Journal of
Clinical Respiratory Diseases and Care

Siler et al., J Clin Respir Dis Care 2019, 5:2

Research Article Open Access

Assessing the Clinical Effect of High Velocity Nasal Insufflation on Improving Ambulation in Patients with Dyspnea: A Feasibility Study

Thomas M Siler[1], Shailesh C Patel[2], Parag kumar Amin[3], Larry Hamon[2], Ronald J DeBellis[4], Leonithas I Volakis[4]* and George C Dungan II[4,5]

[1]*Midwest Chest Consultants, Saint Charles, Missouri, USA*
[2]*Department of Primary Care, Knox Community Hospital, Mount Vernon, OH, USA*
[3]*Riverside Regional Medical Centre, Newport News, VA, USA*
[4]*Department of Science and Innovation, Vapotherm Inc, Exeter, NH, USA*
[5]*Canisius College, Buffalo, NY, USA*

Abstract

Objective: Ambulation and early mobility is used in concert with oxygen therapy, as exercise is linked to improved patient outcomes. Past studies with ambulatory oxygen have evaluated patients with a need for oxygenation and ventilatory support during daily activity. The goal of this study is to establish the feasibility of a low risk model, using High Velocity Nasal Insufflation (HVNI; a form of non-invasive ventilation that augments breathing) providing oxygenation and ventilation support to facilitate ambulation of patients experiencing Dyspnea, and assess the impact of HVNI on outcomes compared to treatment as usual (TAU) in both inpatients and outpatients.

Methods: The study was performed as a prospective, crossover trial of patients across three sites. Patients prescribed ambulation (in the conduct of normal clinical care) were studied on oxygen therapy, and then crossed to HVNI therapy for the subsequent ambulation attempt. Ambulation distance and duration time were primary outcomes, with recovery time, vital signs, patient perception and clinician perception were secondary measurements. Patients with Dyspnea were recruited from both inpatient and outpatient settings.

Results: 32 patients were enrolled, 28 completed both study arms and 25 were analysed after post hoc exclusion. HVNI improved inpatient distance, duration and recovery outcomes: 8.5% increase in walk duration, 12.4% increase in distance walked, 32.5% decrease in recovery time, and the speed was 7.1% faster in HVNI than in TAU. Comparable improvement was not seen among outpatient ambulation.

Conclusion: The study suggests that HVNI during ambulation is feasible and may have more effective improvement in the inpatient acute care population of the study subjects. Enhanced duration and distance whilst reducing recovery time may provide clinical advantage to inpatient ambulation. A larger, randomised controlled study is required to further explore the role of HVNI in rehabilitation and allow for deeper review of outcomes.

Keywords: HVNI; Ambulation; Early mobilization; COPD; Dyspnea; Pulmonary rehabilitation

Abbreviations: 6MWD: Six-Minute Walk Distance; 6MWT: Six-Minute Walk Test; ARDS: Acute Respiratory Distress Syndrome; COPD: Chronic Obstruction Pulmonary Disease; GOLD: Global initiative for chronic Obstructive Lung Disease; HFNC: High Flow Nasal Cannula; HR: Heart Rate; HVNI: High Velocity Nasal insufflation; IQR: Interquartile range; IRB: Institutional Review Board; NIPPV: Non-Invasive Positive Pressure Ventilation; NIV: Non-Invasive Ventilation; PAP: Positive Airway Pressure; QOL: Quality Of Life; RPE: Rated Perceived Exertion; RPD: Rated Perceived Dyspnea; RR: Respiratory Rate; SOC: Standard of Care; SpO_2: Oxygen Saturation Percentage; TAU: Treatment As Usual; VAS: Visual Analog Scale; VTU: Vapotherm Transfer Unit; WOB: Work Of Breathing

Clinical Trial Registrations

Clinical Govt. ID: NCT03885726

Introduction

Chronic obstructive pulmonary disease (COPD) patients have pathology that compromises lung function. Many patients with COPD suffer from hypoxemia, deconditioning and peripheral muscle dysfunction [1]. Immobility and reduced ambulation has been shown to generally cause deconditioning and reduced muscle mass, exercise performance and quality of life, periods as short as two weeks [2-4]. Inactivity among COPD patients has been shown to progress exercise intolerance and muscle depletion [5], with desaturations of 4% during 6MWD may predict long-term mortality [6].

COPD patients may often receive supplemental oxygen *via* low-flow nasal cannula, which emits dry and cool air at rates up to 6 L/min, with associated complaints of nasal dryness, crusting and epistaxis [7]. Non-invasive positive pressure ventilation (NIPPV) during ambulation has been shown to facilitate breathing and promote exercise, with reduced Dyspnea and improved exercise performance [8]. NIPPV has been shown to increase exercise tolerance and reduce exercise desaturation episodes, thereby improving pulmonary rehabilitation [9]. However, current NIPPV systems, those that have tight-fitting masks that provide pressure, are deemed unsuitable for ambulatory care practices [10,11]. This study aims to demonstrate the feasibility of High Velocity Nasal Insufflation (HVNI; a form of non-invasive ventilation [NIV] that augments breathing), in contrast to standard site care practices, when employed in concert to all-comer Dyspneic patients during ambulatory practices. HVNI during ergometry of COPD patients demonstrated

***Corresponding author:** Leonithas I Volakis, Department of Science and Innovation, Vapotherm Inc, Exeter, NH, USA, Tel: +1 603 658 0629; E-mail: lvolakis@vtherm.com

Received September 10, 2019; **Accepted** September 24, 2019; **Published** October 01, 2019

Citation: Siler TM, Patel SC, Amin PK, Hamon L, DeBellis RJ, et al. (2019) Assessing the Clinical Effect of High Velocity Nasal Insufflation on Improving Ambulation in Patients with Dyspnea: A Feasibility Study. J Clin Respir Dis Care 5: 141.

improved arterial oxygenation, reduced respiratory rate and mean arterial pressure and increasing exercise duration. Analogous to NIV, the HVNI therapy mechanisms of action may equally play a role in exercise tolerance improvement when patients are provided HVNI therapy. HVNI flow translates into a high velocity flush of the anatomical respiratory dead space of the upper airways [12]. Clinical effects are direct improvement of ventilation and oxygenation, thus improving efficiency and reducing the work of breathing. In doing so, the optimally conditioned heated and humidified gas of HVNI can lessen the metabolic demand on patients [13].

In a trial comparing NIPPV to HVNI among adult patients presenting with undifferentiated respiratory failure in the Emergency Department, HVNI was non-inferior to NIPPV in management of respiratory distress [14]. Further, a recent follow-on sub-group analysis of ADHF demonstrated HVNI may be non-inferior to NIPPV in patients with respiratory failure secondary to ADHF that do not need emergent intubation [15]. Patient mobilization prevents muscle deconditioning and atrophies [16], which may be amenable to management including ambulation with HVNI therapy. NIPPV has demonstrated improved exercise tolerance in compromised COPD patients with objective data using per cent predicted FEV1 [16-18]. The benefit of NIPPV is that it provides ventilation in addition to simple oxygenation. HVNI is non-inferior to NIPPV leading to the trial hypothesis that HVNI therapy, when implemented in conjunction to ambulatory practices in all-comers, will be more effective than treatment as usual (TAU) to improve patient mobility by reducing the patient's perceived Dyspnea and exertion *via* maintaining oxygenation (reduced desaturation) and supporting ventilation (reduced work of breathing [WOB]).

Materials and Methods

Study design and setting

This was a feasibility study (N=32 enrolled, N=28 completed both study arms, N=25 after post hoc exclusion), with the objective of evaluating the feasibility of using HVNI during ambulation. During this trial, HVNI was evaluated for ability to improve patient ambulation relative to treatment as usual (TAU), by use of a provocation exercise paradigm (ambulation). The exercise model was designed as a conservatively-modified ambulation exercise exposure, similar to a 6-minute walk test (6MWT) model, without a maximum exercise duration. The modified model was designed such that: (1) the exercise matched clinical application at the study sites, (2) reduced the ceiling effect for patient exercise time and (3) allowed for feasible patient improvements beyond 6-minute time-limits. The study was performed as a prospective, crossover trial. Each patient served as their own control, comparing the difference in TAU vs HVNI therapy performance outcomes. The trial was conducted at three sites across the Midwest and Mid-Atlantic United States, including two non-academic inpatient medical centres and one pulmonary outpatient clinic facility. Clinical management of the patients was independent of the study interventions and conducted per individual site provider.

The study was approved by a centralized institutional review board (Advarra IRB) and waivers for expedited review were granted from site specific IRB's, per site requirements. The institutional review boards accepted the study as minimal risk, as it was implemented in conjunction with normal site standard of care. Patients were either mobile, or the sites expected patient ambulation at time of study participation, per the inclusion and exclusion criteria. Data for patients was collected and compiled at each site. This feasibility study was registered at Clinical trials govt. ID: NCT03885726.

Study participants

Subjects were identified and recruited by the study investigators and appropriately trained staff. The feasibility study took place in a clinical setting (e.g. hospital, out-patient facility). To maintain patient safety, all testing was performed with appropriate supervision and staff training. Initial contact was made by study investigators, after which participants decided whether to enroll/participate. Compensation was provided only for patients enrolled at the outpatient facility, to compensate for travel expenses and time during the study. No compensation was provided for participants enrolled as inpatients in the two hospitals.

Criteria for inclusion were: (1) adults over the age of 18 years old, with demonstrated respiratory distress upon mild to moderate exertion (e.g. Dyspnea upon standing, walking etc.) and (2) being a candidate for clinical ambulation/mobilization. Outpatients were considered for the trial if they met GOLD 4 or GOLD 3 criteria for COPD, with significant Dyspnea on exertion and with or without supplemental oxygen therapy [19]. At the outpatient site, to maintain patient safety and per site clinician consult, a limit of 18 minutes was set for any ambulation test.

Exclusion criteria were: (1) hypoxemia at resting baseline with SpO_2<88% with supplemental oxygen, (2) inability to provide informed consent, (3) pregnancy, (4) known contraindication to ambulation per site standard of care (SOC) practice, (5) inadequate respiratory drive or any known contraindications to HVNI (must be spontaneous breathing patient), (6) inability to use nasal cannula and HVNI therapy, (7) agitation or uncooperativeness, and (8) determined by the attending clinician to be sufficiently unstable or unsuitable for the study.

Study procedures

The study was designed to be implemented in conjunction with normal patient clinical management procedures. Subjects were identified and recruited by study investigators and appropriately trained designees. Screened patients only had to meet inclusion criteria, broadly designed for patients that experienced Dyspnea upon mild/moderate exertion. All relevant patient events were tracked for the duration of the study, and if any events were due to testing, it was noted. All pharmaceutical and medical treatment remained the purview of the attending physician and was administered per site standards.

Equipment used in the study for the experimental test arm (HVNI) was property of and provided by the study sponsor (Vapotherm Inc, Exeter, NH, USA). Equipment operation was conducted at each study by trained site personnel who participated in the study. Precision Flow Plus provided the therapy, and the Vapotherm Transfer Unit (VTU, Figure 1) provided an all-inclusive mobile transfer platform for the Precision Flow Plus. The VTU is a product consisting of a mobile stand for the Precision Flow Plus, which includes a rechargeable medical grade battery, a pressure manifold, and auxiliary storage for oxygen and air E-cylinders. The PF unit provides the heated humidified medical grade oxygen and air at high velocity to patients.

Per institutional practice, patient ambulation in an inpatient setting was prescribed by a physician order for a 6MWT or ambulation. Patients who met study criteria were identified for consent. If consent was received, the patient's initial ambulation test served as TAU for this study. During the TAU arm of the test, patients were fitted with appropriate monitoring devices as well as supplemental oxygen delivered *via* nasal cannula (NC) as is considered usual treatment for this activity. The oxygen flow rate varied from room air to titration of a SpO_2 >88%, as determined by pulse oximetry.

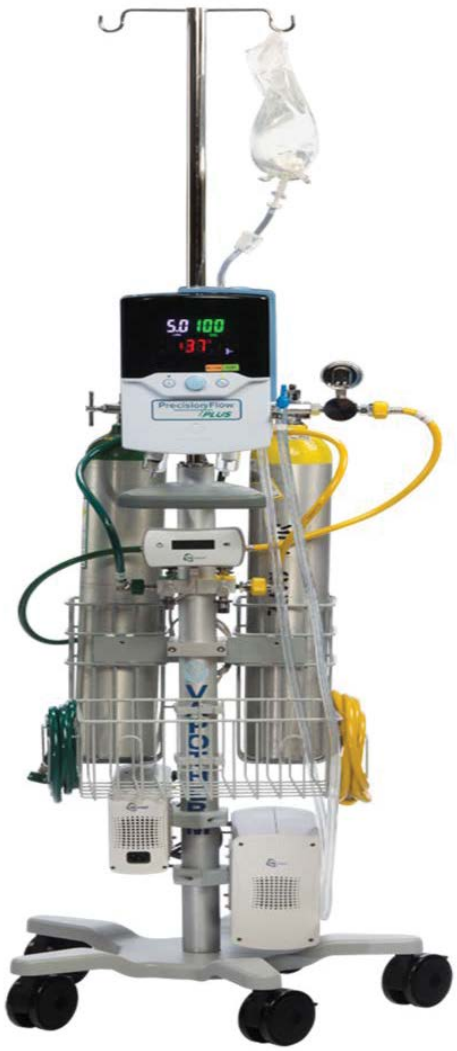

Figure 1: Vapotherm transfer unit.

For outpatients screened and enrolled in the study, the subjects travelled to the study site, underwent a detailed history and physical exam and upon consent were set up in the same manner as the inpatients. The walk time in the outpatients was limited to 18 minutes, since many outpatients were medically well-managed GOLD 3 or 4 patients with Dyspnea, who ambulated at home and were able to come to the clinic under their own power.

As the study commenced, the clinical management of the patient remained unchanged. Subjects wore appropriate gear for walking and, when applicable, had therapy-specific mobile carts to provide supplemental oxygen therapy (e.g. HVNI VTU, oxygen cylinder, etc.) during ambulation. The patient device's FiO_2 and/or flow values were recorded while on any supplemental oxygen. Breaks (per standard 6MWT procedures) were monitored for each study arm. Breaks longer than 10 seconds were deemed ambulation stop.

The TAU period was administered first, followed by an adequate rest period, as determined by measured objective parameters and time, proceeded by the HVNI study period. Both study periods commenced under the same procedure. The appropriate monitoring devices and oxygen *via* NC were set as above in the TAU arm to ensure SpO_2>88%.

In the HVNI arm, all of the same procedures were followed, as previously discussed, with the difference that patients were connected and allowed to acclimate to Vapotherm's VTU for a period of 5-10 minutes instead of using standard oxygen. Subjects were fit with Vapotherm adult NC applied by a healthcare practitioner conducting the study. The initial flow rate was 35 L/min with a FiO_2 of 1.0 and temperature between 35-37°C. The FiO_2 was rapidly adjusted to no greater than 0.6 to maintain a SpO_2>88%. In addition, the flow rate was adjusted down in many cases to rates <35 L/min, as tolerated. If subjects found the temperature of the medical grade vapor produced to be high, the temperature was adjusted to no less than 33°C a temperature that in some cases provided greater comfort without compromising adequate humidification.

Study outcomes and measures

The study objective was to demonstrate the feasibility of using HVNI *via* the VTU to support increased mobility *via* patient ambulation when compared to TAU with oxygen. The primary outcome of this study was exercise performance, defined as the distance and duration of patient ambulation. From distance and duration, a comparative average rate of speed was calculated between the two trial arms of each patient. The secondary outcomes evaluated the patient physiological data (heart rate [HR], respiratory rate [RR], blood pressure [BP], pulse oxygen saturation [SpO_2], rating of perceived exertion [RPE] and rating of perceived Dyspnea [RPD]) and the patient recovery interval, defined as the recovery time (return time to baseline perceived Dyspnea following ambulation). A tertiary outcome evaluated clinician perception scores for each arm of the study. The clinician perception evaluation included five metrics: frequency of technical/clinical difficulties (Never to Frequent), patient comfort & tolerance (Excellent to Insufficient), simplicity of setup and use (Simple to Complex), support/adjustment required for therapy (Minimal to Frequent) and expected/perceived patient response to therapy (Excellent to Insufficient), on a continuous 100 mm Visual Analog Scale (VAS). In instances of patients using room air during control study arm, the VAS did not include a score in all five metrics. For the VAS data, 3 mm was deemed the margin of error in this measurement.

Statistical analysis

The planned enrolment size of N=32 patients (N=26 estimated with 20% fallout rate) was selected for this feasibility study using a desired power of 90% with α=0.05, such that the sample size would show a difference between TAU and HVNI groups, wherein post hoc exclusion criteria only excluded patients that reached maximum 18 minute walk duration safety endpoint in both study arms, thereby artificially truncating data and hindering reliable comparison. Statistical analysis plan and study outcomes were examined, approved, and deemed appropriate by an independent statistician. The statistical analysis was presented with findings reported as median values with interquartile ranges (median [IQR]) and range (min, max) unless otherwise annotated. Categorical variables are presented as proportion of subjects in each category. The analyzed data is described in two forms: inpatient data and outpatient data. Statistical significance was not reported as this is a feasibility study. Analyses were performed using Minitab (v18.1, Minitab Inc, PA, USA) and Sigma Plot (v14.0, Systat Software, San Jose, CA).

Results

Characteristics of study subjects

The patient characteristics include data for analyzed subjects in

both the inpatient and outpatient groups. See Table 1 for a summary of all reported patient characteristics. Each patient provided their own comparison between TAU and HVNI. Of the total study enrolment N=32 only N=28 completed both study arms and N=25 were analysed after post hoc exclusion (Figure 2, CONSORT diagram), 16 acute care inpatients performed ambulation, and 9 outpatients were Gold 3 or 4 COPD who reportedly suffered from Dyspnea coming to an outpatient facility to perform ambulation exercise.

Table 1 shows differences in patient age and weight between inpatients (lower age) and outpatients (lower weight). No differences were noted (Table 1) between the subjects' baseline physiologic parameters (HR, RR, BP, SpO_2, RPE [Borg], RPD [Borg]) before the TAU and HVNI walk tests. In all cases the patients continued prescribed medications for indicated diagnoses. All inpatients and outpatients suffered from symptoms of Dyspnea, and most patients had diagnoses of COPD (N=10 inpatient, N=9 outpatient).

In only two instances of inpatient data did the records indicate a prior mobility assessment during the hospital stay. For inpatients at walk test start, the median FiO_2 in Control group was 2 L/min oxygen (or 28%), and median FiO_2 of HVNI group was 30%. For inpatients at walk test stop, the median FiO_2 in Control group was 2 L/min oxygen (or 28%), and median FiO_2 of HVNI group was 30%. For outpatients at walk test start, the median FiO_2 in Control group was 0 L/min oxygen (or 21%), and median FiO_2 of HVNI group was 21%. For outpatients at walk test stop, the median FiO_2 in Control group was 2 L/min oxygen (or 28%), and median FiO_2 of HVNI group was 33%.

Performance and recovery study outcomes

Table 2 describes both the inpatient and outpatient data of each of the performance and recovery metrics. For the inpatient data, the time to recovery was substantially shorter in HVNI (191.5 [172 – 395.5] sec) than in TAU (283.5 [232 – 462.3] sec). The inpatient data demonstrated a positive trend for HVNI, with an 8.5% increase in walk duration, 12.4% increase in distance walked, 32.5% decrease in recovery time, and speed of the walk was 7.1% faster in the HVNI arm which was second test completed for each patient during the trial. The outpatient data demonstrated a negative trend for the HVNI data; 18.6% decrease

Patient Demographics			**Inpatient**				**Outpatient**			
			N	**Median (IQR)**		**[Range]**	**N**	**Median (IQR)**		**[Range]**
Age (year)			16	66	(58-68.3)	[48-83]	9	72	(63-75)	[61-77]
Height (m)			16	1.65	(1.6-1.8)	[1.52-1.85]	9	1.65	(1.6-1.7)	[1.56-1.91]
Weight (kg)			16	107.1	(90-118.8)	[38.5-149.7]	9	73.9	(57.1-83)	[38-107.1]
Patient Characteristics			**Inpatient**				**Outpatient**			
			N		**No. (%)**		**N**		**No. (%)**	
Gender			16		-		9		-	
	Female		9		56.3		3		33.3	
	Male		7		43.7		6		66.6	
Long Term Oxygen Therapy User			16		-		9		-	
	Yes		5		31.3		6		66.6	
Positive Airway Pressure User			16		-		9		-	
	Yes		3		18.8		3		33.3	
Diagnosis			16		-		9		-	
	COPD		10		62.5		9		100	
	Dyspnea		16		100		9		100	
Baseline Characteristics		**Arm**	**Inpatient**				**Outpatient**			
			N	**Median (IQR)**		**[Range]**	**N**	**Median (IQR)**		**[Range]**
Heart Rate (bpm)		TAU	16	101	(88.3-108.3)	[71-112]	9	81	(72-89)	[61-93]
		HVNI	16	94	(89.8-103.5)	[54-120]	9	79	(75-82)	[70-97]
Respiratory Rate (brpm)		TAU	16	20	(17.5-20)	[16-24]	9	20	(18-20)	[14-24]
		HVNI	16	18	(17.5-20)	[12-26]	9	20	(18-20)	[18-24]
SpO_2 (%)		TAU	16	95	(93-97.3)	[91-100]	9	95	(94-95)	[91-97]
		HVNI	16	95	(93-98)	[90-100]	9	95	(93-97)	[92-98]
Systolic Blood Pressure (mmHg)		TAU	16	125.5	(119.8-152.5)	[103-190]	9	129	(120-132)	[95-142]
		HVNI	16	137	(114.8-141.5)	[106-159]	9	113	(110-120)	[99-141]
Diastolic Blood Pressure (mmHg)		TAU	16	82	(69-88)	[44-117]	9	69	(63-71)	[60-80]
		HVNI	16	79	(68.5-85.5)	[52-109]	9	70	(68-72)	[56-90]
Rated Perceived Exertion (Borg)†		TAU	16	1.5	(0-3)	[0-7]	9	0	(0-0.5)	[0-3]
		HVNI	16	0.5	(0-1.25)	[0-4]	9	0.5	(0-0.5)	[0-2]
Rated Perceived Dyspnea (Borg)†		TAU	16	0.5	(0-2)	[0-3]	9	0	(0-0.5)	[0-0.5]
		HVNI	16	0.75	(0-1)	[0-2]	9	0	(0-0)	[0-0.5]

HVNI: High Velocity Nasal Insufflation; TAU: Treatment as Usual.
† The modified Borg score is a self-reported rating of perceived dyspnea on a scale of 0 to 10.
Data is reported for inpatient and outpatient groups, as number (%) or median (IQR) and range (min-max) for each category.

Table 1: Characteristics of study subjects.

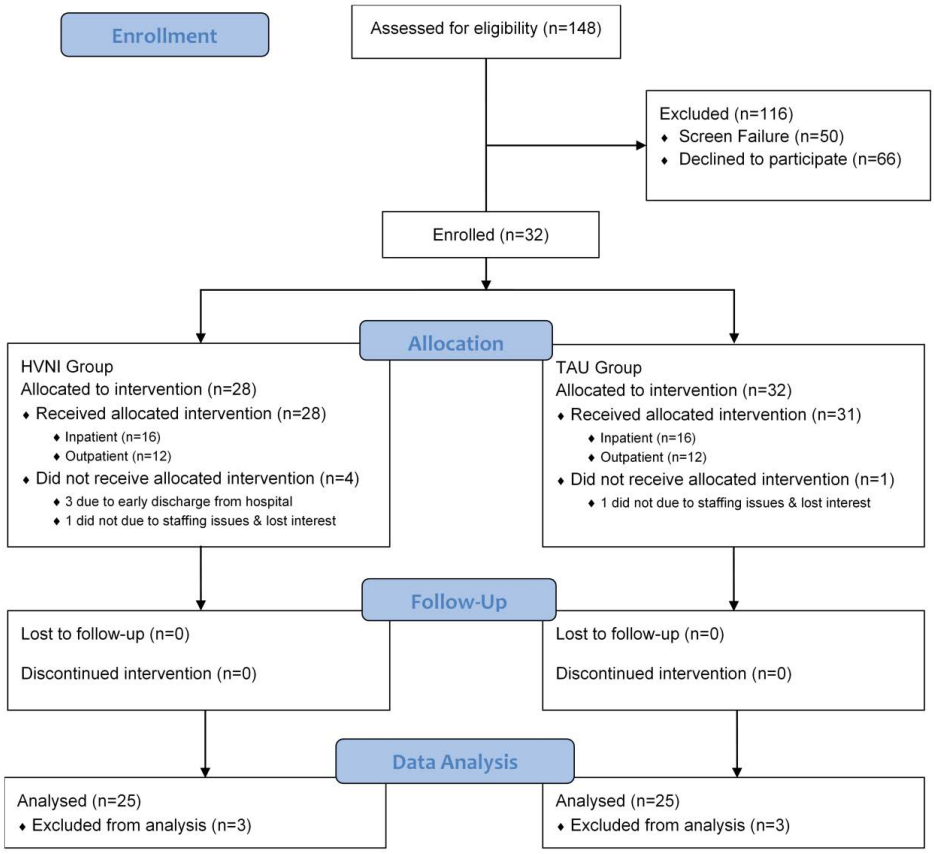

Figure 2: Study CONSORT diagram. High Velocity Nasal Insufflation; TAU: Treatment as Usual (Control).

	TAU			HVNI		
	N	**Median (IQR)**	**[Range]**	**N**	**Median (IQR)**	**[Range]**
Inpatient						
Duration of Walk (s)	16	211.5	(139.5-376.5) [45-575]	16	229.5 164.3-387)	[95-580]
Distance of Walk (m)	16	78.8	(63-144.1) [3.38-281.7]	16	88.6 75.3-172.6)	[6.1-358.8]
Speed of Walk (m/s)	16	0.402	(0.27-0.46) [0.07-0.72]	16	0.43 0.32-0.59)	[0.06-0.86]
Time to Recovery (s)	16	283.5	(232-462.3) [207-631]	16	191.5 172-395.5)	[122-795]
Outpatient						
Duration of Walk (s)	9	307	(192.5-452.5) [105-985]	9	250 180-537)	[131-1080]
Distance of Walk (m)	9	182.9	(134.1-453.4) [42.3-912.9]	9	165.2 136.9-455.2)	[55.7-1176.5]
Speed of Walk (m/s)	9	0.75	(0.6-0.94) [0.4-1.06]	9	0.69 0.62-0.88)	[0.42-1.09]
Time to Recovery (s)	9	239	(143-330) [108-424]	9	245 135.5-359.5)	[99-506]

HVNI: High Velocity Nasal Insufflation; TAU: Treatment as Usual (Control).
Data is presented as inpatient and outpatient data. Data is reported as median (IQR) and range (min-max) for each category.

Table 2: Ambulation performance and recovery outcomes.

in walk duration, 9.66% decrease in walk distance, 2.5% increase in recovery time, and 7.7% slower speed as compared to TAU.

Figure 3 demonstrates plots of the walk distance *vs.* walk duration behaviours of both the outpatient data (Figure 3, left) and the inpatient data (Figure 3, right). The best correlation was a power trend line for the presented data in Table 2. After solving for "x," it was determined that the outpatient data intersected at 64.04 seconds and inpatient data intersected at 186.08 seconds. Figure 3 trend lines demonstrate that patient walking speed may be equivalent before each intersection time point. However, after each intersection time point, the speed increases in the inpatient HVNI data and is not increasing in the outpatient HVNI data.

Physiologic outcomes of study subjects

The physiologic outcomes of this study were analysed for all completed datasets (N=25), then presented as both inpatient and outpatient data. This is available in the Supplementary Information Table. Breaks (per standard 6MWT procedures) for each study arm were

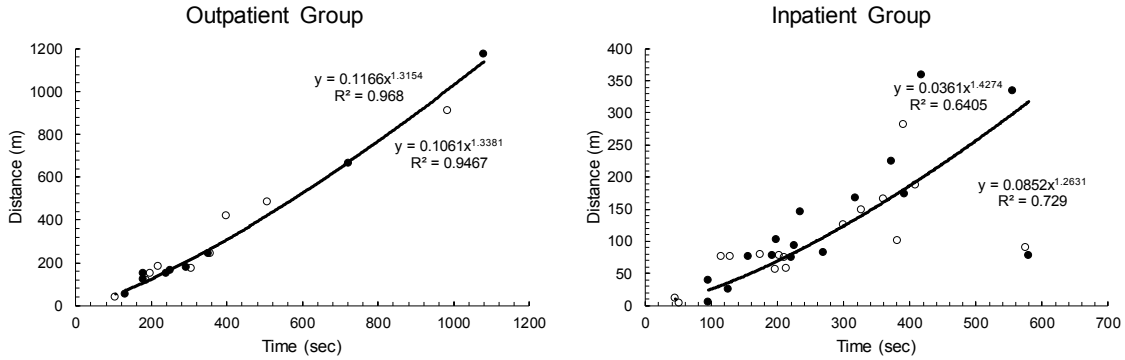

Figure 3: Performance and recovery outcomes. (Left) Outpatient (n=9) only data presented. (Right) Inpatient (n=16) only data presented. TAU: Solid Fill & dotted power trendline. HVNI: Open Fill & dashed power trendline.

similar between inpatient and outpatient groups, wherein ambulation stopped after any 10 second breaks. Assessment of HVNI & TAU study arms at comparable time points in the physiologic parameters suggested some advantage for HVNI. For the inpatient data: (1) the median systolic BP at walk test stop was 7.5 mm Hg higher in HVNI than in TAU, and (2) the diastolic BP at walk test stop was 5 mm Hg higher in HVNI than in TAU. For the outpatient data: (1) the RPD range for both TAU and HVNI study arms trended to be smaller in outpatients versus inpatients and (2) the systolic BP trended to 19 mmHg lower in HVNI than in TAU at walk test stop.

Clinician perception scores of study subjects

The clinician assessment scores evaluated the tertiary study outcomes (Table 3). Figure 4 demonstrates the differences between HVNI and TAU, where the more negative the value in the difference values denoted improved outcome for HVNI, and conversely for the TAU study arm. Figure 4 and Table 3 present the data as the inpatient and outpatient groups.

Of note, the inpatient group demonstrated a favourable patient respiratory response and patient comfort/tolerance in HVNI over TAU. Conversely, the outpatient group noted an opposite trend, denoting less technical difficulties in TAU.

Study and subject notations

There was one recorded protocol deviation in an outpatient. The patient had been receiving 1 L/min oxygen *via* nasal cannula at night for 10 years. The patient started TAU on room air and was titrated up to 3 L/min of oxygen during the TAU arm as RPE increased. The patient stopped the TAU test for shortness of breath. After rest, per protocol, the subject was cleared for HVNI arm and acclimated to a flow of 35 L/min with an FiO_2 of 21% at 35°C. Upon beginning the walk, the patient desaturated (SpO_2 95 to 87%) within the first minute. The flow continued at 35 L/min as the O_2 was titrated upward, 25% to 33%, to raise the patient from a low SpO_2 of 83% to 94%. The subject stopped the test complaining of dizziness. The dizziness correlated with desaturation as recorded by SpO_2 upon review of clinical report form.

Discussion

This pilot study demonstrated that the application of ambulatory HVNI during inpatient and outpatient mobilization/ambulation is

VAS Characteristic	TAU				HVNI			
	N	Median (IQR)		[Range]	N	Median (IQR)		[Range]
Patient Respiratory Response								
Inpatient	16	44.5	(3.38-69.5)	[0-98]	16	8.25	(1.13-61.5)	[0-97.5]
Outpatient	9	9	(3-49.5)	[0-51]	9	37.5	(15-58.5)	[0-86.5]
Technical & Clinical Difficulties								
Inpatient	13	1.5	(1-4.5)	[0-48]	16	1.5	(0.5-6.38)	[0-65]
Outpatient	9	1	(0-2.5)	[0-3]	9	3	(0.5-17.5)	[0-92.5]
Patient Comfort/Tolerance								
Inpatient	16	33.8	(1.75-69.3)	[0-82]	16	4	(1.25-17.1)	[0-68]
Outpatient	9	1	(0-20.5)	[0-68]	9	19	(8.5-82)	[1-93.5]
Simplicity of Setup/Use								
Inpatient	13	1	(0.25-2.25)	[0-6.5]	16	1	(0.5-2.75)	[0-12.5]
Outpatient	9	1.5	(0-2.5)	[0-3]	9	2	(0.75-3)	[0-50]
Monitoring Required								
Inpatient	13	2	(0.25-11.3)	[0-100]	16	2	(0.5-20.3)	[0-88.5]
Outpatient	9	18.5	(1-33.8)	[0-63]	9	18.5	(0.5-48.3)	[0-73]

VAS: Visual Analog Scale; HVNI: High Velocity Nasal Insufflation; TAU: Treatment as Usual (Control). Data presented as continuous VAS scale from 0-100mm, such that a lower score signifies better score. Sample size may be variable due to TAU patients at room air. Data is reported as median (IQR) and range (min-max) for each category.

Table 3: Clinician assessment scores.

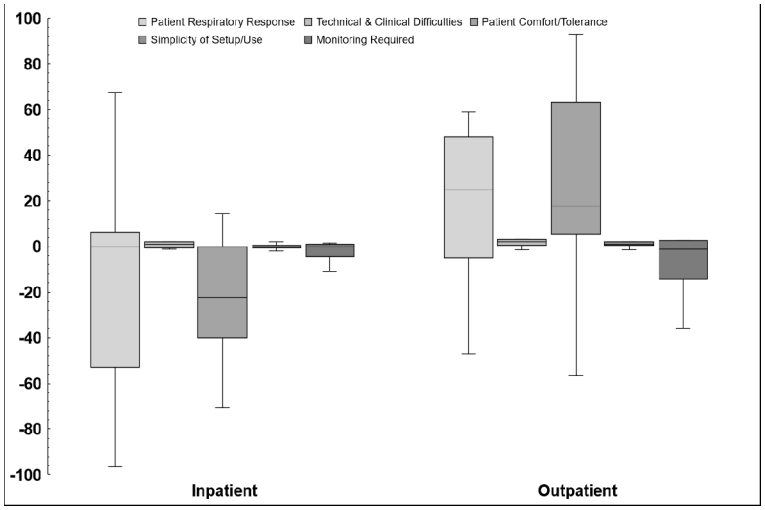

Figure 4: Difference in clinician assessment of study arms. Data presented as difference of a continuous VAS scale from 0-100mm, such that a lower score signifies better score for HVNI study arm. Difference shown is between [HVNI-TAU] for the inpatient (n=16) and outpatient (n=9) groups. Sample size may be variable between VAS scores due to TAU patients at room air.

feasible and may provide ventilatory advantage for inpatients during exercise. This study is different from prior studies by including a mask-free non-pressure-based form of NIV (i.e. HVNI) that augments ventilation. Past studies of respiratory support during ambulation/mobilization have looked at oxygen alone [6,18-20] demonstrating predictable improvement in oxygenation, or a combination of supplemental oxygen and NIPPV [10,11,21,22]. This study evaluated the effect of supplemental oxygen along with HVNI, shown to provide ventilatory support comparable to NIPPV among patients with respiratory distress [14], while employing a comfortable cannula-based interface. Unlike studies showing the benefit of using simple oxygen for oxygenation support preventing desaturation [10,17,22], this study adds to the body of knowledge by using HVNI [14], Both simple oxygen and NIPPV therapy modalities provide respiratory support to alleviate Dyspnea during ambulation, however, for the improved outcomes that NIPPV provides, NIPPV also generates challenges during ambulatory practice [8-11]. The study determined feasibility of HVNI efficacy against TAU during ambulation in both inpatient and outpatient settings. The data demonstrated improved exercise distance, duration, speed, and recovery duration among the inpatient group.

Separating the data into inpatient and outpatient groups was performed due to the fundamental differences in the presentation of the patients. Overall, the outpatient data represented a procedural test of the feasibility of the HVNI outside the acute care setting. Although the data set in this feasibility study for each arm is smaller than in the overall combined group, the time to recovery produced a 32.5% improvement over TAU. We believe this difference is consistent with the anticipated consequences from the mechanisms of action (MOA) of HVNI that provide ventilation in addition to the standard practice of oxygenation alone.

The potential mechanisms of action (MOA's) include: decreasing re-breathed CO_2 by functionally decreasing upper airway anatomic dead space; use of supra physiologic flow that generates high velocity *via* an open system at the nares, allowing for maximal dead space flush; delivery of optimally conditioned gas with physiologic heat and humidity that decreases work of breathing; and provision of modest distending pressure upon exhalation [13]. The MOA's contribute to optimizing each individual patients respiratory state. Moreover, in the inpatient group there was no difference in SpO_2 in either the TAU or HVNI group, which suggests that this inpatient population may have benefitted from optimization of the alveolar ventilation equation by optimizing dead space flush from HVNI therapy as opposed to inspired volume typically delivered by augmenting airway pressure provided by alternative devices that provide ventilation. Interestingly, when graphing distance versus duration, Figure 3 demonstrates that if the walk test duration is longer than 186.08 seconds in the inpatient population, this may suggest that this threshold provides a clear delineation where HVNI provides patients a greater walking speed when compared to TAU. This threshold may also be indicative of an optimal level of lung function where ambulation enhanced by HVNI may prove to be extremely beneficial in recovery. This identified tipping point suggests that HVNI may improve inpatient outcomes more than outpatient group outcomes. In addition, in inpatients prescribed ambulation, this value may provide insight into patients who may benefit from more rapid transition out of the inpatient setting. Further study should be sought in a randomized controlled fashion with endpoints that will statistically and clinically provide information to determine the overall benefit of this therapy in inpatients.

Of note were physiologic parameters relating to breathing, both measured and reported. The higher diastolic BP at walk test stop in HVNI may be due to increased exercise secondary to the presence of HVNI. Conversely, the systolic BP trended to 19 mmHg lower in HVNI at walk test stop, suggestive that patients not suffering from an acute respiratory episode requiring hospitalization may experiencing some sympathetic off-loading due to HVNI [23]. This feasibility study was not designed to take an in-depth look at BP and the relationship between exercise, breathing and any medications the patient may have been on to control blood pressure.

The RPE reported by the patients trended toward improvement with HVNI in both data groupings (inpatient and outpatient). Again, this may be due to a sensation that a patient's normal breathing is enhanced. This is perhaps because patients, while on HVNI, felt that they were able to push themselves during the test more than TAU due to a potential feeling of an enhanced ability to breathe normally.

This could have resulted from either/or a physiologic change from the mechanism of action, namely dead space flush by HVNI and/or a psychological perception advantage from using an alternative technology. Additionally, the optimal heat and humidity that is consistently maintained through the HVNI independent of flow rate and its effect to decrease the work of breathing may have played into the perception. The RPE findings may be consistent with the objective measurement of RR, which trended toward being higher in the HVNI population at walk test end in both groups throughout the study. This could be linked to the fact that duration and distance were both increased in the trial, thus providing an appropriate level of exercise for an individual patient compromised state with a natural compensatory increase in RR.

Excluding the RPE findings previously discussed, overall the outpatient group produced the opposite trend with HVNI demonstrating decreases in distance walked, walk duration, recovery time, walk speed. The outpatients who were selected fell into GOLD 3 or 4 COPD criteria for Dyspnea and were not as physiologically limited at baseline as the inpatients, thus the extra equipment during the HVNI arm of the test may have been more cumbersome and inhibited their progress. In addition, the Gold 3 and 4 patients were extremely well managed and ambulatory upon arriving in the clinic. Data to support this point may be drawn from the VAS results in the outpatient group where the scores were skewed more negatively towards the HVNI arm. This only further illustrates that there are other factors in play with this outpatient group of COPD patients such as the potential for inadequate energy supply to respiratory muscles, locomotor muscles and lower limb muscles as well as varying degrees of dynamic hyperinflation [24]. In this patient population who are not acutely ill, a patient undergoing exercise may be able to activate/recruit additional alveoli for gas exchange in this setting as pulmonary blood flow increased [25,26]. The findings from this feasibility study lend credence to the fact that additional studies are needed to differentiate outpatients with poor baseline gas exchange as opposed to using an inclusion criterion of GOLD 3 or 4 that is consistent with severe or very severe obstruction in order to potentially realize an ambulation benefit from HVNI in this population.

Overall, a greater benefit occurred in inpatients over outpatients, specific to patient therapy response and patient comfort. Of note was that adjustment of therapy trended less towards the HVNI arm of the study. These results were not replicated in the outpatient arm of the trial. Still, this is a feasibility study attempting to determine next step with a small sample split between both inpatients and outpatients. Objectively, the RPE trended favourably for HVNI in the outpatient group suggesting that patients either felt better or other physiologic factors such as unpredictable alveolar perfusion as well as the fact that they may not have been comfortable with the equipment and constraints of the trial.

In the clinician assessment scores in Table 3, a difference was similarly demonstrated between inpatient and outpatient population. For both patient respiratory response and patient comfort and tolerance, there was a noticeable trend toward HVNI in both VAS categories that was consistent with prior HVNI trials [12,27,28]. There were two cases, one inpatient and one outpatient that exemplified the VAS scores. The inpatient was a severely obese female who nearly doubled her walking distance between TAU 3.4 m and HVNI 6.2 m, nearly doubled her walk time from 51 seconds to 95 seconds, and improved her recovery time by nearly 1 minute (433 *vs.* 486 seconds) on HVNI over TAU. A female outpatient similarly nearly tripled her walk distance (422.2 m *vs.* 1176.5 m), nearly tripled her walk time (398 seconds *vs.* 1080 seconds), however her recovery time (174 seconds *vs.* 245 seconds) was 1.4x higher during HVNI due to significantly greater walk performance over TAU. The exemplified VAS scores in both groupings warrant further investigation to determine if these are outliers, or there are true physiological and/or psychological factors that are optimized in these patients with HVNI therapy.

Limitations of this feasibility pilot study stemmed largely from the small sample size in each group, which may have limited the realization of significance in identified trends. The study allowed for open-ended disease enrollment, without a specific focus on COPD or respiratory primary diagnoses alone. The purpose was for patients that are Dyspneic during provocation exercise, no matter the underlying diagnosis. This was a feasibility study only. A larger future study would be designed to accommodate appropriate conclusions instead of the feasibility of HVNI/VTU use during ambulation. The study did not randomize the order of the administration of the two arms – this was due to the feasibility nature of the trial, providing an opportunity to qualify patients with sufficient impairment from which to evaluate the technology in the overall scope of patient ambulation. Further studies would require randomization. Medication was not monitored as was per normal patient treatment plan. Since this was a feasibility study we wanted to focus solely on the effect of the medical device. However, some medications may have influenced physiologic parameters, particularly HR and BP, to what extent was not accounted for in the trial. In this feasibility study planned to determine next steps, we did not feel that subjecting patients to blood gas draws were necessary as the principal investigators along with the investigational review board did not deem this necessary for patient safety.

In the outpatient setting, patients came into a clinic from home under their own effort which may have had some effect on patient energy expenditure, thereby influencing data in both the control and study arms. Also, in the outpatient group, there were two technical items identified. The first involved the wheels on the unit that contained the Vapotherm Transfer Unit (VTU). The health care professional pushing the VTU stepped on the locking mechanism on the wheel on occasion making the device difficult to roll. This may have slowed the pace momentarily on some patients or at minimum disturbed the patient momentum. The second technical item was similarly identified in the outpatient group and involved swapping air tanks mid-test since no wall air/O_2 existed in the outpatient clinic. While the outpatient setting wall air and O_2 availability represented a technical limitation, it is important to note that testing progressed largely unhindered and at no point during the trial were patients compromised

Conclusion

This feasibility study demonstrated that the use of ambulatory HVNI is both technically feasible and potentially clinically beneficial by improving patient exercise performance and recovery measures. The use of HVNI, particularly for support of acute inpatient ambulation requiring attendant oxygenation/ ventilator support is not only possible but may provide selective advantage. In the outpatient setting patients with disease that adversely affects gas exchange as opposed to severity of obstruction may also benefit from HVNI. These findings must be verified in larger properly-powered studies, with greater specificity and more rigorous patient selection and measures of oxygenation and ventilation.

Funding

The study was sponsored by Vapotherm, Inc., Exeter, NH, USA.

Acknowledgments

From the study data collection, the authors would like to acknowledge the following: Emily Johnson, Jessica Hanshaw, Rebecca Brigham, Macie Christian, Krista Haggard, Camalia Woods, Virginia Barch, Christian Mitchell, Alisha Arthur, Sheila McCaffity, Deborah Reed, Jamie Mills, Jamie Orf, Mitchell Champagne, and Manya Harsch (statistician).

Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: All authors attest to meeting the four ICMJE authorship criteria. Dr. Siler reports receiving study related support from Vapotherm, and consulting support for work on study design. Dr. Patel's and Dr. Amin's Institutions received study related support from Vapotherm. Dr. Volakis, Prof. Dungan, and Dr. DeBellis were employed by Vapotherm. The study was sponsored by Vapotherm, which participated in study design and management of each study site. The study sponsor, Vapotherm agreed to publish findings with the principal investigators. The study sponsor provided the study equipment necessary for the study. All analyses and results interpretations were reviewed and approved by an independent statistician. Authors worked in concert to write the first draft, and all authors approved edits to subsequent drafts of article and made the decision to submit for publication.

References

1. Gallagher CG (1990) Exercise and chronic obstructive pulmonary disease. Med Clin North Am 74: 619-641.
2. Suetta C, Hvid LG, Justesen L, Christensen U, Neergaard K, et al. (2009) Effects of aging on human skeletal muscle after immobilization and retraining. J Appl Physiol 107: 1172-1180.
3. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ, et al. (2007) Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 297: 1772-1774.
4. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, et al. (2014) Physical complications in acute lung injury survivors: A two-year longitudinal prospective study. Crit Care Med 42: 849-859.
5. Waschki B, Kirsten AM, Holz O, Mueller KC, Schaper M, et al. (2015) Disease progression and changes in physical activity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 192: 295-306.
6. Casanova C, Cote C, Marin JM, Pinto-Plata V, de Torres JP, et al. (2008) Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. Chest 134: 746-752.
7. Chatila W, Nugent T, Vance G, Gaughan J, Criner GJ, et al. (2004) The effects of high-flow vs low-flow oxygen on exercise in advanced obstructive airways disease. Chest 126: 1108-1115.
8. Porszasz J, Cao R, Morishige R, van Eykern LA, Stenzler A, et al. (2013) Physiologic effects of an ambulatory ventilation system in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 188: 334-342.
9. Corner E, Garrod R (2010) Does the addition of non-invasive ventilation during pulmonary rehabilitation in patients with chronic obstructive pulmonary disease augment patient outcome in exercise tolerance? A literature review. Physiother Res Int 15: 5-15.
10. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, et al. (2007) Pulmonary rehabilitation: Joint accp/aacvpr evidence-based clinical practice guidelines. Chest 131: 4S-42S.
11. Dyer F, Flude L, Bazari F, Jolley C, Englebretsen C, et al. (2011) Non-invasive ventilation (niv) as an aid to rehabilitation in acute respiratory disease. BMC Pulmonary Medicine 11: 58.
12. 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.
13. Dysart K, Miller TL, Wolfson MR, Shaffer TH (2009) Research in high flow therapy: Mechanisms of action. Respiratory Medicine 103: 1400-1405.
14. Doshi P, Whittle JS, Bublewicz M, Kearney J, Ashe T, et al. (2018) High-velocity nasal insufflation in the treatment of respiratory failure: A randomized clinical trial. Ann Emerg Med 72: 73-83.e75.
15. Haywood ST, Whittle JS, Volakis LI, Dungan G 2nd, Bublewicz M, et al. (2019) Hvni vs nippv in the treatment of acute decompensated heart failure: Subgroup analysis of a multi-center trial in the ED. Am J Emerg Med.
16. Brower RG (2009) Consequences of bed rest. Crit Care Med 37: 422-428.
17. Walker ML, Austin AG, Banke GM, Foxx SR, Gaetano L, et al. (2007) Reference group data for the functional gait assessment. Phys Ther 87: 1468-1477.
18. Andrianopoulos V, Franssen FM, Peeters JP, Ubachs TJ, Bukari H, et al. (2014) Exercise-induced oxygen desaturation in COPD patients without resting hypoxemia. Respir Physiol Neurobiol 190: 40-46.
19. Mirza S, Clay RD, Koslow MA, Scanlon PD (2018) COPD guidelines: A review of the 2018 gold report. Mayo Clin Proc 93: 1488-1502.
20. Vainshelboim B, Kramer MR, Izhakian S, Lima RM, Oliveira J, et al. (2016) Physical activity and exertional desaturation are associated with mortality in idiopathic pulmonary fibrosis. J Clin Med 5: 73.
21. Menadue C, Alison JA, Piper AJ, Flunt D, Ellis ER, et al. (2010) Bilevel ventilation during exercise in acute on chronic respiratory failure: A preliminary study. Respir Med 104: 219-227.
22. Ameer F, Carson KV, Usmani ZA, Smith BJ (2014) Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest. Cochrane Database Syst ReV 6:CD000238.
23. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, et al. (2017) Organ dysfunction, injury and failure in acute heart failure: From pathophysiology to diagnosis and management. A review on behalf of the acute heart failure committee of the heart failure association (HFA) of the European society of cardiology (ESC). Eur J Heart Fail 19: 821-836.
24. Aliverti A, Macklem PT (2008) The major limitation to exercise performance in copd is inadequate energy supply to the respiratory and locomotor muscles. J Appl Physiol 105: 758-762.
25. Borghi-Silva A, Oliveira CC, Carrascosa C, Maia J, Berton DC, et al. (2008) Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD. Thorax 63: 910-915.
26. Behnia M, Wheatley CM, Avolio A, Johnson BD (2017) Alveolar-capillary reserve during exercise in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis12: 3115-3122.
27. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G, et al. (2009) Children with respiratory distress treated with high-flow nasal cannula. J Intensive Care Med 24: 323-328.
28. Biselli PJ, Kirkness JP, Grote L, Fricke K, Schwartz AR, et al. (2017) Nasal high-flow therapy reduces work of breathing compared with oxygen during sleep in COPD and smoking controls: A prospective observational study. J Applied Physiol 122: 82-88.