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ORIGINAL ARTICLE

High-velocity nasal insufflation versus noninvasive positive pressure ventilation for moderate acute exacerbation of chronic obstructive pulmonary disease in the emergency department: A randomized clinical trial

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Abstract

Background: Acute exacerbations of chronic obstructive pulmonary disease (COPD) in the emergency department (ED) involve dyspnea, cough, and chest discomfort; frequent exacerbations are associated with increased mortality and reduced quality of life. Noninvasive positive pressure ventilation (NiPPV) is commonly used to help relieve symptoms but is limited due to patient intolerance. We aimed to determine whether high-velocity nasal insufflation (HVNI) is noninferior to NiPPV in relieving dyspnea within 4 h in ED patients with acute hypercapnic respiratory failure.

Methods: This randomized control trial was conducted in seven EDs in the United States. Symptomatic patients with suspected COPD, partial pressure of carbon dioxide (pCO_2) ≥ 60 mm Hg, and venous pH 7.0–7.35 were randomized to receive HVNI ($n = 36$) or NiPPV ($n = 32$). The primary outcome was dyspnea severity 4 h after the initiation of study intervention, as measured by the Borg score. Secondary outcomes included vital signs, oxygen saturation, venous pCO_2, venous pH, patient discomfort level, and need for endotracheal intubation.

Results: Sixty-eight patients were randomized between November 5, 2020, and May 10, 2023 (mean age 65.6 years; 47% women). The initial pCO_2 was 77.7 ± 13.6 mm Hg versus 76.5 ± 13.6 mm Hg and the initial venous pH was 7.27 ± 0.063 versus 7.27 ± 0.043 in the HVNI and NiPPV groups, respectively. Dyspnea was similar in the HVNI and NiPPV groups at baseline (dyspnea scale score 5.4 ± 2.93 and 5.6 ± 2.41)

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and HVNI was noninferior to NiPPV at the following time points: 30 min (3.97 ± 2.82 and 4.54 ± 1.65, $p = 0.006$), 60 min (3.09 ± 2.70 and 4.07 ± 1.77, $p < 0.001$), and 4 h (3.17 ± 2.59 and 3.34 ± 2.04, $p = 0.03$). At 4 h, there was no difference between the groups in the pCO_2 mm Hg (68.76 and 67.29, $p = 0.63$). Patients reported better overall comfort levels in the HVNI group at 30 min, 60 min, and 4 h ($p = 0.003$).

Conclusions: In participants with symptomatic COPD, HVNI was noninferior to NiPPV in relieving dyspnea 4 h after therapy initiation. HVNI may be a reasonable treatment option for some patients experiencing moderate acute exacerbations of COPD in the ED.

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) contribute to 600,000–1,500,000 emergency department (ED) visits and 140,000 deaths annually in the United States.[1,2] The annual economic burden of the condition is approximately $50 billion.[3,4] COPD represents a collection of respiratory diseases that result in airflow obstruction and breathing difficulties, including emphysema and chronic bronchitis. Acute exacerbations of COPD are distinct episodes of symptom exacerbation that involve dyspnea, cough, and chest discomfort. These episodes are typically associated with increased airway inflammation, mucus hypersecretion, and gas trapping.[5] Frequent COPD exacerbations are associated with increased mortality, reduced quality of life, and a higher likelihood of lung function decline.[1,4]

The standard treatment for acute exacerbations of COPD in the ED includes oxygen therapy in the presence of hypoxia, inhalational bronchodilators, and corticosteroids.[6] For patients with persistent respiratory distress, hypoxemia, or respiratory acidosis, noninvasive positive pressure ventilation (NiPPV) is used to assist with respiration.[7] BiPAP ventilation significantly improves patient comfort, respiratory parameters, and oxygenation, while reducing the need for intubation in patients with respiratory failure and COPD.[8-10] However, its use is limited by patient discomfort, risk of aspiration due to vomiting, difficulty in administering concomitant oral medication, inability to create a seal on the face due to the anatomy or facial hair, and concerns about pulmonary barotrauma.[11] Some patients require sedation to minimize the adverse effects of NiPPV.[12,13] Therefore, an effective alternative is highly desirable for managing acute exacerbations of COPD in some patients.

One potential alternative for ventilatory support is high-velocity nasal insufflation (HVNI), which provides warm humidified oxygenated air to the nares at a higher rate than possible with a standard nasal cannula. Because HVNI provides pressurized, warmed, and humidified oxygen via a less constrictive nasal cannula, HVNI may be a more tolerable alternative to NiPPV and may not require sedation.[14,15] Other potential benefits of HVNI over NiPPV include ease in speech, possibility of clearing secretions through coughing, consumption of food, and use of oral and inhaled medications.[16] The ability to address sputum production with suctioning and deliver bronchodilator medication has been demonstrated in clinical practice.[17] The European Respiratory Society (ERS) recommends NIPPV over HVNI in patients with COPD and acute hypercapnic respiratory failure; however, this recommendation was made considering the insufficient evidence confirming a clinically significant benefit of HVNI. Currently, ERS does suggest a conditional recommendation of utilizing HVNI prior to NiPPV due to HVNI's higher tolerability for patients and recommends HVNI over conventional oxygen therapy during NIPPV breaks for COPD patients. Therefore, additional investigation of HVNI in COPD and hypercapnic respiratory failure is necessary to elucidate the clinical benefits or harms of HVNI in this patient population to justify increased usage during COPD exacerbation events.[18]

The ability of HVNI to improve oxygenation especially during the COVID-19 pandemic led to widespread availability of the technology over the past several years.[19] A recent multicenter randomized clinical trial demonstrated the noninferiority of HVNI to NiPPV in the treatment of undifferentiated respiratory distress in patients presenting to the ED.[20] However, it is unknown whether HVNI is a reasonable alternative to NiPPV to improve ventilation and to reduce dyspnea in patients with acute exacerbation of COPD with hypercapnia. There exists clinical equipoise that HVNI may be an effective alternative treatment option for these patients.[11] Therefore, we conducted a multicenter randomized clinical trial to evaluate whether HVNI is noninferior to NiPPV in reducing dyspnea within 4 h in ED patients with acute exacerbations of COPD.

METHODS

Study design

This prospective, multicenter, noninferiority, randomized controlled clinical trial was conducted to assess whether HVNI is noninferior to NiPPV in relieving dyspnea primarily within 4 h in ED patients with acute exacerbation of COPD. Seven EDs in geographically diverse U.S.-based hospital groups, which included three community hospitals, three academic hospitals, and one military hospital (eTable S1). Study was approved by a central institutional review board (IRB)

Sterling IRB. After randomization in the ED, patients were assigned to treatment, either with HVNI or with NiPPV and assessed at baseline, 30 min, 60 min, and 4 h. All other care was provided at the discretion of the treating team.

Participants

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) a known history of COPD or high clinical suspicion for COPD, based on a history of smoking or secondhand smoke exposure, and prior history of wheezing, chronic cough, bronchospasm, or hypercapnia; (3) partial pressure of carbon dioxide (pCO_2) equal or greater than 60 mm Hg on blood gas analysis; and (4) serum pH between 7.0 and 7.35 on venous blood gas analysis. The exclusion criteria were as follows: (1) need for immediate endotracheal intubation; (2) presence of respiratory or cardiac arrest; (3) dyspnea that was more likely due to any alternative cause such as congestive heart failure, pneumonia, neurologic dysfunction, or toxicologic exposure; (4) a known intolerance to NiPPV or HVNI; (5) determination by the treating emergency physician that the patient is clinically unstable to participate; (6) altered mental status; or (7) a known or suspected pregnancy. Written or verbal consent was obtained before participation and randomization. In cases where verbal consent was initially provided, patients provided written consent once the symptoms improved to the point where they were able to provide written consent. Sex, race, and ethnicity were self-reported by participants.

Randomization

The study intervention was assigned using block randomization with a block size of four participants. Both interventions were implemented with standard initial settings and then titrated according to standard practice for optimal effect. Random allocation sequence was implemented via sealed envelopes at each site and envelopes were opened after the participant consent was given. Sequence was generated a priori by statistician who was not involved in enrollment.

Procedures

Hospital respiratory therapists who were not a part of the study initiated all the ventilatory regimens. The initial settings for HVNI (Vapotherm Inc.) included fraction of inspired oxygen (FiO_2) 0.50, flow 30 L/min, and temperature 37°C. The initial settings for NiPPV included FiO_2 0.50 and pressure settings of 10–12 cmH_2O in inspiration and 5–6 cmH_2O in expiration were chosen for a targeted tidal volumes of 6–8 mL/kg ideal body weight as a volume goal, with each center's standard humidification settings. The settings for both HVNI and NiPPV were titrated according to standard practice to determine the optimal effect. Details about changes in settings during titration and the final settings of each ventilatory support were recorded as part of study protocol. The treating clinician at each center decided on the need for intubation, specific medication treatment regimen, and final disposition per routine practice.

Outcome

The primary outcome was the degree of dyspnea at 4 h, measured using the modified Borg scale (Borg), a validated measure that is scored on a scale of 0 (no dyspnea) to 10 (unbearable dyspnea).[21-24] Secondary outcomes included (1) dyspnea at 30 and 60 min, (2) need for intubation, (3) change in heart rate, (4) change in respiratory rate, (5) change in oxygen saturation, (6) change in pCO_2, (7) change in pH, and (8) patient and physician perceptions of clinical stability and comfort.

Treatment failure was defined as follows: (1) failure to tolerate device, if the patient was unable to tolerate the mask, nasal prongs, air flow, or pressure, or had persisting asynchrony; (2) failure to oxygenate, if the modality was unable to sustain an oxygen saturation > 88% or partial pressure of oxygen > 60 mm Hg despite treatment with 100% FiO_2 and optimal manipulations of flow rate and airway pressures; (3) failure to ventilate, if patients remain acutely hypercapnic and acidemic with lack of reduction in pCO_2 or improvement in pH despite optimal settings per institutional standard; or (4) deteriorating medical status correlating with worsening venous blood gas levels related to respiratory distress, which is manifested as worsening mental status or hemodynamics, which is in turn manifested as hypotension (systolic blood pressure < 90 mm Hg), unremitting tachycardia (>140 beats/min or an increase by >20% during therapy), or other conditions as determined by the treating physician.

Perception of comfort by the participant was measured on a continuous 10-point Visual Analog Scale (VAS), with responses ranging from insufficient to excellent. Finally, we asked the clinicians three questions: (1) "How satisfied were you with the degree of respiratory support that this patient received since presenting and enrolling in the study?" (2) "How satisfied were you with the degree of comfort and tolerance exhibited by this patient with the received therapy since presentation and enrollment in the study?" (3) "During the study procedures, what degree of challenge did you find setting up and using/adjusting the device providing therapy to this patient?"

Outcomes were chosen to match those used in prior NIPPV efficacy studies. The rationality for choosing a noninferiority design is that NIPPV is an established treatment modality; however, it is associated with patient discomfort and delayed relief while HVNI is generally perceived to be more comfortable for patients. Demonstrating that HVNI is equivalent to controlling dyspnea would suffice to establish it as a more desirable treatment option. The noninferiority margin of 1.0 was selected based on clinical experience with the dyspnea score and a review of literature. While there are no equivalent prior studies used to establish a minimally significant difference, in a study of ED patients with acute heart failure, a similar change was used as the minimal clinically important difference for improvement in dyspnea over 6 h.[25]

Statistical analysis

This trial was designed to randomize participants in a 1:1 ratio into the HVNI and NiPPV arms to assess the hypothesis that HVNI is noninferior to NiPPV in providing relief from moderate-to-severe hypercapnic dyspnea within 4 h of ED presentation. A sample size of 64 (approximately 32 per arm) was calculated to attain a one-sided alpha of 0.025 in providing at least 80% power to demonstrate noninferiority. This sample size assumed a difference of 0.9 between treatment and control arms with standard deviations (SDs) of 2.4 and 2.9 for the treatment and control arms, respectively, and a noninferiority margin of 1.0. The minimal clinically significant difference in Borg is reported as 1.0.

Planned data analyses were based both on "per protocol" and on "intention-to-treat" models. The baseline patient demographics and characteristics were summarized and compared. Group data were compared for equality, inequality of variance, and nonnormality. Continuous variables were presented as means and compared between groups using appropriate independent group *t*-tests after assessing for equality of variance. Discrete or categorical variables were presented as proportions and compared between groups using the chi-square test. The mean differences between the groups in secondary outcome variables were also assessed after adjustment for baseline measures. To do this the analysis of covariance (ANCOVA) model was used for continuous data. Similarly, the logistic regression model with adjustment for baseline scores was used to compare noncontinuous proportion data between group where appropriate. Additional statistical testing done after the noninferiority testing to test whether the treatment was not just inferior, but actually superior to the control. Noninferiority analyses were performed using the *t*-test with a special feature of the Statgraphics (ver. 19) software. IBM SPSS Statistics for Windows Version 27 (IBM Corp.) was also used. A minimum significance interval of 0.05 was used for all comparison tests.[26,27]

Role of the funding source

The funders assisted in the design of the study, but had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

RESULTS

From November 5, 2020, to May 10, 2023, a total of 404 patients were assessed for eligibility, of whom 73 patients were consented and randomized. Five patients were excluded postrandomization prior to receiving treatment for a variety of reasons (Figure 1). Among randomized participants who received allocated study treatment, 36 participants were in the HVNI group and 32 were in the NiPPV group (Figure 1). Five participants were identified by the study investigators to be excluded from the summaries and were not included because of screening failures or attrition (eTable S1).

The groups were matched adequately according to sex, age, race, and comorbidities (Table 1). Baseline laboratory results and vital signs were matched adequately between the groups. The average baseline pH was 7.27 in both groups. The average baseline pCO_2 values were 77.7 mm Hg and 76.5 mm Hg and the average Borg scores were 5.4 and 5.6 in the HVNI and NiPPV groups, respectively (Table 1). The proportion of patients who received additional medications and other respiratory therapies was similar between the two groups (eTable S1). We observed low rates of COVID-19–positive patients with one patient testing positive in each group. When analyzing for our primary outcome, the modified Borg scale scores at 4 h in the HVNI group were noninferior to those in the NiPPV group (3.17 ± 2.59 vs. 3.34 ± 2.04, $p = 0.03$; Table 2). Noninferiority was also observed at 60 and 30 min (Table 2). In addition, noninferiority was observed for venous pCO_2 levels and pH (Figure 2A,B). A significantly higher proportion (0.41 vs. 0.08, $p = 0.01$) of patients in the HVNI group attained minimal dyspnea in 60 min than of those in the NIPPV group (Figure 2C).

Patients in the HVNI group reported less discomfort than those in the NiPPV group (Figure 2D). No patients in either group were intubated; however, more patients in the HVNI group were admitted to the intensive care unit (ICU; 0.38 vs. 0.27, $p = 0.42$). Four patients in the HVNI group were discharged directly from the ED, whereas none in the NiPPV group were discharged. (Table 3) Additionally, no adverse events were reported, and no significant difference was seen in tolerability between the devices (0.11 vs. 0.19, $p = 0.38$; Table 2).

Finally, the patient and clinician acceptability scores were similar between the two groups (Table 4). There were no significant differences in the clinicians' ratings for patient stability, outcomes, comfort, or ease of use. On a VAS of 0 to 100, where lower scores represented greater comfort, patients described HVNI as having greater comfort than NiPPV (20.13 vs. 43.25, $p = 0.003$). Post hoc ANCOVAs and logistic regression analyses showed results similar to those above.

DISCUSSION

In this randomized clinical trial that included 68 adult patients in the ED with respiratory distress due to acute exacerbation of COPD, patients treated with HVNI had a dyspnea score of 3.17, while patients treated with NiPPV had a dyspnea score of 3.34 after 4 h of treatment, indicating a noninferior difference ($p = 0.03$). This finding correlated with other measures of respiratory distress, such as intubation rates, changes in respiratory rate, and changes in pCO_2 and pH. Despite there being no significant improvement seen in the patients treated with HVNI, we similarly did not see a significant advantage with NiPPV when comparing measures of respiratory distress. All values for respiratory distress, such as intubation

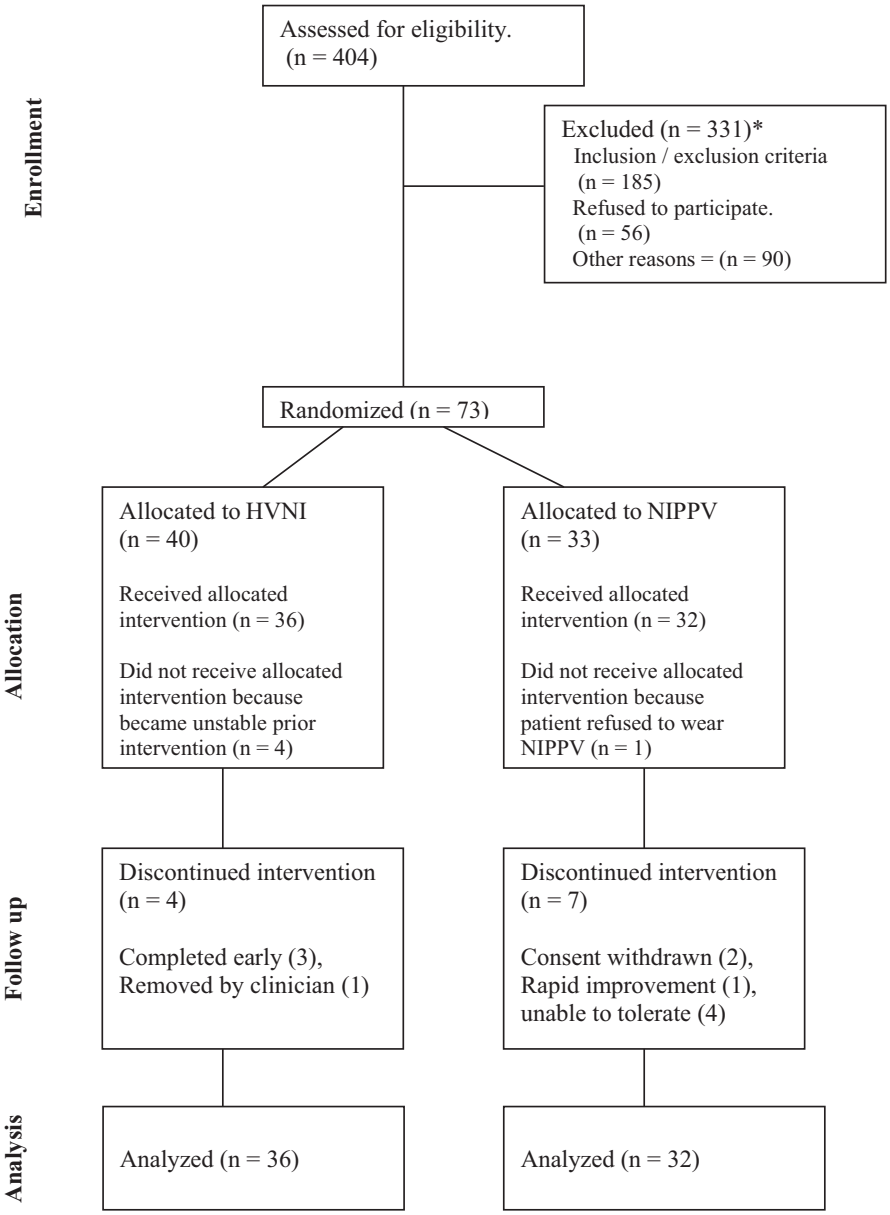

FIGURE 1 CONSORT diagram showing the flow of participants. *Reasons for exclusion ($n = 185$): CHF without COPD ($n = 96$), pneumonia without COPD ($n = 23$), non–English-speaking ($n = 22$), major medical complications including active cancer ($n = 11$), DVT/PE ($n = 8$), AMS/unable to consent ($n = 8$), respiratory or cardiac arrest prior to enrollment ($n = 5$), seizure ($n = 3$), renal failure ($n = 3$), pulmonary hypertension ($n = 3$), metabolic derangement ($n = 2$), anaphylaxis ($n = 1$), patient declined study and/or refused care ($n = 56$). Other reasons ($n = 90$): no respiratory support needed ($n = 37$), no research staff available ($n = 34$), treated prior to randomizing ($n = 12$), clinician declined to agree to enrollment ($n = 3$), police custody ($n = 2$), inability to draw blood ($n = 1$), previously enrolled ($n = 1$). AMS, altered mental status; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; HVNI, high-velocity nasal insufflation; NIPPV, noninvasive positive pressure ventilation; PE, pulmonary embolism.

rates and changes in pCO_2 and pH, were all not statistically different between the two treatment groups. Since the findings of this study suggest that HVNI is noninferior to NiPPV in relieving dyspnea within 4 h in COPD patients presenting to the ED primarily with uncomplicated acute hypercapnia, we believe these findings warrant further investigation into the usage of HVNI in patients with acute COPD exacerbation.

NiPPV has long been recommended for ED management of patients with COPD who show respiratory acidosis or hypoxia. The use of NiPPV has increased since its introduction in the 1980s and has contributed to a reduced overall mortality from acute exacerbations of COPD.[28] Early management with NIPPV is associated with reduced need for endotracheal intubation as well as reduced mortality for COPD patients.[7] However, an alternative to NiPPV is required because between 5% and 30% of patients with hypercapnic COPD do not tolerate NiPPV.[29,30]

Multiple physiological studies have assessed the effectiveness of HVNI or a similar technology known as high-flow nasal insufflation.[20,31] The use of HVNI has shown physiological improvements in respiratory rate and pCO_2.[20,31,32] In general, the physiological benefits of HVNI appear to be due to its ability to wash out the anatomical dead space and generate positive end-expiratory pressure.[33] Although HVNI has been found to be effective in improving gas exchange and reducing the work of breathing, its ability to address hypercapnic respiratory distress is controversial.[34-41]

HVNI has a well-established role in improving oxygenation for infectious causes of respiratory distress but its role in improving ventilation for COPD is unclear. In our study population, we had low rates of COVID-19 infections. The small proportion of COVID-19 patients in each treatment arm alleviates a concern that these patients had a combination of hypercapnic respiratory failure from COPD exacerbation and hypoxemic respiratory failure from severe COVID-19.

TABLE 1 Baseline characteristics of randomized patients.

	HVNI ($n=36$)	NiPPV ($n=32$)	p-value
Female	0.44 (16/36)	0.50 (16/32)	0.81
Age (years), mean ± SD	63.8 ± 11.18	67.7 ± 9.44	0.12
Black	0.58 (21/36)	0.63 (20/32)	0.72
Body mass index (kg/m^2), mean ± SD	29.3 ± 9.23	28.3 ± 9.58	0.64
Chronic heart failure	0.22 (8/36)	0.16 (5/32)	0.55
Hypertension	0.47 (17/36)	0.44 (14/32)	0.81
Diabetes	0.11 (4/36)	0.22 (7/32)	0.33
Obstructive sleep apnea	0.14 (5/36)	0.16 (5/32)	1.00
Coronary artery disease	0.11 (4/36)	0.06 (2/32)	0.68
COVID-19 positive	0.03 (1/36)	0.03 (1/32)	0.94
Chronic cough	0.37 (13/35)	0.42 (13/31)	0.80
Smoker	0.66 (23/35)	0.78 (25/32)	0.29
Long-term oxygen therapy	0.66 (21/32)	0.47 (14/30)	0.20
Sodium (mEq/L)	139.9 ± 3.5	140.4 ± 3.1	0.54
Potassium (mEq/L)	4.4 ± 0.63	4.4 ± 0.66	0.94
Chloride (mmol/L)	97.7 ± 6.4	99.9 ± 5.3	0.13
Bicarbonate (mEq/L)	33.0 ± 5.20 (33/36)	33.8 ± 6.60	0.60
Blood urea nitrogen (mg/dL)	17.6 ± 10.68	20.5 ± 15.85	0.38
Creatinine (mg/dL)	1.0 ± 0.44	1.0 ± 0.59	0.83
Glucose (mg/dL)	133.8 ± 54.83	137.2 ± 40.03	0.84
Lactate (mmol/L)	1.6 ± 1.25	1.2 ± 0.84	0.24
Temperature (°C)	36.6 ± 0.41	36.7 ± 0.41	0.49
Heart rate (beats/min)	93.2 ± 17.37	85.9 ± 16.58	0.08
Systolic blood pressure (mm Hg)	141.4 ± 21.33	138.8 ± 26.32	0.66
Respiratory rate (breaths/min)	20.9 ± 5.00	21.2 ± 6.09	0.81
Oxygen saturation (%)	94.4 ± 7.42	96.8 ± 3.37	0.11
Venous pH	7.27 ± 0.063	7.27 ± 0.043	0.86
pCO_2 (mm Hg)	77.8 ± 13.6	76.5 ± 13.6	0.69
Base excess	6.7 ± 4.79	7.7 ± 5.56	0.67
Severe hypercapnia ($pCO_2 > 70$)	66.7% (24/36)	56.2% (18/32)	0.47
Partial pressure of oxygen (mm Hg)	43.5 ± 17.0 (35/36)	41.4 ± 16.4 (29/32)	0.61
Glasgow coma scale score < 14	2.8% (1/36)	6.5% (2/31)	0.59
Patient stability index	62.0 ± 28.00	62.5 ± 23.09	0.93
Dyspnea scale score (0–10)	5.4 ± 2.93	5.6 ± 2.41	0.83
Proportion with dyspnea score < 2 baseline	0.13 ± 0.34 (32)	0.10 ± 0.27 (26)	0.56
Patient reported discomfort (0–100)	34.8 ± 24.81	38.5 ± 22.19	0.11

Abbreviations: HVNI, high-velocity nasal insufflation; NIPPV, noninvasive positive pressure ventilation; pCO_2, partial pressure of carbon dioxide.

Asthma, chronic heart failure, chronic atelectasis.

While we described our patient population as having "mild to moderate" COPD exacerbation due to the low rates of intubation at 48 h, this description contrasts with other definitions of severity. Both the European Respiratory Society and the American Thoracic Society describe acute exacerbations of COPD as "severe" if the patient has respiratory acidosis.[5,42] In addition, hypercapnia is traditionally defined as mild if $pCO_2 \leq 50$ mm Hg, moderate if 55–70 mm Hg, and severe if ≥70 mm Hg. All participants had hypercapnic respiratory acidosis >60 mm Hg as an inclusion criterion, with one pCO_2 having a level of 120 mm Hg.

This study lends more evidence to the expanding role of HVNI in respiratory conditions. This work builds off prior clinical studies

TABLE 2 Outcome scores for patients that tolerated treatment.

	HVNI ($n=36$)	NiPPV ($n=32$)	Mean difference p-value	Mean difference	SE	95% upper CI (one-sided)	Noninferiority p-value
Dyspnea scale score at 30 min (mean)	3.97 ± 2.82 (32)	4.54 ± 1.65 (26)	0.37	−0.57	0.59	0.43	0.0055[b]
Dyspnea at 60 min (mean)	3.09 ± 2.70 (32)	4.07 ± 1.77 (26)	0.12	−0.98	0.59	0.006	0.0007[b]
Dyspnea at 4 h (mean)	3.17 ± 2.59 (32)	3.34 ± 2.04 (25)	0.79	−0.17	0.61	0.86	0.0310[b]
				Mean diff	SE	95% C.L.	
Proportion with minimal dyspnea (<2), baseline	0.12 ± 0.34 (32)	0.08 ± 0.27 (26)	0.56	0.05	0.08	0.11, 0.21	
Proportion with minimal dyspnea (<2), 30 min	0.31 ± 0.47 (32)	0.08 ± 0.27 (26)	0.03[a]	0.23	0.10	0.04, 0.43	
Proportion with minimal dyspnea (<2), 60 min	0.41 ± 0.50 (32)	0.08 ± 0.27 (26)	0.004[a]	0.33	0.10	0.12, 0.54	
Proportion with dyspnea (<2), 4 h	0.41 ± 0.50 (32)	0.24 ± 0.44 (25)	0.193	0.17	0.12	−0.08, 0.41	
Other medical and laboratory outcome values							
pCO_2 at 4 h	68.76 (31)	67.29 (25)	0.63	1.47	4.70	−8.01 10.96	
pH at 4 h	7.31 (31)	7.31 (25)	0.50	0.00	0.01	−0.03, 0.03	
Respiratory rate at 4 h	20.97 (32)	20.92 (25)	0.37	0.05	1.47	−3.012, 3.11	
Heart rate at 4 h	91.22 (32)	82.40 (25)	0.72	8.82	4.40	−0.04, 17.68	
Intubated for 4 h	0.0 (0/32)	0.0 (0/26)	1.000	0.0	0	NA	
Admitted to the ICU	0.38 (12/32)	0.27 (7/26)	0.42	0.11	0.12	0.14, 0.35	

Abbreviations: C.L., confidence limit; HVNI, high-velocity nasal insufflation; ICU, intensive care unit; NiPPV, noninvasive positive pressure ventilation; pCO_2, partial pressure of carbon dioxide.

[a]HVNI had a significantly higher proportion by chi-square test, $p<0.05$.

[b]Significant noninferiority of HVNI using a margin more than one unit, t-test, $p<0.05$.

that have regarding the use of HVNI for nonspecific respiratory distress[35,43] and comparing HVNI to conventional oxygen therapy.[44,45] Observational studies have analyzed the sequential use of HVNI and NiPPV,[46,47] HVNI's role in preventing reintubation after extubating.[48,49] Most recently, in a study of 225 patients comparing HVNI to NiPPV for acute COPD patients who were admitted to the ICU, outcomes were not different during the first 48 h of care. However, intubation rates were higher in the HVNI group between Day 4 and Day 28 of ICU stay with no differences in hospital length of stay or 28-day mortality.[50]

Several prior studies have also shown results that cumulatively support the potential usage of HVNI in the treatment of acute exacerbations.[5,35,40,41,42] One study with 92 patients supported the use of HVNI for the acute management of COPD exacerbation.[51] In another study of 82 patients with COPD and moderate hypercarbia due to acute respiratory failure, compared to NiPPV, the use of HVNI led to fewer nursing interventions and skin breakdown episodes in the HVNI group.[52] Further, in a subgroup analysis of 65 patients with hypercapnic respiratory failure who randomized to HVNI or NiPPV groups, the impact on pCO_2, pH, intubation rate, and treatment failure rate was similar.[53] HVNI is also been shown effective in patients with mixed OSA and COPD.[52,54]

In this study, treatment was noninferior at secondary outcomes of 30 min and at 1 h. The longer 4-h time interval set as the primary outcome allowed the control group to catch up to the treatment group, but significant noninferiority was still detected. While lowering our significance level due to multiple comparisons, we continue to detect similar results and conclusions about the noninferiority of the treatment group for relieving dyspnea. Since all participants in this study who tolerated respiratory devices would be expected to eventually achieve minimal dyspnea, the study outcome was subject to "ceiling effects" at the longer time interval of 4 h. To avoid missing true differences between groups, a 5% error band was used. Since the treatment had the advantage of being more comfortable for the HVNI participants, we felt it was reasonable to adjust the significance level per guidelines that support a wider noninferiority margin for efficacy.[55]

LIMITATIONS

While the pragmatic nature of the trial can be viewed as a strength, this study has several limitations. First, the participants, providers, and assessors were not blinded to the treatment arms; however,

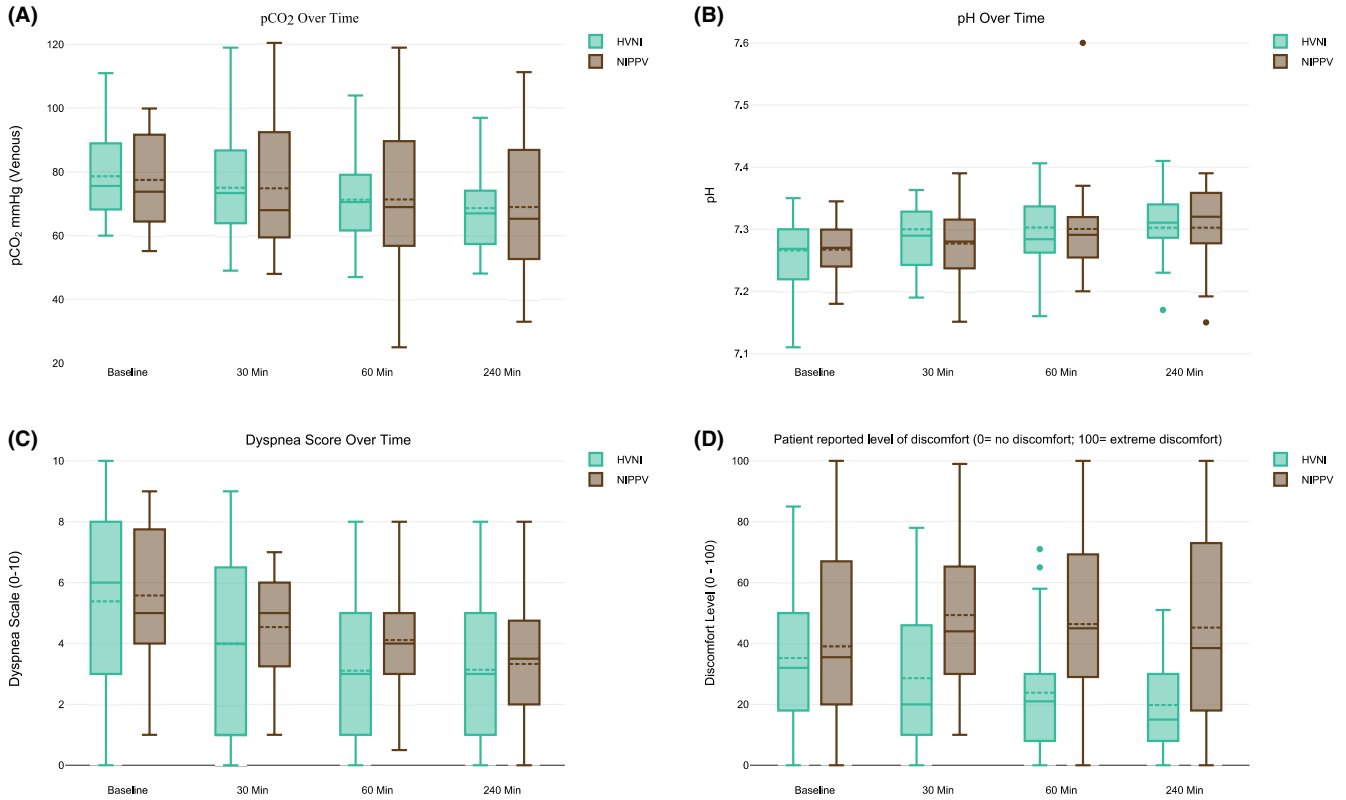

FIGURE 2 (A) pCO_2 over time. (B) pH over time. (C) Modified dyspnea score over time dyspnea scale. (D) Patient reported level of discomfort. HVNI, high-velocity nasal insufflation; NIPPV, noninvasive positive pressure ventilation; pCO_2, partial pressure of carbon dioxide.

TABLE 3 Proportion of all study patients who failed treatment by group.

	HVNI	NiPPV	*p*-value	Mean difference	SE	95% confidence limits
Failure to tolerate device	0.11 (4/36)	0.19 (6/32)	0.38	0.08	0.09	−0.25, 0.10
Discharge from the ED	0.11 (4/36)	0.0 (0/32)	0.04[a]	0.11	0.12	−0.014,0.35

Abbreviations: HVNI, high-velocity nasal insufflation; NiPPV, noninvasive positive pressure ventilation.

[a]Significant difference, chi square test, $p < 0.05$.

TABLE 4 Mean visual analog scale scores at 4 h according to group.

	HVNI			NiPPV			Mean difference	95% confidence limits	*p*-value
	Mean	*N*	SD	Mean	*N*	SD			
Clinicians' ratings from 0 to 100 (lower scores are better)									
Patient stability	82.28	32.00	17.69	82.00	25.00	19.37	0.28	−9.72, 10.28	0.79
Outcomes as expected	23.26	31.00	14.33	16.32	25.00	14.53	6.93	−0.85, 14.73	0.08
Patient comfort and tolerance	17.58	31.00	13.61	22.04	25.00	20.87	−4.46	−14.24, 5.32	0.34
Ease of use	16.45	31.00	16.25	15.08	25.00	18.68	1.37	−8.16, 10.90	0.77
Patient ratings from 0 to 100 (lower scores are better)									
Dyspnea relief	28.48	31.00	24.09	24.58	24.00	21.80	3.9	−8.55, 16.35	0.54
Comfort and tolerance	20.13	31.00	23.45	43.25	24.00	32.02	−23.12	−38.82, −7.41	0.003[a]

Abbreviations: HVNI, high-velocity nasal insufflation; NiPPV, noninvasive positive pressure ventilation.

[a]HVNI group: significantly better, $p < 0.05$, *t*-test.

participants did not know which group they would be assigned prior to consent, allocation, and enrollment. Second, patients typically presented with undifferentiated dyspnea presumed to be due to COPD; although, patients with respiratory distress due to mixed reasons may have been included as undifferentiated complaints are typical in the ED settings. Third, this study only enrolled patients who were not in imminent respiratory arrest and were able to provide at least initial verbal consent; therefore, caution should be exercised when extrapolating the results of this study to patients in extreme distress. Fourth, all patients in the study received standard care according to the treating physician and the respiratory therapist. As such, the protocol did not dictate exactly how the HFNC or NiPPV settings should be titrated nor specify the use of adjunct medication such as bronchodilators, antibiotics, and steroids. There is an inherent variability among individual clinicians regarding standard of care. Fifth, we used a subjective measure as a primary outcome, the degree of dyspnea. However, this subjective outcome was augmented by more quantitative measures such as pH and pCO_2. Finally, this study was initiated during the COVID-19 pandemic, which made enrollment, staffing, and clinical research challenging. While fewer patients completed the study than initially planned, reducing the overall power of the study, this did not significantly impact the study's findings, as we were still able to detect significant effects.

CONCLUSIONS

In conclusion, high-velocity nasal insufflation was noninferior to noninvasive positive pressure ventilation in reducing subjective dyspnea at 4 h in ED patients presenting with moderate acute exacerbation of chronic obstructive pulmonary disease. In addition, we found that patients treated with high-velocity nasal insufflation had similar pH and pCO_2 levels to noninvasive positive pressure ventilation–treated patients. Based on these data it is reasonable to use high-velocity nasal insufflation in patients with moderate chronic obstructive pulmonary disease exacerbations, especially when noninvasive positive pressure ventilation is not tolerated.

AUTHOR CONTRIBUTIONS

Study concept and design: Amy Bergeski, Jessica S. Whittle, George C. Dungan II, Richard Maisiak, Andrew C. Meltzer. Acquisition of the data: David P. Yamane, Christopher W. Jones, R. Gentry Wilkerson, Joshua J. Oliver, Soroush Shahamatdar, Aditya Loganathan, Taylor Bolden, Ryan Heidish, Connor L. Kelly, Andrew C. Meltzer. Analysis and interpretation of the data: David P. Yamane, Christopher W. Jones, R. Gentry Wilkerson, Joshua J. Oliver, Connor L. Kelly, Amy Bergeski, Jessica S. Whittle, George C. Dungan II, Richard Maisiak, Andrew C. Meltzer. Drafting of the manuscript: David P. Yamane, Christopher W. Jones, R. Gentry Wilkerson. Critical revision for intellectual content: David P. Yamane, Christopher W. Jones, R. Gentry Wilkerson, Joshua J. Oliver, Soroush Shahamatdar, Aditya Loganathan, Taylor Bolden, Ryan Heidish, Connor L. Kelly, Amy Bergeski, Jessica S. Whittle, George C. Dungan II, Richard Maisiak, Andrew C. Meltzer. Statistical expertise: Richard Maisiak. Acquisition of funding: David P. Yamane, Christopher W. Jones, R. Gentry Wilkerson, Joshua J. Oliver, Connor L. Kelly, Amy Bergeski, Jessica S. Whittle, George C. Dungan II, Richard Maisiak, Andrew C. Meltzer.

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Vapotherm, Inc., sponsored the study.

CONFLICT OF INTEREST STATEMENT

DY: Grant funding for research by Vapotherm; Received compensation for participating in Webinar sponsored by Vapotherm. CJ: Grant funding for research by Vapotherm. GW: Grant funding for research by Vapotherm. JO: Grant funding for research by Vapotherm. AB: Employee of Vapotherm. JW: Employee of Vapotherm. GD: Employee of Vapotherm. RM: Consultant with Vapotherm. CK: Grant funding for research by Vapotherm. AM: Grant funding for research by Vapotherm; Received compensation for participating in Webinar sponsored by Vapotherm. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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