) but significantly more for the Vapotherm device at all flow rates ($p < 0.001$).

"This is even more important with certain specialty gases such as helium, where the thermal conductance is much greater than air and can therefore strip energy from the nasal tissues faster, leading to greater deterioration."

In a randomized crossover study, Woodhead and colleagues evaluated the impact of Vapotherm compared to conventional nasal cannula therapy on the nasal mucosa of preterm infants post extubation.[14] Thirty infants received either Vapotherm or HFT by way of a conventional cannula setup for 24 hours and then were switched to the opposite modality (conventional or Vapotherm) for an additional 24 hours. Using a blinded scoring system accounting for nasal erythmia, edema, thick mucus and hemorrhage, where a subjective value was assigned ranging from 2 to 10 in arbitrary units, Vapotherm infants had much better tolerance compared to conventional humidification (2.7 ± 1.2 vs. 7.8 ± 1.7; $p < 0.001$).

In summary, the Vapotherm devices have demonstrated superior gas conditioning and delivery capabilities that have been shown to be protective of the nasal tissues with constant high gas flows. This is arguably even more important with certain specialty gases such as helium, where the thermal conductance is much greater than air and can therefore strip energy from the nasal tissues faster, leading to greater deterioration. Thus, the Vapotherm platform is ideally suited for the administration of these gases.

Mechanisms of Action for Vapotherm HFT

With Vapotherm technology, the conditioning of respiratory gases is therefore adequate for delivering flow rates that would otherwise result in significant drying and damage to the nasal mucosa.[4,5,14] As described below, it is the relatively precise use of these higher gas flows that is defined by Vapotherm as HFT. In the acute care setting, HFT has been used to treat respiratory distress or failure, and in these applications has been shown to improve respiratory gas exchange[15] and mechanics.[16] The mechanisms of action for HFT are summarized here, however, a more complete description of these mechanisms can be found in a review paper by Dysart, Miller and colleagues.[17]

HFT is the delivery of respiratory gas by nasal cannula in an open system at a flow rate that exceeds a patient's spontaneous inspiratory flow. In simplest terms, this means that the cannula provides enough flow to meet a patient's inspiratory flow requirement so they will not have to breathe room air, and will only inhale cannula gas to the lung. For the typical adult in the hospital setting, this would be between 25 and 35 L/min based on normative values for adult pulmonology. Infants are more complex because of their proportionally greater extrathoracic dead space[18] and they typically require flow between 4 and 8 L/min. With these nasal flows, and without the aid of non-rebreather masks, intubation or some other form of elaborate airway control, a patient will inhale the intended gas mixture despite the perceived openness of the interface. Moreover, during exhalation cannula flow continues to purge the anatomical dead space of the upper airway, creating an internal reservoir of cannula gas ready for the next inhalation. This aspect of HFT actually improves respiratory efficiency and results in a ventilation effect. HFT has a number of other influences that result in more favorable gas equilibrium values in the lungs and reduced respiratory effort. The key factors considered to be mechanisms of action for HFT are as follows:

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.[19, 20]

2) The distensibility of the nasopharynx provides significant resistance on inspiratory efforts relative to expiratory efforts.[21] HFT provides adequate flow rates to match inspiratory flow and thus eliminates the inspiratory resistance associated with the nasopharynx and the related work of breathing.

3) The provision of adequately warmed and humidified gas to the conducting airways is associated with improved conductance and pulmonary compliance compared to dry, cooler gas.[22]

4) The provision of adequately warmed and humidified gas through the nasal and pharyngeal regions reduces the metabolic work associated with gas conditioning.

5) When manipulated correctly, the flow that flushes the nasopharynx can be restricted to provide positive distending pressure for lung recruitment.[23]

6) The ideal humidification of the inspired gas has been shown to restore mucocilliary function and reduce symptoms of airway exacerbations.[24, 25]

Based on these factors, HFT has been shown to be effective in adults[26, 27] as well as children.[28] Certainly, the provision of high gas flows through the nasopharynx will tend to develop mild distending pressure[29-31] which often intuitively seems to be the cause for the level of clinical efficacy observed. However, mechanistic research suggests that the most impactful of these factors is the nasopharyngeal flush, which results in the purging of CO_2 from the dead space gas volume that would otherwise be re-breathed during a subsequent inhalation.[19] As such, Vapotherm has focused research on the dynamics of flow through the nasopharynx and the dependency on cannula design. Using computational fluid dynamics modeling, we have learned that cannula design related to nasal prong size and orientation can create a tradeoff between purge efficiency and pressure development in the nasopharynx. Moreover, pressure in the nasopharynx is variable based on the flow patterns and the development of vortices. Therefore, cannula design can affect the points at which pressure is generated throughout the geometry of the nasopharyngeal space. This information has been used to refine the patient interface for the multiple applications to which HFT can be applied.

Some of the most recent clinical data in HFT pertains to the long term use of humidification therapy. A study by Hasani and colleagues described how HFT used for humidification therapy over a one-week period in bronchiectasis patients resulted in improved clearance of labeled markers from the airway.[24] Another study by Rea and colleagues demonstrated reduced exacerbation days and increased time to exacerbations of COPD patients who used HFT for humidification treatment over a longer term.[25] These lessons could have an important carryover to understanding the efficacy of a flow therapy when gas is soothing the airway, versus delivery of a cool dry gas that appears to be promoting airway reactivity and potentially, inflammation.

Heliox Ventilation

Heliox has been used as a breathing medium since the 1930's.[32] A body of literature exists which evaluates heliox ventilation as an alternative to nitrogen-oxygen mixtures for use as a respiratory therapy that reduces airway resistance. Heliox ventilation results in a marked reduction in respiratory resistance when the gas is undiluted by room air and the helium balance gas represents at least 50-60% of the mixture. This section is a redacted report of the key research pertaining to heliox ventilation, which has been well-studied over the past few decades.

A detailed paper by Myers on the theory of various therapeutic gases describes how helium reduces airway resistance and therefore work of breathing.[33] Helium has a lower density than nitrogen and thus contributes to a lower Reynolds number. Reynolds number predicts the pattern of flow for a liquid through a passage. A higher Reynolds number predicts more turbulent flow and vice versa. With a less turbulent flow pattern, the resistance to flow is reduced, as is the pressure gradient needed to drive the gas through the airway (i.e. work of breathing). Meyers also discusses Graham's law which states that the rate of diffusion for a gas is inversely proportional to the square root of its density. Based on this principle, a less dense gas moves faster with less driving force.

"Corcoran and Gamard propose that the impact of heliox is not truly a matter of making flow more often laminar, but rather reducing resistance to flow where it is turbulent."

In an invited review on aerosol drug delivery using heliox, Corcoran and Gamard further explain that the effects of heliox are more pronounced in the upper airway.[34] Within the respiratory system, the upper airways normally provide the greatest resistance to flow. Also, gas flow in the upper airways is likely always turbulent, even with heliox, whereas in the most distal airways flow is likely always laminar. Corcoran and Gamard propose that the impact of heliox is not truly a matter of making flow more often laminar, but rather reducing resistance to flow where it is turbulent. Unlike laminar flow, when flow is turbulent the pressure gradient needed to drive flow is directly related to gas density.[35] As such, when flow is turbulent in the upper airways, heliox gas mixtures require less driving force to generate flow or will have greater flow with any given driving force, compared to respiratory gas mixtures where the balance gas in nitrogen.

In addition to the impact of helium density on airway resistance, another property of helium may contribute to better ventilation. In a paper by Mildner and colleagues evaluating the use of heliox with high-frequency oscillatory ventilation, the authors describe how gases such as carbon dioxide diffuse faster in helium than in nitrogen.[36] In this study, CO_2 transit time through heliox was substantially less than through a nitrogen-oxygen mixture. These results indicate that heliox may be a more effective medium for diffusive mixing at the alveolar level, and therefore more effective at removal of CO_2.

Putting theory into practice, Jolliet and Colleagues discuss the use of heliox gas mixture in patients receiving mechanical ventilation.[37] These authors describe how the lesser density of heliox resulting in decreased airway resistance may also facilitate exhalation time and end-expiratory lung volumes. Using heliox, they saw a reduction in dynamic hyperinflation and intrinsic positive end-expiratory pressure. This effect in turn decreases necessary lung inflation pressures, respiratory acidosis, and work of breathing. These authors also discuss how the use of heliox could be a valuable approach to decrease post-extubation respiratory distress.

Heliox ventilation has been demonstrated effective in pediatric/infant populations as well. Migliori and colleagues showed that heliox ventilation improved gas exchange and work of breathing to reduce the need for mechanical ventilation in infants.[38] Grosz and colleagues shows that heliox ventilation was safe and effective at relieving upper airway obstruction in pediatric patients.[39] In infants with bronchopulmonary dysplasia, a study by Wolfson and colleagues, demonstrated decreased pulmonary resistance and work of breathing while spontaneously breathing heliox.[40] These later authors also showed a reduced risk of respiratory muscle fatigue and discussed the possibility that the reduced energy expenditure may allow more calories to be used for growth and development.

In terms of safety, the most comprehensive evaluation of the effects of helium exposure was done by Singhaus and colleagues.[41] These authors assessed the safety of a chronic heliox incubator environment on developing rabbit pups. They showed that there were no differences in growth parameters or a developmental milestone between the pups grown in a heliox environment compared to controls. Furthermore, in a piglet model of respiratory distress, Nawab and colleagues showed that breathing heliox attenuated lung inflammation,

Figure 3.
The Precision Flow® Heliox Device

This device is designed to blend, heat, humidify, and deliver heliox gas mixtures through a nasal cannula. The device is calibrated for use with an 80/20 heliox mixture as a balance gas (actually, 79% helium and 21% oxygen), and can be blended with oxygen to increase the fraction of oxygen up to 100%. Note that whatever the fraction of oxygen is set to, helium makes up the balance of the mixture; e.g. if oxygen is set to 40%, then helium is 60%.

presumably by reducing mechanical and oxidative stress.[42]

Because of the high safety record and known tolerance, as well as the indications for efficacy in reducing the resistive work of breathing, heliox is an existing mode of therapy used in many hospitals throughout the world. As such, there are numerous medical devices such as respiratory gas blenders and mechanical ventilators already cleared to deliver heliox mixtures. The combination of HFT with heliox offers no increased risk and there are distinct advantages of this combination.

Summary: Combination of HFT with Heliox

The delivery of heliox with the Vapotherm Precision Flow Heliox device (Figure 3) 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.

Key References: Vapotherm High Flow Therapy

This section summarizes the major research that pertains to the use of HFT. This table presents relevant reports and key findings published in peer-reviewed journals.

STUDY	MAJOR CONCLUSIONS
Dysart et al.[17]	Comprehensive literature review describing the mechanisms of action for HFT: • Washout of the nasopharynx • Attenuates the inspiratory resistance associated with the nasopharynx • Improves conductance and pulmonary compliance compared to dry, cooler gas • Reduces the metabolic work associated with gas conditioning • Provide positive distending pressure for lung recruitment
Frizzola et al.[19]	• Mechanistic preclinical research demonstrating that the core mechanism of action is dead space flush • Demonstrated ventilation effect • More pronounced effect with less occlusive prongs
Chatila et al.[15]	• Crossover prospective trial in 10 COPD patients • High flows of humidified oxygen improved exercise performance and oxygen dependency in part by enhancing oxygenation • Patients were able to exercise longer on higher flows with less dyspnea, better breathing pattern and lower arterial pressure compared to low flow oxygen delivery
Roca et al.[43]	• Crossover trial in acute respiratory failure: HFT compared to face mask oxygen therapy • HFT resulted in higher blood oxygenation and lower respiratory rate without changing blood pCO_2 • Patients found the cannula interface to be more tolerable and more comfortable
Price et al.[44]	• Retrospective analysis of 72 patients with Type 1 hypoxemic respiratory failure using HFT • HFT reduced respiratory rate and improvement in oxygenation for treated patients
Calvano et al.[45]	• Case study of an end-stage respiratory failure patient with multilobar pneumonia • Patient had a DNR order and could not tolerate a NIV mask • HFT reduced her agitation and improved her dyspnea, oxygenation, tolerance of oxygen therapy, and comfort at the end of life
Dewan & Bell.[20]	• Prospective trial of 10 COPD patients who were receiving transtracheal oxygen (TTO) through a stoma • TTO compared to both high and low flow nasal cannula oxygen • HFT, but not low flow nasal cannula, resulted in the same exercise tolerance and dyspnea score as TTO
Parke et al.[31]	• Prospective trial in postoperative cardiac patients • Aim was to demonstrate the level of airway pressure generated by HFT in adults • HFT generates a low level of distending pressure in adults: 2.7 +/- 1.04 cmH_2O
Hasani et al.[24]	• Prospective trial in bronchiectasis patients • Aim to investigate the impact of HFT on airway clearance • HFT with humidified breathing gas improves airway function via enhanced mucocilliary clearance

Key References: Heliox Ventilation

This section summarizes significant research that pertains to the use of heliox as a respiratory gas mixture. This table presents relevant reports and key findings published in peer-reviewed journals.

STUDY	MAJOR CONCLUSIONS
Myers.[33]	• Comprehensive review of the concepts behind heliox ventilation • Lesser density gas reduces airway resistance and therefore work of breathing • Reynolds Number: Lower density support laminar flow • Graham's law: Helium diffuses faster than nitrogen
Jolliet et al.[37]	• Discussion of heliox use in ventilation of adults • Resulted in decreased airway resistance • Reduced dynamic hyperinflation and intrinsic positive end-expiratory pressure, which reduces needed lung inflation pressures, respiratory acidosis and work of breathing
Migliori et al.[38]	• Study of heliox gas delivery in infants • Improved gas exchange and work of breathing • Reduced the need for mechanical ventilation
Wolfson et al.[40]	• Study respiratory mechanics in spontaneously breathing infants with bronchopulmonary dysplasia receiving heliox • Decrease pulmonary resistance and work of breathing • Reduced risk of respiratory muscle fatigue
Singhaus et al.[41]	• Safety study: rabbits pups raised in heliox environment compared to controls • No difference in growth parameters or developmental milestones
Nawab et al.[42]	• Piglet model to assess markers of inflammation with heliox ventilation versus control • Lung morphology showed improved distribution of heliox gas through the lung • Proinflammatory mediators and matrix remodeling proteins levels were significantly lower with heliox versus nitrogen-oxygen mix

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