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HVNI *vs* NIPPV in the treatment of acute decompensated heart failure: Subgroup analysis of a multi-center trial in the ED

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ABSTRACT

Background and objective: Managing respiratory failure (RF) secondary to acute decompensated heart failure (ADHF) with non-invasive positive-pressure ventilation (NIPPV) has been shown to significantly improve morbidity and mortality in patients presenting to the emergency department (ED). This subgroup analysis compares high-velocity nasal insufflation (HVNI), a form of high-flow nasal cannula, with NIPPV in the treatment of RF secondary to ADHF with respect to therapy failure, as indicated by the requirement for intubation or all-cause arm failure including subjective crossover to the alternate therapy.
Methods: The subgroup analysis is from a larger randomized control trial of adults presenting to the ED with RF requiring NIPPV support. Patients were randomly selected to therapy, and subgroup selection was established *a priori* in the original study as a discharge diagnosis. The primary outcome was therapy failure at 72 h after enrolment.
Results: Subgroup analysis included a total of 22 HVNI and 20 NIPPV patients which fit discharge diagnosis ADHF. Baseline patient characteristics were not statistically significant. Primary outcomes were not statistically significant: intubation rate ($p = 1.000$), therapy success ($p = 1.000$). Repeated measures (vitals, dyspnea, blood gases) showed comparable differences over initial 4 h. Physicians scored HVNI superior on patient comfort/tolerance ($p < 0.001$), ease of use ($p = 0.004$), and monitoring ($p = 0.036$). Limitations were technical inability to blind the clinician team and lack of power of the subgroup analysis.
Conclusion: In conclusion, this subgroup analysis suggests HVNI may be non-inferior to NIPPV in patients with respiratory failure secondary to ADHF that do not need emergent intubation.

1. Introduction

Acute decompensated heart failure (ADHF) is a common diagnosis encountered in the Emergency Department. Between 2000 and 2010 there were over 1 million hospital admissions annually for heart failure [1]. Patients presenting with Respiratory Failure secondary to ADHF have shown significant morbidity and mortality benefits when Non-Invasive Positive-Pressure Ventilation (NIPPV) is utilized [2]. High flow nasal cannula (HFNC) use has

Abbreviations: ADHF, acute decompensated heart failure; ANOVA, analysis of variance; BMI, body mass index; ED, emergency department; FiO_2, fraction of inspired oxygen; HFNC, high flow nasal cannula; HF, heart failure; HVNI, high-velocity nasal insufflation; IRB, institutional review board; IPAP, inspiratory positive airway pressure; IQR, interquartile range; NIPPV, non-invasive positive-pressure ventilation; RF, respiratory failure.

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shown some benefit in patients with cardiogenic pulmonary edema [3].

To date, there has been no head to head comparison with NIPPV and HFNC in patients with respiratory failure (RF) secondary to ADHF.

Recently, a large, prospective, randomized control trial showed that HFNC in the form of High-Velocity Nasal Insufflation (HVNI) was non-inferior when compared to NIPPV in patients with RF of all causes. Respiratory Failure was determined by the clinical judgment of the treating physician that there was a requirement to escalate to NIPPV or to maintain NIPPV if the patient was delivered to the ED from an out-of-hospital setting on either type of ventilation. [4] Patients with the *a priori* discharge diagnosis of ADHF as the cause of RF were pre-specified for further analysis. HFNC has been shown to create a mild positive intrathoracic pressure [5]. Positive intrathoracic pressure has been postulated to decrease the preload to the right ventricle and increase the hydrostatic pressure in the alveoli improving the cardiopulmonary status of heart failure patients [6,7]. While the intrathoracic pressure is less with HFNC, has shown that it can significantly reduce cardiac preload in patients with heart failure [8]. Patients in ADHF typically have hypoxic respiratory failure [9]. HFNC has the ability to deliver a high FiO2 to compensate for this hypoxia while additional therapies are utilized to treat the patient. The refined form of HFNC, HVNI also creates a rapid flush of the extra-thoracic deadspace, facilitating ventilation and thereby reducing work of breathing [10]. This decrease in metabolic demand will also decrease myocardial load. The combination of distending pressure, ability to deliver high FiO2, and reduction of work of breathing could prove beneficial in the acute management of respiratory failure associated with acute decompensated heart failure (HF).

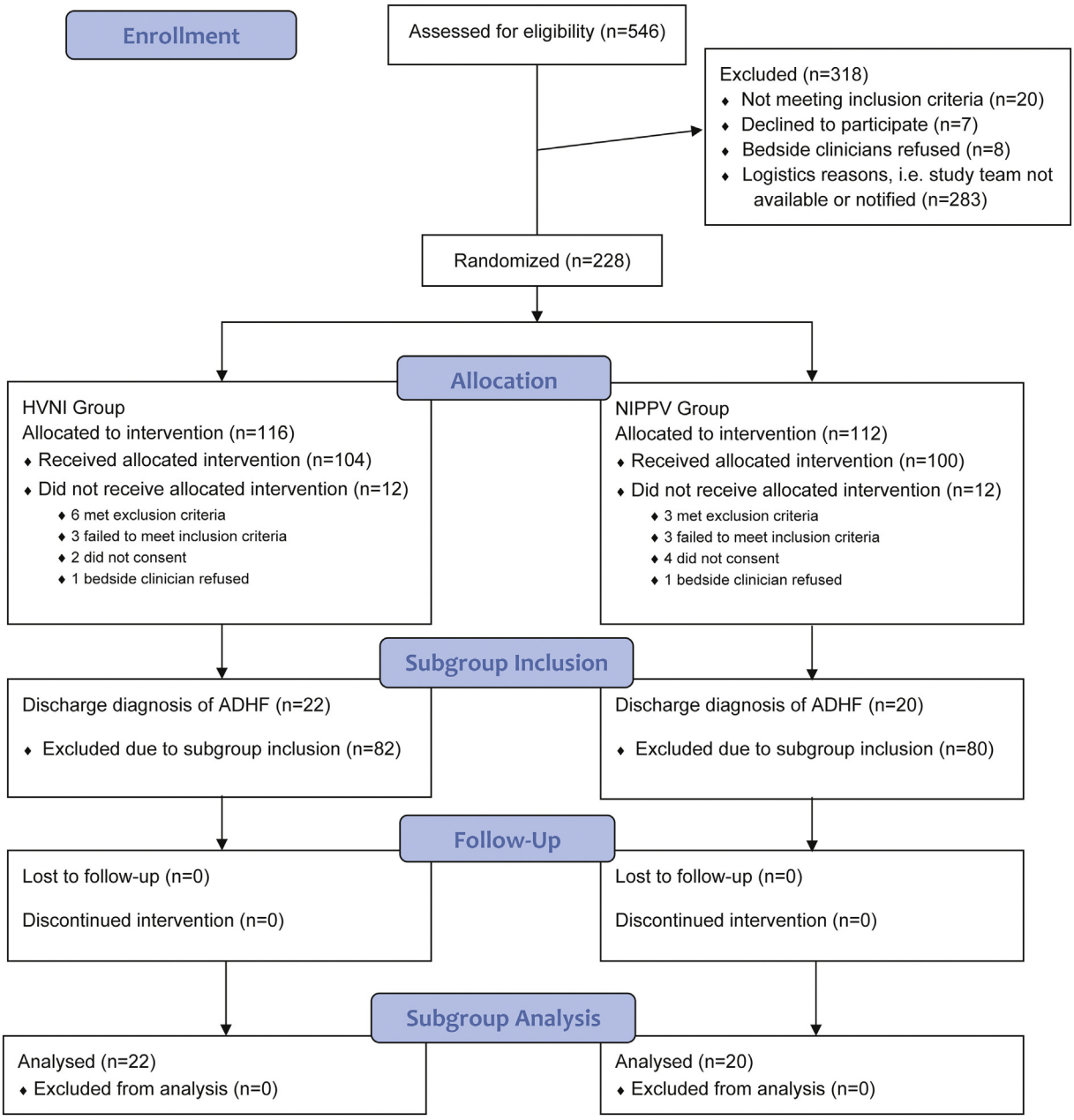

Fig. 1. Screening, randomization, enrollment, and subgroup selection of study participants.From October 2014 to September 2016, patients presenting to the ED with respiratory failure were screened and data was selected per *a priori* determined criteria of ADHF discharge diagnosis for this subgroup analysis. Screening failures were largely due to logistical reasons. For this subgroup analysis the distribution of patients was relatively even between HVNI ($N = 22$) and NIPPV ($N = 20$).

Based on our literature review, treatment of patients in RF secondary to ADHF with HFNC has previous only been discussed with case reports and case series [11,12]. The largest case series we identified only had 5 patients [11]. There has never been a head to head comparison between NIPPV and HFNC in this population. NIPPV has contraindications including uncooperative patients and aspiration risk [13]. NIPPV has also been associated with patient compliance challenges (30–50%) [14]. In a head to head comparison with NIPPV, HVNI has been shown to be more comfortable and tolerable, [4] and HFNC has also been shown to improve patient comfort [11,15-17]. In patients who cannot tolerate NIPPV, there is currently no other treatment option other than conventional oxygen therapy or intubation and mechanical ventilation. If HVNI can be shown to be non-inferior to NIPPV in ADHF patients presenting with RF, these patients would have an alternative therapeutic option.

The hypothesis of the original trial was that HVNI is non-inferior to NIPPV in treatment of undifferentiated RF with respect to therapy failure, as indicated by the requirement for intubation or all-cause arm failure including subjective crossover to the alternate therapy. The goal of this study was to assess in a subgroup analysis of a larger trial the ability of HVNI to support patients with RF secondary to ADHF in the ED who required ventilatory support. This subgroup analysis may provide important insight into the possible use of HVNI in the management of RF in ADHF and guide further research.

2. Methods

2.1. Study design

This subgroup analysis is from a previously published prospective, multicenter, parallel-group, randomized controlled trial of two non-invasive ventilatory support modalities: HVNI and NIPPV with a non-inferiority model. The original clinical trial was conducted in 2 academic and 3 community centers across the southeastern United States, with clinical management retaining site standard of care. The clinical study was approved by the site-specific institutional review boards (IRB; Committee for the Protection of Human Subjects, College of Medicine Chattanooga Scientific Review Board, McLeod Health IRB, Athens Regional Medical Center IRB, and University of Georgia IRB), and an independent data and safety monitoring board supervised study safety.

After randomization, all respiratory interventions were tracked for 72 h. After 72 h, patient conditions were marked long-term or progressive per ventilatory support needs. The primary endpoint of failure requiring intubation was used to build the statistical rationale for the original study. To maintain non-significant risk, the ability to disposition the patient *via* crossover to the alternative therapy was left to the clinician's discretion. This crossover was included in a co-primary endpoint of all-cause arm failure. All data was collected by each site team and compiled in a database. No individual de-identified participant data was shared. Data management & analysis was performed by a third-party data capture and management provider. Complete protocol of the original clinical study can be found online at http://www.annemergmed.com/ [4]. Discharge diagnosis was recorded for all patients in the original study dataset, and from this a subgroup patient data set was determined by patient discharge diagnosis of "acute decompensated heart failure". This discharge diagnosis was not differentiated for preserved or reduced injection factor due to pre-determined discharge designations.

2.2. Participant criteria

In the original study, adult patients with respiratory failure requiring escalation to NIPPV were enrolled upon presentation in the ED. Inclusion criteria were adults (over 18 years of age) presenting a clinical requirement by clinician with acute respiratory failure requiring an escalation of treatment to NIPPV or if patient was presented to ED while on NIPPV. Exclusion criteria are articulated in the original study [4]. Inclusion into this subgroup analysis was patients from the original study with a discharge diagnosis of

Table 1
Baseline characteristics of ADHF subgroup subjects.Data is reported as number (%) or median (IQR) and range (min–max) for each category. All sample sizes (N) are reported. Statistical significance ($p < 0.05$) was determined by Fisher's Exact (top) or Wilcoxon Rank Sum (bottom).

Characteristic	HVNI			NIPPV			*p*-Value
	N			N			
Gender	22	No. (%)		20	No. (%)		0.107
Female		17	(77.3)		10	(50)	
Male		5	(22.7)		10	(50)	
Race	22			20			0.1662
African		6	(27.3)		10	(50)	
Latino		3	(13.6)		3	(15)	
Caucasian		13	(59.1)		6	(30)	
Other		0	(0)		1	(5)	

Characteristic	N	Median (IQR)		[Range]	N	Median (IQR)		[Range]	*p*-Value
Age (yrs)	22	64.5	(59–77)	[41–95]	20	60	(53–71.5)	[44–90]	0.2074
BMI	22	32	(27.1–39.1)	[19.2–54.6]	20	32.8	(26.8–41.2)	[20.6–61.6]	0.7529
APACHE II score[b]	22	31.5	(30–37)	[24–45]	20	29	(28–34)	[22–42]	0.1689
Therapy setup time (min)	22	5	(5–15)	[3–30]	20	10	(5.5–13)	[5–26]	0.2102
Time to crossover (min)	22	0	(0–0)	[0–6]	20	0	(0–0)	[0–0]	0.365
Heart rate (beats/min)	22	93	(84–101)	[58–142]	20	106	(92–110)	[56–128]	0.0554
Respiratory rate (breaths/min)	22	33	(28–38)	[22–53]	20	34	(28–36)	[22–47]	0.8006
SpO_2 (%)	22	95.5	(93–100)	[76–100]	20	98.5	(94–100)	[78–100]	0.5587
Modified Borg score[a]	22	6	(3–9)	[0–10]	20	7	(5–9)	[3–10]	0.3909
pH	22	7.38	(7.27–7.45)	[7.2–7.65]	19	7.33	(7.32–7.38)	[7.16–7.46]	0.2717
PCO_2 (mm Hg)	22	42.5	(32–55)	[18–83]	19	42	(39–49)	[35–86]	0.5827
PaO_2, arterial (mm Hg)	15	82	(60–162)	[54–404]	16	116.5	(81–283.5)	[32–418]	0.206
Ratio of PaO_2/FiO_2, arterial	15	118	(60–166)	[54–404]	16	153.5	(81.8–283.5)	[32–418]	0.277

ADHF: Acute Decompensated Heart Failure; APACHE: Acute Physiology and Chronic Health Evaluation; BMI: body mass index.
[a] The modified Borg score is a self-reported rating of perceived dyspnea on a scale of 1 to 10.
[b] APACHE II scores were calculated from 15 variables at enrollment and health status and information obtained at admission.

Table 2
Primary study outcomes of ADHF subgroup.Statistical significance ($p < 0.05$) was determined by Fisher's Exact test. All categories and groups analyzed reported sample size $N = 22$ (HVNI) and $N = 20$ (NIPPV)

Characteristic	HVNI (N = 22)		NIPPV (N = 20)		p-Value
Success	No. (%)		No. (%)		1.000
No	1	(4.5)	0	(0)	
Yes	21	(95.5)	20	(100)	
Intubation					1.000
No	22	(100)	20	(100)	
Crossover					1.000
No	21	(95.5)	20	(100)	
Yes	1	(4.5)	0	(0)	

ADHF: Acute Decompensated Heart Failure.

acute decompensated heart failure. "Acute Decompensated Heart Failure" was established *a priori* in the original study as a discharge diagnosis of importance. Patients provided informed consent and the original study was performed under IRB approval, from which this subgroup data was collected.

2.3. Interventions

Patients were randomized to receive one of two therapies for the management of acute respiratory failure, NIPPV and HVNI. Randomization was performed using computer generated block randomization cards, sequentially numbered at each site, and maintained in opaque envelopes. Therapies included HVNI (Precision Flow, Vapotherm, Inc., Exeter, NH, USA) and NIPPV (Respironics Vision V60; Philips Healthcare, Murrysville, PA, USA). Both interventions were targeting relief of respiratory distress, indicated by reduction of respiratory rate to below 25 breaths per minute, and improved patient comfort, with fraction of inspired oxygen (FiO_2) also adjusted to maintain a pulse oxygen saturation above 88%. HVNI was implemented using a small-bore nasal cannula starting at a flow rate of 35LPM at 35-37C and $FiO_2 = 1.0$, and titrated to target. NIPPV was initiated *via* an oronasal mask, with initial pressures set at Inspiratory Positive Airway Pressure (IPAP) of 10 cmH_2O and Expiratory Positive Airway Pressure set at 5 cmH_2O, FiO_2 at 1.0, and titrated to target effect. During the first 4 h of the interventions, a respiratory therapist or other research clinician was present at bedside to adjust interventions as needed.

2.4. Measurements & collected outcomes

The primary outcome of failure of therapy, either requiring intubation or crossover to the alternative therapy, was recorded if occurring within the first 72 h after randomization and initiation of therapy. Criteria for recognition of therapy failure requiring intubation were stated in the original study (Failure criteria are further described in Doshi et al. Appendix E2, available online at

Table 3
Repeated time measures of ADHF subgroup data.Data presented as median (IQR) & range (min–max) for each characteristic with variable sample size (N). Blood gases are presented as arterial and venous, expect in the oxygenation measure of PaO_2.

Characteristic	HVNI				NIPPV			
	N	Median (IQR)		[Range]	N	Median (IQR)		[Range]
Heart rate (beats/min))								
Baseline	22	93	(84–101)	[58–142]	20	106	(92–110)	[56–128]
30 min	21	88	(76–96)	[58–125]	20	90	(84–101)	[52–123]
60 min	21	90	(76–98)	[51–125]	20	86.5	(72.5–99.8)	[52–118]
90 min	21	87	(78–93.5)	[54–126]	20	86.5	(73.3–98)	[54–118]
240 min	21	85	(76.5–97)	[49–126]	19	78	(74–95)	[58–113]
Respiratory rate (breaths/min)								
Baseline	22	33	(28–38)	[22–53]	20	34	(28–36)	[22–47]
30 min	21	27	(23–28)	[16–36]	20	26.5	(22–30)	[20–37]
60 min	21	24	(22–26)	[14–38]	20	24	(18.5–27)	[13–33]
90 min	21	23	(20–25)	[18–38]	20	22.5	(20–28)	[16–34]
240 min	21	20	(20–26)	[16–39]	19	21	(20–24)	[16–34]
SpO_2 (%)								
Baseline	22	95.5	(93–100)	[76–100]	20	98.5	(94–100)	[78–100]
30 min	21	99	(99–100)	[96–100]	20	100	(100–100)	[94–100]
60 min	21	99	(98–100)	[94–100]	20	100	(98–100)	[95–100]
90 min	21	98	(97–100)	[95–100]	20	99	(97–100)	[91–100]
240 min	21	99	(98–100)	[94–100]	19	98	(97–100)	[95–100]
Modified Borg score[†]								
Baseline	22	6	(3–9)	[0–10]	20	7	(5–9)	[3–10]
30 min	21	4	(2.5–6.5)	[0–8]	20	4	(3–7)	[1–8]
60 min	21	3	(2–4)	[0–7]	19	4	(3–4)	[1–7]
90 min	21	3	(2–5)	[0–6]	20	3	(2–3.75)	[0–8]
240 min	21	2	(1–3)	[0–7]	17	2	(1.5–2.5)	[0–3]
pH								
Baseline	22	7.38	(7.27–7.45)	[7.2–7.65]	19	7.33	(7.32–7.38)	[7.16–7.46]
60 min	21	7.37	(7.31–7.42)	[7.23–7.54]	20	7.35	(7.32–7.40)	[7.22–7.54]
240 min	21	7.39	(7.34–7.42)	[7.23–7.53]	19	7.38	(7.35–7.40)	[7.25–7.48]
PCO_2 (mm Hg)								
Baseline	22	42.5	(32–55)	[18–83]	19	42	(39–49)	[35–86]
60 min	21	45	(38–53)	[27–86]	20	40.5	(37.5–46.2)	[28–66]
240 min	21	43	(38–49)	[22–94]	19	39	(36–47.2)	[32–64]
PaO_2, arterial (mm Hg)								
Baseline	15	82	(60–162)	[54–404]	16	116.5	(81–283.5)	[32–418]
60 min	15	90	(77–197)	[23–296]	17	171	(128–260)	[71–502]
240 min	15	98	(71–140)	[25–154]	16	79	(65.25–93.5)	[39–120]
Ratio of PaO_2/FiO_2, arterial								
Baseline	15	118	(60–166)	[54–404]	16	153.5	(81.8–283.5)	[32–418]
240 min	15	200	(106.7–260)	[50–260]	16	202.9	(159.1–272.5)	[85.3–306.7]

ADHF: Acute Decompensated Heart Failure.
[†] The modified Borg score is a self-reported rating of perceived dyspnea on a scale of 1 to 10.

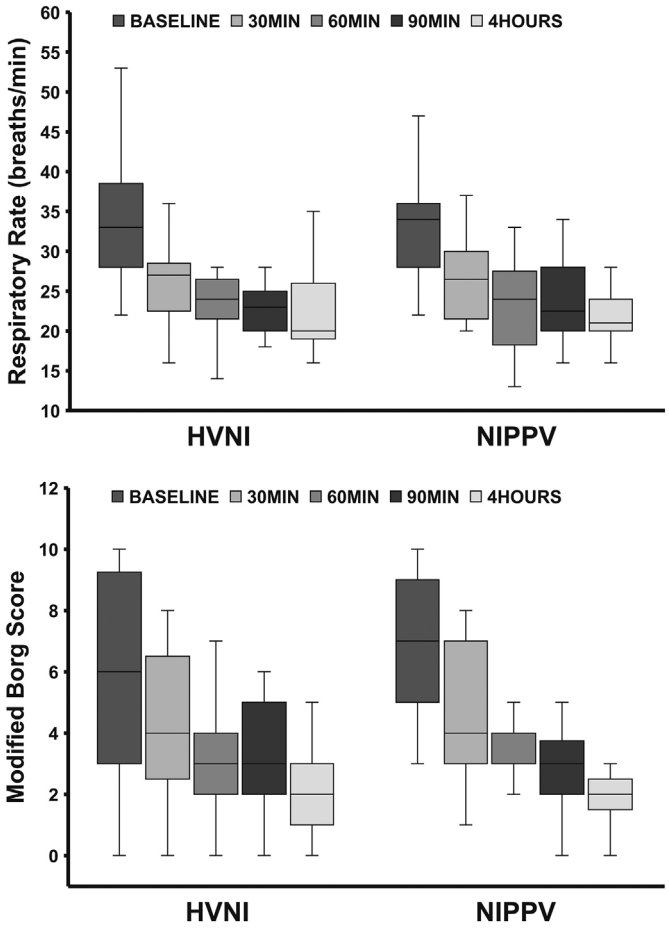

Fig. 2. Respiratory rate and Modified BORG score over 4 h after therapy initiation. Selected repeated measures are presented as a box plot. HVNI and NIPPV demonstrate a downward trend in the respiratory rate (top) and the modified Borg score (bottom). Data is reported over initial monitoring period (4 h) of the original study. The modified Borg score is a self-reported rating of perceived dyspnea on a scale of 1 to 10.

http://www.annemergmed.com) [4]. The additional criteria of clinician perception were added for a decision to crossover to the alternative therapy.

Secondary outcomes of the original study included evaluation of HVNI and NIPPV over time to affect patient blood gases, and other signs or symptoms of respiratory failure, including vital signs and perceived dyspnea and exertion scores reported by the patients. Vital signs were recorded at baseline and every 30 min for the first 90 min, and at 4 h after therapy initiation. Baseline and post-initiation blood samples were drawn at 0, 1, and 4 h. Blood gases could be either arterial or venous, but were methodically consistent across all time points per patient. FiO2 data was recorded at therapy initiation and 4 h post-initiation, which allowed for calculation of patient PaO_2/FiO_2 ratios when complete arterial blood gas data was recorded. While PaO_2/FiO_2 ratio is frequently used to determine ARDS, it is also commonly used as a measure of a patient's oxygenation status [18]. Our patient population did not have ARDS as left sided heart failure patients are excluded from the diagnosis of ARDS [18]. Physician assessment (based on a scale of 1 to 5, with 5 being a more positive value) of the therapy included respiratory response, technical or clinical difficulties, patient comfort and tolerance, simplicity of setup and use, and monitoring and support required for the therapy.

2.5. Data analysis

The initial study was designed and appropriately powered for evaluating the failure (intubation and all-cause) rate for HVNI v NIPPV in an adult undifferentiated respiratory failure group presenting in the ED. [4] This was a subgroup data analysis of the primary randomized clinical study participants. There was no requirement for the original study to power for subgroup analyses. An independent statistician performed all analyses presented in this study. Statistical significance was accepted where $p < 0.05$. Statistical analysis was performed using SAS (version 9.3; SAS Institute, Inc., Cary, NC) and MedCalc (v 18, MedCalc Software bvba, Brussels, Belgium). Statistical tests implemented were Wilcoxon Rank Sum test, or Fisher's Exact test. For the time course measures a two-way repeated measures (RM) ANOVA was performed for time and therapy. Categorical data reported as number and percent of population. Continuous data are reported as median with interquartile range (IQR), and range as minimum to maximum.

3. Results

3.1. Characteristics of ADHF study subjects

Patients were recruited from October 2014 to September 2016. This subgroup analysis was from an original study of 228 patients, of which 204 were randomized and enrolled into the two study arms: the HVNI group with 104 patients, and the NIPPV group with 100 patients. The subgroup analysis included a total of 22 HVNI and 20 NIPPV patients which fit inclusion criteria of discharge diagnosis acute decompensated heart failure, established *a priori* in original study (Fig. 1). For this subgroup analysis, the patient demographics (Table 1) are all comparable between HVNI and NIPPV, with no statistical difference in gender, race, age, and body mass index (BMI). The baseline patient characteristics (Table 1) were not statistically significantly different between HVNI and NIPPV, including therapy setup time ($p = 0.210$), time to crossover ($p = 0.365$), patient vitals, and blood gases. Patient blood gases (PCO_2 and pH) are analyzed and reported for both arterial and venous. Patient oxygenation measures for blood gases (PaO_2 and SaO_2) are analyzed and reported for arterial only.

Table 4
Clinician perception scores of ADHF subgroup.Data presented as median (IQR) & range (min–max) for each characteristic. All categories and groups analyzed reported sample size $N = 20$. Statistical significance ($p < 0.05$) was determined by Wilcoxon Rank Sum test.

Characteristic	HVNI (N = 20)			NIPPV (N = 20)			p-Value
	Median (IQR)		[Range]	Median (IQR)		[Range]	
Patient respiratory response (1-insufficient, 3-adequate, 5-excellent)	5	(4–5)	[2–5]	4	(3–5)	[2–5]	0.081
Patient comfort/tolerance (1-insufficient, 3-adequate, 5-excellent)	5	(5–5)	[3–5]	3	(3–4)	[2–5]	<0.001
Technical & clinical difficulties (1-frequent, 3-occasional, 5-excellent)	5	(5–5)	[3–5]	5	(3–5)	[3–5]	0.979
Simplicity of use (1-complex, 3-typical, 5-simple)	5	(4–5)	[3–5]	3	(3–5)	[3–5]	0.004
Monitoring required (1-complex, 3-typical, 5-simple)	5	(3–5)	[1–5]	3	(3–4.5)	[2–5]	0.036

3.2. Main results of ADHF study subjects

The primary outcomes of the ADHF subgroup analysis are presented in Table 2, specifically therapy success, intubation rate, and crossover. The intubation rate for patients assigned to both HVNI and NIPPV was not statistically significant ($p = 1.000$), with no intubations (0%) in both groups of the ADHF patients. Similarly, the success of HVNI (95.5%, $N = 21/22$) was not statistically significant (p = 1.000) from success of NIPPV (100%, $N = 20/20$). There was a single instance of crossover in the HVNI group (4.5%) to NIPPV with no crossover from NIPPV (0%) to HVNI. Table 1 demonstrates that for this single patient in the HVNI group, the crossover time was within 10 min of therapy initiation. Table 1 also demonstrated that the crossover time for the two study groups was not statistically significant ($p = 0.365$). All patient data was available for the primary outcomes of the ADHF patients within this subgroup analysis of the HVNI ($N = 22$) and NIPPV (N = 20) study arms.

3.3. Repeated measures results of CHF study subjects

The repeated measures results of the ADHF subjects consist of patient vitals, perceived dyspnea, and blood gases (see Table 3). Patient blood gases (PCO_2 and pH) are analyzed and reported for both arterial and venous. Patient oxygenation measures of PaO_2 and PaO2/FiO2 ratio are analyzed and reported for arterial only. Two-way repeated measures (RM) ANOVA (time and therapy) tests were performed for the patient vitals (Heart Rate, Respiratory Rate, SpO_2), perceived dyspnea (modified Borg score), and blood gases (pH, PCO_2, PaO_2). Fig. 2 demonstrates the downward trend of the respiratory rate (Fig. 2 top) and the modified Borg score (Fig. 2 bottom) in both study arms. Two-way RM ANOVA demonstrated comparable differences over time between HVNI and NIPPV for the patient vitals and perceived dyspnea over initial 4 h of therapy. Two-way RM ANOVA demonstrated comparable differences over time between HVNI and NIPPV for the patient blood gases over initial 4 h of therapy.

3.4. Clinician perception scores of CHF study subjects

The original clinical study recorded the clinician perception measures of each randomized and enrolled patient. These scores included patient respiratory response, patient comfort and tolerance, technical and clinical difficulties, simplicity of therapy use, and level of required monitoring (see Table 4). The physicians gave superior scores for HVNI for patient comfort and tolerance ($p < 0.001$), simplicity of use ($p = 0.004$), and monitoring required ($p = 0.036$).

4. Discussion

Acute decompensated heart failure presents regularly in the emergency department, where NIPPV has been utilized to improve morbidity and mortality [2]. The data in our study supports the hypothesis that HVNI is non-inferior to NIPPV in patients presenting to the Emergency Department in RF secondary to ADHF. Our primary outcome of treatment failure showed no difference, with a p value of 1.

An important finding of our study was the improvement in the physician perceived patient comfort of HVNI compared to NIPPV. This finding is consistent with previous studies that showed an improved patient comfort level with HFNC [15-17]. A large contributor to the cardiopulmonary decompensation of patients in heart failure is increased catecholamine release which redistributes splanchnic blood flow [19]. Many of our current therapies for acute treatment of this population are directed at countering this increased sympathetic surge. In many patients, a tight-fitting mask increases agitation. This may increase sympathetic tone, thereby counter acting our resuscitative efforts.

In addition to fighting the sympathetic surge, HFNC has been shown to decrease myocardial preload as measured by inferior vena cava dynamics using ultrasound [8]. Several factors could be contributing to this decrease in preload. First, the positive intrathoracic pressure exerted by HFNC is hypothesised to cause this effect. Secondly, HFNC has been demonstrated to decrease the patient's inspiratory force exerted as it decreases the patient's work of breathing [16]. In previous studies, this was demonstrated by increased esophageal pressures during inspiration before and after HFNC was applied. This improvement will also increase the patient's intrathoracic pressure. The combined effect of the positive pressure and causing the patient to create less negative pressure would account for the demonstrated decrease in myocardial preload.

For patients that require extended respiratory support, those treated with HVNI can more easily communicate, receive oral medications, and eat without interruption of therapy, which are limitations of NIPPV. Physician perception scores further demonstrated HVNI provided improved ease of use and reduced monitoring needs. Lastly, the subjects of this study come from a generalizable patient population across multiple care settings [4]. The trial was conducted in 5 centres (2 academic and 3 community) across the southeastern United States.

Among the limitations of this study, the most important was the fact that this study was not powered for subgroup analysis. Since this cohort was a subgroup, frequency of use and dose of non-respiratory treatments for ADHF such as nitrates and diuretics were not recorded. This lack of data does present a potential unmeasured variable. We also were limited by our 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. Although criteria for failure were presented in the protocol, the determination of arm failure and crossover were ultimately at the discretion of the attending physician. While no patients in our analysis required intubation, based on the initial PaO_2/FiO_2 ratios, our patients consistently had an oxygenation deficit. Additionally, a 2013 Cochrane review showed only around 13% of patients with ADHF treated with NIPPV require intubation [2]. While we were underpowered, the numbers of patients in our study far exceeds those of previous observational studies that we identified. In addition, none of the previous studies have utilized a comparison group.

This subgroup analysis suggests that HVNI may be non-inferior to NIPPV in patients presenting to the ED with respiratory failure secondary to ADHF that do not require emergent intubation. This provides permission to use HVNI in these cases. A subsequent, prospective randomized control trial is needed to confirm our results.

Disclosure statement

All authors attest to meeting the four ICMJE authorship criteria. All authors, except for primary author Steven T Haywood, report receiving study-related support from Vapotherm, Inc. Dr. Doshi reports receiving funding from Zoll Inc. for coordination of the clinical trial. Dr. Miller, Dr. Volakis, and George Dungan MPhil (Med) were employed by Vapotherm. The original clinical study was sponsored by Vapotherm, which participated in study design and selection/management of each site. The study sponsor, Vapotherm, agreed *a priori* to allow publication of study findings at discretion of the principal investigators. For the study's subgroup analyses, all analysis and results interpretations were determined by the pri-

mary author and principal investigators. Primary author and principal investigators wrote the first draft, approved edits to subsequent drafts of article, and made decision to submit for publication.

ADHF: acute decompensated heart failure.

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References

[1] Writing Group, M, et al., Heart Disease and Stroke Statistics-2016 *Update: A Report From the American Heart Association* Circulation, 2016. 133(4): e38–360.
[2] Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev 2013(5):CD005351.
[3] Makdee, O., et al., High-flow nasal cannula versus conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. Ann Emerg Med, 2017. 70(4): p. 465–472 e2.
[4] Doshi P et al. High-velocity nasal insufflation in the treatment of respiratory failure: a randomized clinical trial. Ann Emerg Med 2018;72(1):73–83 (e75).
[5] Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. Respir Care 2013;58(10):1621–4.
[6] Kuhn BT et al. Management of mechanical ventilation in decompensated heart failure. J Cardiovasc Dev Dis 2016;3(4).
[7] Luecke T, Pelosi P. Clinical review: positive end-expiratory pressure and cardiac output. Crit Care 2005;9(6):607–21.
[8] Roca O et al. Patients with New York Heart Association class III heart failure may benefit with high flow nasal cannula supportive therapy high flow nasal cannula in heart failure: high flow nasal cannula in heart failure. J Crit Care 2013;28(5):741–6.
[9] Kormos, R.L. and L.W. Miller, Mechanical Circulatory Support: Companion to Braunwald's Heart Disease. 1 ed. Companion to Braunwald's Heart Disease. 2012: Saunders. 384.
[10] Miller TL, Saberi B, Saberi S. Computational fluid dynamics modeling of Extrathoracic airway flush: evaluation of high flow nasal cannula design elements. Journal of Pulmonary & Respiratory Medicine 2016;6(5):376.
[11] Carratalá Perales JM et al. High-flow therapy via nasal cannula in acute heart failure. Revista Española de Cardiología (English Edition) 2011;64(8):723–5.
[12] Moriyama K et al. High-flow nasal cannula therapy in a patient with reperfusion pulmonary edema following percutaneous transluminal pulmonary angioplasty. Case Rep Pulmonol 2014;2014:837612.
[13] Marino, P.L., *Marino's the ICU book*. Fourth edition ed. 2014: Lippincott Williams & Wilkins xv, 1059 pages.
[14] Carron M et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. Br J Anaesth 2013;110(6):896–914.
[15] Rittayamai N et al. Use of high-flow nasal cannula for acute dyspnea and hypoxemia in the emergency department. Respir Care 2015;60(10):1377–82.
[16] Vargas F et al. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. Respir Care 2015;60(10):1369–76.
[17] Nishimura M. High-flow nasal cannula oxygen therapy in adults. J Intensive Care 2015;3(1):15.
[18] Parrillo, J.E., Critical care medicine : principles and diagnosis and management in the adult. 5th ed. 2019, Philadelphia, PA: Elsevier. Chapter 36 pp 591–604.
[19] Harjola VP et al. 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 2017;19(7):821–36.