High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial

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Study objective: We compare high-velocity nasal insufflation, a form of high-flow nasal cannula, with noninvasive positive-pressure ventilation in the treatment of undifferentiated respiratory failure with respect to therapy failure, as indicated by requirement for endotracheal intubation or cross over to the alternative therapy.

Methods: This was a multicenter, randomized trial of adults presenting to the emergency department (ED) with respiratory failure requiring noninvasive positive-pressure ventilation. Patients were randomly assigned to high-velocity nasal insufflation (initial flow 35 L/min; temperature 35°C (95°F) to 37°C (98.6°F); FiO_2 1.0) or noninvasive positive-pressure ventilation using an oronasal mask (inspiratory positive airway pressure 10 cm H_2O; expiratory positive airway pressure 5 cm H_2O). The primary outcome was therapy failure at 72 hours after enrollment. A subjective outcome of crossover was allowed as a risk mitigation to support deferment of informed consent. Noninferiority margins were set at 15 and 20 percentage points, respectively.

Results: A total of 204 patients were enrolled and included in the analysis, randomized to high-velocity nasal insufflation (104) and noninvasive positive-pressure ventilation (100). The intubation rate (high-velocity nasal insufflation=7%; noninvasive positive-pressure ventilation=13%; risk difference=−6%; 95% confidence interval −14% to 2%) and any failure of the assigned arm (high-velocity nasal insufflation=26%; noninvasive positive-pressure ventilation=17%; risk difference 9%; confidence interval −2% to 20%) at 72 hours met noninferiority. The effect on PCO_2 over time was similar in the entire study population and in patients with baseline hypercapnia. Vital signs and blood gas analyses improved similarly over time. The primary limitation was the technical inability to blind the clinical team.

Conclusion: High-velocity nasal insufflation is noninferior to noninvasive positive-pressure ventilation for the treatment of undifferentiated respiratory failure in adult patients presenting to the ED. [Ann Emerg Med. 2018;72:73-83.]

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INTRODUCTION

Background

Dyspnea and acute respiratory failure are among the top 5 reasons for patients to present to the emergency department (ED).[1] Tools available to emergency physicians for respiratory support include oxygen therapy, noninvasive positive-pressure ventilation, and mechanical ventilation. More recently, oxygen through a high-flow nasal cannula has been used to provide respiratory support as an escalation from simple oxygen therapy. In contrast to traditional nasal cannula therapy, a high-flow nasal cannula can deliver up to 100% oxygen by nasal cannula.[2,3] Additionally, it has been shown to induce a mild distending pressure[4] and improve ventilation efficiency by way of extrathoracic dead-space clearance.[5-7]

High-velocity nasal insufflation, a form of high-flow nasal cannula, focuses on optimum efficiency of the dead-space purge to augment ventilation (removal of carbon dioxide from the dead space between breaths), in addition to providing other effects of high-flow nasal cannula.[6,8] This is accomplished by use of small-bore nasal cannulae (typically 2.7-mm internal diameter for adult patients) to produce high velocity flow that is approximately 360% greater than that of the larger-bore cannulae used in previous studies. According to flow analyses[8] and clinical experience,[9] high-velocity nasal insufflation typically requires a flow of 25 to

Editor's Capsule Summary

What is already known on this topic

Noninvasive positive-pressure ventilation is an established emergency department (ED) treatment for patients requiring respiratory support. High-velocity nasal insufflation by nasal cannula might be easier to apply but is less studied.

What question this study addressed

This randomized, nonblinded, noninferiority trial compared high-velocity nasal insufflation with noninvasive positive-pressure ventilation in 204 ED patients with respiratory distress. Treatment failure was defined as intubation or crossover to alternate therapy.

What this study adds to our knowledge

High-velocity nasal insufflation had a treatment failure rate that was noninferior to that of noninvasive positive-pressure ventilation.

How this is relevant to clinical practice

High-velocity nasal insufflation may be a reasonable treatment option for select ED patients with respiratory distress.

35 L/min in adults to accomplish a complete purge of the extrathoracic anatomic reservoir between breaths.

Importance

The application of high-flow nasal cannula in the ED has not been well studied, and when it has, the focus has been on oxygen delivery.[10,11] Patients presenting to the ED with respiratory distress often require interventions before determination of the underlying pathology, and can be hypoxic, hypercapnic, or both. Conventionally, noninvasive positive-pressure ventilation is used in this setting because of its ability to support both type 1 (hypoxic) and type 2 (hypercapnic) respiratory failure, and has been well established for the treatment of chronic obstructive pulmonary disease and cardiogenic pulmonary edema.[12] Several trials have demonstrated high-flow nasal cannula to be efficacious as a means of supporting hypoxic patients who are not hypercarbic.[13-16] Experience[9] and preclinical data[6,8] suggest that high-velocity nasal insufflation may be effective in patients requiring ventilatory support as well. Therefore, it is important to assess whether high-velocity nasal insufflation can be used in the early management of respiratory distress patients in the same manner as noninvasive positive-pressure ventilation.

Goals of This Investigation

The goal of this study was to assess the ability of high-velocity nasal insufflation to support patients with undifferentiated respiratory failure in the ED who required ventilatory support. The hypothesis of this trial was that high-velocity nasal insufflation is noninferior to noninvasive positive-pressure ventilation in treatment of undifferentiated respiratory failure with respect to therapy failure, as indicated by the requirement for intubation or crossover to the alternate therapy.

MATERIALS AND METHODS

Study Design and Setting

This study was a prospective, multicenter, parallel-group, randomized controlled trial of 2 noninvasive ventilatory support modalities, high-velocity nasal insufflation and noninvasive positive-pressure ventilation, using a noninferiority model. The trial was conducted at 5 centers across the southeastern United States, 2 academic and 3 community centers (Table E1, available online at http://www.annemergmed.com). Clinical management independent of the study interventions was conducted according to standard care in each facility. All respiratory interventions were tracked for 72 hours after randomization; beyond 72 hours, patients requiring ventilatory support were reasoned to be in a long-term or progressive condition.

The study was approved by the institutional review board at each of the centers, and safety was monitored by an independent data and safety monitoring board. The nature of the study required a mitigation of risk owing to the state of duress at the point of randomization. Hence, the study design necessitated the a priori option to cross over to the alternate therapy (high-velocity nasal insufflation or noninvasive positive-pressure ventilation) at the request of the treating physician. Although escalation to intubation was the intended primary endpoint, a subjective crossover was treated as a failure of the assigned therapy if the patient was not in need of immediate intubation.

Data were collected by research teams at each site and placed in a database. Data management and analysis were performed by third-party data capture and management providers who were not the sponsor. The full trial protocol is included in Appendix E1, available online at http://www.annemergmed.com.

Selection of Participants

Patients presenting to the ED with respiratory compromise were screened for eligibility. Each site screened consecutive

patients during the study period according to the site-specific process that was based on available resources at the sites. For example, the primary site enrolled patients between 7 AM and 5 PM, whereas other sites enrolled patients during their peak volume times when others enrolled 24 hours a day. Patients were randomized to either high-velocity nasal insufflation or noninvasive positive-pressure ventilation therapy and enrolled if they met the inclusion criteria. If exclusion criteria were identified as laboratory or diagnostic results became available, the patient was withdrawn from the study. Patients assented to the trial at randomization and informed consent was obtained when they were medically stable.

Criteria for inclusion were older than 18 years, with clinical judgment of the treating clinician of acute respiratory failure requiring escalation to noninvasive positive-pressure ventilation or to maintain noninvasive positive-pressure ventilation if the patient was delivered to the ED while receiving either type of ventilation from the out-of-hospital setting. Exclusion criteria were suspected drug overdose, cardiovascular instability (hypotension requiring immediate intervention), end-stage cancer, life expectancy less than 6 months, significant respiratory depression on presentation (eg, drug overdose), Glasgow Coma Scale score less than 9, cardiac or respiratory arrest on presentation, need for emergency intubation, known or suspected cerebrovascular accident, known or suspected ST-segment elevation myocardial infarction, and patients with increased risk of pulmonary aspiration, agitation, or uncooperativeness.

A computer-generated block-randomization schedule was used to produce the randomization sequence. Sealed, sequentially numbered envelopes were prepared to provide a 1:1 randomization ratio for each center in the study and were opened when the decision was made to randomize a patient.

Interventions

High-velocity nasal insufflation (Precision Flow; Vapotherm, Inc, Exeter, NH) (Figure 1) using a small-bore nasal cannula was initiated with a flow rate set to 35 L/min, with a starting temperature between 35°C and 37°C and FiO_2 at 1.0. Adjustments in flow (up to 40 L/min) and temperature (typically between 35°C and 37°C) were made to alleviate respiratory distress and optimize comfort. Noninvasive positive-pressure ventilation (Respironics Vision V60; Philips Healthcare, Murrysville, PA) was initiated with an oronasal mask, with inspiratory and expiratory positive airway pressures (IPAP, EPAP) set at the lower end of the following settings and increased as necessary to alleviate respiratory distress: IPAP 10 to 20 cm H_2O (or 5 to 15 cm H_2O above EPAP), and EPAP 5 to 10 cm H_2O. FiO_2 was initiated at 1.0 for noninvasive positive-pressure ventilation. The target for each intervention was to decrease breathing rate to fewer than 25 breaths/min and optimize comfort, whereas FiO_2 was adjusted to maintain a pulse oximetry reading (SpO_2) greater than 88%. The study model provided for having a respiratory therapist at bedside for the first 4 hours, which facilitated rapid changing of settings as needed.

Methods of Measurement and Outcomes Measures

The primary outcomes were treatment failure rate, defined as the need for intubation, and arm failure rate, defined as the decision for crossover to the alternate therapy, within 72 hours of initiation of assigned therapy. Failure of the assigned noninvasive ventilatory therapy was defined as failure to tolerate therapy, failure to oxygenate, failure to ventilate, failure to alleviate respiratory distress, or deteriorating medical status. Intubation was performed as needed for refractory respiratory failure (persistent hypoxemia and worsening hypercarbia), failure to cooperate, altered mental status, worsening hemodynamic status, or clinical judgment. Failure criteria are further described in Appendix E2, available online at http://www.annemergmed.com.

Secondary outcomes included evaluation of the ability of high-velocity nasal insufflation versus noninvasive positive-pressure ventilation to affect the degree and timing of changes of PCO_2, pH, and other signs or symptoms of respiratory distress, including vital signs and perceived exertion scores reported by the patients.[17] Vital signs were recorded before initiation of therapy; at 30, 60, and 90 minutes; and at 4 hours after therapy initiation. Baseline and posttherapy blood samples were drawn at 0, 1, and 4 hours. Blood gases could be either arterial or venous, consistently per patient. Treating physicians assigned assessment scores (based on a scale of 1 to 5, with 5 being a more positive value) in the following areas of respiratory response: technical or clinical difficulties, patient comfort and tolerance, simplicity of setup and use, and monitoring and support required for the therapy. Disposition and length of stay in any unit were at the discretion of the medical team and were recorded to determine any differences between groups.

Primary Data Analysis

Sample size calculation was based on an assumed 16.1% intubation rate for the control arm from published noninvasive positive-pressure ventilation studies in chronic obstructive pulmonary disease[18] and was cross-referenced with published noninvasive positive-pressure ventilation

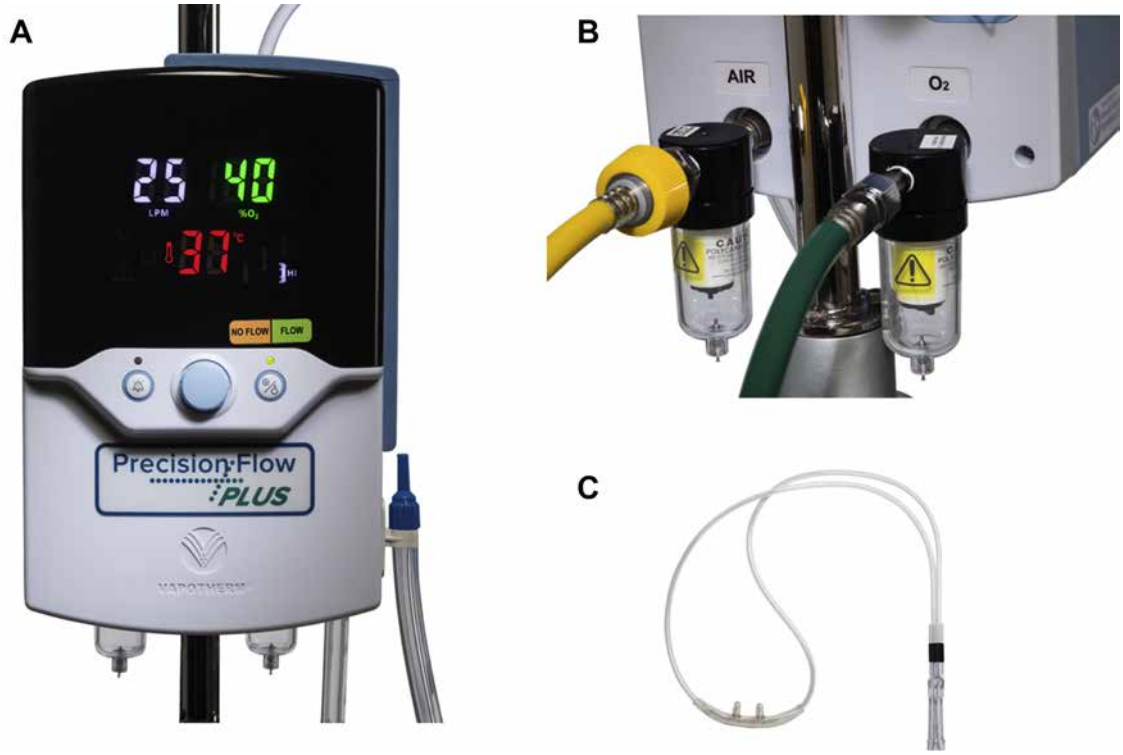


Figure 1. High-velocity nasal insufflation device platform. *A*, The main device unit (Precision Flow; Vapotherm, Inc) allows the clinician to set the flow rate (liters/minute), FiO_2 (percentage of oxygen), and temperature (degrees Celsius). The unit connects directly to oxygen and compressed air inputs (*B*), and delivers high-velocity flow through a modified nasal cannula (*C*).

studies in cardiogenic pulmonary edema in which the intubation rate was 16.7% in studies in which the sample size was greater than or equal to 20.[19] A sample size of 204 patients (102 in each arm) was calculated such that a test of proportions with a .05 significance level and 90% power with a noninferiority margin for intubation of 15 percentage points. The Wald test for noninferiority was used for primary outcomes of intubation and treatment arm failure. The prespecified noninferiority margins of 15 and 20 percentage points for differences in intubation and failure rates, respectively, were selected owing to the substantial variability in intubation rates from the literature, and the anticipated increase associated with the subjective decision for crossover. The 15 percentage points are the result of wide confidence intervals (CIs) in rates of intubation in the literature; CIs in the Cochrane review assessing noninvasive positive-pressure ventilation in chronic obstructive pulmonary disease and congestive heart failure were 7% and 9%, respectively. Thus, for the purposes of power analysis, a 10% difference was used to incorporate the limits of the CI, and an additional 5% was considered the accepted difference in the outcome of intubation for high-velocity nasal insufflation to be considered noninferior to noninvasive positive-pressure ventilation.

All analyses were based on an intention-to-treat model defined according to the protocol. Subanalyses of intubation or failure rates within the ED and within 4 hours, as well as differences between treatment arm and reason for intubation or failure, are presented as point and interval estimates of effect magnitude. Rates of intubation and failure were also described with Kaplan-Meier plots. Baseline demographic factors were summarized by study arm. For secondary outcomes, data for physiologic parameters were summaries by group, with point and interval estimates of effect magnitude when applicable. All analyses were performed with SAS (version 9.3; SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Subjects

Patients were recruited from October 2014 to September 2016. During this period, 228 patients were randomized and 204 were enrolled in the trial (Figure 2). The 24 patients randomized but not enrolled were excluded for meeting exclusion criteria (10), consent not obtained or withdrawn (6), bedside clinician not comfortable with enrollment after randomization (2), and patient identified to not need noninvasive positive-pressure ventilation after initial evaluation, thus failing to meet inclusion criteria (6). A total of 104 enrolled patients

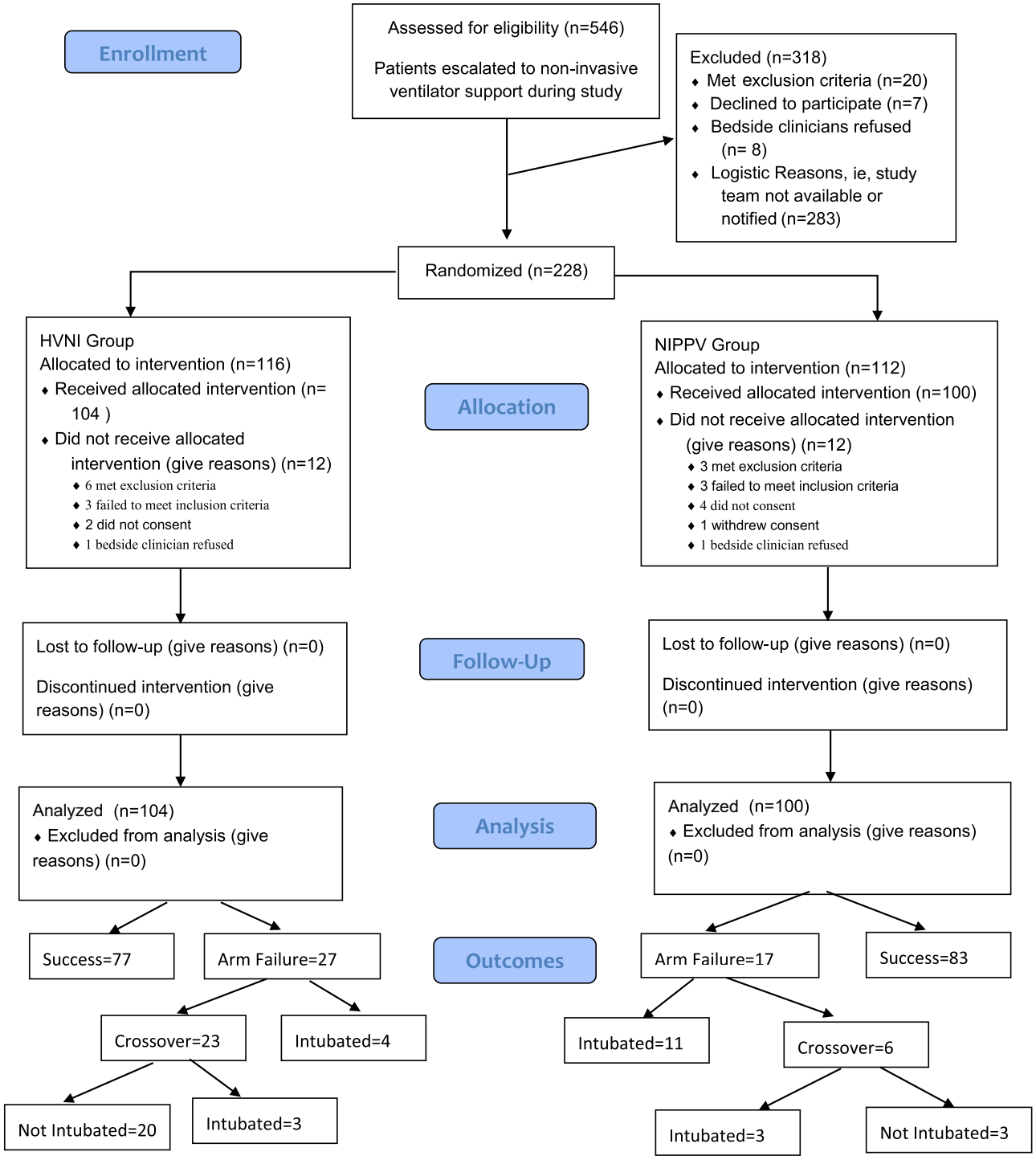


Figure 2. Screening, randomization, and enrollment of study participants. From October 2014 to September 2016, patients presenting to the ED with respiratory failure were screened according to the clinical need for advancement to noninvasive ventilatory support. Patients meeting eligibility were randomized to either high-velocity nasal insufflation through high-flow nasal cannula (HVNI) or NIPPV. If exclusion criteria were observed after randomization, patients were not subsequently enrolled. The large number of screen failures because of logistic reasons represents patients who presented and began receiving noninvasive support but who could not be enrolled because of resources and activity level in the units. *HVNI*, High-velocity nasal insufflation; *NIPPV*, noninvasive positive-pressure ventilation.

were randomized to receive high-velocity nasal insufflation; 100 patients, to receive noninvasive positive-pressure ventilation. The median time from presentation to initiation of therapy was 35 minutes (interquartile range 15 to 73 minutes) and setup time was 10 minutes (interquartile range 5 to 15 minutes) (Table 1).

Demographics and baseline characteristics of the study cohort are presented in Table 1. Mean baseline PCO_2 level was 53.4 mm Hg in the high-velocity nasal insufflation group and 58.7 mm Hg in the noninvasive positive-pressure ventilation group, and 60% of the patients enrolled (n=121) had a baseline PCO_2 of greater than 45 mm Hg. The most common condition treated was chronic obstructive pulmonary disease, both in terms of presenting condition (39%) and discharge diagnosis (26%). The second most common presenting condition was general dyspnea (36%); this classification was clarified for specific diagnoses at discharge. The second most common discharge diagnosis was acute decompensated heart failure (21%), followed by pneumonia (14%) and acute multifactorial hypoxic and hypercapnic respiratory failure (14%).

High-velocity nasal insufflation was titrated to a mean flow rate of 30 L/min (with a standard deviation of 6 L/min.), with a temperature setting of 35 °C (with a standard deviation of 1 °C). Noninvasive positive-pressure ventilation was titrated to mean settings for IPAP and EPAP of 13 cm H_2O (with a standard deviation of 3 cm of H_2O) over 6 cm H_2O (with a standard deviation of 1 cm of H_2O). FiO_2 was 0.62 (with standard deviation of 0.17) in the high-velocity nasal insufflation group compared with 0.57 (with a standard deviation of 0.18) in the noninvasive positive-pressure ventilation group. Medications and other relevant treatments provided during the 72 hours of the trial did not differ between treatment groups.

Table 1. Baseline characteristics of the patients, according to study group.

Characteristic	HVNI (N=104)	NIPPV (N=100)
Age (SD), y	63.4 (13.6)	63.3 (14.8)
Body mass index (SD), kg/m^2	31.8 (11.2)	31.2 (11.3)
APACHE II score (SD)*	31.2 (6.3)	30.7 (6.5)
Male sex, No. (%)	44 (42)	46 (46)
Race, No. (%)		
Indian	0	0
Asian	1 (1)	1 (1)
African	28 (27)	33 (33)
Latino	8 (8)	8 (8)
White	67 (64)	57 (57)
Other	0	1 (1)
Presenting condition, No. (%)		
Asthma	8 (8)	6 (6)
Congestive heart failure	19 (18)	14 (14)
Chronic renal failure	2 (2)	2 (2)
COPD	38 (37)	41 (41)
General dyspnea	37 (36)	37 (37)
Discharge diagnosis, No. (%)		
Asthma	4 (4)	3 (3)
Acute decompensated heart failure	22 (21)	20 (20)
Acute COPD exacerbation	29 (28)	24 (24)
Acute hypercapnic respiratory failure	5 (5)	7 (7)
Acute hypoxic respiratory failure	13 (13)	13 (13)
Acute hypercapnic and hypoxic respiratory failure	16 (15)	13 (13)
Pneumonia/sepsis	15 (14)	20 (20)
Time to initiation of therapy (SD), min	69.9 (128.3)	76.9 (133.8)
Time to setup of therapy (SD), min	11.1 (7.7)	11.2 (8.8)
Pulse rate (SD), beats/min	100.4 (21.2)	101.0 (21.3)
Respiratory rate (SD), breaths/min	31.3 (8.0)	29.3 (8.2)
SpO_2 (SD), %	93.2 (7.0)	93.5 (8.9)
PCO_2 (SD), mm Hg	53.4 (20.6)	58.7 (25.0)
Arterial pH (SD)	7.35 (0.10)	7.33 (0.08)
Modified Borg score† (SD)	6.3 (3.0)	6.4 (2.6)

APACHE, Acute Physiology and Chronic Health Evaluation; *COPD*, chronic obstructive pulmonary disease.
*APACHE II scores were calculated from 15 variables at enrollment and health status and information obtained at admission.
†The modified Borg score is a self-reported rating of perceived dyspnea on a scale of 1 to 10.

Main Results

The intubation rate for patients assigned to high-velocity nasal insufflation was 7% (95% CI 2% to 12%), and for noninvasive positive-pressure ventilation, it was 13% (95% CI 6% to 20%), independent of whether patients were determined to have failed their assigned therapy arm, meeting the criteria for high-velocity nasal insufflation noninferiority compared with noninvasive positive-pressure ventilation (risk difference –6%; 95% CI –14% to 2%) (Table 2). The number of arm failures, independent of subsequent intubation or crossover, was 26% (95% CI 17% to 34%) in the high-velocity nasal insufflation group and 17% (95% CI 9.6% to 24.4%) in the noninvasive positive-pressure ventilation group, which met the noninferior criterion (risk difference 9%; 95% CI –2% to 20%) (Table 2). The complete presentation of CIs and risk differences is available in Table E2, available online at http://www.annemergmed.com. Kaplan-Meier plots for intubation and arm failure rates during the 72 hours of the trial are presented in Figure 3. Heterogeneity with respect to intubation rates and crossover rates was evaluated in an aggregate manner comparing academic centers with community centers, and no significant differences were noted.

In the patients who failed the primary therapy, there was a substantial difference between groups in the number of those who were crossed to the opposite modality after arm failure versus going directly to intubation. Of the patients determined as not responding to high-velocity nasal insufflation, 85% (23/27) began receiving noninvasive

Table 2. Primary outcomes, according to study group.

	HVNI (N=104)	NIPPV (N=100)	% Risk Difference (95% CI)
Intubation at 72 h, No. (%)*	7/104 (6)	13/100 (13)	−7 (−14 to 2)
Reasons for intubation, No. (%)			
Inability to tolerate	0/7	0/13	
Oxygenate	1/7 (17)	0/13	
Ventilate	3/7 (33)	7/13 (54)	
Mental status	0/7	2/13 (15)	
Worsening CV status	2/7 (33)	2/13 (15)	
Clinical judgment	1/7 (17)	2/13 (15)	
Arm failure at 72 h, No. (%)*	27/104 (26)	17/100 (17)	9 (−2 to 20)
Arm failure in the ED, No. (%)	18/104 (17)	12/100 (12)	5 (−4 to 15)
Arm failure in the first 4 h, No. (%)	17/104 (16)	8/100 (8)	8 (0 to 17)
Reasons for arm failure, No. (%)			
Tolerate	1/27 (4)	5/17 (29)	
Oxygenate	3/27 (11)	0/17	
Ventilate	12/27 (44)	6/17 (35)	
Alleviate distress	10/27 (37)	1/17 (6)	
Deteriorating status	1/27 (4)	5/17 (29)	
Time to intubation, h†	4.0 (2.1 to 5.5)	2.5 (1.0 to 6.4)	
Time to arm failure, h†	2.0 (1.2 to 8.0)	3.3 (0.9 to 6.4)	

CV, Cardiovascular.
*HVNI is noninferior to NIPPV at the 15% margin for intubation and the 20% margin for arm failure.
†Values are median (interquartile range).

positive-pressure ventilation, of whom 3 (13%) were intubated within the 72 hours. Only 35% of patients (6/17) determined as not responding to noninvasive positive-pressure ventilation began receiving high-velocity nasal insufflation, and 3 (50%) were intubated within 72 hours (Figure 2).

Vital signs and blood gas analyses trended similarly between high-velocity nasal insufflation and noninvasive positive-pressure ventilation groups, and each parameter showed improvement over time (Tables E3*A* and E4, available online at http://www.annemergmed.com). Seventeen percent of the samples were venous, and the venous sample was uniform between groups (18% [high-velocity nasal insufflation] versus 16% [noninvasive positive-pressure ventilation] of samples). The effect of high-velocity nasal insufflation on PCO_2 over time was similar to that of noninvasive positive-pressure ventilation in the entire study population (Figure E1, available online at http://www.annemergmed.com) and when analyzed for the subgroup who presented with baseline PCO_2 greater than 45 mm Hg (Figure E2, available online at http://www.annemergmed.com).

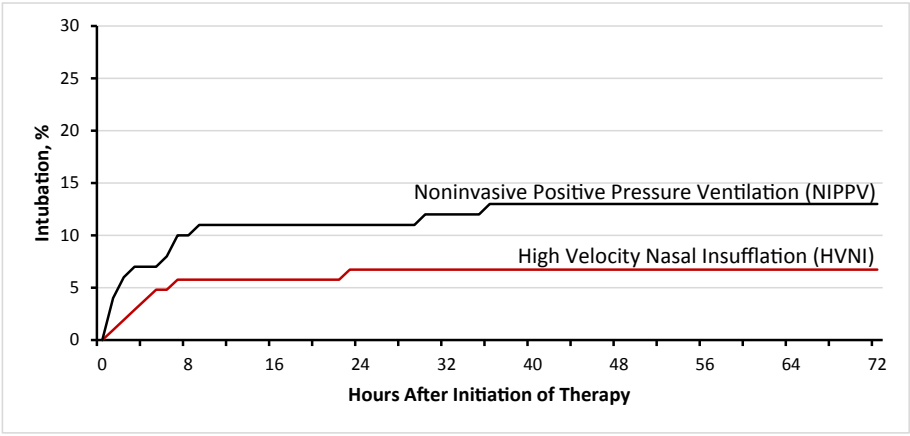
Patient perception of dyspnea was similar between groups for Borg and visual analog scale scores (Table E3*B*, available online at http://www.annemergmed.com). Assessment scores for attending physicians' perceptions are presented in Table 3. Physicians gave superior scores for high-velocity nasal insufflation for respiratory response, patient comfort and tolerance, and simplicity of use. There were similarities in ED, ICU, and overall hospital length of stay between groups (Table E5, available online at http://www.annemergmed.com).

LIMITATIONS

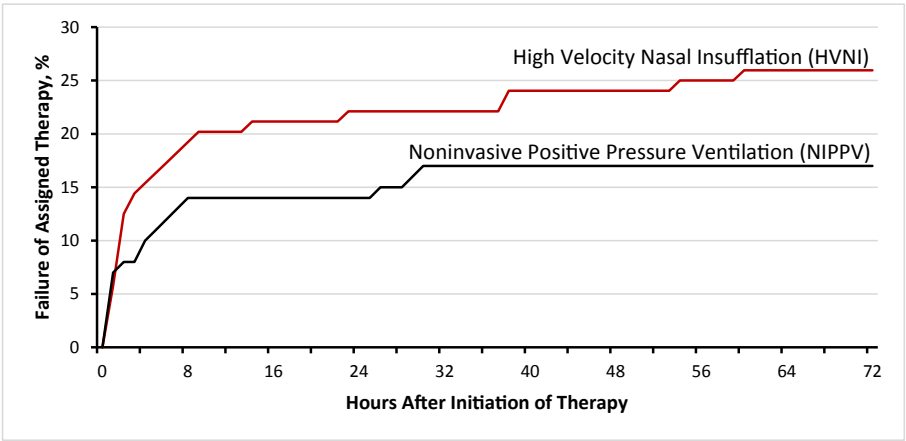
Among the limitations of this study, the most important was the technical inability to blind the treating team. The lack of blinding can contribute to bias, especially when clinical judgment affects an outcome that is being evaluated. This study was also not powered for subanalyses across specific respiratory failure causes. Although criteria for failure were presented in the protocol, the determination of arm failure and need for intubation were ultimately at the discretion of the attending physician. Last, the mix of arterial and venous blood samples limited the interpretation of blood gas parameters such as PaO_2. Because of lack of invasive monitoring to assess various respiratory physiologic variables, it is difficult to define all the potential clinical benefits of these therapies.

DISCUSSION

The principal finding of this study demonstrates that high-velocity nasal insufflation is noninferior to noninvasive positive-pressure ventilation for the treatment of adult ED patients with respiratory failure from various causes. The most meaningful outcome is avoidance of intubation; however, the model also evaluated the failure rate for patients to continue receiving their assigned noninvasive therapy. The 13% intubation rate for noninvasive positive-pressure ventilation was in line with



No. at Risk										
HVNI	104	98	98	97	97	97	97	97	97	97
NIPPV	100	90	89	89	88	87	87	87	87	87



No. at Risk										
HVNI	104	84	82	81	81	79	79	78	77	77
NIPPV	100	86	86	86	83	83	83	83	83	83

Figure 3. Kaplan-Meier plots of time to intubation and time to failure to 72 hours. The top plot illustrates intubation rate over time as a function of assigned therapy, regardless of whether the assigned therapy was determined to have failed during the course of treatment. The bottom plot illustrates the rate of failure of the assigned arm over time, regardless of whether the patient was ultimately intubated. Patients assigned to HVNI were less likely to be intubated, despite the greater trend for therapy failure.

the historical data used to power the study, which makes the 7% intubation rate for high-velocity nasal insufflation noteworthy.

The noninferiority margins, designated a priori, must account for both the acceptable difference in failure percentages and an estimation of the 95% CI. In accordance with the methodology for the noninferiority analysis, the lower limit of the 95% CI for the test group needed to be within (above) this margin relative to the control condition to demonstrate noninferiority. The acceptable difference in failure percentages was determined from a survey of clinicians, who indicated either 5 or 10 percentage points, to which we added an estimated 10 percentage points to account for the relatively large 95% CIs observed in the literature for noninvasive positive-pressure ventilation failure (intubation) rates. The more conservative of these margins, 15 percentage points, was applied to the intubation rate, given that the 95% CI was based on this outcome. The less conservative of these margins, 20 percentage points, was applied to the all-cause failure allowing crossover, given the inherent increase in variability that could be expected from the additional subjectivity of a failure determination when intubation was not imminent.

The crossover (arm failure) component of this study was a limitation of the model included as a safety measure

Table 3. Attending physician perceptions, according to study group.

	HVNI (N=104)	NIPPV (N=100)
Patients' respiratory response, No. (%)		
1, insufficient	8/104 (8)	7/100 (7)
2	2/104 (2)	6/100 (6)
3, adequate	18/104 (17)	32/100 (32)
4	15/104 (14)	11/100 (11)
5, excellent	57/104 (55)	40/100 (40)
Technical/clinical difficulties, No. (%)		
1, frequent	0/104	0/100
2	1/104 (1)	0/100
3, occasional	9/104 (9)	14/100 (14)
4	8/104 (8)	6/100 (6)
5, never	82/104 (79)	76/100 (76)
Patients' comfort/tolerance, No. (%)		
1, insufficient	2/104 (2)	4/100 (4)
2	1/104 (1)	3/100 (3)
3, adequate	16/104 (15)	45/100 (45)
4	6/104 (6)	10/100 (10)
5, excellent	75/104 (72)	34/100 (34)
Simplicity of use, No. (%)		
1, complex	0/104	1/100 (1)
2	0/104	0/100
3, typical	27/104 (26)	48/100 (48)
4	8/104 (8)	3/100 (3)
5, simple	65/104 (63)	44/100 (44)
Monitoring required, No. (%)		
1, frequent	1/104 (1)	2/100 (2)
2	1/104 (1)	1/100 (1)
3, typical	34/104 (33)	46/100 (46)
4	9/104 (9)	1/100 (1)
5, minimal	55/104 (53)	45/100 (45)

associated with the need for deferred consent; therefore, the arm failure rate that induced an element of subjectivity was expected to be greater than the intubation rate. Despite this, the arm failure rate met the a priori noninferiority criteria. These data reveal a tendency to cease high-velocity nasal insufflation if patients are not immediately responsive, and as such, much of the observed difference in arm failure rates may be due to less clinical familiarity with high-velocity nasal insufflation in this diverse population. As mentioned in the "Limitations," because of a lack of invasive monitoring to assess for other physiologic variables, there may be benefits that are not accounted for in this study.

Another important finding of this study is the demonstration of the ventilatory effect with high-velocity nasal insufflation that is similar to that of noninvasive positive-pressure ventilation, as evidenced by the improvement in the PCO_2 level over time in both arms, at a similar rate in all patients, as well as the subgroup with initial PCO_2 greater than 45. Recent studies of high-flow nasal oxygen for adults in hypoxemic respiratory failure indicate that, generally, high-flow nasal cannula may be as effective in the treatment of hypoxemia as noninvasive positive-pressure ventilation.[14-16] Although these studies report positive outcomes for oxygenation support, they focused specifically on patients with stable ventilatory parameters and therefore did not show differences in ventilatory indices. Of these trials, Stephan et al[14] presented PCO_2 and breathing frequency data without significant and clinically meaningful reductions.

These findings of our trial may be attributed to the physiologic effects of small-bore cannulae used in high-velocity nasal insufflation. Mechanistic evidence suggests that high-flow nasal cannulae will purge the anatomic dead space of expired carbon dioxide between breaths, thus providing a ventilatory effect.[7,20] Moreover, the ventilatory effect may be attributed to flow parameters generated by a small-bore, high-velocity cannula. Frizzola et al[6] demonstrated in an animal model of respiratory failure that a cannula design optimizing the potential to flush extrathoracic dead space results in improved physiologic ventilation outcomes compared with one that was designed more for airway-pressure generation. Subsequent computation fluid modeling work demonstrated that cannula flow velocity plays the major role, in that greater velocity adds turbulent energy and accelerates the vortices formed on the nasal cavity.[8] This trial translates the clinical effect of these theoretical flow properties to an adult respiratory failure population.

In light of our findings, the nasal cannula application offers several distinct advantages over noninvasive positive-pressure ventilation. High-flow nasal cannula systems, by necessity, provide humidification superior to that of noninvasive positive-pressure ventilation systems and provide support without the need to secure a seal on the face, which preserves the nasal and facial tissue from lesions.[21,22] In addition, our clinical experience has shown that for many patients, the full face mask of some noninvasive positive-pressure ventilation systems can be anxiety provoking, which may further exacerbate the adrenergic response often associated with respiratory distress. Patients treated with high-velocity nasal insufflation can more easily communicate, receive oral medications, and eat without interruption of therapy, which are limitations of noninvasive positive-pressure ventilation.

Last, the findings of this trial are generalizable across care settings. The trial was conducted across the southeastern United States in 5 centers with different characteristics. Two of the centers were academic centers, one a large urban center and second a tertiary care center with large catchment area. Three of the centers were community centers with volumes ranging from 50,000 to 70,000 patient visits per year.

In summary, within the described limitations of this trial, specifically, being a nonblinded trial and not powered to assess performance within any specific respiratory failure cause, high-velocity nasal insufflation is noninferior to noninvasive positive-pressure ventilation for the treatment of respiratory failure from various causes in adult patients presenting to the ED who do not require emergency intubation.

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Author contributions: PD led the trial. PD, JSW, MB, JK, TA, RG, S. Salazar, TEW, DM, RD, AT, MH, MG, and S. Spivey gathered the data. PD, CD, and TLM were involved in the study design and protocol development. NG performed the data management and statistical analysis. PD, JSW, MB, JK, and TLM prepared the article. All authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol, and reviewed the article and agreed to the content. PD takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The sponsor agreed a priori to allow publication of the findings of the trial at the discretion of the principal investigators. A steering committee composed of the principal investigators oversaw the analysis and interpretation of the data, wrote the first and subsequent drafts of the article, and made the decision to submit the article for publication.

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(continued from p. 25)

DIAGNOSIS:

Periorbital phytophotodermatitis. The plant was identified to be *Ruta graveolens*, more commonly known as rue, or *ruda* in Spanish. Found worldwide, it is used sparingly in the culinary world because of its bitter taste but has had many purported uses, including as an abortifacient, emmenagogue, and a mosquito and snake repellant.[1,2] In literature, it was used in John Milton's *Paradise Lost* to give sight to Adam.[3] The leaves of rue contain multiple phytotoxic agents, including 8-methoxypsoralen, a furocoumarin.[4] Dermal exposure to rue can cause phytophotodermatitis, whereby the combination of ultraviolent light and chemicals in the plant can inhibit dermal mitosis, usually within 24 hours of exposure.[2] In our patient's case, the dermal application of the rue coupled with the outdoor setting of the flea market triggered her rash.

After diagnosis, the patient was discharged home with instructions to avoid further plant exposure. On follow-up at 1 week, all symptoms had resolved.

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APPENDIX E2

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to Doshi P, Whittle J, Bublewicz, et al. High velocity nasal insufflation in the treatment of respiratory failure. *Ann Emerg Med.* 2017.

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Contribution to the Study. This was a sponsored multicenter trial led by Pratik Doshi. All investigators mentioned as coauthors gathered the data except for Charles Dunlap, Tom Miller, and Nancy Gordon. Charles Dunlap and Tom Miller were involved in the study design and protocol development along with Pratik Doshi. Nancy Gordon, with Gordon and Associates, performed the data management and statistical analysis. Data were checked by the clinical research team and electronic data capture system was Imednet (Mednet system, Minnetonka, MN), and the database build was performed by Fuel Studios, which was financed by study funding.

The manuscript was prepared by Pratik Doshi, Jessica Whittle, Michael Bubblewicz, Joe Kearney, and Tom Miller. The manuscript was reviewed by all the coauthors and they agreed to the content and plan for submission to *Annals of Emergency Medicine*.

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Table E1. Study sites and enrollment periods.

Study Site	Enrollment Open	Enrollment Closed	Total Enrolled
Memorial Hermann Hospital - Texas Medical Center, Houston, TX	Oct 2014	Sept 2016	71
Erlanger Health System, Chattanooga, TN	Feb 2015	Sept 2016	23
Memorial Hermann The Woodlands Hospital, The Woodlands, TX	Apr 2015	Sept 2016	56
Athens Regional Medical Center, Athens, GA*	Jun 2015	Apr 2016	25
	Aug 2016	Sept 2016	1
McLeod Regional Medical Center, Florence, SC	Mar 2016	Sept 2016	28

*Enrollment was paused at Athens Regional Medical Center for four months associated with a reorganization of the IRB; this was unrelated to the conduct of the trial.

Methods: Failure Criteria and Study Interventions.

Treatment Failure. Treatment failure will be defined as 1) Failure to tolerate if the patient is unable to tolerate the mask, nasal prongs, air flow or pressure, has persisting asynchrony, and is unable to cooperate with the therapy; 2) Failure to oxygenate if the modality is unable to sustain an O_2 sat > 88 - 92% or PaO_2 > 60 – 65 mmHg despite maximal treatment with $FI0_2$ 100% and optimal manipulations of flow rate and/or airway pressures; 3) Failure to ventilate if the patients remain acutely hypercarbic and academic with lack of reduction in $PaCO_2$ or improvement in pH; 4) Failure to alleviate respiratory distress if the patient has no alleviation of moderate to severe dyspnea or tachypnea (RR remains > 30/min) with inability to reduce work of breathing as manifested by sustained increase in accessory muscle use; 5) Deteriorating medical status manifested by worsening mental status or hemodynamics, manifested by hypotension (systolic P < 90 mm Hg), unremitting tachycardia (>140 or increase by >20% during therapy), or other conditions interpreted by the patient's clinicians as constituting evidence of deterioration.

Criteria for Intubation. Intubation will be undertaken for unremitting respiratory failure despite maximal use of initial and/or crossover therapy as manifested by failure to maintain $SaO_2 \geq 88\%$ despite FIO_2 1.0 and optimization of flow and/or PEEP settings, progressive increase > 10 mmHg in $PaCO_2$ and concomitant drop in pH despite maximal attempts to enhance ventilation, inability to cooperate with therapy in the face of persisting evidence of respiratory failure, unremitting agitation interfering with ability to cooperate and with persisting evidence of respiratory failure, deteriorating mental status despite maximal therapy with HVNI and/or NIPPV, worsening hemodynamic status (systemic SBP <90 mmHg or MAP < 60 mmHg despite fluid resuscitation and use of low dose pressors), unremitting life-threatening arrhythmias, cardiac or respiratory arrest, or any other condition, which, in the judgment of the clinical care team, warrants intubation.

Crossover. Treatment failures on initial therapy wherein immediate intubation is not required will be eligible for crossover to the alternative therapy. The decision to intubate is entirely at the discretion of the clinical team caring for the patient without input from the investigators. Crossover will be offered to Treatment Failures only if deemed safe by the clinical care team.

The Initial and Subsequent Settings for Application of Each Therapeutic Arm. These initial settings in the two arms are designed as a standardization of usual medical treatment for the respective therapies, and were devised to provide critical intervention and rapid abatement of both dyspnea and increased work of breathing. Once the patient has been placed upon the initial settings, the medical staff may, and should, manipulate and titrate the settings to optimize effectiveness and subject's tolerance.

HVNI

$FiO_2 = 1.0$

Flow = 35 L/min

Temperature = 35 -37 C

Patients will be fit with a Vapotherm adult nasal cannula that will be applied by a respiratory therapist or other clinician skilled in management of HVNI. Initial flow will be set to 35 L/min but can be decreased or increased as rapidly as necessary to alleviate respiratory distress and optimize patient comfort. Targets should be to lower respiratory rate to the low 20s and with a HVNI flow rate between 20 to 35 L/min. Starting temperature will be between 35°C and 37°C; if patients find the gas temperature to be uncomfortable, it can be lowered as necessary down to 33°C to enhance tolerance.

FIO_2 will be 1.0 initially to assure adequate oxygenation, but should be adjusted promptly to

maintain an FIO_2 of no greater than 0.6 to maintain a $PaO_2 > 88\%$.

NIPPV

$FiO_2 = 1.0$

IPAP = 10 – 20 cmH_2O (or 5 to 15 cmH_20 pressure support above EPAP)

EPAP = 5-10 cmH_2O

Backup Ventilation Rate = 0 - 4 breaths/min (lowest setting)

Applied with humidification per individual hospital practice

Patients will be fit with an oronasal mask using a fitting gauge that will be applied by a respiratory therapist or other clinician skilled in management of NIPPV. Initial pressures will be at low end of suggested range but can be increased as rapidly as necessary to alleviate respiratory distress. Targets should be to lower respiratory rate to the low 20s and achieve tidal volumes of 6-8 ml/kg ideal body weight. If patients find pressures uncomfortably high, they can be lowered as necessary by 1 to 2 cmH_2O decrements to enhance tolerance. EPAP (PEEP) can also be adjusted upward as needed to reduce triggering effort (by counterbalancing auto-PEEP) or to improve oxygenation.

FIO_2 will be 1.0 initially to assure adequate oxygenation, but should be adjusted promptly to maintain an FIO_2 of no greater than 0.6 with an EPAP (PEEP) of not more than 10 cm H_2O to maintain a $PaO_2 > 88\%$.

Table E2. Primary outcomes.

	HVNI		NIPPV		(HVNI – NIPPV)	
Outcome	**Risk**	**95% Confidence Limits**	**Risk**	**95% Confidence Limits**	**Risk Difference**	**95% Confidence Limits**
Intubation	0.0673	0.0192 to 0.1155	0.1300	0.0641 to 0.1959	-0.0627	-0.1443 to 0.0189
Arm Failure	0.2596	0.1754 to 0.3468	0.1700	0.0964 to 0.2436	0.0896	-0.0223 to 0.2015

Table E3*A*. Secondary outcomes: vitals.*

Characteristic	**HVNI**	**NIPPV**	**Difference (95% CI)**
Heart Rate (beats•min^{-1})			
Baseline (n=204, HVNI=104, NIPPV=100)	100.4 (21.2)	101.0 (21.3)	-0.6 (-6.5 to 5.3)
30 min (n=189, HVNI=96, NIPPV=93)	95.6 (20.4)	96.4 (22.0)	-0.8 (-6.9 to 5.3)
60 min (n=180, HVNI=92, NIPPV=88)	94.0 (18.4)	93.7 (20.4)	0.3 (-5.4 to 6.0)
90 min (n=167, HVNI=84, NIPPV=83)	91.8 (17.8)	92.2 (21.6)	-0.4 (-6.4 to 5.6)
240 min (n=149, HVNI=73, NIPPV=76)	92.1 (17.4)	89.6 (18.2)	2.5 (-3.3 to 8.3)
Treatment Failure (n=22, HVNI=12, NIPPV=10)	106.4 (29.8)	108.9 (33.5)	-2.5 (-30.6 to 25.6)
Respiratory Rate (breaths•min^{-1})			
Baseline (n=204, HVNI=104, NIPPV=100)	31.3 (8.0)	29.3 (8.2)	2.0 (-0.2 to 4.2)
30 min (n=189, HVNI=96, NIPPV=93)	26.0 (6.1)	25.6 (7.6)	0.4 (-1.6 to 2.4)
60 min (n=180, HVNI=92, NIPPV=88)	23.9 (5.5)	23.4 (6.6)	0.5 (-1.3 to 2.3)
90 min (n=167, HVNI=84, NIPPV=83)	22.9 (5.8)	22.7 (6.4)	0.2 (-1.7 to 2.1)
240 min (n=149, HVNI=73, NIPPV=76)	22.2 (4.7)	22.1 (4.8)	0.1 (-1.4 to 1.6)
Treatment Failure (n=23, HVNI=13, NIPPV=10)	26.4 (11.4)	27.4 (10.2)	-1.0 (-10.5 to 8.5)
SpO_2 (%)			
Baseline (n=204, HVNI=104, NIPPV=100)	93.2 (7.0)	93.5 (8.9)	-0.3 (-2.5 to 1.9)
30 min (n=189, HVNI=96, NIPPV=93)	97.5 (3.4)	97.8 (3.3)	-0.3 (-1.3 to 0.7)
60 min (n=180, HVNI=92, NIPPV=88)	97.6 (3.0)	97.8 (3.0)	-0.2 (-1.1 to 0.7)
90 min (n=167, HVNI=84, NIPPV=83)	97.8 (2.3)	97.7 (2.3)	0.1 (-0.6 to 0.8)
240 min (n=148, HVNI=73, NIPPV=75)	96.8 (2.8)	97.2 (2.3)	-0.4 (-1.2 to 0.4)
Treatment Failure (n=23, HVNI=13, NIPPV=10)	93.3 (3.8)	91.4 (6.1)	1.9 (-2.4 to 6.2)

*Values are mean (SD). HVNI denotes high velocity nasal insufflation via high flow nasal cannula, and NIPPV denotes noninvasive positive pressure ventilation.

Table E3*B*. Secondary outcomes: Borg & VAS.

Characteristic	HVNI	NIPPV	Difference (95% CI)
Discomfort VAS[†1] (breaths•min^{-1})			
Baseline (n=195, HVNI=103, NIPPV=92)	4 (0,5)	4 (0,5)	
30 min (n=180 HVNI=95, NIPPV=85)	3 (0,5)	3 (0,5)	
60 min (n=170, HVNI=91, NIPPV=79)	2 (0,5)	2 (0,5)	
90 min (n=159, HVNI=84, NIPPV=75)	2 (0,5)	2 (0,5)	
240 min (n=141, HVNI=72, NIPPV=69)	2 (0,4)	2 (0,5)	
Treatment Failure (n=17, HVNI=10, NIPPV=7)	3 (2,5)	4 (3,5)	
Modified Borg Score[‡1]			
Baseline (n=195, HVNI=102, NIPPV=93)	6.3 (3.0)	6.5 (2.6)	-0.2 (-1.0 to 0.6)
30 min (n=180, HVNI=94, NIPPV=86)	4.4 (2.3)	4.3 (2.7)	0.1 (-0.6 to 0.8)
60 min (n=171, HVNI=90, NIPPV=81)	3.5 (2.1)	3.3 (2.2)	0.2 (-0.4 to 0.8)
90 min (n=161, HVNI=83, NIPPV=78)	3.3 (2.1)	2.9 (2.2)	0.4 (-0.3 to 1.1)
240 min (n=142, HVNI=71, NIPPV=71)	2.6 (2.0)	2.2 (1.8)	0.4 (-0.2 to 1.0)
Treatment Failure (n=17, HVNI=10, NIPPV=7)	4.9 (3.5)	7.1 (3.0)	-2.2 (-5.7 to 1.3)

HVNI denotes high velocity nasal insufflation via high flow nasal cannula, and NIPPV denotes noninvasive positive pressure ventilation.
[†]VAS – Visual Analog Satisfaction score – 0-5, 5 extreme discomfort (frown face). Shown as median (min, max)
[‡]Modified Borg score is a self-reported rating of perceived dyspnea on a scale of 1 to 10. Show as mean (SD).

Table E4. Secondary outcomes: blood gas analysis.*

Characteristic	HVNI	NIPPV	Difference (95% CI)
pH			
Baseline (n=203, HVNI=104, NIPPV=99)	7.35 (0.10)	7.33 (0.08)	0.02 (-0.00 to 0.04)
60 min (n=178, HVNI=92, NIPPV=86)	7.36 (0.08)	7.34 (0.07)	0.02 (-0.00 to 0.04)
240 min (n=146, HVNI=74, NIPPV=72)	7.38 (0.07)	7.36 (0.06)	0.02 (-0.00 to 0.04)
Treatment Failure (n=16, HVNI=10, NIPPV=6)	7.25 (0.07)	7.19 (0.04)	0.06 (-0.01 to 0.13)
PCO_2 (mmHg)			
Baseline (n=203, HVNI=104, NIPPV=99)	53.4 (20.6)	58.7 (25.0)	-5.3 (-11.6 to 1.0)
60 min (n=178, HVNI=92, NIPPV=86)	52.0 (19.6)	55.2 (21.5)	-3.2 (-9.3 to 2.9)
240 min (n=146, HVNI=74, NIPPV=72)	46.3 (12.7)	52.5 (17.8)	-6.2 (-11.2 to -1.2)
Treatment Failure (n=16, HVNI=10, NIPPV=6)	69.2 (32.1)	66.2 (33.3)	3.0 (-33.0 to 39.0)
HCO_3^- (mEq/L)			
Baseline (n=203, HVNI=104, NIPPV=99)	28.6 (8.6)	29.8 (9.5)	-1.2 (-3.7 to 1.3)
60 min (n=178, HVNI=92, NIPPV=86)	28.4 (8.4)	29.4 (9.5)	-1.0 (-3.6 to 1.6)
240 min (n=146, HVNI=74, NIPPV=72)	26.9 (6.1)	29.3 (9.2)	-2.4 (-5.0 to 0.2)
Treatment Failure (n=16, HVNI=10, NIPPV=6)	30.1 (13.7)	26.5 (15.4)	3.6 (-12.3 to 19.5)
Base Excess (mmol/L)			
Baseline (n=203, HVNI=104, NIPPV=99)	2.35 (8.12)	2.87 (7.76)	-0.52 (-2.72 to 1.68)
60 min (n=178, HVNI=92, NIPPV=86)	2.30 (7.95)	2.71 (7.92)	-0.41 (-2.76 to 1.94)
240 min (n=146, HVNI=74, NIPPV=72)	1.47 (5.48)	3.14 (7.79)	-1.67 (-3.87 to 0.53)
Treatment Failure (n=16, HVNI=10, NIPPV=6)	2.29 (12.88)	-2.12 (13.75)	4.41 (-10.21 to 19.03)

*Values are mean (SD). HVNI denotes high velocity nasal insufflation via high flow nasal cannula, and NIPPV denotes noninvasive positive pressure ventilation. Blood gas from arterial or venous samples.

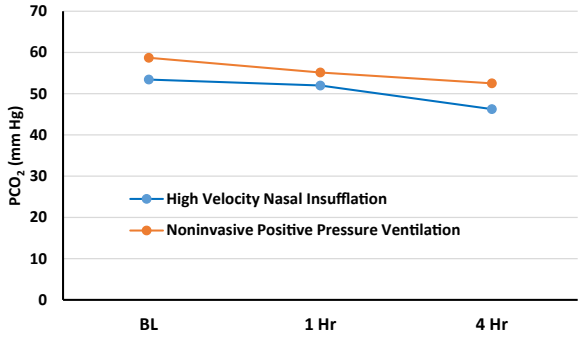

Figure E1. Blood carbon dioxide tension over time as a function of group: all patients (n=204).

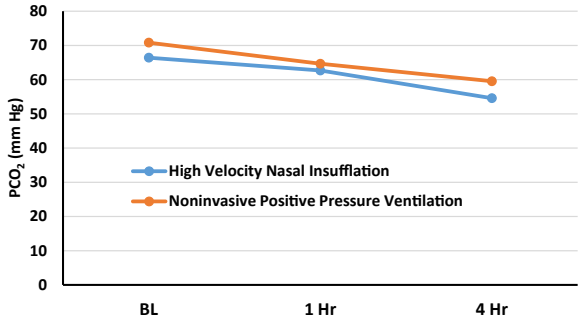

Figure E2. Blood carbon dioxide tension over time as a function of group: patients with a baseline PCO_2 less than 45 (n=121).

Table E5. Secondary outcomes: length of stay.*

	HVNI		NIPPV		
	n	Duration	n	Duration	Difference (95% CI)
ED, hours	104	7.6 (5.0)	100	8.0 (8.5)	-0.4 (-2.3 to 1.5)
ICU, days	48	3.3 (3.7)	47	3.9 (4.1)	-0.6 (-2.2 to 1.0)
Medical floor, days	83	3.8 (3.4)	77	3.3 (2.8)	0.5 (-0.5 to 1.5)
Step-down unit, days	39	4.6 (4.3)	43	2.9 (2.2)	1.7 (0.2 to 3.2)
Other, days	3	6.4 (6.5)	2	0.1 (0.1)	6.3 (-9.1 to 21.7)
Overall hospital, days	104	6.8 (5.7)	100	6.0 (4.4)	0.8 (-0.6 to 2.2)

*Values are mean (SD). HVNI denotes high velocity nasal insufflation via high flow nasal cannula, and NIPPV denotes noninvasive positive pressure ventilation.

REFERENCE

1. Burdon JG, Juniper EF, Killian KJ, et al. The perception of breathlessness in asthma. *Am Rev Respir Dis*. 1982;126:825-828.