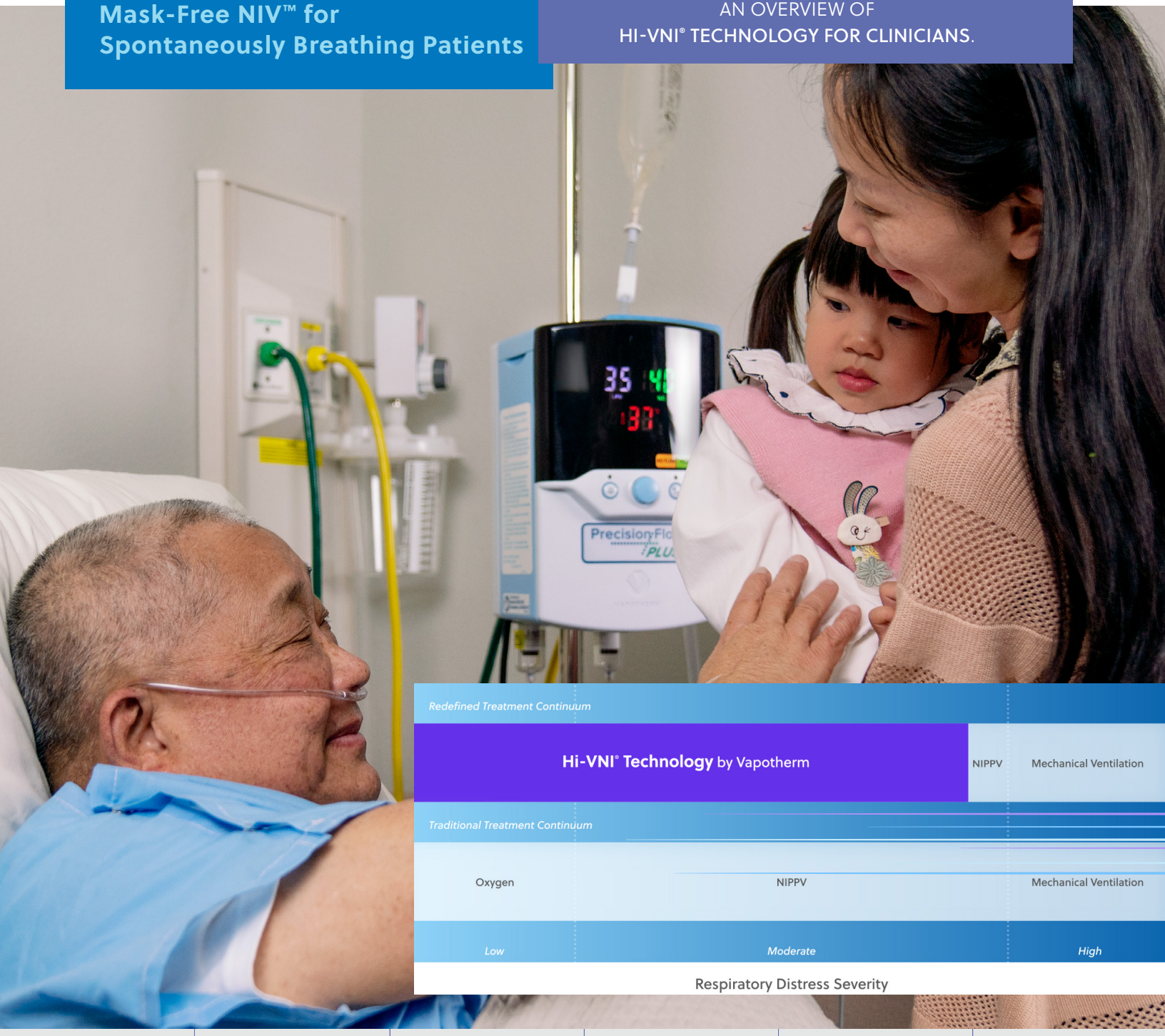
VAPOTHERM®

No Mask. No Problem.™

Mask-Free NIV™ for Spontaneously Breathing Patients

AN OVERVIEW OF
HI-VNI® TECHNOLOGY FOR CLINICIANS.



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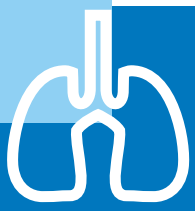
Introduction

The Ventilatory Support of NiPPV with the Comfort of Humidified High Flow

Clinicians managing patients in respiratory distress traditionally have had three categories of tools to relieve symptoms. There is oxygen therapy for low severity patients, non-invasive positive pressure ventilation (NiPPV) for moderate distress, and then mechanical ventilation for severe cases of respiratory distress. Hi-VNI Technology by Vapotherm® offers clinicians a new tool to treat a broad range of patients experiencing respiratory distress, including hypercapnia, hypoxemia, and dyspnea.



HI-VNI TECHNOLOGY BY VAPOTHERM IS MASK-FREE NIV FOR SPONTANEOUSLY BREATHING PATIENTS. THE TECHNOLOGY PROVIDES VENTILATORY SUPPORT FOR PATIENTS IN UNDIFFERENTIATED RESPIRATORY DISTRESS.

Hi-VNI Technology offers some of the best aspects of both NiPPV and commodity high flow oxygen systems.

Hi-VNI Technology provides high velocity nasal insufflation (HVNI), a viable alternative to NiPPV in treating adults in undifferentiated respiratory distress. It provides both oxygenation and ventilatory support to reduce hypercapnia.[1] Hi-VNI Technology has also been demonstrated to have comparable outcomes to CPAP when it comes to neonatal patients.[2]

Unlike NiPPV Hi-VNI Technology is low pressure and mask-free. The Hi-VNI Cannula interface delivers optimally humidified breathing gases and allows patients to eat, drink, and speak while receiving therapy. Although Hi-VNI Technology operates in part based on L/min selection, it is not a commodity high flow oxygen system, and although it can offer ventilatory support, it is not an NiPPV device.

1) Doshi, Pratik et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Annals of Emergency Medicine, 2018, 2018; 72:73-83 e5.

2) Lavizarri A, Colnaghi M, Ciuffini F, Veneroni C, Musumeci S, Cortinovis I, Mosca F. "Heated, humidified high-flow nasal cannula vs nasal continuous positive airway pressure for respiratory distress syndrome of prematurity – a randomized clinical noninferiority trial." JAMA Pediatr. 2016 Aug 8.

Introduction

New FDA Product Category

The FDA has recently created a new product category for a device which uses high velocity nasal insufflation. As of the time of this writing, Vapotherm's Precision Flow Hi-VNI™ is the only device in this category. It has an indication that the product can be used to augment breathing in spontaneously breathing patients suffering from respiratory distress in a hospital setting. This is a way of saying **that Hi-VNI Technology didn't quite fit into any of the previously existing categories for medical devices treating respiratory distress**.

The FDA's new category is supported by substantial clinical evidence that Hi-VNI Technology is non-inferior to NiPPV in spontaneously breathing patients. This evidence includes Doshi and colleagues' recent controlled, multi-center, randomized clinical trial which we will cover in Section 4.

THE PRECISION FLOW Hi-VNI BY VAPOTHERM IS CURRENTLY THE ONLY PRODUCT IN THE NEW FDA CATEGORY. ITS PRODUCT CODE IS QAV.

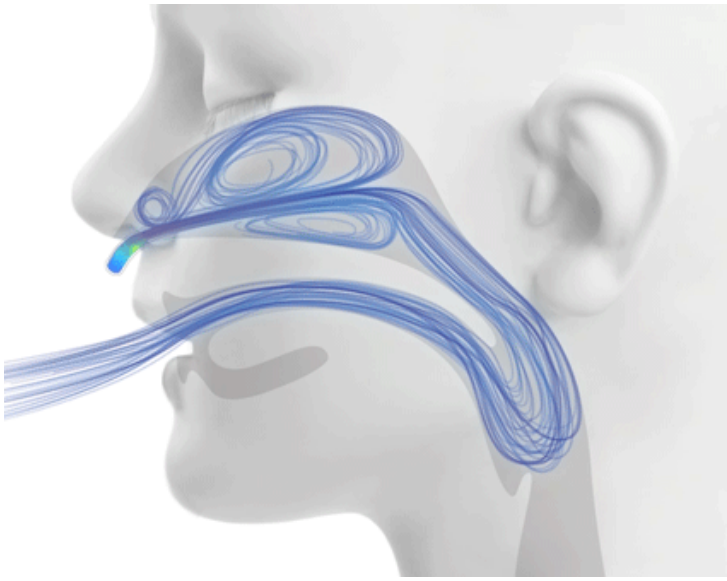
We should also note that although the category is new, Vapotherm's Hi-VNI Technology—which is incorporated in all of its Precision Flow systems—is already **trusted and used by over 1,250 hospitals, and has been used for over 1.5 million patients**. While it doesn't entirely replace NiPPV in the clinical toolkit, it offers an appealing alternative for clinicians treating most patients in undifferentiated respiratory distress. In particular, those patients who have difficulty tolerating a mask, are difficult to fit, or have a risk of vomiting and aspiration. It is also a good choice for patients where clinicians feel there is benefit to the patient being able to talk, eat, and drink while receiving therapy.

So, how does this technology work?

Mechanisms of Action

Eliminating End-Expiratory CO_2 and Reducing the Functional Dead Space

The primary mechanism of action of HVNI delivered by Vapotherm's Hi-VNI Technology, is the flushing of end-expiratory CO_2 from the upper airway between breaths. This is accomplished rapidly and efficiently with a high velocity stream of optimally conditioned breathing gas. Because Hi-VNI Technology is an open system, the fresh gas is insufflated through the nares and the end-expiratory CO_2 is flushed out through the mouth. This reduces the CO_2 content of the next inspiration and fills the nasopharyngeal cavity with fresh gas. **Like a tracheostomy that mechanically bypasses the dead space, the high velocity purge functionally minimizes it by changing the dead space to a fresh gas reservoir**.



Other Mechanisms of Action

Although the flush of end-expiratory CO_2 is the primary mechanism of action, Hi-VNI Technology also achieves its efficacy in part through the following[3]:

Some distending airway pressure

Primarily during exhalation against the high velocity flow

Warming gas flow (typically 33-37°C)

Which decreases inspiratory resistance

Humidification

Optimal humidity preserves mucociliary function and aids in mucus clearance from airways

3) Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: Mechanisms of action. Respir Med 2009; 103:1400-1405

Mechanisms of Action

Difference between Hi-VNI Technology and NiPPV

Clinicians used to NiPPV as the gold standard treatment for patients with hypercapnia may be skeptical about how a mask-free device that does not deliver pressure as a primary mechanism of action could achieve alveolar ventilation in patients. In reality NiPPV and Hi-VNI Technology are just two different approaches toward the same goal. Let's look at the basics:

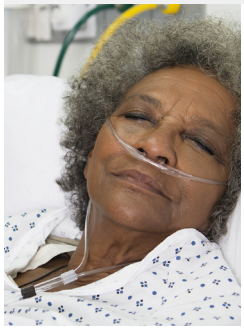
Ventilation with NiPPV

Alveolar Ventilation = (**Tidal Volume** — Dead Space) x Respiratory Rate

In order to achieve ventilation, NiPPV most greatly affects the Tidal Volume aspect of the above equation.[4] The machine ensures ventilation by using positive pressure to deliver target Tidal Volume. Because there is a risk of over-pressurization, clinicians generally start low and adjust up for effect to stabilize a patient.

Ventilation with Hi-VNI Technology

Alveolar Ventilation = (Tidal Volume — **Dead Space**) x Respiratory Rate



However, it is also possible to achieve alveolar ventilation by affecting the other parameter in the equation: Dead Space.

The rapid flushing out of the upper airway Dead Space is the mechanism of action by which Hi-VNI Technology facilitates alveolar ventilation.5,[6]

Unlike NiPPV, Hi-VNI Technology is an open system de-escalation therapy—it is safe to turn on high and stabilize the patient fast. The clinician can then titrate down upon patient response.

4) Mehta, Sangeeta and Nicholas S. Hill. Noninvasive Ventilation. American Journal of Respiratory and Critical Care Medicine 163(2).

5) Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: Mechanisms of action. Respir Med 2009; 103:1400-1405

6) Miller TL, Saberi B, Saberi S (2016) Computational Fluid Dynamics Modeling of Extrathoracic Airway Flush: Evaluation of High Flow Nasal Cannula Design Elements. J Pulm Respir Med 6:376. doi: 10.4172/2161-105X.1000376

Mechanisms of Action

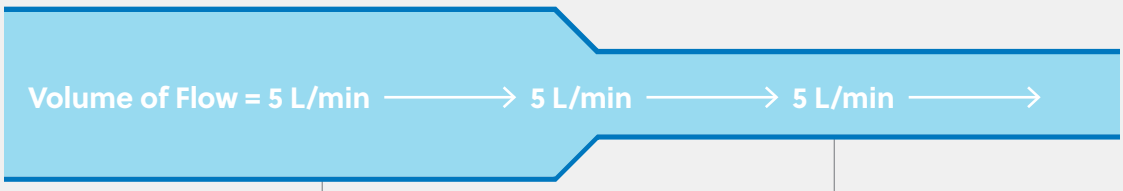
Difference between Hi-VNI Technology and Commodity High Flow Oxygen Systems

Hi-VNI Technology is frequently confused with commodity high flow oxygen systems, also commonly known as high flow nasal cannula (HFNC). This comparison is understandable at first glance—both deliver high liter flows of conditioned gas though a cannula interface. However, there are some significant differences between these devices and the likely explanation for the difference in clinical outcomes. Hi-VNI Technology has been clinically demonstrated to be comparable to NiPPV in treating patients in undifferentiated respiratory distress.

Why Velocity Matters

Hi-VNI Technology is designed to deliver High Velocity Nasal Insufflation, and as the name suggests, velocity is a key component of the efficacy of this therapy. Unlike most conventional large-bore HFNC, Hi-VNI Technology uses small-bore cannulas. This matters because velocity, at a constant volume of flow, varies inversely with the cross sectional area of a tube, as depicted below.

A HELPFUL WAY TO THINK ABOUT IT IS TO ENVISION A GARDEN HOSE WITH WATER FLOWING OUT. IF YOU PLACE YOUR THUMB TO NARROW THE DIAMETER OF THE HOSE, THE WATER INSTANTLY MOVES FASTER.



Velocity = 16.4 cm/sec
A = 5.08cm²

Velocity = Distance/Time

Velocity = 32.8 cm/sec
A = 2.54cm²

Velocity = Distance/Time

From Kacmarek, Robert M., James K. Stoller, Albert J. Heuer, and Donald F. Egan. Egan's Fundamentals of Respiratory Care. St. Louis, MO: Elsevier/Mosby, 2013.

In other words, the smaller the diameter of the cannula, the faster the gas will travel so long as the volume remains constant. The Precision Flow system is specifically designed to withstand the back pressure high velocity creates.

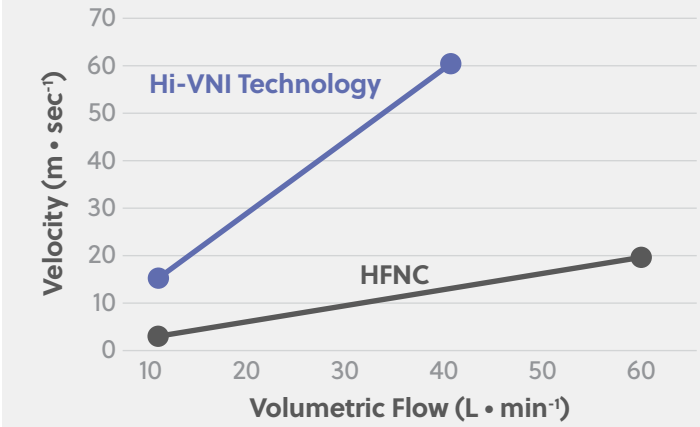
Mechanisms of Action

The Greater the Velocity, The Faster the Flush

In the 2016 study "Computational Fluid Dynamics Modeling of Extrathoracic Airway Flush: Evaluation of High Flow Nasal Cannula Design Elements" Miller and colleagues demonstrated that small-bore cannula prongs flush the upper airway dead space faster than large-bore cannulas. More precisely, the Hi-VNI small-bore cannula achieves a flush in 2.2 seconds while the large-bore cannulas flush in 3.6 seconds.

This is clinically meaningful because with the velocity the small-bore cannulas generate, a lower flow rate is needed to achieve an effective flush. Figure 1 illustrates how Hi-VNI Technology compares to commodity high flow oxygen systems when generating velocity. For example, Hi-VNI Technology achieves the same velocity at approximately 15 L/min that HFNC systems require 60 L/min to achieve.

Figure 1: Hi-VNI Technology



We are sometimes asked why Hi-VNI Technology only goes up to 40 L/min in its settings when some commodity high flow oxygen systems require higher flow rates. As illustrated, the answer is that Hi-VNI Technology is clinically effective below 40 LPM.

Flush Time is Crucial for Patients in Respiratory Distress

Ultimately this differentiator wouldn't matter if it didn't have real-life impact on the treatment of patients. So, the bottom line is that the more tachypneic a patient, the more important it is that their end-expiratory CO2 be flushed out fast – before they take their next breath in. The patient breathes in more oxygenated gas, reducing the work of breathing and augmenting alveolar ventilation.

Mechanisms of Action

Why Humidification Matters

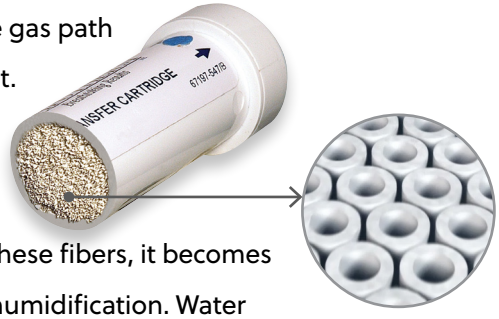
Although velocity is a salient difference between Hi-VNI Technology and systems that don't deliver HVNI, it is not the only difference. Humidification is another key component.

As we know, optimal humidification is crucial for maintaining airway health and mucociliary transport of secretions. Inspired gas at core temperature and optimal humidity is moisture neutral and preserves maximum mucociliary function.[7] At lower levels of inspired humidity, water is removed from the mucus and periciliary fluid by evaporation, causing increased viscosity of mucus and loss of periciliary fluid depth. This in turn leads to negative consequences from thickening of secretions to atelectasis. This is why any system with high flows of gas offers some kind of humidification.

Membrane Humidification vs. Passover Humidification

The difference between Hi-VNI Technology and commodity high flow oxygen systems is that the temperature in the system never exceeds the gas delivery temperature in order to create or maintain humidification. High flow oxygen products use higher than set temperatures in both the creation and maintenance of humidification.

While Hi-VNI technology uses membrane humidification, high flow oxygen humidifiers use a pass-over humidification system. With pass-over humidification, breathing gas passes over highly heated water to add moisture and humidify the gas. Hi-VNI Technology, on the other hand, uses a vapor transfer cartridge to deliver water molecules to the gas path across a membrane to create Medical Grade Vapor™ without high heat.



When we look at a cross section of the Vapor Transfer Cartridge in Hi-VNI Technology, we see hundreds of tiny, semi-permeable "straws". The straws are surrounded by water and as gas flows down these fibers, it becomes optimally humidified[8]. This method is quite different from pass-over humidification. Water molecules enter the gas pathway through tiny .05 micron pores in the fibers by osmotic pressure.

7) Williams, RB. Respir Care Clin N Am 1998 Jun; 4 (2): 215-28

8) Waugh J, Granger W. An evaluation of 2 new devices for nasal high-flow gas therapy. Respiratory Care. 2004 Aug; 49(8): 902-906.

Mechanisms of Action

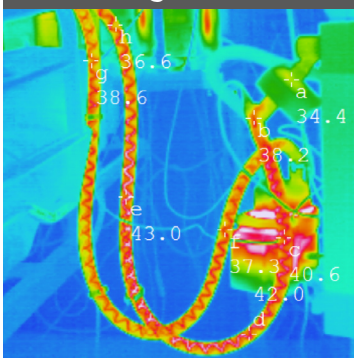
Delivering Optimally Conditioned Gas to the Patient

Generating optimally conditioned gas is just the first step. To be clinically effective, the gas also needs to be delivered in its humidified state all the way to the patient. This is where yet another difference between Hi-VNI Technology and commodity high flow oxygen products comes in.

The oxygen systems largely use a heated wire circuit for dewpoint control as they deliver the gas. As the heat mapping image in Figure 2 illustrates, the wire circuit does not provide uniform heating and leaves parts of the tubing cooler. Each time the humidified gas hits a cold spot in the tubing, there is an opportunity for water to condense out and create rainout. The patient may receive less than optimally humidified breathing gas, and may also experience the discomfort of water droplets being delivered through the cannula.

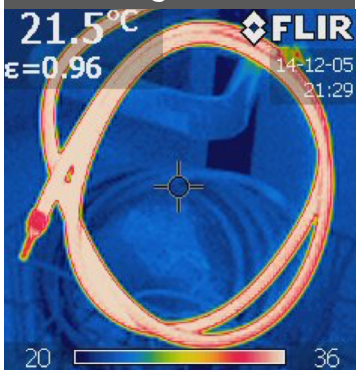
In contrast, Hi-VNI Technology ensures that the delivery tubing is uniformly heated and thereby reduces the chance of rainout, as shown in Figure 3. This is accomplished through a triple-lumen—or three-channel—delivery tube. In essence, the tube creates a warm-water jacket that keeps the Medical Grade Vapor energetically stable all the way from the Vapor Transfer Cartridge to the Hi-VNI® Cannula, where the short supply tubing continues to ensure that the possibility of rainout is further reduced.

Figure 2

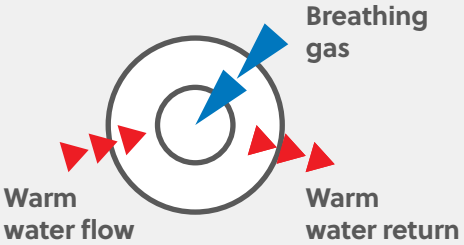


Heated wire circuit of commodity high flow oxygen systems.

Figure 3



Triple lumen delivery tube of Hi-VNI Technology.



AN ADDED BENEFIT TO THE TRIPLE LUMEN DELIVERY TUBE IS THAT IT'S SAFE TO THE TOUCH AND WILL NOT CAUSE BURNS

Mask-Free Interface Selection and Application

Hi-VNI Cannula Selection and Application

Now that we've covered why Hi-VNI Technology could be a great treatment for patients in undifferentiated distress and how it works, we'll address how to apply the therapy.

Maintaining an Open System

Given that the primary mechanism of action in Hi-VNI Technology is not pressure, but flush, it is important to maintain an open system at the patient. This is why the **Hi-VNI Cannula prongs should never occlude more than 50% of the diameter of the nare**. It allows gas flow out around the cannula as well as through the patient's mouth helping to create the turbulence that efficiently clears CO_2. Vapotherm manufactures 8 different Hi-VNI Cannula sizes to accommodate all patient populations from premature neonate to adult.

HI-VNI TECHNOLOGY PARAMETERS (FLOW RATE AND FIO_2) CAN BE CONTROLLED INDEPENDENTLY OF EACH OTHER. ADJUSTMENT IN FIO_2 GENERALLY TARGETS OXYGENATION STATUS OF THE PATIENT (E.G., SPO_2), AND FLOW RATE (L/MIN) TARGETS VENTILATORY WORK (WORK OF BREATHING).

Maintaining an open system not only provides an exit path for the purging of end-expiratory CO_2, but it also ensures that no inadvertent pressure is built up.

Vapotherm recommends applying the cannula to the patient while the Precision Flow system comes to temperature. This allows the cannula tubing to warm to body temperature. When the system is warmed up and primed (usually less than 5 minutes) it is time to start delivering respiratory support.

Starting Settings Across Patient Populations

Once the proper interface has been selected and applied, it is time to select the starting parameters of the therapy.

Flow is independent of FiO_2. FiO_2 starting settings should be chosen to achieve target SpO_2.

Typical L/min Recommendations

Adults: 25 – 35 L/min[9]
It is also okay to start at 40 L/min, then titrate down based on the clinical response from the patient.

Pediatrics: Approximately 2 L/min/kg[10] of ideal bodyweight.

Neonates: 4 – 8 L/min[11]

Vapotherm does not practice medicine. These guidelines are based on published literature and physiologic modeling. Providers should refer to the full indications for use and operating instructions before using Precision Flow®.

9) Doshi, Pratik et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Annals of Emergency Medicine, 2018, 2018; 72:73-83 e5.

10) Weiler, Thomas MD, Asavari Kamerkar DO, Justin Hotz RRT, Patrick A.Ross MD, Christopher J.L.Newth MD, FRCPC, Robinder G.Khemani MD, MsCI. The Relationship between High Flow Nasal Cannula Flow Rate and Effort of Breathing in Children. The Journal of Pediatrics Volume 189, October 2017, Pages 66-71.e3.

11) Yoder BA, B Manley, C Collins, K Ives, A Kugelman, A Lavizzari, and M McQueen. "Consensus approach to nasal high-flow therapy in neonates." Journal of Perinatology (2017) 00, 1–5.

Overview of Controlled Multi-Center Randomized Trial

In July 2018 the Annals of Emergency Medicine published the results of a controlled multi-center randomized trial by Doshi and colleagues titled *High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial*.[12] The trial found no difference between Vapotherm HVNI and NiPPV in intubation rates or treatment failure rates. The authors conclude that Vapotherm High Velocity Nasal Insufflation is non-inferior to NiPPV for the treatment of adult patients experiencing undifferentiated respiratory failure in the Emergency Department. This was the first randomized controlled trial (RCT) of HVNI that included undifferentiated respiratory distress in the adult patient, including hypercapnia.

Hypothesis/Methods

The hypothesis was that HVNI is non-inferior to NiPPV in the treatment of undifferentiated respiratory failure.

This was a prospective multi-center RCT of two methods of ventilatory support—HVNI delivered by Vapotherm Hi-VNI Technology and NiPPV. The trial used a non-inferiority design with a sample size of 204 (100 NiPPV, 104 HVNI), calculated such that test of proportions with 0.05 significance and 0.90 power, based on intubation rate of 16.1%. It should be noted that the non-inferiority margin includes broad variability in NiPPV intubation rates – mean difference including 95%CI.

15%
For intubation

20%
For all-cause arm failure including subjective cross-over

The study was conducted at three community hospitals and two academic hospital Emergency Departments. After randomization, the patients were monitored for 72 hours.

12) Doshi, Pratik et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Annals of Emergency Medicine, 2018, 2018; 72:73-83 e5.

Overview of Controlled Multi-Center Randomized Trial

Patient Selection and Characteristics

Inclusion Criteria:

- Patients >18 years in Acute Respiratory Failure, presenting to the ED requiring escalation to NiPPV in judgment of the clinical team.

Exclusion Criteria:

- Suspected drug overdose
- Cardiovascular instability (hypotension req Tx)
- End stage cancer, life expectancy < 6mo
- Significant respiratory depression / GCS score <9
- Cardiac or respiratory arrest / emergent intubation
- Known/suspected CVA or STEMI
- Patients with increased risk of aspiration (NiPPV contraindication)

Patient Characteristics:

There was no significant difference between the randomization groups and there was an array of diverse presenting conditions of undifferentiated respiratory distress, including asthma, CHF, CRF, COPD, and general dyspnea.

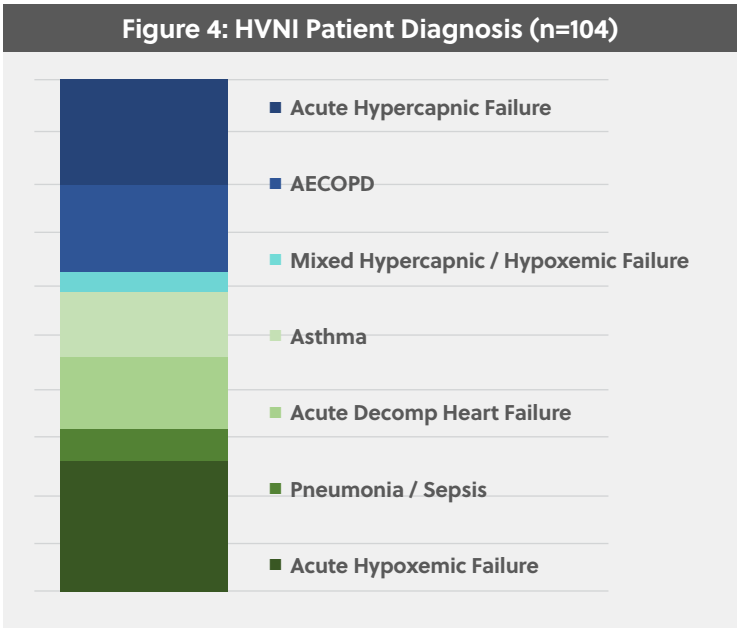
- Age mean 63 years (both)
- Mean BMI >30 (both)
- Apache II score mean 31 (both)

The discharge diagnoses of all patients showed the following breakdown:

- 33% COPD/Hypercapnia
- 20% CHF
- 15-20% Pneumonia
- 28% hypoxic / mixed respiratory failure

Figure 4 depicts the breakdown for the HVNI arm of the study.

Figure 4: HVNI Patient Diagnosis (n=104)



Overview of Controlled Multi-Center Randomized Trial

Endpoints

Primary Endpoint:

- Treatment Failure
- Failure requiring intubation / Mechanical Ventilation
- Failure of primary assignment including crossover to other arm

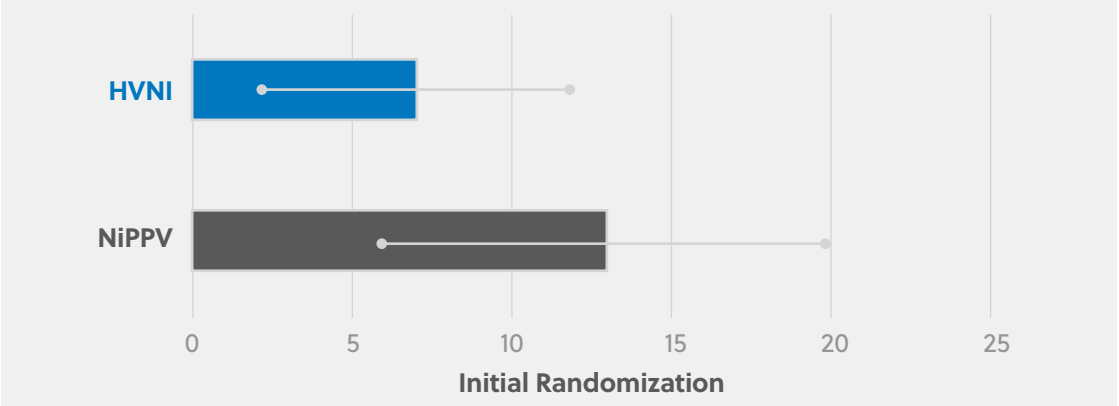
Secondary Endpoint:

- The ability of HVNI versus NiPPV to affect indices of breathing, including PCO_2, RR, HR, SpO_2.
- The patients' perception of dyspnea and discomfort.
- The treating physician's perception of efficacy at end of the treatment period.
- The disposition of patient and length of stay.

Primary Outcomes

The primary outcome is that HVNI delivered by Vapotherm Hi-VNI Technology is non-inferior to NiPPV for failure to intubation. The percentage of intubations on the HVNI arm were 7% (95%CI 2% to 12%) v. 13% (95%CI 6% to 20%) on the NiPPV arm as depicted in Figure 5. The risk difference of HVNI to NiPPV was -6% (95%CI -14% to 2%).

Figure 5: Intubation Rage (%)



Graph based on results of Doshi, Pratik et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Annals of Emergency Medicine, 2018, 2018; 72:73-83 e5.

Overview of Controlled Multi-Center Randomized Trial

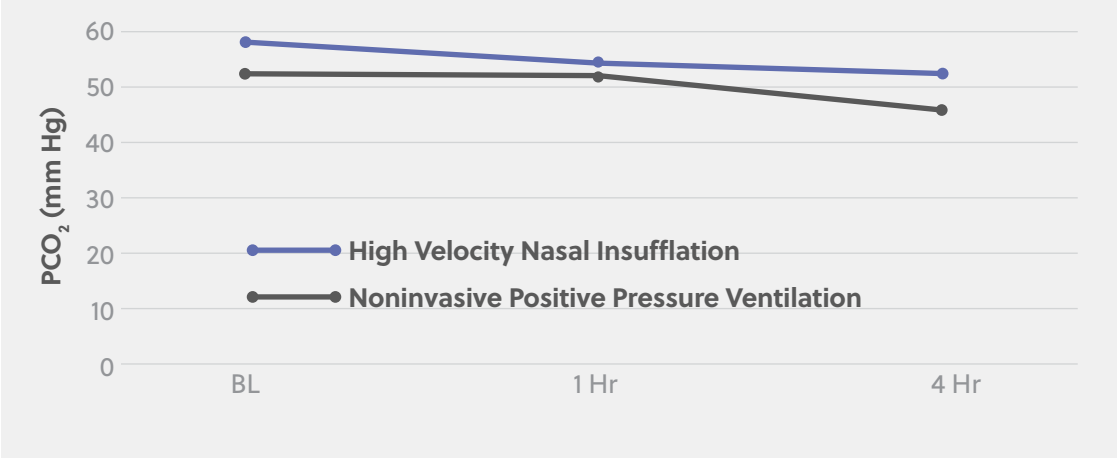
Additionally, HVNI was found non-inferior to NiPPV for all-cause arm failure with HVNI arm failure at 26% (17% to 34%) and NiPPV arm failure 17% (10% to 24%). The risk difference was HVNI-NiPPV 9% (-2% to 20%).

Secondary Outcomes

Markers of Ventilatory Effect

There was no significant difference regarding HVNI's ability to affect indices of breathing, including PCO_2, RR, HR, SpO_2 versus NiPPV. Additionally, there was a comparable change over time when it came to CO_2 reduction as shown in Figure 6.

Figure 6: Hi-VNI Technology



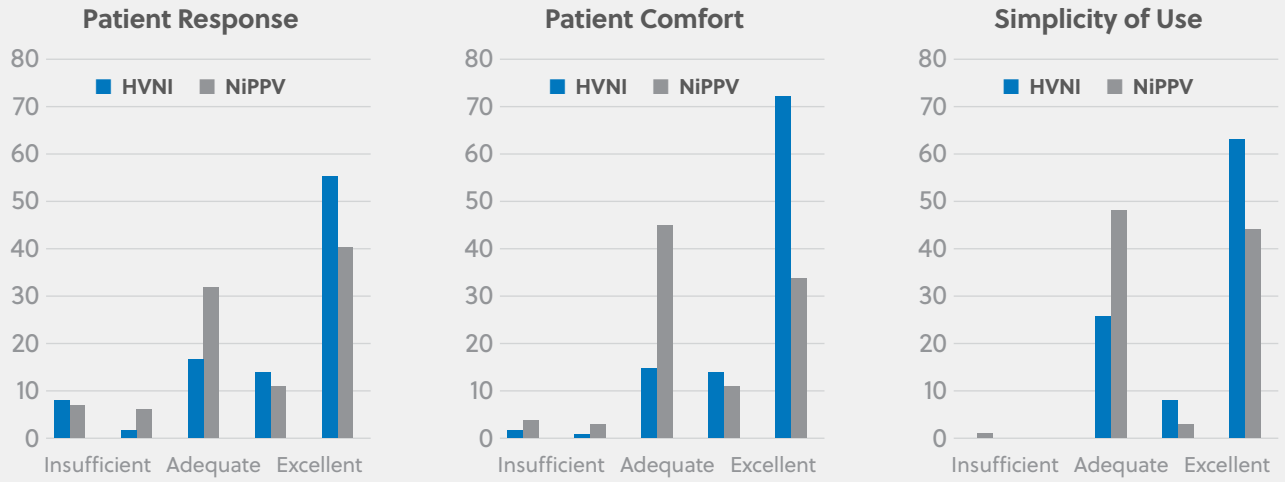
Graph based on results of Doshi, Pratik et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Annals of Emergency Medicine, 2018, 2018; 72:73-83 e5.

Overview of Controlled Multi-Center Randomized Trial

Physician Perception

The physician perception of patient comfort, patient response, and simplicity favors HVNI as shown in Figure 7:

Figure 7: Providers Rated Hi-VNI Technology Higher



MEDIAN	
HVNI	NiPPV
5	4

MEDIAN	
HVNI	NiPPV
5	3

MEDIAN	
HVNI	NiPPV
5	3

Selected Secondary Outcomes — monitoring need and technical difficulty had similar results. Used from Doshi et al. HVNI in the Treatment of Respiratory Failure, Ann of Emerg Med, 2017;1:11. (Adult, Multi, Clinical trial, Prospective, Randomized, Multi-Center, n=201)

Regarding the physician perception of need for monitoring and technical complexity, there was no significant difference. In other words, physicians perceived that Hi-VNI Technology provided the patient with greater comfort, a better response, and was easier to use than NiPPV. With that said, we should note that there were limitations.

Limitations include:

- unblinded due to technical limitation (mask v cannula)
- subjective character of crossover decision—some physicians may have chosen to cross over due to unfamiliarity with Hi-VNI Technology
- mix of arterial and venous blood gases – however each patient had same method over time

"HIGH-VELOCITY NASAL INSUFFLATION MAY BE A REASONABLE TREATMENT OPTION FOR SELECT ED PATIENTS WITH RESPIRATORY DISTRESS."

— study authors, Doshi, Pratik et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Annals of Emergency Medicine, 2018, 2018; 72:73-83 e5.

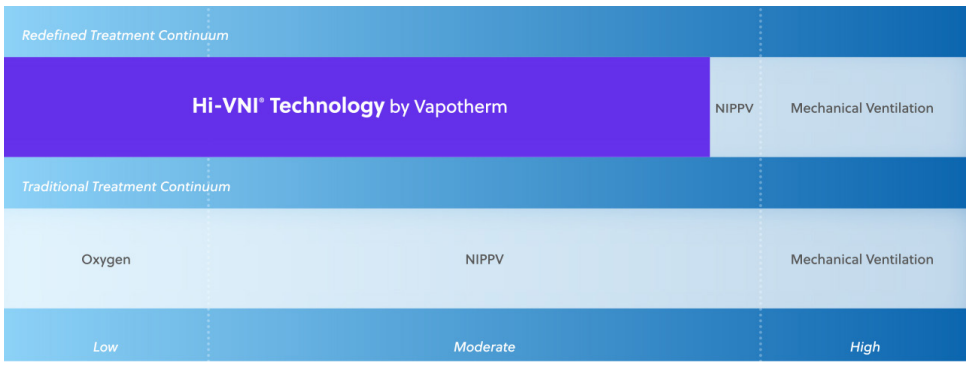
Summary

A New Continuum of Care

ALTHOUGH THE RANDOMIZED CONTROLLED TRIAL REVIEWED IN THIS BOOK IS RELATIVELY NEW, IN THE MORE THAN 18 YEARS THAT VAPOTHERM HAS BEEN BINGING INNOVATION TO THE FIELD OF RESPIRATORY SUPPORT, HI-VNI TECHNOLOGY HAS PROVEN ITSELF ON OVER 1.5 MILLION PATIENTS ACROSS MORE THAN 1250 HOSPITALS.

Hi-VNI Technology has been clinically proven to be a viable alternative to NiPPV in the treatment of undifferentiated respiratory distress in adults, including hypercapnia. When it comes to the neonatal population, Hi-VNI Technology has also been demonstrated to have comparable outcomes to NCPAP and bi-level PAP.[14] Yet, it has an easy-to-tolerate, mask-free interface and delivers optimally humidified breathing gases.

We are excited that this breakthrough helps to redefine the toolkit that clinicians have available to them when treating patients on the front lines of care. Where traditionally you only had masked therapies available for those patients who were too sick for oxygen therapy, but not sick enough for intubation, you now can facilitate your workflow with an easy-to-use yet efficacious technology.



Respiratory Distress Severity

Our expert field team is always available to demonstrate Hi-VNI technology, provide education, technical support, or answer questions. Vapotherm provides 24/7 technical support 365 days per year. Contact **855-557-8276** or reach us through the website **www.vapotherm.com**

13) Lavizarri A, Colnaghi M, Ciuffini F, Veneroni C, Musumeci S, Cortinovis I, Mosca F. "Heated, humidified high-flow nasal cannula vs nasal continuous positive airway pressure for respiratory distress syndrome of prematurity – a randomized clinical noninferiority trial." JAMA Pediatr. 2016 Aug 8.

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